MUSCULOSKELETAL PAIN AND AGEING

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To Barbara
Candidate’s Statement

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Abstract

Musculoskeletal pain is a complex phenomenon involving biomechanics, inflammation and central pain processing pathways. The ageing process and age-related conditions can affect the course of musculoskeletal pain; conversely, the presence of pain can affect the ageing process, contributing to increased risks of adverse health outcomes. Despite the importance of managing pain in older adults, questions remain in terms of the best approach as the use of analgesics in this population is associated with increased risks of adverse events. This thesis contributes to the current knowledge of how age-related conditions such as multimorbidity and frailty interact with musculoskeletal pain and its management. The specific aims are: a) to determine whether frailty status is a risk factor for development of chronic or intrusive musculoskeletal pain; b) to determine whether pain increases the risk of developing the frailty phenotype; c) to describe the current management of vertebral compression fractures, a common and painful musculoskeletal condition typically seen in older adults; and d) to review and appraise the literature on the efficacy and safety of opioid analgesics for older adults with musculoskeletal pain.

To address the first and the second aims, longitudinal data from the Concord Health and Ageing in Men Project (CHAMP), a prospective population based cohort study, were used. A total of 1705 men aged 70 years or older, living in an urban area of New South Wales, Australia, were included in the CHAMP baseline study. Data on the presence of chronic pain (daily pain for at least 3 months), intrusive pain (pain causing moderate to severe interference with activities) and the criteria for the Cardiovascular Health Study frailty phenotype were collected in three waves, from
January 2005 to October 2013. After adjusting for potential confounders, no association between frailty and future chronic or intrusive pain was observed. However, non-frail (robust and pre-frail) men who reported chronic pain were 1.60 (95% confidence interval (CI): 1.02 to 2.51, p=0.039) times more likely to develop frailty at follow-up, compared to those with no pain. For those reporting intrusive pain, the odds of developing future frailty were 1.64 (95%CI: 0.97-2.78, p=0.063). In summary, the presence of chronic pain increased the risk of developing the physical frailty phenotype in community-dwelling older men.

To address the third aim, data from the Bettering the Evaluation And Care of Health (BEACH) program collected between April 2005 and March 2015 were used. Each year, a random national sample of approximately 1,000 GPs each recorded information on 100 consecutive patient encounters. All encounters at which vertebral compression fracture was managed were selected. Vertebral compression fractures were managed in 211 (0.022%; 95% CI: 0.018–0.025) of the 977,300 BEACH encounters recorded April 2005–March 2015. At encounters with patients aged 50 years or over, prescription of opioids analgesics (47.1 per 100 vertebral fractures; 95% CI: 38.4–55.7) was the most common management action. Prescriptions of paracetamol (8.2 per 100 vertebral fractures; 95% CI: 4-12.4) or non-steroidal anti-inflammatory drugs (4.1 per 100 vertebral fractures; 95% CI: 1.1-7.1) were less frequent. Non-pharmacological treatment was provided at a rate of 22.4 per 100 vertebral fractures (95% CI: 14.6-30.1). In summary, prescription of oral opioid analgesics remains the commonest general practice approach for vertebral compression fractures management, despite the lack of evidence to support this approach.
The fourth aim concerns the efficacy and safety of using opioid analgesics in older adults with musculoskeletal pain. A systematic review with meta-analysis was performed including 23 randomized controlled trials with mean population age of 60 years or older that compared the efficacy and safety of opioid analgesics with placebo for musculoskeletal pain conditions. Opioid analgesics had a small effect on decreasing pain intensity (Standardised mean difference (SMD): -0.27; 95% CI: -0.33 to -0.20) and improving function (SMD: -0.27, 95%CI: -0.36 to -0.18), which was not associated with daily dose or treatment duration. The risk of adverse events was three times higher (OR: 2.94; 95% CI: 2.33 to 3.72) and treatment discontinuation four times higher (OR: 4.04; 95% CI: 3.10 to 5.25) in opioid treated patients. The systematic review concluded that, in older adults suffering from musculoskeletal pain, using opioid analgesics had only a small effect on pain and function at the cost of a higher risk of adverse events and treatment discontinuation. Therefore, for this specific population, the opioid-related risks may outweigh the benefits.

From the results presented in the chapters of this thesis, important conclusions can be drawn: a) chronic musculoskeletal pain increases the risk of developing frailty in older adults and therefore, pain management should be part of a potential strategy to prevent frailty; b) despite being commonly prescribed for musculoskeletal pain in older adults, opioid analgesics alone are not likely to result in significant relief of chronic pain in these patients; c) instead of recommending opioid analgesics for persistent pain in older patients, guidelines should recommend comprehensive pain assessment, multimodal strategies and multidisciplinary approaches.
CHAPTER ONE

Introduction
Treating older patients suffering from musculoskeletal pain, particularly chronic musculoskeletal pain, is quite complex. Not only the ageing process and age-related health conditions affect the course and the management of musculoskeletal diseases but also the presence of pain can affect how well these patients age. This thesis reviews the mechanisms of pain underlying the most common musculoskeletal conditions affecting older adults; the influence of ageing and age-related health conditions on pain; and the current literature on pharmacological pain management in older adults. In addition, important gaps in the literature are identified. In order to bridge these gaps, this thesis has focused in addressing the following clinical questions: a) Are frail older adults at increased risk of developing chronic or intrusive pain? b) Does the presence of pain increase the risk of developing the frailty phenotype? c) How have clinicians been treating pain in patients with vertebral compression fractures (a condition typically seen in older adults)? d) What is the role of opioid analgesics in the management of older patients with musculoskeletal pain?

1.1 The burden of musculoskeletal pain in older adults

The prevalence of degenerative musculoskeletal conditions increases steadily with age, as does the prevalence of musculoskeletal pain. Around one in every two adults older than 65 years is affected by symptomatic arthritis (1), most commonly in the knees (2, 3) and hips (4); and one in every five reports back pain (5). Musculoskeletal pain is known to result in severe disability and impaired quality of life in older adults (6). Scudds and Robertson have conducted a cross-sectional study including 885 community-dwelling older Canadians and found that the presence of severe pain increased fourfold the odds of disability (7). This could be explained by the higher number
of associated comorbidities, reduced physiologic reserves, slower rate of tissue healing (8) and accelerated muscle loss after a period of rest (9) observed in people aged 60 or older. In another cross-sectional study, at least one third of community-living older women attributed their difficulties in basic and instrumental activities of daily living (ADL) to musculoskeletal pain; and one quarter of women who had difficulties walking 0.25 miles reported hip or knee osteoarthritis as the main cause for their mobility impairment (10). Musculoskeletal pain in older adults is not only highly prevalent and frequently disabling but also very costly, particularly considering the increasing role of surgical treatment in this condition (11, 12).

Despite the burden associated to musculoskeletal pain in older adults, there is limited research guiding the best and most appropriate management for this condition. Older adults constitute a very heterogeneous group of individuals and probably the best management of musculoskeletal pain depends on factors other than the age itself. Particularly, the presence of comorbidities, pain-related functional impairment and the frailty status seem to be important variables to be considered managing musculoskeletal pain in older adults.

1.2 The contribution of coexisting conditions to the burden of musculoskeletal pain

As the population ages, the prevalence of multiple coexisting diseases has increased substantially (13). In Australia, 57.2% of people aged 65 years or more attending to primary care services have three or more diagnosed chronic conditions and 9.4% have seven or more diagnosed chronic conditions (14). The effects of accumulated comorbid load (i.e. multi-morbidity) in individuals with musculoskeletal pain, however, are not fully understood.
Individuals dealing with the management of multiple conditions are exposed to chronic stress and usually have more psychological, behavioural and social demands (15). While short-term fluctuations in stress-induced responses are needed to successfully deal with a particular stressor, excessive activation of stress, arousal and attentional circuits could increase nociception from periphery (16, 17) resulting in changes in pain modulation and processing.

Frailty is also an important contributor to the burden of musculoskeletal pain. Several studies have shown the association between pain and frailty in different populations (18-24). Frailty-related changes in the brain might impair descending inhibitory pain pathways increasing pain intensity in frail individuals. Moreover, hypothalamic-pituitary-adrenal (HPA) axis dysfunction, commonly associated with frailty (25), might contribute to chronic pain (26). Another explanation for such association is that persistent pain might lead to mobility impairment, depressive symptoms, lack of sleep, loss of appetite, and increase in the burden of medical comorbidities, a phenomenon called “pain homeostenosis”, that could precipitate or worsen frailty (22).

Therefore, in order to understand the burden of musculoskeletal pain in older adults, frailty status as well as age, gender, presence of multi-morbidity and other health-related features must be considered. Those health-related aspects of the older patient, added to non-health-related factors such as socioeconomic status, cultural background, health beliefs and locus of control (27) bring greater complexity, to the clinical management of musculoskeletal pain in this population.
1.3 Pain in musculoskeletal conditions

It is known that more than 50% of older adults are affected by symptomatic arthritis (1), most commonly in their knees, hips, hands and spine. Around 25% of people over 55 years have knee pain, mostly due to osteoarthritis (3). Also, 5% of people over 65 years have radiologic signs of hip osteoarthritis (4). In the spine, radiographic signs of disc or joint degeneration can be found in more than 90% of older adults and around 20% will report back pain (5). It is important to highlight that painful musculoskeletal conditions in older adults often occur together as comorbidities. In the following sections, the most common musculoskeletal conditions affecting older patients will be discussed. Particular attention will be paid to the mechanisms of pain underlying these conditions.

1.3.1 Osteoarthritis

The source of pain in osteoarthritis is not fully understood. Mechanical and inflammatory factors are not sufficient to explain the differences between pain intensity and the degree of joint damage in a lot of patients (28). In the past, osteoarthritic pain was believed to be mostly of nociceptive nature (i.e. caused by damage to body tissues). However, the observation that some patients with osteoarthritis can feel pain at sites distant from the inflamed joints and also report increased tenderness over supposedly normal tissues suggests changes in central modulation of pain might contribute to pain in osteoarthritis (29). Damage to articular cartilage has received substantial attention in the pathophysiology of osteoarthritis; however, its importance in the mechanism of pain is limited. Since cartilage tissue is both avascular and aneural, pain must be
arising from other structures such as joint capsules, ligaments, synovium or bones (30). Particularly, synovium inflammation (31) and bone marrow lesions (32) seem to be important sources of pain in osteoarthritis.

1.3.2 Degenerative spine conditions

Mechanical low back pain can originate from many structures of the spine, including intervertebral discs, facet joints, ligaments, paravertebral musculature and fascia, and spinal nerve roots (33). Lumbar disc degeneration is believed to be the most common cause of low back pain in older adults. Unfortunately, there is no clear boundary between the aging changes and pathological degeneration of the disc (34). Degenerative spine conditions are very common in older adults, but are often asymptomatic. For instance, disc herniation is found in around 40% of asymptomatic 80-years-old individuals, whilst signs of disc degeneration are found in almost all of them (35).

Another common source of low back pain in older people is osteoarthritis of the facet joints (36). Facet joints are synovial joints in the spine and subject to the same degenerative and inflammatory changes observed in other synovial joints (37). Particularly in older adults, two conditions contribute to higher prevalence of facet joint osteoarthritis: disc degeneration and paraspinal muscle weakness. Degenerative disc disease and facet joint osteoarthritis are frequently associated given that lesions which affect the disc tend to also have an effect on the facet joints (36). In some patients, the degenerative process in the spine can lead to hypertrophy of vertebral joint facets, bulging of the intervertebral disc and thickening of ligamentum flavum,
narrowing the spinal canal (38). This condition, called spinal stenosis, can result in symptoms of neurogenic claudication (39), low back pain and radiculopathy.

Besides the above mentioned conditions, osteoporotic vertebral fractures should also be considered as a possible cause of low back pain in older adults (40, 41). These fractures are seldom seen in younger adults but are particularly common in older women (42, 43). They can cause significant acute pain at the time of their occurrence (44, 45) and can also cause persistent pain, compromising function and quality of life (46-51). Chapter Three of this thesis will focus on this condition.

1.3.3 Myofascial syndrome and fibromyalgia

The two most common conditions associated with muscular pain in older adults are myofascial pain syndromes and fibromyalgia. Despite their overlapping features, these are separate entities. In myofascial pain syndromes, the pain is often regional and occurs in physiologically abnormal muscles as the presence of taut bands are usually necessary for the development of trigger points (52). On the other hand, no structural or functional abnormalities are found in the muscle tissue of fibromyalgia patients, and pain is caused by dysfunctional pain processing mechanisms in the central nervous system (53). The augmentation of pain signals within the spinal cord through central sensitisation seems to be the most important factor in the development of fibromyalgia (54).
1.4 Pain processing

In bones and joints, pain signals are carried by A-delta and C fibres (peripheral nociceptors). The thinly myelinated A-delta fibres are involved in the rapid detection and signalling of nociceptive stimuli such as pin pick and noxious mechanical stimuli, leading to an acute sensation of sharp pain. The unmyelinated C fibres, on the other hand, respond to a broader range of painful stimuli, producing slow, burning, and long lasting pain (55).

The peripheral nociceptor neuron enters the spinal cord through the dorsal horn, where it synapses with a second-order neuron. Depending on stimulation frequency and intensity, a postsynaptic output may be produced. Pain-related signals then ascend in contralateral spinothalamic tract to the thalamus (56).

The thalamus receives pain inputs from spinothalamic tract and brainstem, acting as a relay centre for cortical afferent information. In the lateral thalamus, the second-order neuron synapses with the third-order neuron, which projects via the internal capsule and corona radiata to the primary somatosensory cortex (S1). This pathway is responsible for the sensory discriminative component of pain. The medial thalamus, on the other hand, projects diffusely to wide areas of the cortex making up the “medial pain system” that modulates the affective dimension of pain and control autonomic activity (57). As a result, the involvement of the cortex in pain processing is not restricted to S1. Indeed, others cortical and subcortical brain regions were found to be commonly activated by nociceptive stimulation, such as the secondary somatosensory cortex (S2), anterior cingulate cortex, anterior insula, prefrontal cortex, posterior
parietal cortex and amygdala (58, 59). The amygdala, particularly, which is associated with biological responses to emotions, anxiety, and stress, is believed to be very important in central pain processing, integrating pain, fear and anxiety.

As soon as the painful stimulus reaches the brain, the descending pain modulatory circuit, which includes the amygdala, thalamus, periaqueductal grey region, locus ceruleus, rostral ventromedial medulla and dorsal reticular nucleus, is activated. The activation of this descending circuit results in decreased pain perception in areas away from the stimuli. The presence of persistent musculoskeletal pain can decrease the efficacy of the descending pain control (60) and can contribute to the development of widespread pain in patients with musculoskeletal conditions. Higher cortical functions can also positively or negatively modulate nociceptive inputs and contribute to this endogenous pain regulatory system. Anxiety (61) and attention (62) seems to be particularly important.

In summary, pain processing is highly complex and dynamic, and involves tissue damage, nociceptive inputs, cortical pain responses (activation of the descendental pain inhibitory pathways), attention, anxiety, cultural factors, past experiences and many other variables (63). That makes pain a feeling that varies in intensity according not only to the source of pain but also the individual who is suffering from pain.
1.5 The effect of age and age-related conditions on musculoskeletal pain

1.5.1 Effect of age on osteoarthritis and degenerative spine conditions

Like most of the age-related conditions, osteoarthritis results in part from loss in the efficiency of cells and tissues to maintain homeostasis, notably under stress. Chondrocyte senescence caused by oxidative stress, low grade inflammation, decreased levels or decreased growth factors responsiveness, decreased autophagy and increased matrix calcification are some mechanisms probably involved in the loss of joint homeostasis (64, 65). It is rare to find older adults without radiographic signs of osteoarthritis in at least one joint. Besides degenerative changes in meniscus and joint ligaments, increased joint laxity, increased bone turnover, subchondral bone marrow lesions and calcification of joint tissues (65, 66) sarcopenia and altered proprioception are also relevant factors involved in the higher susceptibility to osteoarthritis in older adults.

In the spine, ageing-related degeneration begins in the discs, in which decreased vascularization affect the ability of disc cells to synthesize the extracellular matrix (34), causing the discs to lose fluids and proteoglycans (33). Macroscopically, the disc height decreases, the border between nucleus and annulus become less distinct and concentric fissuring and radial tears may appear. Disc degeneration, in turn, causes osteoarthritis of facet joints, which is characterized by joint hypertrophy, apophyseal malalignment, degenerative instabilities including spondylolisthesis, and osteophyte formation. The ageing-related spinal changes are also responsible for foraminal and central canal stenosis, frequently observed in older adults (36, 38).
1.5.2 Effect of age-related inflammation on the joint

Several studies have shown higher levels of C-reactive protein (CRP), interleukin-6 (IL-6) and tumour necrosis factor alpha (TNF-α) in older people. This low-grade pro-inflammatory state produced by the ageing process seems to be critical in many ageing-related diseases such as Alzheimer’s disease, atherosclerosis and macular degeneration (67).

Although osteoarthritis has been traditionally classified as a non-inflammatory arthritis, synovitis is present in a significant proportion of patients (68). In addition to local inflammation, age-related systemic inflammation, also referred to as “inflamm-ageing”, have been associated with joint tissue destruction, pain and disability (69). This is particularly true in older adults with higher levels of CRP (70) or IL-6 (71).

1.5.3 Effect of age on pain processing

Although some studies have shown that older adults have relatively lower levels of pain complaints in several clinical conditions such as myocardial ischemia, intra-abdominal infections, cancer, and inflammatory diseases (72), it does not necessarily mean that there is an age-related decrease in pain sensitivity per se. Actually, the effect of age on pain perception cannot be simply summarized as increase or decrease in sensitivity to pain. Age-related changes in pain perception depend on the kind of noxious stimuli used, its duration and the region where it is applied. For instance, while older adults present increased pain thresholds for heat stimuli (72), they present decreased pain thresholds for mechanical stimuli (73, 74), reflecting differences in the effect of ageing on superficial and deep tissue nociception. Moreover, even in situations in which the pain
threshold is increased, once it is reached, older adults tend to be less tolerant to pain and usually experience pain for longer periods after the tissue damage (75).

Several mechanisms are involved in age-related changes in pain sensitivity. In the aged peripheral nervous system, A-delta fibre nociceptive function seems to be impaired while the C nociceptive fibres function remains intact (76), which means that older adults rely mostly on unmyelinated fibres carrying the painful stimuli to the second-order neuron. In the central nervous system, the altered cerebral processing of signals from pain stimuli and the reduced ability to down-regulate pain through descending inhibitory pain pathways (77) are the main differences observed in some older adults. However, these ageing-related changes vary considerably among individuals, reflecting genetics, the presence of comorbidities, mental health, lifestyle and socio-economic factors.

1.5.4 Effect of non-pain comorbidities on pain

Most individuals accumulate chronic non-painful conditions throughout their ageing process. There is vast evidence suggesting that these conditions are associated with changes in pain processing, inflammation or osteoarthritis progression. Hypertension, for instance, can stimulate baroreceptors in aorta and carotid arteries, which send afferent signals to the brain areas involved in the descending pain inhibitory pathways (78). This would cause a “BP-related hypoalgesia” (79-81). However, in older adults experiencing chronic hypertension, the continuous input might lead to exhaustion or failure of the systems responsible for the “BP-related hypoalgesia”, explaining the positive association between hypertension and chronic pain.
Likewise, there is an association between chronic obstructive pulmonary disease (COPD) and chronic pain. More patients with COPD have chronic pain and use pain medication than patients with other non-rheumatic chronic comorbidities (83). However, that mechanisms underlying these associations are not fully elucidated. As previously mentioned, there are also clinical conditions associated with inflammation, such as obesity and diabetes, which can contribute to the progression of osteoarthritis. In obese older adults, cytokines produced by adipose tissue act as a systemic mediator in osteoarthritis progression producing a low grade inflammation environment (84). Likewise, hyperglycaemia can cause joint tissue damage by increasing the local formation of advanced glycation end products (AGEs) and by inducing a low grade inflammation state (85).

Besides physical comorbidities, mental conditions commonly present in older adults can also affect musculoskeletal pain. Depressed mood, for instance, has been associated with alterations in central pain processing (86), particularly dysfunctions in central pain inhibitory mechanisms (87). This is consistent with the finding that individuals with depressive symptoms have reduced effectiveness of pain interventions (88). On the other hand, older adults with chronic pain have more chances of subsequent depressed mood (89). It means that depression can adversely affect musculoskeletal pain and vice versa.

Anxiety can also affect musculoskeletal pain. It is known that anxiety disorders in patients with chronic arthritic pain are two times more prevalent than anxiety disorders in the general population (90). Anxious patients usually have lowered physiological threshold for alarm
reactions facing a stressor (90), causing them to develop chronic autonomic nervous system arousal (91) and dysregulation of the endogenous opioid system (92). This might reduce the threshold for musculoskeletal pain.

1.5.5 Multimorbidity

The co-occurrence of multiple chronic conditions in the same patient is usual in older people (93, 94) and health practitioners should keep this in mind managing musculoskeletal pain in this population. The presence of other conditions usually affects an index condition through a synergistic effect, i.e., when two or more conditions co-exist, the effect is greater than what would be expected from the adding the effects of the conditions alone (95). Moreover, there may be a reason for the co-occurrence of diseases. The presence of a given disease can be a risk factor for the other, different conditions can share the same risk factors, or a third condition can be a risk factor for two diseases (27). Besides assessing the effects of each clinical condition in pain, models addressing ageing and musculoskeletal pain should take into account the number of comorbidities since this variable seems to have a greater impact than each disease taken alone.

1.5.6 Effect of frailty in musculoskeletal pain

Frailty is a medical syndrome characterized by a state of vulnerability in which decreased physiologic reserves lead to reduced ability to maintain or regain homeostasis after a stressor (96). Assessing frailty, however, can be challenging since it is not possible to measure physiological reserves in clinical practice. In the last decades, several tools to identify and screen for frailty in older adults have been proposed (97) and, two instruments, the Frailty Index (FI) and
the Cardiovascular Health Study (CHS) frailty phenotype, have become widely used (98).

Although both measures were designed to detect frailty, they are not interchangeable (98). In the FI, a count of accumulated multidimensional deficits is used to assess frailty (99) and so, the presence of comorbidities and disabilities plays an important role determining the degree of frailty. On the other hand, the CHS frailty phenotype has tried to distinguish frailty from comorbidity or disability (100), operationalizing a physical frailty phenotype, which could be considered a pre-disability condition. The development of the CHS frailty phenotype criteria was based on a conceptual framework of a frailty cycle, which was validated in the CHS study. According to the authors, the core clinical presentations of the frailty phenotype are: a) unintentional weight loss, b) weakness, c) poor endurance and energy, d) slowed waking speed and e) low physical activity (101) and the presence of three of these criteria defines frailty. Studies addressing the association between pain and frailty are mostly cross-sectional (18, 20, 23), preventing us from determining causal relationships, or used the FI to assess frailty (22, 24), which has the risk of potential confounders, as the FI combines items related to physical frailty, comorbidity and disability.

In 2008, Blyth et al. published the first study exploring the relation between physical frailty and intrusive pain. A significant association was found, even adjusting for demographic characteristics, number of comorbidities, opioid use and specific conditions such as depressed mood and arthritis (18). Afterwards, higher rates of moderate to severe pain and intrusive pain were found in frail Mexican American (19). Chen et al. also found an association between pain
and frailty in the Survey of Health and Living Status of the Elderly in Taiwan. In this survey, the prevalence of pain in non-frail was less than half the prevalence in frail elders (40.7% vs 87.9%) (20). In 2012, Shega et al. found that the self-report of moderate or greater pain was independently associated with frailty in a cross-sectional analysis of the second wave of the Canadian Study of Health and Ageing (CSHA). The authors suggested that persistent pain might precipitate or accelerate the frailty development through a phenomenon which they called “pain homeostenosis” (21, 22). The association between pain and frailty was reinforced by the finding that pain assessed by the Pain Impact Questionnaire (PIQ6) was associated with the presence of frailty in a sample of Portuguese community dwelling elderly (23). Past evidence is, however, based on results of cross-sectional studies and does not allow for the ascertainment of cause-effect relationships between pain and frailty.

The first longitudinal analysis testing the hypothesis that chronic widespread pain is a risk factor for frailty development was published in 2015. In this study, however, the association between pain and frailty did not take in consideration the possibility of a bidirectional relationship. Moreover, the authors used the FI approach to assess frailty and so, it is not known if the same association would be found using the frailty phenotype to assess frailty. Chapter Two of this thesis addresses the gaps above, using longitudinal results of the CHAMP (Concord Health and Ageing in Male Project), one of the world’s largest and most comprehensive epidemiological studies of ageing in men. The aims of this chapter are: a) to assess the risk of developing the frailty phenotype in community-dwelling older men with chronic musculoskeletal pain and b) to assess how frailty status influences the risk of developing chronic pain in this same population.
1.6 The management of musculoskeletal pain in older adults

Musculoskeletal pain in older adults has well established characteristics. Although little is known about the influence of age and ageing-related conditions on musculoskeletal pain, some conclusions can be drawn: i) musculoskeletal pain is highly prevalent and frequently disabling in older adults ii) information derived from studies in the general population cannot be extrapolated to older individuals, particularly to those who are frail or have multimorbidity. As a consequence, what constitutes optimal pain management in older adults is still unclear. Older adults are the highest users of analgesics, however pain remains under-treated in the greater part of this population (102). Achieving optimal pain control in older people can be very challenging as drug-related adverse events frequently prevents dose progressions or drug combinations. Moreover, the presence of comorbidities can contraindicate the use of some analgesic classes.

The population of older adults suffering from musculoskeletal pain is heterogeneous in terms of physiological reserves and presence of comorbidities, resulting in a less predictable response to analgesics (103). It is unlikely that frail elders and those with multiple morbidities will respond to analgesic drugs or other interventions in the same way healthy older adults do and so, it is suboptimal to extrapolate results from studies conducted in otherwise healthy older adults to all the population of aged people. Unfortunately, frail older people have been under-represented in most clinical trials (104), including those designed to investigate musculoskeletal pain management strategies, and the evidence for any kind of recommendation in this population is
scarce (103). The lack of evidence based guidelines on management of musculoskeletal pain management in older adults leaves clinicians to their own experience dealing with this condition. This is particularly true for pain associated with vertebral compression fractures, a prevalent condition in which the medical literature has focused more on the osteoporosis treatment to prevent future fractures than on the pain management required. Most vertebral compression fractures are seen in older patients and they can cause both acute and chronic pain. Therefore, this condition was used as the basis to study the pain management in older adults. Chapter Three aims to describe current management of an important source of musculoskeletal pain in older adults – vertebral compression fractures. Data from the BEACH (Bettering Evaluation and Care of Health) program was use to describe how Australian general practitioners have been treating vertebral compression fractures in the last ten years. The BEACH program is a continuous, cross-sectional national study that collects information of about 100,000 encounters with general practitioners annually, providing reliable data to describe general practice activity.

Our results suggest that the most common approach to older adults with vertebral compression fracture-related pain is the prescription of analgesic drugs. Three classes of analgesics are particularly common: paracetamol, non-steroidal anti-inflammatories (NSAIDs) and analgesic opioids.

1.6.1 Paracetamol

Most of the guidelines endorse the use of paracetamol as the first line care for several musculoskeletal conditions (105-109). Traditionally viewed as an effective analgesic with
excellent tolerability, recent data have changed this view questioning both the safety and efficacy of paracetamol (110-112). Recent systematic review found that while the risk of having abnormal liver function tests increases fourfold in patients taking paracetamol, the effect of this analgesic in patients with pain due to osteoarthritis is quite small (<4 points in a 1-100 points pain scale) and probably not clinically meaningful (113).

Paracetamol is considered to be a weaker inhibitor of the synthesis of prostaglandins (PGs) and its spectrum of action resembles particularly the selective cyclooxygenase-2 (COX-2) inhibitors, except for a weaker analgesic and anti-inflammatory effect and differences in sites of action (114, 115). While paracetamol acts in preferentially in central nervous system, NSAIDs selective COX-2 inhibitors act in peripheral sites. The effect of ageing in paracetamol pharmacokinetics is more significant in the drug clearance, which is significantly lower in older adults, especially in frail elders (103, 116, 117). Given the concerns related to dose-dependent hepatotoxicity and, in a lesser extent, gastrointestinal complications (118) and nephrotoxicity (119), the daily use of the maximum recommended dose (4g/day) in frail elders might be inappropriate, particularly considering that paracetamol is contained in many over-the-counter combination products frequently used by older people.

The evidence on the effectiveness of paracetamol for the management of certain musculoskeletal diseases is still unclear. However, when compared to other pharmacological treatment options, paracetamol is more tolerable and has fewer adverse effects. It makes this drug relatively more suitable for use in frail elders.
1.6.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

Although NSAIDs are considered more effective for the management of inflammatory pain compared to paracetamol, gastrointestinal (120), cardiovascular (121) and renal (122) adverse effects have raised concerns about the use of NSAIDs in older adults. According to the American Geriatric Society (AGS) 2009 Panel on the Pharmacological Management of Persistent Pain in Older Persons, “NSAIDs and cox-2 selective inhibitors may be considered rarely and with extreme caution, in highly selected individuals” (109). The Osteoarthritis Research Society International (OARSI) also recommends caution in the use of NSAIDs in patients with cardiovascular risk factors or increased gastrointestinal risks (108). Considering that most of the older patients will present cardiovascular risk factors (123-125) and older age is itself a risk factor for gastrointestinal bleeding (126) this concern can be extended to older adults. Unfortunately, since many pain conditions are ageing-related, the use of NSAIDs increases with age. Older adults using NSAIDs are at risk of peptic ulcer, acute kidney injury, increased blood pressure and cardiovascular risk, hepatic injury, allergic reactions, dizziness, confusion, falls and even delirium (127). Because upper gastrointestinal ulcers, gross bleeding, or perforation caused by NSAIDs occur in 1% of patients treated for 3-6 months, and individuals aged 75 years or over have even higher risk, the AGS Beers Criteria for Potentially Inappropriate Medication Use in Older Adults strongly recommends avoiding chronic use of NSAIDs. However, the AGS Beers Criteria consider its use acceptable when no other alternatives are effective and the patient can take gastro-protective agents.
Although all the recommendations above mentioned, the use of NSAIDs among older adults is still significant (128) and therefore, NSAIDs-related adverse events are the leading cause of hospital admissions due to drug reactions (129). As many NSAIDs are available as over-the-counter (OTC) drugs and the pain relief is rapidly felt by patients, NSAIDs are very popular among older adults who frequently are not aware of potential risks.

A recent meta-analysis of the effectiveness of NSAIDs compared to placebo for low back pain found this drug is slightly more effective than placebo, at a cost of increased risk of gastrointestinal adverse events (130). In patients with knee osteoarthritis, a meta-analysis of placebo-controlled trials addressing the efficacy of NSAIDs found similar results, i.e. NSAIDs are slightly more effective than placebo reducing pain (131). The modest benefits of NSAIDs in pain are probably outweighed by the risk of serious adverse events, particularly among older adults.

1.6.3 Opioids
The doubts regarding the efficacy of paracetamol in musculoskeletal conditions and the concerns about the long-term use of NSAIDs have placed opioid analgesics as one of the most popular choices for the management of acute and chronic musculoskeletal pain. Recent meta-analyses have shown some evidence for short-term efficacy of opioids to treat chronic low back pain (132) and knee or hip osteoarthritis (133), however, in low doses (median daily dose in morphine equivalency of 51 mg), the modest benefits observed were offset by increased risks of adverse effects (133). For older adults, even though clinical trials have shown evidence of short-term efficacy and less likelihood of abuse or misuse behaviours (134), the higher rates of adverse
events such as constipation, nausea, dizziness and somnolence seems to limit the use of opioids in this population. One in four opioid-treated patients enrolled in clinical trials involving older adults discontinued treatment because of adverse events (134).

In the United States, a population-based survey found that approximately 2 per cent of the respondents reported opioid use for at least one month. Arthritis and back pain were the most prevalent chronic conditions among opioid users (135). Although opioids have been commonly used for chronic musculoskeletal conditions, their safety and efficacy in older adults with musculoskeletal pain is still unclear. Chapter four presents a systematic review with meta-analysis of randomised controlled trials with mean population age of 60 years or over, comparing opioid analgesics with placebo for musculoskeletal conditions on pain, function and quality of life, as well as the risks of opioids-related adverse events.

1.7 Aims of the thesis

The aims of this thesis were to:

i) Investigate whether musculoskeletal pain is an independent risk factor for development of the frailty phenotype in older men (Chapter Two);

ii) Investigate whether the frailty status is an independent risk factor for development of chronic or intrusive musculoskeletal pain (Chapter Two);

iii) Describe the current management of vertebral compression fractures, a painful and disabling musculoskeletal condition commonly seen in older adults (Chapter Three);
iv) Systematically review and appraise the literature on the efficacy and safety of opioid analgesics for older adults with musculoskeletal pain (*Chapter Four*).
1.8 References


CHAPTER TWO

Association between pain and frailty in older men: longitudinal results from the CHAMP

Chapter Two has been submitted as:

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Statement from co-authors confirming authorship contribution of the MPhil candidate

The co-authors of the paper “Association between pain and frailty in older men: longitudinal results from the CHAMP” confirm that Rodrigo Zunzarren Megale has made the following contributions:

I. Conception and design of the research
II. Analysis and interpretation of the findings
III. Writing of the manuscript and critical appraisal of the content

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Rodrigo Zunzarren Megale
Date: 01.07.2017

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Manuela Loureiro Ferreira
Date: 01.07.2017
Association between pain and the frailty phenotype in older men:
longitudinal results from the CHAMP

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Abstract

Objectives: To determine whether pain increases the risk of developing the frailty phenotype and whether frailty increases the risk of developing chronic or intrusive pain, using longitudinal data.

Design/Setting: Longitudinal data from the Concord Health and Ageing in Men Project (CHAMP), a prospective population based cohort study.

Participants: A total of 1705 men aged 70 years or older, living in an urban area of New South Wales, Australia.

Measurements: Data on the presence of chronic pain (daily pain for at least 3 months), intrusive pain (pain causing moderate to severe interference with activities) and the criteria for the CHS frailty phenotype were collected in three waves, from January, 2005 to October, 2013. Data on age, living arrangements, education, smoking status, alcohol consumption, body mass index, comorbidities, cognitive function, depressive symptoms and history of vertebral or hip fracture were also collected and included as covariates in the analyses.

Results: 1,705 participants were included at baseline, of whom 1,332 provided data at the 2-year follow-up and 940 at the 5-year follow-up. Non-frail (robust and pre-frail) men who reported chronic pain were 1.60 (95% confidence interval (CI): 1.02 to 2.51, p=0.039) times more likely to develop frailty at follow-up, compared to those with no pain. Intrusive pain did not significantly increase the risk of future frailty. Likewise, the frailty status was not associated with future chronic or intrusive pain in the adjusted analysis.

Conclusions: The presence of chronic pain increases the risk of developing the physical frailty phenotype in community-dwelling older men.
Key words: Ageing, Pain, Frailty, Male Health
Introduction

Pain is very common among older adults (1-5). A wealth of evidence has established the association between pain and disability in the older population (6-10) and, more recently, between pain and frailty (11-17). Although positive association between pain and frailty has been showed in past research, a causal association has not been established yet. All but one of the previous studies addressing the association between pain and frailty are cross-sectional studies. The only longitudinal study (17) to look at this association found chronic widespread pain to be associated with worsening frailty as assessed using a Frailty Index (FI).

Another common approach to assessing frailty is the use of the Cardiovascular Health Study (CHS) frailty phenotype criteria. The frailty phenotype distinguishes frailty from comorbidity and disability, defining a pre-disability syndrome based on specific clinical signs and symptoms (18). Therefore, CHS frailty criteria identify a group of frail older people sharing a common pathophysiological chain (19), which provides a framework for identifying etiologic factors and interventions to prevent further functional decline. While pain seems to be a risk factor for frailty as measured by deficit accumulation (17), whether it is also risk factor for physical frailty assessed using the CHS frailty criteria is still unknown. Moreover, it is possible pain and frailty hold a bidirectional risk relationship.

We aimed to explore the association between pain and frailty using longitudinal data collected over 5 years. The objectives of this study were:

1. To establish whether chronic pain or intrusive pain at baseline would increase the risk
of future frailty defined using the CHS criteria in older Australian men;

2. To establish whether frailty status at baseline would predict the occurrence of future
chronic or intrusive pain in older Australian men.

Methods

Study design and sample population

The Concord Health and Ageing in Men Project (CHAMP) is a population-based cohort study of
men aged 70 years or over, living in a defined geographical region near Concord Hospital in
Sydney (20). The sampling frame used for the study was the New South Wales Electoral Roll.
Eligible men in the study area were sent a letter describing the study and, if they had a listed
telephone number, were contacted about one week later. Men without listed telephone
numbers who did not respond to the first letter were sent a second invitation letter. Recruitment
occurred sequentially across the geographic study area, with invitation letters being sent out
each week during the recruitment period. The only exclusion criterion was living in a residential
aged care facility.

Baseline data were collected between January 28, 2005 and June 4, 2007. Invitation letters were
sent to 3,627 men and contact was made with 3,005 men. One hundred and ninety of the
contacted men were not eligible for the study because they had moved out of the study area,
had moved into a nursing home or had died. Of the 2,815 eligible men with whom contact was
made, 1,511 participated in the study (54%). An additional 194 eligible older men who lived in
the study area heard about the study from friends or the media and asked to be in the study
before receiving an invitation letter. Two-year follow-up assessments were conducted between January 2007 and October 2009, and the 5-year follow-up was conducted between January 2012 and October 2013.

**Pain assessment**

**Chronic pain**

The presence of chronic pain was assessed through the question: “In the last 6 months, have you experienced pain in any part of your body which has lasted for 3 months or more, that is pain experienced every day for at least 3 months?”; this question has been widely used in population studies (4). Data were collected at baseline and at 2 and 5-year follow-ups.

**Intrusive pain**

The following question from the SF-12 questionnaire (21) was used to assess the impact of pain on an individual’s life: “During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?” Men who reported that their pain interfered “moderately”, “quite a bit” or “extremely” on normal work were classified as individuals with intrusive pain.

**Frailty assessment**

Frailty was assessed using the CHS frailty phenotype definition: weight loss/shrinking, weakness, exhaustion, slowness and low activity. The assessment of weakness and slowness used the standard CHS definition and cut-offs, but adapted criteria were used for weight loss/shrinking,
exhaustion, and low activity. The following definitions were used: a) weight loss/shrinking: defined as current weight 15% or more less than self-reported heaviest weight; b) weakness: defined as being in the lowest CHS study quintile for grip strength, adjusted for BMI; c) exhaustion: defined according to responses to the following question from the SF12: “How much of the time during the past 4 weeks did you have a lot of energy?”; d) slowness: defined as being in the lowest CHS study quintile for walking speed, adjusted for height; e) low physical activity: defined as being in the lowest quintile on the Physical Activity Scale for the Elderly (PASE) (cut-off score <73). Individuals who met 3 or more criteria were classified as frail. Those meeting less than 3 criteria were classified as pre-frail (1 or 2 criteria) or robust (0 criteria). The presence of frailty and the frailty score were assessed at baseline and at 2-year and 5-year follow-ups.

Socio-demographic and life-style factors

Age, living arrangements (living alone vs. living with others) and level of education (no post-school qualification vs. post-school qualification) were used to assess socio-demographic status of included participants. Participants were classified as having a post-school qualification if they answered “yes” to the following question: “Since leaving school have you obtained a trade qualification, certificate, diploma or any other qualifications?”

Smoking status was classified as “never smoked” (those who smoked less than 100 cigarettes in their entire life), “ex-smokers” or “current smokers”. Alcohol abuse was assessed through the CAGE questionnaire (22), with two or more positive answers in the questionnaire used to determine “alcohol abuse”. Height and weight were measured, and body mass index (BMI) was
calculated as kilograms per square metre.

**Comorbidities**

The comorbidity count was calculated for each participant by summing the presence of 18 self-reported, doctor-diagnosed conditions: diabetes; thyroid disease; osteoporosis; Paget’s disease; stroke, blood clot in the brain or bleeding in the brain; Parkinson’s disease; kidney stones; epilepsy or fits; hypertension or high blood pressure; heart attack, coronary or myocardial infarction; angina; congestive heart failure or enlarged heart; intermittent claudication or pain in the legs from a blockage of the arteries; chronic obstructive lung disease, chronic bronchitis, asthma, emphysema or COPD; liver disease; chronic kidney disease or kidney failure; arthritis or gout; and cancer (excluding non-melanoma skin cancer).

**Cognitive function and depressive symptoms**

The mini-mental state exam (MMSE) (23) score was used as a continuous measure to assess cognitive function. Depressive symptoms were evaluated with the Geriatric Depression Scale (GDS) 15-item version (24). A total of five or more depressive symptoms were considered as indicating a possible depressed mood.

**Statistical analysis**

The statistical analysis was carried out using STATA v13 (Stata Corp, College Station, TX). Descriptive characteristics were expressed as means and standard deviation (SD) for continuous variables and absolute number and percentage for categorical variables. The statistical
significance threshold was set at 0.05.

Generalised estimating equations (GEE) were used to explore the association between pain and frailty. GEE takes into account the time-varying nature of included variables allowing for the inclusion of all three waves of data collection in the analyses. The analyses were performed using a time lag model in which predictors were always assessed in the previous wave. For the GEE models, exchangeable working correlation structure and robust standard errors were used. Unadjusted, age-adjusted and multivariate analyses were carried out. Covariates selected for the multivariate analysis were those significantly associated with the outcome of interest (p<0.1) when included in the model. The results are expressed as odds ratios (OR) and 95% confidence intervals (95%CI).

**Risk of developing frailty in participants with chronic pain or intrusive pain**

To ascertain evidence of the role of chronic pain or intrusive pain in frailty development, individuals who were classified as frail at baseline were excluded from this analysis. The GEE model included data from baseline, 2- and 5-year follow-ups. Participants without chronic pain and participants without intrusive pain were considered the reference group.

**Risk of developing chronic or intrusive pain in frail participants**

To ascertain the role of frailty status as a risk factor for pain, men who reported chronic pain or intrusive pain at baseline (according to the outcome of interest) were excluded from the analysis. The GEE model included data from baseline, 2 and 5-year follow-up. Robust participants were
considered the reference group.

**Ethics approval and informed consent**

All participants gave written informed consent. The study was approved by the Sydney Local Health District Human Research Ethics Committee, Concord Repatriation General Hospital, Sydney, Australia.

**Results**

1,705 patients were included in the baseline assessments. At the 2-year follow-up, frailty status was assessed in 1,332 participants and at the 5-year follow-up in 940 participants. Death was the main reason for nonparticipation at 2 years and at 5 years. The other main reason for failure to attend the follow-up clinic visits was illness.

The mean (SD) age of the study population at baseline was 76.9 (5.5) years. Chronic pain was reported by 29.5% (n=501) of the participants and intrusive pain by 23.4% (n=392). Also at baseline, 50% (n=833) of the participants were classified as robust, 40.7% (n=679) as pre-frail and 9.4% (n=158) as frail. Other baseline characteristics of the participants are summarized in Table 1, as reported by the CHAMP researchers previously.

*Risk of developing frailty in participants with chronic pain and intrusive pain*

In GEE analyses presence of chronic pain in the previous wave was independently associated with increased odds of future frailty (OR 1.60, 95%CI 1.02-2.51, p=0.039) (Table 2).
Likewise, the GEE analyses suggested that the odds of developing frailty were higher in participants who reported intrusive pain (see Table 2). However, the association did not quite reach statistical significance in the fully adjusted model (OR 1.64, 95%CI 0.97-2.78, p=0.063).

**Risk of developing chronic pain or intrusive pain in pre-frail and frail participants**

Compared to robust individuals, pre-frail or frail individuals were not at a higher risk of reporting future chronic pain (OR 1.07, 95%CI 0.80-1.44; p=0.649 for pre-frail and OR 0.82, 95%CI 0.38-1.79; p=0.618 for frail men) or intrusive pain (OR 0.91, 95%CI 0.67-1.23; p=0.551 for pre-frail and OR 1.38, 95%CI 0.70-2.74; p=0.356 for frail men) at follow-up, after adjusting for covariates (Table 3).

**Discussion**

This study has shown that chronic pain in older men is a risk factor for developing frailty, as assessed using the CHS frailty criteria. However, frailty status is not associated with increased risk of developing chronic or intrusive pain.

This is not the first study to demonstrate that chronic pain is associated with increased risk of frailty. Similar results were found in the European Male Ageing Study (EMAS), a cohort study with a younger population (mean age population of 59 years). However, both the chronic pain assessment and the frailty measure in the EMAS study were different from ours. The EMAS study assessed chronic widespread pain using the American Rheumatology Association (ARA) criteria for fibromyalgia (25) whereas we used the International Association for Study of Pain (IASP)
definition for chronic pain ("pain which has persisted beyond normal tissue healing", usually taken as 3 months duration (26)) and intrusive pain (pain-related interference with activities (11)). In addition, the EMAS study assessed frailty using the FI whereas we used the CHS frailty phenotype criteria. Despite all these differences, EMAS and CHAMP found similar results regarding the association between chronic pain and frailty.

The association between pain and physical frailty could be explained in several ways. The presence of pain might be acting as persistent stressor, demanding continuous activation of stress-related systems, which would consume physiological reserves and increase the risk of frailty (14, 15). Alternatively, systemic inflammation and the hypothalamic-pituitary-adrenal axis dysfunction, often found in patients with chronic pain (27, 28), could contribute to frailty development (29, 30). Regardless of the mechanisms underlying pain and frailty association, it has been suggested that persistent pain should be included as a sixth CHS frailty criterion because it usually occurs in association with other frailty criteria, increasing the risk of adverse outcomes (31).

As frailty-related changes in the brain might cause impairments in descendent inhibitory pain modulation (14), it was expected that frailty would be a risk factor for pain. However, our study has shown that frailty status is not independently associated with increased risk of developing chronic or intrusive pain.

In 2008, Blyth et al. published one of the first studies exploring the relation between frailty and
pain using baseline data from this same cohort study (11). The authors concluded that frailty was associated with intrusive pain at CHAMP’s baseline. Our longitudinal results, however, are not so clear regarding the association between intrusive pain and frailty development. Although the odds ratio for the association between intrusive pain and frailty is quite similar to the odds ratio for chronic pain and frailty association, the significant threshold was not met.

The findings reported in this study have important clinical implications. If chronic pain increases the risk of frailty, then better pain management could reduce the frailty trajectory among older adults. However, randomised clinical trials are still needed to test whether and which pain interventions have any effect on frailty progression.

Our study has a number of strength: a) data were collected prospectively in this large cohort of older men (mean age 77 years) which is significantly older that the previous study (17); b) standardised criteria for frailty were used with a standardised approach to definitions for all clinical variables; c) the longitudinal nature of this study is a major strength, with measurement of variables up to 5 years. Nevertheless, there are limitations that must be pointed out. Our results cannot be extrapolated to women, since men and women have different behaviours regarding pain (32) and frailty (33). Other important limitations are not including disease severity when examining comorbidities and the exclusion of information on pain medication from the analyses, given pain medication might mediate the association between pain and frailty (34).

This study represents a step forward understanding the influence of chronic pain, a common
problem in aged populations, on frailty dynamics. However, many questions remain unanswered, for example, the biological mechanisms responsible for this association, the influence of pain characteristics (such as origin and intensity) on frailty progression and the impact of pain management on vulnerable populations.

Conclusion

We have established that the presence of chronic pain increases the risk of developing physical frailty phenotype in community-dwelling older men, even after adjusting for potential confounders. Conversely, we found that frailty is not an independent risk factor for chronic or intrusive pain. Future studies should focus on the efficacy of different pain management strategies in reducing the risk of frailty.

Key Points

- Chronic pain is an independent risk factor for developing the CHS frailty phenotype among older men
- The frailty status does not independently increase the risk of developing chronic or intrusive pain among older men
- Future studies should focus on the role of pain management as a potential strategy to prevent frailty in older people
Acknowledgments

Conflict of interests: None declared

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References


### Table 1. Baseline characteristics of population (n=1705).

<table>
<thead>
<tr>
<th>Demographic factors</th>
<th>n (% or SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD)</strong></td>
<td>76.9 (5.5)</td>
</tr>
<tr>
<td><strong>Living alone, n (%)</strong></td>
<td>318 (18.8)</td>
</tr>
<tr>
<td><strong>Post-school qualification, n (%)</strong></td>
<td>915 (54.5)</td>
</tr>
<tr>
<td><strong>Alcohol abuse (CAGE&gt;=2), n (%)</strong></td>
<td>76 (4.5)</td>
</tr>
<tr>
<td><strong>Cigarette-smoking status</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Never smoked, n (%)</strong></td>
<td>630 (37.3)</td>
</tr>
<tr>
<td><strong>Ex-smoker, n (%)</strong></td>
<td>956 (56.7)</td>
</tr>
<tr>
<td><strong>Current smoker, n (%)</strong></td>
<td>101 (6.0)</td>
</tr>
<tr>
<td><strong>BMI, mean (SD)</strong></td>
<td>27.8 (4.0)</td>
</tr>
<tr>
<td><strong>Mini-Mental, mean (SD)</strong></td>
<td>27.1 (3.0)</td>
</tr>
<tr>
<td><strong>Depressive mood (GDS&gt;=5)</strong></td>
<td>246 (14.6)</td>
</tr>
<tr>
<td><strong>Hip or vertebral fracture, n (%)</strong></td>
<td>50 (2.9)</td>
</tr>
<tr>
<td><strong>Comorbidity count, mean (SD)</strong></td>
<td>1.4 (1.3)</td>
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<tr>
<td><strong>Chronic pain, n (%)</strong></td>
<td>501 (29.5)</td>
</tr>
<tr>
<td><strong>Intrusive pain, n (%)</strong></td>
<td>392 (23.4)</td>
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<tr>
<td><strong>Frailty status</strong></td>
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<tr>
<td><strong>Robust, n (%)</strong></td>
<td>833 (49.9)</td>
</tr>
<tr>
<td><strong>Pre-frail, n (%)</strong></td>
<td>679 (40.7)</td>
</tr>
<tr>
<td><strong>Frail, n (%)</strong></td>
<td>158 (9.4)</td>
</tr>
</tbody>
</table>

Missing: living alone = 14, post-school qualification = 25, alcohol abuse = 14, smoking status = 18, BMI = 28, MMSE = 186, depression = 24, comorbidity count = 16, chronic pain = 8, intrusive pain = 30, frailty status = 35
Table 2. Unadjusted, age adjusted and multivariate GEE analyses with a time lag assessing chronic or intrusive pain as a risk factor for frailty development (n=1,512)

<table>
<thead>
<tr>
<th>Frailty</th>
<th>OR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model 1. Chronic pain vs. Frailty</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>1.71 (1.22-2.41)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age-adjusted model</td>
<td>1.77 (1.24-2.53)</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.19 (1.15-1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate model¹</td>
<td>1.60 (1.02-2.51)</td>
<td>0.039</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.17 (1.12-1.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Living alone</td>
<td>0.92 (0.52-1.64)</td>
<td>0.789</td>
</tr>
<tr>
<td>Post-school qualification</td>
<td>0.86 (0.54-1.37)</td>
<td>0.522</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.91 (0.87-0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Count of comorbidities (0-18)</td>
<td>1.40 (1.24-1.60)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE (0-30)</td>
<td>0.88 (0.83-0.94)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>4.20 (2.57-6.86)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Model 2. Intrusive pain vs. Frailty</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>2.32 (1.59-3.38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age-adjusted model</td>
<td>2.45 (1.65-3.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.19 (1.15-1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Multivariate model²</td>
<td>1.64 (0.97-2.78)</td>
<td>0.063</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.17 (1.12-1.23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Living alone</td>
<td>0.96 (0.54-1.69)</td>
<td>0.879</td>
</tr>
<tr>
<td>Post-school qualification</td>
<td>0.85 (0.53-1.34)</td>
<td>0.474</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.91 (0.87-0.96)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Count of comorbidities (0-18)</td>
<td>1.38 (1.21-1.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE (0-30)</td>
<td>0.87 (0.82-0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression</td>
<td>3.99 (2.43-6.53)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Smoking status, alcohol abuse and history of hip/vertebral fracture were not included because these variables were not significantly associated (p<0.1) with frailty when included in the GEE model.

Smoking status, alcohol abuse and history of hip/vertebral fracture were not included because these variables were not significantly associated (p<0.1) with frailty when included in the GEE model.
Table 3. Unadjusted, age adjusted and multivariate\(^1\) GEE analyses with a time lag assessing frailty status in the previous wave as a risk factor for development of chronic pain or intrusive pain.

<table>
<thead>
<tr>
<th></th>
<th>Chronic pain (n=1,196)</th>
<th>Intrusive pain (n=1,283)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
</tr>
<tr>
<td><strong>Unadjusted model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-frail</td>
<td>1.15 (0.89-1.49)</td>
<td>0.286</td>
</tr>
<tr>
<td>Frail</td>
<td>1.26 (0.70-2.27)</td>
<td>0.440</td>
</tr>
<tr>
<td><strong>Age-adjusted model</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-frail</td>
<td>1.07 (0.82-1.40)</td>
<td>0.603</td>
</tr>
<tr>
<td>Frail</td>
<td>1.12 (0.62-2.04)</td>
<td>0.706</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03 (1.00-1.05)</td>
<td>0.030</td>
</tr>
<tr>
<td><strong>Multivariate model(^1)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-frail</td>
<td>1.07 (0.80-1.44)</td>
<td>0.649</td>
</tr>
<tr>
<td>Frail</td>
<td>0.82 (0.38-1.79)</td>
<td>0.618</td>
</tr>
<tr>
<td>Age (years)</td>
<td>1.03 (1.00-1.06)</td>
<td>0.021</td>
</tr>
<tr>
<td>Post-school qualification</td>
<td>0.74 (0.55-0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td>Smoking status(^2)</td>
<td>1.53 (1.17-2.00)</td>
<td>0.002</td>
</tr>
<tr>
<td>BMI (kg/m(^2))</td>
<td>1.00 (0.97-1.04)</td>
<td>0.959</td>
</tr>
<tr>
<td>Count of comorbidities (0-18)</td>
<td>1.10 (1.01-1.20)</td>
<td>0.024</td>
</tr>
<tr>
<td>MMSE score (0-30(^3))</td>
<td>1.06 (1.00-1.12)</td>
<td>0.060</td>
</tr>
<tr>
<td>Depression</td>
<td>1.63 (1.07-2.50)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

\(^1\) Living alone, alcohol abuse, and history of hip/vertebral fracture were not included because these variables were not significantly associated (p<0.1) with frailty when included in the GEE model.

\(^2\) Smoking status: never smoked, ex-smokers and current smokers.
MMSE score was not significantly associated (p<0.1) with intrusive pain when included in the GEE model.
CHAPTER THREE

Management of vertebral compression fracture in general practice: BEACH program

Chapter Three has been published as:

Statement from co-authors confirming authorship contribution of the MPhil candidate

The co-authors of the paper “Management of vertebral compression fracture in general practice: BEACH program” confirm that Rodrigo Zunzarren Megale has made the following contributions:

I. Conception and design of the research

II. Analysis and interpretation of the findings

III. Writing of the manuscript and critical appraisal of the content

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Rodrigo Zunzarren Megale  
Date: 01.07.2017

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Manuela Loureiro Ferreira  
Date: 01.07.2017
RESEARCH ARTICLE

Management of vertebral compression fracture in general practice: BEACH program

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Abstract

Importance
The pain associated with vertebral compression fractures can cause significant loss of function and quality of life for older adults. Despite this, there is little consensus on how best to manage this condition.

Objective
To describe usual care provided by general practitioners (GPs) in Australia for the management of vertebral compression fractures.

Design, setting and participants
Data from the Bettering the Evaluation And Care of Health (BEACH) program collected between April 2005 and March 2015 was used for this study. Each year, a random sample of approximately 1,000 GPs each recorded information on 100 consecutive encounters. We selected those encounters at which vertebral compression fracture was managed. Analyses of management options were limited to encounters with patients aged 50 years or over.

Main outcome(s) and measure(s)
I) patient demographics; II) diagnoses/problems managed; III) the management provided for vertebral compression fracture during the encounter. Robust 95% confidence intervals, adjusted for the cluster survey design, were used to assess significant differences between group means.

Results
Vertebral compression fractures were managed in 211 (0.022%; 95% CI: 0.018–0.025) of the 977,300 BEACH encounters recorded April 2005–March 2015. That provides a national annual estimate of 26,000 (95% CI: 22,000–29,000) encounters at which vertebral fractures
were managed. At encounters with patients aged 50 years or over (those at higher risk of primary osteoporosis), prescription of analgesics was the most common management action, particularly opioids analgesics (47.1 per 100 vertebral fractures; 95% CI: 38.4–56.7). Prescriptions of paracetamol (8.2; 95% CI: 4.4–12.4) or non-steroidal anti-inflammatory drugs (4.1; 95% CI: 1.1–7.1) were less frequent. Non-pharmacological treatment was provided at a rate of 22.4 per 100 vertebral fractures (95% CI: 14.6–30.1). At least one referral (to hospital, specialist, allied health care or other) was given for 12.3 per 100 vertebral fractures (95% CI: 7.8–16.8).

Conclusions and relevance

The prescription of oral opioid analgesics remains the common general practice approach for vertebral compression fractures management, despite the lack of evidence to support this. Clinical trials addressing management of these fractures are urgently needed to improve the quality of care patients receive.

Introduction

Vertebral compression fractures (VCFs) are of increasing public health concern due to a rising prevalence in an ageing Australian population. Around 725,000 Australians are at risk of developing an osteoporotic vertebral fracture every year [1], and in fact, one in four women aged 80 years or over will have sustained one or more vertebral fractures [2, 3]. In general practice, the burden of this condition is likely underestimated as only around one third of vertebral fractures will be clinically diagnosed [4]. Even in the acute phase, most cases are not recognised at the time of their occurrence [5].

Acute pain is a common clinical presentation of symptomatic VCFs. Recent observational studies have shown that patients may report moderate to severe pain intensity after a VCF, with an average score of 7 on a 10-point visual analogue pain scale [6, 7]. Further, some patients may develop persistent pain with reduced function and quality of life [8–13].

Significant attention is currently paid to the secondary prevention of vertebral and non-vertebral fractures given that the presence of a VCF is an important predictor of future osteoporotic fractures [14]. However, pain relief is as important as osteoporosis treatment in older adults, because each additional day of immobility due to pain will result in further loss of muscle mass, strength, and functional capacity [15, 16]. Effective pain management may prevent prolonged bed rest, deconditioning and further losses of physiological and functional capacity, especially important among frail older adults. Unfortunately, there is no consensus on the clinical pathway for pain management in patients with VCF. The available guidelines differ markedly in their recommendations [17–20] and the scientific evidence on the effective management of VCF is scarce [21].

The lack of consensus in VCF management means that clinicians must rely on their own expertise when managing patients with symptomatic VCF, resulting in significant variation in usual care. Descriptive studies reporting such variation would provide valuable information to be used in public health planning. In Australia, general practitioners (GPs) are usually the first port of call and those who first manage VCF in outpatient settings. The aim of this study is to describe the usual management of VCF in older adults at consultations in Australian general practice and to identify gaps to be addressed in future research to inform best practice.
Methods
Population and settings
We analysed data from the Bettering Evaluation and Care of Health (BEACH) program, collected April 2005 to March 2015 inclusive. The data collection methods are described in detail elsewhere [22, 23]. In summary, the BEACH program is a continuous, national cross-sectional study of general practice activity in Australia. Each year, an ever-changing random sample of approximately 1,000 GPs each records details of 100 consecutive encounters with consenting patients (total approximately 100,000 encounters/year) on structured paper encounter forms. GPs are randomly selected from a national list of active GPs, defined as those for whom at least 375 GP services were claimed for Government rebates in the previous quarter. Patient reasons for the encounter (up to three), problems managed (which includes evaluated, treated or otherwise dealt with) (up to four), and treatments (linked by the GP) to each problem, are recorded as free text. The status of each problem—new (first presentation to a medical practitioner), or follow-up (previously managed problem)—was also indicated. Completed forms are returned to the research team, centrally coded in an Australian general practice interface terminology ICP-C-2 PLUS [24], classified according to the International Classification of Primary Care, Version 2 (ICPC-2) [25]. Pharmaceutical were classified at generic level according to the World Health Organization’s (WHO) Anatomic Therapeutic Chemical (ATC) classification [26].

In this study, we used data from encounters at which VCFs were managed. VCF problems were defined as ICP-C-2 PLUS code L8491 ("Fracture; compression (of); spine"). Analyses of management actions for VCF were limited to encounters with patients aged 50 years or over. This age group is considered to be at higher risk of VCF consequent to primary osteoporosis, than patients aged less than 50 years, among whom VCF is more likely to be associated with secondary osteoporosis or with major trauma [27].

The data elements used in this study of VCF management were: i) patient demographics; ii) co-morbidities managed iii) the management provided for during the consultation (medications prescribed or supplied by the GP and their prescribed daily dose; clinical treatments such as general and specific advice, counselling or education; procedural treatments including therapeutic actions and diagnostic procedures undertaken at the encounter; referrals to specialists, and to allied health services; and orders for pathology and imaging tests). Opioid analgesics included in the 5-digit ATC code as N02AA (except codeine and dihydrocodeine), N02AE or N02AB were considered “strong” opioids. Codeine (N05DA04 or N02AA59), dihydrocodeine (N02AA08) or opioid analgesics included in the 5-digit ATC code as N02AC and N02AX were considered “weak” opioids. The Australian and New Zealand College of Anaesthetists (ANZCA) opioid conversion table [28] was used to convert the daily opioid analgesic dose to morphine equivalents.

Antidepressants (N06AA, N06AB and N06AX), antiepileptics (N03AE, N03AF, N03AG, N03AX), anxiolytics (N05BA) or glucocorticoids (H02AB) were considered adjuvant pain medications when used in VCF management. In this analysis bisphosphonates (M05BA), combinations of bisphosphonates with other compounds (M05SR), strontium ranelate or denosumab (M05RX) were pooled under the label "anti-osteoporotic medication"). Non-pharmacological management approaches included clinical treatments involving general and specific advice, counselling or education, administrative processes and procedural treatments involving physical medicine/rehabilitation.

In Australia, there is a universal medical insurance scheme (Medicare Australia), which covers all or part of an individual’s cost for a GP visit. The national annual number of encounters at which VCF was managed was therefore estimated as the proportion of BEACH
encounters at which VCF was managed multiplied by the national average annual number of GP consultation items claimed from Medicare over the period 2005–15.

Statistical analysis

Descriptive analyses are presented as frequencies and mean rates. Using SAS® 9.3, robust 95% confidence intervals (CI), adjusted for the cluster survey design are reported, except if less than three observations. Differences between group means were regarded as significant when 95% CIs did not overlap.

Results estimating the caseload of VCFs are reported as management rates per 100 GP encounters. As more than one problem could be managed at each encounter, management actions (such as medication prescription) are only those linked by the GP to the VCF problem and are reported as rates per 100 VCF problems managed.

The BEACH program is approved by the Human Research Ethics Committee of the University of Sydney and the Ethics Committee of the Australian Institute of Health and Welfare (project number 2012/130).

Results

In this sample, for all age groups, 211 VCF problems were managed at 211 (0.022%); 95% CI: 0.018–0.025) of the 977,300 encounters recorded from April 2005–March 2015. These data were extrapolated to an estimated national annual average of 26,000 (95% CI: 22,000–29,000) encounters at which VCFs were managed by GPs.

Description of encounters at which VCFs were managed

The majority of patients at VCF encounters were: female (65.1%); 65 years and over (64.8%); previously seen at the recording GP’s practice (95.7%). Of 211 VCF encounters, 186 (88.7%) were claimable from Medicare, and, of these, 85.2% were surgery consultations, whereas home, hospital or residential aged care visits accounted for 8.5%. Follow-up management of previously diagnosed VCFs (59.2%; 95% CI: 52.4–66.1) was more frequent than management of new cases (40.8%; 95% CI: 33.9–47.6) (Table 1).

Additional investigations were ordered for less than half of the VCF problems managed. At least one imaging test was ordered for 31.8% (25.2–38.3) and at least one pathology test for 4.7% (1.8–7.6) of VCF problems. Pharmacological treatment was the most common management action for VCF, at least one medication being prescribed, supplied or advised for 60.7% (54.1–67.2) of VCF problems managed. At least one referral (to hospital, specialist, allied health care or other) was given for 12.3% (7.8–16.8) (Table 1).

Patient’s reason for encounter and other problems managed

Patients described 331 (156.9 per 100 VCF encounters) reasons for encounter (RFEs). Classified by ICF-C3 chapter, musculoskeletal complaints (n = 145) were the most common (68.7 per 100 VCF encounters), representing 42.8% of all RFEs. Back complaint (68.3 per 100 VCF encounters), trauma/injury (not otherwise specified) (6.2) and fracture (5.7) were the top 3 musculoskeletal RFEs.

On average, 75.4 (62.2–88.5) problems (other than VCF) were managed per 100 VCF encounters, most commonly being circulatory (13.3 (7.7–18.9) per 100 VCF encounters), musculoskeletal (12.8 (7.8–17.8)) and psychological (9.5 (5.3–13.7)). Hypertension (4.5 per 100 VCF encounters), lipid disorders (3.8), osteoporosis (3.8), sleep disturbance (3.3) and depression (2.4) were the top 5 individual problems co-managed in VCF encounters (Table 2).
OF VCF encounters, 170 (80.6%) were with patients aged 50 years or over (those at higher risk of primary osteoporosis). In this group the proportions of women, patients previously seen by GP, and first presentation of VCFs; the likelihood of additional investigations, pharmacological treatment and referrals did not significantly differ from those of the total sample. Likewise, the rates of the top 3 musculoskeletal RPs and the top 5 other problems managed were similar to the rates presented for the whole sample (data not shown).

Pharmacological and non-pharmacological VCF treatment at encounters with patients aged 50 years or over

At VCF encounters with patients aged 50 years or over, opioids were the top analgesic class prescribed for VCF (47.1 per 100 problems; 95% CI: 38.4–55.7) (Table 3). For new cases of VCF weak opioid analgesics (20.3; 95% CI: 10.1–30.4) were more often prescribed than strong opioids (12.7; 95% CI: 5.3–20.0). In contrast at follow-up encounters prescriptions for strong opioids analgesics were more common than for weak opioids (47.3; 95% CI: 35.1–59.4 vs. 12.1; 95% CI: 5.5–18.7). The prescription of paracetamol (8.2) was less frequent than opioids for all VCF problems. No significant difference was found in the paracetamol prescription rate for new cases (10.1; 95% CI: 3.4–16.9) and previously diagnosed VCF cases (6.6; 95% CI: 1.4–11.8). Non-steroidal anti-inflammatory drugs (NSAIDs) were less frequently prescribed (4.1; 95% CI: 1.1–7.1) and adjuvant pain medication prescriptions were rare.

Table 1. Main characteristics of encounters at which vertebral compression fractures (VCFs) were managed—BEACH, 2005–2015, all patient ages.

<table>
<thead>
<tr>
<th>Encounters characteristics</th>
<th>N (N = 211 VCF encounters)</th>
<th>Rate per 100 VCF encounters (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td>136</td>
<td>65.1 (58.3–71.8)</td>
</tr>
<tr>
<td>Male</td>
<td>73</td>
<td>34.9 (28.2–41.7)</td>
</tr>
<tr>
<td>Age &lt;50 years</td>
<td>40</td>
<td>19.9 (13.3–24.6)</td>
</tr>
<tr>
<td>Age = 50 years</td>
<td>170</td>
<td>81.0 (75.2–86.7)</td>
</tr>
<tr>
<td>Age &gt;= 65 years</td>
<td>136</td>
<td>64.8 (57.9–71.7)</td>
</tr>
<tr>
<td>Patient new to practice</td>
<td>9</td>
<td>4.9 (1.5–7.1)</td>
</tr>
<tr>
<td>Patient seen previously</td>
<td>200</td>
<td>95.7 (92.9–98.5)</td>
</tr>
<tr>
<td>Surgery consultations</td>
<td>161</td>
<td>76.3 (70.8–82.3)</td>
</tr>
<tr>
<td>Hospital, residential aged care and home visits</td>
<td>16</td>
<td>7.6 (3.8–11.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VCF management</th>
<th>N (N = 211 VCF problems)</th>
<th>Rate per 100 VCF problems (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First presentation of VCFs</td>
<td>86</td>
<td>40.8 (33.3–48.6)</td>
</tr>
<tr>
<td>Follow-up of previously assessed VCFs</td>
<td>125</td>
<td>59.2 (52.4–66.1)</td>
</tr>
</tbody>
</table>

Additional investigation
- At least 1 imaging exam | 67 | 31.8 (25.3–39.3)
- At least 1 pathology exam | 10 | 4.7 (1.9–7.6)
- At least 1 medication prescribed | 128 | 60.7 (54.1–67.2)
- At least 1 referral | 26 | 12.3 (4.2–32.9)
- Hospital | 5 | 2.4 (0.3–4.4)
- Specialist | 12 | 5.7 (2.5–8.8)
- Allied health services | 8 | 3.8 (1.2–6.4)
- Other referrals | 1 | 0.6*

a) Vertebral compression fracture.
b) Confidence interval.
c) N missing: sex 2; age 1; patient new to practice 2.
* 95% CI not reported for n=3.

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Table 2. Reasons for encounter (RFEs) and other problems managed at vertebral compression fracture (VCF) encounters—BEACH, 2005–2015, all patient ages.

<table>
<thead>
<tr>
<th>Category</th>
<th>Number of RFEs</th>
<th>Rate per 100 VCF-encounters (95% CI) N = 211</th>
</tr>
</thead>
<tbody>
<tr>
<td>All RFEs recorded</td>
<td>931</td>
<td>156.9 (146.3–167.5)</td>
</tr>
<tr>
<td>RFEs from ICPC-2(^a) musculoskeletal (MSK) chapter</td>
<td>145</td>
<td>68.7 (61.6–76.0)</td>
</tr>
<tr>
<td>Top 3 RFEs from ICPC-2 MSK(^a) chapter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back complaints</td>
<td>102</td>
<td>48.3 (41.3–55.3)</td>
</tr>
<tr>
<td>Trauma/injury NOS(^b)</td>
<td>13</td>
<td>6.2 (2.6–9.7)</td>
</tr>
<tr>
<td>Fracture</td>
<td>12</td>
<td>5.7 (2.5–8.9)</td>
</tr>
<tr>
<td>RFEs from other (non-MSK) ICPC-2 chapters</td>
<td>186</td>
<td>88.2 (76.4–99.9)</td>
</tr>
<tr>
<td>Top 3 RFEs from other ICPC-2 chapters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test results</td>
<td>46</td>
<td>21.8 (15.1–28.5)</td>
</tr>
<tr>
<td>Prescriptions</td>
<td>29</td>
<td>13.7 (8.8–18.7)</td>
</tr>
<tr>
<td>General check-up</td>
<td>5</td>
<td>2.4 (0.9–4.4)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Problems (other than VCF) managed</th>
<th>Number of other problems managed</th>
<th>Rate per 100 VCF-encounters (95% CI) N = 211</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>9</td>
<td>4.3 (1.5–7.0)</td>
</tr>
<tr>
<td>Lipid disorders</td>
<td>8</td>
<td>3.8 (1.2–6.4)</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>8</td>
<td>3.8 (1.2–6.4)</td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>7</td>
<td>3.3 (0.9–5.8)</td>
</tr>
<tr>
<td>Depression</td>
<td>5</td>
<td>2.4 (0.9–4.4)</td>
</tr>
</tbody>
</table>

\(^a\) Vertebral compression fracture.  
\(^b\) Confidence interval.  
\(^c\) Reasons for encounter.  
\(^d\) International Classification for Primary Care-2.  
\(^e\) Musculoskeletal.  
\(^f\) Not otherwise specified.

Anti-osteoporotic medications including bisphosphonates, strontium ranelate or denosumab, were prescribed in new cases at a rate of 5.5 (0.7–10.3) per 100 VCF problems, and in follow-up care at 15.2 (6.6–23.8) per 100. There were 22.4 (14.6–30.1) non-pharmacological treatments (counselling, advice, education or physical medicine/rehabilitation) per 100 VCF problems. (Table 3).

The mean and median daily dose of oral opioids analgesics prescribed for VCF pain management is shown in Table 4. Except for one prescription for 90 mg of morphine sulphate per day, opioid medications were prescribed in relatively low doses, with a mean daily dose ranging from 18 to 40 mg morphine equivalents.

### Discussion

This descriptive study provides important information about current management of VCF by GPs in Australia. This information was derived from data collected through the BEACH program, which has been previously shown to accurately reflect how GPs manage primary care conditions [23, 29].

While this study found that VCFs were managed at a rate of 2/1000 GP encounters, this figure does not reflect the incidence or prevalence of the condition in Australia, but rather the caseload of VCFs in general practice. In the absence of specific protocols, it is difficult to determine the real burden of this condition because: a) most VCFs are asymptomatic [30]; b) even symptomatic VCFs can be undiagnosed in older patients with acute low back pain [31, 32];
Table 3. Pharmacological and non-pharmacological treatment for new (first presentation) vertebral compression fracture (VCF) problems and for previously-assessed VCF problems - BEACH, 2005–2015, patients aged 50 years and over.  

<table>
<thead>
<tr>
<th>Pharmacological treatment</th>
<th>First presentation of VCF (new problem) (N = 79)</th>
<th></th>
<th>Follow-up of VCF (previously-assessed problem) (N = 91)</th>
<th></th>
<th>All VCF problems (N = 170)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of medications or treatments</td>
<td>Rate per 100 VCF problems (95% CI)</td>
<td>Number of medications or treatments</td>
<td>Rate per 100 VCF problems (95% CI)</td>
<td>Number of medications or treatments</td>
</tr>
<tr>
<td>Medications prescribed</td>
<td>54</td>
<td>68.4 (48.9–87.8)</td>
<td>78</td>
<td>85.7 (67.6–103.9)</td>
<td>132</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>26</td>
<td>32.9 (21.5–44.4)</td>
<td>54</td>
<td>59.9 (47.1–71.5)</td>
<td>80</td>
</tr>
<tr>
<td>“Strong” opioid</td>
<td>10</td>
<td>12.7 (5.3–20.0)</td>
<td>43</td>
<td>47.3 (35.1–68.4)</td>
<td>59</td>
</tr>
<tr>
<td>“Weak” opioid</td>
<td>16</td>
<td>20.3 (10.1–30.4)</td>
<td>11</td>
<td>12.1 (5.5–18.7)</td>
<td>27</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>8</td>
<td>10.1 (3.4–16.9)</td>
<td>6</td>
<td>6.6 (1.4–11.6)</td>
<td>14</td>
</tr>
<tr>
<td>NSAIDs*</td>
<td>2</td>
<td>2.5*</td>
<td>5</td>
<td>5.5 (0.7–10.3)</td>
<td>7</td>
</tr>
<tr>
<td>Adjuvant pain medication</td>
<td>0</td>
<td>0.0*</td>
<td>4</td>
<td>4.4 (0.1–8.7)</td>
<td>4</td>
</tr>
<tr>
<td>Anti-osteoporotic medication</td>
<td>5</td>
<td>5.5 (0.7–10.3)</td>
<td>12</td>
<td>15.2 (6.6–23.8)</td>
<td>17</td>
</tr>
<tr>
<td>Non-pharmacological treatment</td>
<td>16</td>
<td>20.3 (9.3–31.2)</td>
<td>22</td>
<td>24.2 (13.2–35.2)</td>
<td>38</td>
</tr>
</tbody>
</table>

* Vertebral compression fracture problems managed.
* Confidence interval.
* Non-steroidal anti-inflammatory drugs.
* 95% CI not reported for n<3.

https://doi.org/10.1371/journal.pone.0176351.s003

and c) diagnosed VCFs are frequently under-reported [33, 34]. Our study has shown that, on average, nationally, each year over the 10 years of this study, 26,000 (22,000–29,000) encounters in general practices involved management of VCF. This represents an average of approximately 70 (60–80) VCFs being managed every day in Australia.

At about 20% of VCF encounters patients were under 50 years of age and, therefore secondary osteoporosis or major trauma (burst fractures) was probably associated with some vertebral fractures. To assess a subsample in which primary osteoporosis was most likely to be a reason for the VCF, we separately analysed the data for encounters with patients aged 50 years or over. This cut-off age has been used in previous clinical trials addressing the treatment efficacy of VCF [13, 35–41]. However, we found, that management of VCFs is quite consistent across age groups, and no significant difference was observed when the whole sample was compared to the older subgroup in terms of likelihood of investigation, pharmacological and non-pharmacological treatment and referral.

Table 4. Mean daily dose of prescribed oral opioid analogues for VCF-related pain in encounters with patients aged 50 years and over.  

<table>
<thead>
<tr>
<th>Number of prescriptions</th>
<th>Opioid mean daily dose</th>
<th>Opioid median daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mg morphine equivalent</td>
<td>mg morphine equivalent</td>
</tr>
<tr>
<td>Oxycodeine</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Oxycodeine/ Naloxone</td>
<td>7</td>
<td>21</td>
</tr>
<tr>
<td>Tramadol</td>
<td>13</td>
<td>200</td>
</tr>
<tr>
<td>Paracetamol/ Codeine</td>
<td>6</td>
<td>170</td>
</tr>
<tr>
<td>Paracetamol/ Dextropropoxyphene</td>
<td>2</td>
<td>179</td>
</tr>
<tr>
<td>Morphone sulphate</td>
<td>1</td>
<td>90</td>
</tr>
</tbody>
</table>

https://doi.org/10.1371/journal.pone.0176351.s004
In almost half of the VCF encounters, back complaint was one of the patients’ expressed reasons for seeking medical care, and prescription of analgesic drugs was the most frequent management action for the VCF. Interestingly, management of other problems was very common in VCF encounters (75.4 per 100 VCF encounters), probably reflecting the fact that most patients with vertebral fractures are older and have comorbidities. Although most guidelines are developed for patients with a single disease and rarely deal with comorbidities, future guidelines on management of VCF should consider the number and types of comorbidities that may be present when recommendations are being developed.

The most important information extracted from this study concerns VCF management in the last decade. The REACH program directly links management actions to the specific condition being managed and so it was possible to get accurate information on VCF management. Based on REACH data, it seems that GPs focused their management on pain relief. Unfortunately, we currently lack robust evidence supporting a specific pharmacological treatment for VCF pain in older adults. In the past, the World Health Organisation pain ladder management [44] was commonly used for guiding pain relief treatment options, but concerns about the use of NSAIDs in older patients [45–48] is resulting in an increased use of opioids analgesics.

Our data suggest that Australian GPs are more likely to prescribe opioids analgesics in low doses rather than paracetamol or NSAIDs for VCF-related pain. This practice, supported in part by the American Geriatric Society (AGS) [49], comes at a high cost to the patient, given the well-known side effects associated with opioids, including constipation, nausea and vomiting, sedation, impaired judgment, impaired psychomotor function and respiratory depression [48, 50].

In addition, our findings raise concerns regarding a significant number of strong opioid analgesic prescriptions for patients at follow-up for their VCFs. This could suggest that patients are remaining on strong opioids after an acute VCF and also that the need for strong opioids did not decrease over time. The increasing prevalence of opioid analgesic use in Australia has been reported in previous studies [51, 52]. The rates of opioid analgesic prescription at VCF follow-up encounters in our study support this concern.

According to the AGS 2009 Panel on the Pharmacological Management of Persistent Pain in Older Persons, use of opioid analgesics is recommended for patients with moderate to severe pain, pain-related functional impairment or diminished quality of life because of pain [49]. However, the AGS recommendations are not evidence-based but based on the clinical experience and the consensus of panel members.

The use of opioid analgesics as first-line therapy, common practice for pain management in our study, should be re-evaluated. Only two studies [53, 54] comparing the use of opioid analgesics with other analgesics or placebo were found in a recent systematic review addressing non-surgical treatment for VCF [21]. Of these, one had insufficient statistical power to enable comparative efficacy analyses due to the premature cessation of the study [53] and the second included only 7 participants in the opioid analgesic treatment group [54]. Although in both trials the groups receiving opioid analgesics had lower pain intensity than controls, immediate and short-term effects of opioid analgesics on pain were found inconsistent across trials with different comparators. Thus, there is very little evidence for the benefits of opioid analgesics in patients with pain due to VCF, and new high-quality trials are needed to address the best approach for this condition before opioid medication is recommended as first-line therapy for VCF.

Interestingly, in only a few encounters were the patients referred to allied health professionals (3.8 per 100 VCF problems). Although the scientific evidence on the effectiveness of most non-pharmacological treatments in VCF is conflicting [21, 55–57], a multimodal approach, using both pharmacological and non-pharmacological treatments, is strongly recommended.
for pain treatment in older patients. Non-pharmacologic treatment including physiotherapy has considerably less frequent and less severe adverse events, and is central in improving pain, muscle strength, posture and mobility in these patients.

Our results have shown that anti-osteoporotic medication was prescribed for only 10% of the VCFs managed at the recorded encounters. This is a very low rate, however, we acknowledge it might not represent the total rate of prescription of osteoporosis treatments for patients with VCF, given we do not have access to medication already in use or prescribed at follow-up encounters for VCFs for the sampled patients. Anyhow, this data raises suspicion that underdiagnosis and undertreatment of osteoporosis after a VCF might have been taking place in Australia.

Readers must be aware the diagnosis method used by GPs to come to the diagnosis of VCFs or the date of VCFs was not available in the BEACH program and therefore it is not possible to distinguish acute and chronic fractures in our dataset. The term "new fractures" refers to the first visit for a VCF in any one patient rather than acute fractures. There are also other limitations to our study. First, there might be inconsistencies in diagnostic coding, even considering that the coding of GP diagnoses of VCF was determined by trained coders using the ICPC-2 PLUS terminology. In addition, the BEACH program does not follow the patient over time; therefore we cannot identify changes in an individual’s VCF management. Finally, our data describes Australian general practice activity and may not reflect the clinical practice in other international settings.

Although patients with VCF might suffer from both nociceptive and neuropathic pain [58], which could play a role on analgesics prescription, our data have not provided details on the nature of pain for included encounters. Medication prescription in this study was done at the general practitioner’s own discretion. Providing recommendations for or against the use of specific analgesic approach is beyond the scope of this study. However, we are concerned that long-term prescription of opioid analogues seems to be a common practice for VCF-related chronic pain whereas non-pharmacological approaches seem to be neglected.

**Conclusion**

The caseload of vertebral compression fractures in primary care cannot be ignored. We estimate that in Australia around 70 GP encounters will take place every day to manage VCFs. The prescription of analgesics drugs, particularly oral opioid analogues, is the most common management action despite the lack of evidence supporting this practice. Referrals to allied health professionals were rarely reported for VCF management. Although we lack evidence on what constitutes the best treatment for symptomatic VCF in older adults, it seems sensible to begin with treatments that may reduce pain and improve mobility without the risk of significant adverse side effects. This means that a greater use of allied health professionals to deliver a multimodal approach to pain may be preferable to the current long-term prescription of opioid analogues.

**Acknowledgments**

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**Author Contributions**

Conceptualization: RM HB JL AM VN MF.
Formal analysis: AP HB.
Funding acquisition: MF.
Investigation: HB AP.
Methodology: RM AP HB MF.
Project administration: MF.
Supervision: MF.
Writing – original draft: RM MF.
Writing – review & editing: RM HB JL AM VN MF.

References


Letter to the Editor – correction request

Dear Professor Michael G. Fehlings,


In the Discussion, page 6, line 15, instead of "While this study found that VCFs were managed at a rate of 2/1000 GP encounters", it should read as follows "While this study found that VCFs were managed at a rate of 2/10,000 GP encounters". We apologise for this error and would like to request the correction, please.

Yours truly,

Rodrigo Zunanrren Megale, corresponding author of the paper “Management of vertebral compression fracture in general practice: BEACH program”
CHAPTER FOUR

Efficacy and safety of oral and transdermal opioid analgesics for musculoskeletal pain in older adults: a systematic review of randomized, placebo-controlled trials

Chapter Four has been submitted as: Megale RZ, Deveza LA, Blyth FM, Naganathan V, Ferreira PH, McLachlan AJ, Ferreira ML. Efficacy and safety of oral and transdermal opioid analgesics for musculoskeletal pain in older adults: a systematic review of randomized, placebo-controlled trials. The Journal of pain. 2017; [Submitted on July 2017]. This chapter has been formatted according to the guidelines from The Journal of Pain.

Statement from co-authors confirming authorship contribution of the MPhil candidate
The co-authors of the paper “Efficacy and safety of oral and transdermal opioid analgesics for musculoskeletal pain in older adults: a systematic review of randomized, placebo-controlled trials” confirm that Rodrigo Zunzarren Megale has made the following contributions:

I. Conception and design of the research

II. Analysis and interpretation of the findings

III. Writing of the manuscript and critical appraisal of the content

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Rodrigo Zunzarren Megale

Date: 01.07.2017

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Manuela Loureiro Ferreira

Date: 01.07.2017
Efficacy and safety of oral and transdermal opioid analgesics for musculoskeletal pain in older adults: a systematic review of randomized, placebo-controlled trials

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Word count (abstract): 254
Word count (text): 2,776
Abstract

Objectives: This systematic review with meta-analysis was performed to evaluate the efficacy and safety of using opioid analgesics in older adults with musculoskeletal pain.

Methods: We searched Cochrane Library, MEDLINE, EMBASE, Web of Science, AMED, CINAHL and LILACS for randomized controlled trial with mean population age of 60 years or older, comparing the efficacy and safety of opioid analgesics with placebo for musculoskeletal pain conditions. Reviewers extracted data, assessed risk of bias and evaluated the quality of evidence using the GRADE approach. Random-effects models were used to calculate standardized mean differences (when different scales were used across trials), mean differences and odds ratios with respective 95% CIs. Meta-regressions were carried out to assess the influence of opioid analgesics daily dose and treatment duration on our main outcomes.

Results: We included 23 randomised placebo-controlled trials in the meta-analysis. Opioid analgesics had a small effect on decreasing pain intensity (Standardised mean difference (SMD): -0.27; 95% CI: -0.33 to -0.20) and improving function (SMD: -0.27, 95%CI: -0.36 to -0.18), which was not associated with daily dose or treatment duration. The risk of adverse events was three times higher (OR: 2.94; 95% CI: 2.33 to 3.72) and treatment discontinuation four times higher (OR: 4.04; 95% CI: 3.10 to 5.25) in opioid treated patients.

Conclusions: In older adults suffering from musculoskeletal pain, using opioid analgesics had only a small effect on pain and function at the cost of a higher risk of adverse events and treatment discontinuation. For this specific population, the opioid-related risks may outweigh the benefits.

Systematic review registration: PROSPERO registration number CRD42016037154
Introduction

Although the use of opioid analgesics to treat acute pain or cancer related chronic pain is widely accepted, the benefits of using them to treat chronic musculoskeletal pain are still unclear. However, the use of opioids for chronic non-cancer pain has been endorsed by different clinical practice guidelines (1-3) based on the belief that these medicines can relieve pain and improve mood and function in selected patients (4). As a result, the rate of regular use of opioid analgesics has continued to increase in recent decades (5-8), raising concerns about the safety of these medicines and the risk of overuse and opioid-related adverse events (9, 10). This is particularly true for older patients, commonly affected by musculoskeletal pain conditions (11-13). Despite the increasing popularity of these medicines, there is currently a lack of evidence regarding the efficacy and safety of opioid analgesics in older populations suffering from musculoskeletal pain.

Previous systematic reviews addressing the use of opioid analgesics for patients with musculoskeletal pain (14-17) have not provided age-relevant recommendations on the efficacy and safety of these medicines for the older patient. To our knowledge, only one systematic review, published in 2010, addressed the efficacy of opioid analgesics compared to placebo for older adults (18). The authors concluded that, in older adults, short-term use of opioid analgesics was associated with modest but favourable effects on chronic musculoskeletal pain. Since then seven new randomized trials including a large proportion of people aged over 60 years have been published in the field. How effective and safe opioid analgesics are in older people with
musculoskeletal pain is an important clinical question. A systematic, contemporary and comprehensive review of the literature may shed more light on this.

The aims of this systematic review were: a) to investigate the efficacy of opioid analgesics compared to placebo, for the outcomes of pain, function and quality of life, in older adults with musculoskeletal pain; b) to investigate the safety of opioid analgesics in older patients looking at the outcomes of adverse events and treatment withdrawal reported in clinical trials.

Methods

Data sources and searches

This systematic review was conducted following the PRISMA statement (19). A systematic electronic search was performed of the following databases: Cochrane Library, MEDLINE, EMBASE, Web of Science, AMED, CINAHL and LILACS. A combination of relevant keywords around randomised placebo-controlled clinical trials, opioid analgesics and musculoskeletal pain were used to construct the search strategy (see supplementary material).

The first screening of potential relevant records was conducted by one author based on titles and abstract (R.Z.M.), and two authors (R.Z.M. and L.A.D.) independently performed the final selection of included trials based on full text evaluation. Consensus between the two reviewers was used to resolve any disagreement.
Study selection

Only randomized controlled trials comparing the efficacy of opioid analgesics versus placebo for acute or chronic musculoskeletal pain were included in this review. Eligible trials needed to have a mean study population age of 60 years or older. When the mean was not available, a median age of 60 years or older was considered. Trials were included if they reported at least one of the following outcome measures: pain, disability, quality of life, treatment discontinuation due to lack of efficacy or adverse events or rate of adverse events. Studies including population with a range of pain conditions were included only if separated data were reported for musculoskeletal pain.

Data extraction

Using a standardized data extraction form, study characteristics (details of participants, interventions, and outcomes) were extracted from the included trials. Relevant data for outcome assessment were extracted by two independent authors (R.Z.M., L.A.D.). Any disagreement was resolved by consensus or with a third author (M.L.F.) as necessary. For pain intensity, disability and quality of life measures, change scores, final scores, standard deviations, and sample sizes were extracted. When more than one pain scale was reported, we extracted data from the scale reporting more severe pain at baseline. Missing standard deviations were estimated from standard errors, confidence intervals or p-values, using the methods described in the Cochrane Handbook (20). Data on treatment discontinuation (due to adverse events or lack of efficacy) and
adverse events were extracted as rates or number of cases. Only between-participant data from cross-over trials were included in the meta-analyses.

**Quality assessment**

Risk of bias was assessed by two independent raters (R.Z.M. and L.A.D.) using the Cochrane Collaboration’s tool for assessing risk of bias (20). The tool classifies the risk of bias in random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other sources of bias as low, unclear or high (20).

**Data synthesis and analysis**

As included trials reported measures of pain and physical function using different scales, the results are presented as standardized mean differences (SMD) and 95% confidence intervals (95% CI). We considered a standardised effect size of 0.2 to represent a small effect, 0.5 as a moderate effect, and 0.8 as a large effect (21). Data regarding quality of life was reported using normalized versions of the Short-Form 36 (SF-36) across included trials and, therefore, results for this outcome are presented as mean differences (MD) and 95% CIs.

Outcomes were grouped according to: a) follow-up time: immediate-term (less than two weeks), short-term (between two weeks and three months), intermediate-term (between three and
twelve months) or long-term (more than twelve months); and b) source of pain: back pain vs. hip and knee osteoarthritis pain.

When there were multiple comparisons (i.e. multiple drugs or multiple dosages of the same drug) in a single study, the number of participants in the placebo group was divided by the number of comparisons (20). Pooled analyses were conducted using random effects model and $I^2$ statistic was used to assess heterogeneity between trials (22). Meta-analyses were conducted using RevMan review management software (version 5.3, Biostat). Meta-regression analyses were conducted in Stata v13 (Stata Corp, College Station, TX).

The quality of evidence for each outcome was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (23). The quality of evidence was downgraded by one or two levels according to the following criteria: (i) study limitations (when most of information is from studies at moderate or high risk of bias) (24), (ii) inconsistency of results (statistically significant heterogeneity [$I^2 >50\%$] or $\leq 75\%$ of trials with findings in the same direction) (25), (iii) imprecision (wide confidence intervals or total number of participants <400 for each pooled analysis) (26) and (iv) publication bias (assessed using funnel plot analysis and Egger test) (27). The indirectness criterion was not assessed because this review included a specific population with relevant outcomes and direct comparisons (28). The quality of evidence was defined as: high, moderate, low, and very low.
Post-hoc analyses

We conducted a meta-regression to determine the association between the log-transformed morphine equivalent dose and the size of treatment effects on pain or function. The morphine equivalent dose was calculated according to the Consortium to Study Opioid Risk and Therapeutics (CONSORT) morphine equivalent conversion factor per milligram of opioid (29), and the European Palliative Care Research Collaboration (30). For tapentadol conversion, we considered morphine 10 mg equivalent to oral tapentadol 33 mg (31). When reported, the mean daily dose in the opioid group was used to calculate the daily dose in oral morphine equivalent. In trials where participants could use a range of capsules or patches and the mean daily dose of opioid was not reported (n=10), we estimated the mean daily dose from the range reported. We also conducted a meta-regression to determine the association between the treatment duration and the size of treatment effect on pain and function.

Results

The studies selection process is summarized in Figure 1. The initial search strategy retrieved 9940 studies whose titles were screened for eligibility after duplicates were removed, leading to 292 studies for abstracts review. This resulted in the assessment of 120 full-texts for eligibility. Of these, 25 randomised placebo-controlled trials of opioid analgesics for musculoskeletal pain in populations with mean age of 60 years and over were included in this review (a total of 6,455 participants). The characteristics of the included studies are summarized in Table 1. Two of the included trials used a cross-over design but failed to provide between-participant data (32, 33).
Data from these two trials were not included in the meta-analyses. The duration of treatment ranged from 10 days to 24 weeks across the trials. Only immediate post-treatment data (i.e. within 14 days from end of intervention) were reported in included randomised controlled trials. The mean daily dose of opioid, in oral morphine equivalents, ranged from 10 to 300 mg morphine equivalents.

The methodological quality assessment of each included studies is shown in supplementary figure S1. Overall, studies were of good quality and the risk of attrition bias was the major concern given that the rate of participants’ withdrawal was high (more than 20%) in all but one clinical trial. The quality of the evidence for each of the outcomes of interest is shown in Table 2, as well as the reason for downgrading the evidence.

**Efficacy Analysis**

**Pain intensity**

From 24 trials that assessed the effects of opioid analgesics on pain intensity, only 16 provided enough data to be included in the meta-analysis. There is moderate quality evidence from 4,998 participants that opioid analgesics decrease musculoskeletal pain (SMD: -0.27; 95% CI: -0.33 to -0.20), when compared to placebo (Table 2 and Supplementary Figure S3).

According to the musculoskeletal condition, there is moderate quality evidence from 13 studies (4565 participants) of a small effect of opioid analgesics on relieving hip or knee osteoarthritis
pain (SMD: -0.26; 95%CI: -0.33 to -0.19), and low quality evidence from 2 studies (283 participants) on relieving back pain (SMD: -0.34; 95% CI: -0.59 to -0.09) (Figure 2).

The meta-regression analysis showed that there is no association between daily doses (meta-regression coefficient: -0.06; 95% CI: -0.14 to 0.01; p=0.107) or treatment duration (meta-regression coefficient: 0.01; 95% CI: -0.07 to 0.19; p=0.369) and the size of treatment effect on pain.

**Function**

Fourteen trials assessed the effects of opioid analgesics on function but only 9 were included in the meta-analysis. There is moderate quality evidence from the included trials (2989 participants) of a small effect of opioid analgesics on function (SMD: -0.27, 95%CI: -0.36 to -0.18) (Table 2 and Supplementary Figure S4).

Analyses were conducted also by specific musculoskeletal conditions, showing moderate quality evidence from 8 studies (2819 participants) of a small effect of opioid analgesics on improving disability due to hip or knee osteoarthritis (SMD -0.27; 95%CI: -0.36 to -0.17) (Table 2 and Figure 3). There is very low quality evidence from a single study (170 participants) on disability improvements in patients with low back pain (SMD: -0.31; 95% CI: -0.61 to -0.01) (Table 2 and Figure 3).
Our meta-regression showed that daily doses (meta-regression coefficient: -0.05; 95% CI: -0.15 to 0.05; p=0.273) or treatment duration (meta-regression coefficient: 0.02; 95% CI: -0.01 to 0.04; p=0.128) are not associated with the size of treatment effect on function.

**Quality of life**

Studies have reported the SF-36 physical and mental component summary score only in patients with hip or knee osteoarthritis (Table 2 and Supplementary Figure S5). There is low quality evidence from 6 studies (2478 participants) of an effect of opioid analgesics on the physical component of quality of life (MD: -1.49; 95% CI: -2.27 to -0.72; on a 1 to 100 scale) and very low quality evidence from 5 studies (2123 participants), of no effect of opioids on the mental component of quality of life (MD: 0.59; 95% CI: -0.31 to 1.54), compared to placebo.

**Safety Analysis**

**Rate of adverse events**

Fourteen studies reporting the rate of participants who presented at least one adverse event during the trial were included in the meta-analysis (4288 participants). The most common adverse events reported were nausea, constipation, drowsiness, vomiting, dizziness, headache and dry mouth. There is very low quality evidence of an increase in the incidence of adverse events among participants allocated to the opioid treated groups (OR: 2.94; 95% CI: 2.33 to 3.72) (Table 2 and Figure 4).
**Discontinuation due to adverse events or lack of efficacy**

Twenty-two studies reporting rates of participant withdrawal due to adverse events were included in the meta-analysis. There is moderate evidence from these studies (6368 participants) of an increased risk of discontinuation due to adverse events in participants allocated to opioid treated groups (OR: 4.04; 95% CI: 3.10 to 5.25) (Table 2 and Supplementary Figure S6).

There is low quality evidence from 20 studies (5803 participants) that the allocation to an opioid group reduces the incidence of discontinuing treatment due to lack of efficacy by 63% (OR: 0.37; 95% CI: 0.29 to 0.47) (Table 2 and Supplementary Figure S7).

**Discussion**

This systematic review suggests that the regular use of opioid analgesics (from 10 days to 24 weeks) for older adults with musculoskeletal pain at daily doses from 10 to 300 mg of oral morphine equivalents results in only a small benefit in terms of pain and function. In addition, the risk of any adverse event is three times higher for opioid analgesics compared to placebo, and the rate of withdrawal due to adverse events is four times higher among older adults allocated to the opioid group compared to the placebo group. While this systematic review aimed to address the efficacy and safety of opioid analgesics specifically in older adults with musculoskeletal pain, the trials conducted to date that were included in this review had study populations with mean ages ranging from 60 to 72 years. Our findings are more applicable to
what would now be considered in developed countries “older” middle-aged adults rather than older people, letting alone frail older people as usual (34).

We have found that the use of opioid analgesics in older adults resulted in only small benefits on pain relief compared to placebo. This benefit can be translated to a 6.8 mm decrease in pain intensity on a 100-mm visual analogue scale (VAS), on the basis of a median pooled SD of 25 mm found in 167 osteoarthritis trials using the same scale (15). Our findings are consistent with a magnitude of treatment effect found in previous systematic reviews of opioid analgesics for OA (14) and back pain (17) in younger populations.

The effect of opioid analgesics on function and quality of life was also small. We found an effect equivalent to 0.56 units on a 0-10 point WOMAC disability subscale, on basis of a median pooled SD of 2.1 found in osteoarthritis trials that assessed pain using same scale (15). While the American Geriatrics Association recommends the use of opioid analgesics in older adults with pain-related functional impairment or diminished quality of life due to pain (1), our results suggest that analgesic opioids have only a small effect on these outcomes. Interestingly, the effect of opioids on pain or function does not seem to vary for different classes of opioids, prescribed at different daily doses or even for different painful musculoskeletal conditions.

Our systematic review also showed the potential risk associated with taking opioid analgesic for musculoskeletal pain. The small benefits in terms of pain and function may be outweighed by the
increased risk of harm. We might have found even higher adverse events in the opioid group compared to placebo group, had the study samples been older.

The strengths of this systematic review is that the pooled analyses results are based on randomized placebo-controlled clinical trials found using a comprehensive search strategy. Individual studies were assessed for validity and the GRADE approach was used to grade the quality of evidence and the strength of our recommendations. In addition, this systematic review was prospectively registered and we strictly followed all Cochrane’s recommendations for systematic review of interventions (20). A limitation was that we used aggregated data rather than individual participant data in the pooled analyses.

For all conclusions drawn from our meta-analysis, the quality of evidence based on GRADE criteria was moderate or lower. The main reason for downgrading of GRADE rating was study bias more commonly due to high risk of attrition bias due to a higher withdrawal rate. Regardless of this limitation, the finding that opioid analgesics have only a modest effect on musculoskeletal pain may not justify the risks imposed by these drugs in older populations. Our finding would support the view that given opioids are of limited benefit, non-pharmacological approaches need to be emphasized in the management of persistent musculoskeletal pain in older adults (36). The growing understanding that no currently available analgesic class is highly efficacious in achieving adequate pain relieve without the risk of major side effects is a key step towards a wider use of non-pharmacological strategies (37).
Acknowledgments

RM was supported by Fundação Hospitalar do Estado de Minas Gerais (FHEMIG) during his Masters of Philosophy.

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Conflicts of Interest

AJM is an investigator on the PACE trial funded by the National Health and Medical Research Council of Australia and GlaxoSmithKline (ACTRN 12609000966291), PRECISE trial funded by the National Health and Medical Research Council of Australia with in kind research support from Pfizer (ACTRN12613000530729) and the OPAL trial funded by the National Health and Medical Research Council of Australia (ACTRN12615000775516).
<table>
<thead>
<tr>
<th>Source</th>
<th>Baseline population</th>
<th>Intervention</th>
<th>Length of treatment</th>
<th>Outcomes</th>
<th>Eligible outcome measures</th>
<th>Main findings</th>
<th>Industry funding</th>
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<tbody>
<tr>
<td>Arai et al., 2015 (38)</td>
<td>150 participants with chronic MSK pain (OA or LBP) and previous use of non-opioid analgesics. Mean age: 66.3 years in the opioid group and 66.6 years in the placebo group</td>
<td>Fentanyl transdermal 12.5 - 50 mcg/h (n=73) or placebo (n=77). Mean daily opioid dose: 25.63 mcg/h</td>
<td>12 weeks</td>
<td>Primary outcome: number of days until withdrawal because of insufficient analgesic efficacy. Secondary outcomes: change in VAS score in the double-blind period, subject's overall assessment score, number of times rescue medication was used, BPI-SF score, SF-36v2 physical and emotional scores, and physician's overall assessment score</td>
<td>Pain intensity: VAS 0-100; Quality of life: SF-36 - PCS and MCS scores; rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: fentanyl transdermal superior to placebo (p=0.0215). SF-36 PCS: NS; SF-36 MCS: NS</td>
<td>Yes (Janssen)</td>
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<td>Babul et al., 2004 (39)</td>
<td>246 participants with chronic pain due to knee OA that had warranted treatment for at least 75 of 90 days prior to the study. Mean age: 61.2 (10.0) years in the opioid group and 61.5 (10.2) years in the placebo group</td>
<td>Tramadol ER 200 - 400 mg/day (n=124) or placebo (n=122)</td>
<td>12 weeks</td>
<td>Analgesia evaluated by the Arthritis Pain Intensity VAS and by the WOMAC OA Index pain subscale, improvements in physical function and stiffness evaluated by the WOMAC OA Index, and effects on sleep evaluated by the CPSI</td>
<td>Pain intensity: Arthritis Pain Intensity VAS (0-100); Disability: WOMAC physical function subscale (0-1700); rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: tramadol superior to placebo (p&lt;0.001). Disability: tramadol superior to placebo (p&lt;0.001)</td>
<td>Unclear</td>
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<tr>
<td>Breivik et al., 2010 (40)</td>
<td>199 participants with chronic pain due to hip or knee OA who were taking NSAIDs or coxibs one month prior to the screening visit. Mean age: 62.9 (9.9) years in the opioid group and 62.9 (9.0) years in the placebo group</td>
<td>Buprenorphine transdermal 5 - 20 mcg/h (n=100) or placebo (n=99)</td>
<td>24 weeks</td>
<td>Primary outcome: change in WOMAC OA Index pain subscale from the baseline to the end of the 6-month double-blind period. Secondary outcomes: changes in WOMAC stiffness, physical function and total scores, daily rescue medication used, number of nights woken because of pain, and Patient's Global Impression of Change (PGIC)</td>
<td>Pain intensity: WOMAC LK 3.1 – pain subscale (0-20); Disability: WOMAC LK 3.1 – functional ability subscale (0-96); rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: NS Disability: NS</td>
<td>Yes (Norpharma and Mundipharma)</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Description</td>
<td>Duration</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
<td>Pain Intensity</td>
<td>Other Information</td>
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<td>Burch et al., 2007 (41)</td>
<td>646 participants with persistent pain due to knee OA who were taking NSAIDs, coxibs or tramadol one month prior to the enrolment. Mean age: 62 (9) years in the opioid group and 62 (9) in the placebo group.</td>
<td>Tramadol Contramid OAD 200 - 300 mg/day (n=432) and placebo (n=214). Mean daily opioid dose: 275.4 mg</td>
<td>12 weeks</td>
<td>Primary outcome: score on the PI - NRS® after 12 weeks of double-blind treatment. Secondary outcomes: percentage of patients who experienced an improvement of one to five in the PI-NRS, patient's and physician's global impressions of change.</td>
<td>Pain intensity: PI-NRS (0-10); discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: tramadol superior to placebo (p&lt;0.001)</td>
<td>Unclear</td>
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<td>Caldwell et al, 2002 (42)</td>
<td>295 participants with moderate-to-severe pain due to hip or knee OA on treatment with NSAIDs, acetaminophen or intermittent opioid analgesic therapy. Mean age &gt; 60 years in all groups.</td>
<td>Once-daily morphine (Avinza) 30 mg QAM (n=73), Once-daily morphine (Avinza) 30 mg QPM (n=73), morphine sulphate controlled-release (MS Contin) 30 mg/day (n=76) or placebo (n=73)</td>
<td>4 weeks</td>
<td>Primary outcomes: analgesia evaluated by WOMAC OA Index pain - sub scale and Overall Arthritis Pain Intensity scores. Secondary outcomes: WOMAC physical function and stiffness, and the effects of treatment on sleep.</td>
<td>Pain intensity: Overall Arthritis Pain Intensity (0-100); Disability: WOMAC physical function subscale (0-1700); discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: Avinza QAM, Avinza QPM and MS Contin superior to placebo (p&lt;0.05) when analgesia evaluated by WOMAC OA Index Pain Disability: NS</td>
<td>Unclear</td>
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<tr>
<td>DeLemos et al. 2011 (43)</td>
<td>1011 participants with moderate-to-severe pain due to hip or knee OA that had warranted treatment for at least 75 of 90 days prior to the study. Mean age of 60 years.</td>
<td>Tramadol ER in different doses: 100 (n=202), 200 (n=203) or 300 mg/day (n=201), Celecoxib (n=203 or placebo (n=202)</td>
<td>12 weeks</td>
<td>Primary outcomes: improvements in WOMAC pain and physical function sub scales, and patient’s global assessment of disease activity. Secondary outcomes: reduction in daily arthritis pain intensity, WOMAC stiffness sub scale and composite index, physician’s global assessment, SF-36 and overall quality of sleep.</td>
<td>Pain intensity: WOMAC Pain subscale (0-500); Disability: WOMAC physical function subscale (0-1700); Quality of life: SF-36 PCS; rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: tramadol 100 mg vs. placebo: NS; tramadol 200 mg vs. placebo: NS; tramadol 300 mg vs. placebo: NS; Disability: tramadol 100 mg vs. placebo: NS; tramadol 200 mg vs. placebo: NS; tramadol 300 mg vs. placebo: NS;</td>
<td>Yes (Biovail and Ortho-McNeil Janssen)</td>
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<td>Emkey et al. 2004 (44)</td>
<td>306 participants with symptomatic OA of the knee or hip for more than 1 year (at least moderate pain) despite treatment with coxibs for at least 2 weeks preceding the study.</td>
<td>Tramadol/acetaminophen (Ultracet) 150 - 300 mg/day (n=153) or placebo (n=153). Mean daily opioid dose: 154 mg/day</td>
<td>13 weeks</td>
<td>Primary outcome: improvements in pain VAS scores. secondary outcomes: pain relief scores, patient’s and physician’s overall medication assessment, time to discontinuation due to lack of efficacy, proportion of subjects</td>
<td>Pain intensity: VAS (0-100); Disability: WOMAC physical function subscale (0-10); Quality of life: SF-36 PCS and MCS scores; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: tramadol superior to placebo (p=0.025). Disability: tramadol superior to placebo (p=0.025). SF-36 PCS: NS SF-36 MCS: NS</td>
<td>Unclear</td>
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<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>Duration</td>
<td>Outcome Measures</td>
<td>Findings</td>
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<td>Fishman et al., 2007 (45)</td>
<td>520 participants with pain due to knee OA. Mean age of 63 (8), 61 (9) and 60 (9) years in the opioid group and 61 (10) years in the placebo group.</td>
<td>Tramadol Contramid OAD 100 mg (n=103), 200 mg (n=107) or 300 mg/day (n=105) or placebo (n=224).</td>
<td>12 weeks</td>
<td>Patients’ Global Rating of Pain Relief, WOMAC pain sub scale and WOMAC physical function sub scale.</td>
<td>Pain intensity: WOMAC Pain subscale (0-500); Disability: WOMAC physical function subscale (0-1700); rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy. Pain intensity: tramadol 100 mg vs. placebo: NS; tramadol 200 mg vs. placebo: p=0.05; tramadol 300 mg vs. placebo: p=0.016; Disability: tramadol 100 mg vs. placebo: p=0.0268; tramadol 200 mg vs. placebo: p=0.0450; tramadol 300 mg vs. placebo: p=0.0211;</td>
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<td>Fleischmann et al. 2001 (46)</td>
<td>129 participants with pain associated with knee OA. Mean age: 62.5 (8.68) years in the opioid group and 62.45 (9.62) years in the placebo group.</td>
<td>Tramadol 200 - 400 mg/day (n=63) or placebo (n=66).</td>
<td>13 weeks</td>
<td>Primary outcome: pain intensity experienced in target knee within 48 hours before the final visit. Secondary outcomes: pain relief scores, patients and investigator overall assessments, WOMAC scores, and time to failure of effectiveness.</td>
<td>Pain intensity: Pain intensity score (0-4); Disability: WOMAC physical function subscale (0-10); discontinuation due to AE; discontinuation due to lack of efficacy. Pain intensity: tramadol superior to placebo (p=0.045, t test / p=0.082, ANCOVA); Disability: tramadol superior to placebo (p=0.033);</td>
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<td>Hyup Lee et al., 2013 (47)</td>
<td>248 participants with moderate to severe chronic low back pain despite the use of NSAIDs or coxibs. Mean age: 60 years</td>
<td>Extended release tramadol/paracetamol (Ultracet ER) 150 - 300 mg/day (n=125) or placebo (n=120)</td>
<td>29 days</td>
<td>Primary outcome: percentage of patients with a pain intensity change rate &gt; 30%. Secondary outcomes: pain relief, quality of life and functionality measurements, and patients and investigator global assessment of treatment.</td>
<td>Pain intensity: VAS (0-100); Disability: Korean Oswestry Disability Index (0-100); Quality of life: Korean SF-36; rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy. Pain intensity: tramadol/paracetamol superior to placebo (p=0.0095) Disability: tramadol/acetaminophen superior to placebo (p=0.0449);</td>
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<td>Kivitz et al., 2006 (48)</td>
<td>370 participants with symptomatic knee or hip OA who had been taking acetaminophen, NSAIDs or opioid analgesics for</td>
<td>Oxymorphone extended release 20 mg (n=95), 80 mg (n=93) or 100 mg/day</td>
<td>2 weeks</td>
<td>Primary outcome: mean change in arthritis pain intensity. Secondary outcomes: change in WOMAC sub scales, physical health component.</td>
<td>Pain intensity: Arthritis Pain Intensity - VAS (0-100); Disability: WOMAC physical function subscale (0-1700); Quality of life: Pain intensity: oxymorphone 20 mg BID vs. placebo: NS; oxymorphone 40 mg BID vs. placebo: Yes (Endo Pharmaceutics);</td>
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<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
<td>Duration</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
<td>Pain Intensity</td>
<td>Disability</td>
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<td>Langford et al., 2006 (49)</td>
<td>416 participants with chronic pain due to hip or knee OA and requiring joint replacement surgery. Mean age: 66 (0.7) years.</td>
<td>Fentanyl transdermal 25-100 mcg/h (n=202) or placebo (n=197). Mean daily opioid dose: 42.5 mcg/h</td>
<td>6 weeks</td>
<td>Primary outcome: pain relief expressed as the difference in the average AUC of the VAS scores (pain diary) over the time. Secondary outcomes: function assessed by WOMAC score and individuals aspects of pain affecting mobility and quality of life (SF-36 scores)</td>
<td>SF-36 PCS score; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: VAS (0-100); Disability: WOMAC physical function subscale (0-10); Quality of life: SF-36 PCS and MCS scores; rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: fentanyl transdermal superior to placebo (p=0.025). Disability: NS SF-36 PCS: NS SF-36 MCS: fentanyl transdermal inferior to placebo (p=0.041)</td>
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<td>Malonne et al., 2004 (50)</td>
<td>230 participants with pain due to hip or knee OA requiring regular treatment with analgesics for more than 1 month. Mean age of 67.1 (7.1) for the opioid group and 66.4 (9.2) for the placebo group</td>
<td>Sustained-release tramadol 200 mg/day (n=111) or placebo (n=119)</td>
<td>2 weeks</td>
<td>Primary outcome: change in the global pain score from the baseline to the end of the study. Secondary outcomes: Lequesne functional discomfort index, patient’s and investigator’s assessment of global efficacy, time to improvement, and use of rescue medication</td>
<td>Pain intensity: VAS (0-100); Disability: Lequesne functional discomfort index (0-20); rate of AE; discontinuation due to AE.</td>
<td>Pain intensity: tramadol superior to placebo (p=0.010). Disability: NS</td>
<td>Unclear</td>
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<td>Markenson et al., 2005 (51)</td>
<td>107 participants with OA (defined by ACR guidelines) and</td>
<td>Controlled-release oxycodone (CR Oxycontin) 20 - 120</td>
<td>90 days</td>
<td>Primary outcome: Brief Pain Inventory (BPI) average pain intensity at stable dosing,</td>
<td>Pain intensity: BPI (0-10); Disability: WOMAC physical function subscale</td>
<td>Pain intensity: oxycodone superior to placebo (p=0.042).</td>
<td>Yes (Purdue Pharma)</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Treatment</td>
<td>Outcome Measures</td>
<td>Key Findings</td>
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<td>Moderate-to-severe pain requiring regular treatment with NSAIDs, acetaminophen or intermittent opioid therapy for at least 2 weeks prior to the study. Mean age of 62 (38.8) years in the opioid group and 64 (41.89) years in the placebo group.</td>
<td>mg/day (n=56) or placebo (n=51). Mean daily opioid dose: 44 mg/day</td>
<td>WOMAC scores at days 30 and 60 and number of patients who discontinued the study due to inadequate pain control. Secondary outcomes: BPI, WOMAC, PGI scores, time to stable dosing, average daily dose, patient-reported acceptability of and satisfaction with medication, ratings of average and current pain intensity from patients diary</td>
<td>(0-1700); Quality of life: SF-36 PCS and MCS scores; rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
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<td>Markman et al., 2015 (32)</td>
<td>24 participants with neurogenic claudication associated with lumbar stenosis and mean age of 71.8 years.</td>
<td>Oxycontin 5 mg, propoxyphene/paracetamol 100 mg or placebo</td>
<td>Primary outcome: time to first reported pain of moderate intensity during a treadmill test. Secondary outcomes: pain at rest before starting the test, area under the pain-intensity curve, pain intensity after 15 minutes, time and distance walked in the treadmill, and time to return to baseline pain. Other outcome measures assessed 45 minutes after the treatment: global assessment of low back pain, RMDQ, BPI, Oswestry Disability Index, Swiss Spinal Stenosis Questionnaire</td>
<td>Pain intensity: Pain at rest (0-10) measured 90 minutes after study drug in each period</td>
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<td>Matsumoto et al., 2005 (52)</td>
<td>491 participants with typical hip or knee OA symptoms that had warranted treatment for at least 75 of 90 days prior to the study. Mean age: 61.4 (1.0), 63.4 (0.9) and 62.7 (1.0) years in the opioid groups and 61.7 (1.0) years in the placebo group</td>
<td>Oxymorphone extended-release 20 mg BID (n=121), 40 mg BID (n=121), oxycodone 20 mg BID (n=125) or placebo (n=124)</td>
<td>Primary outcome: changes in Arthritis Pain Intensity (API) score from baseline to the week 3 visit in the oxymorphone 40 mg group compared with that in placebo group. Secondary outcomes: comparison with oxymorphone 20 mg, WOMAC OA index, patient’s and physician’s global assessments of therapy, withdrawal due to lack of</td>
<td>Pain intensity: VAS (0-100); Disability: WOMAC physical function subscale (0-10); Quality of life: SF-36 PCS and MCS scores; rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
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<td>Disability: oxycodone superior to placebo (p&lt;0.001)</td>
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<td>Study Reference</td>
<td>Study Design</td>
<td>Population</td>
<td>Intervention</td>
<td>Duration</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
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<td>Munera et al., 2010 (53)</td>
<td>315 men and women with hip or knee OA whose pain was inadequately controlled with NSAIDs (ibuprofen 1,600 mg/day). Mean age population: 60 years in the opioid group and 62 in the placebo group</td>
<td>Buprenorphine transdermal system (BTDS) 5-20 mcg/h (n=152) or placebo (n=163)</td>
<td>4 weeks</td>
<td>Primary outcome: percentage of patients who achieved treatment success (patient satisfaction scale 2 or more on a 5-point scale). Secondary outcomes: average pain intensity score, patient's satisfaction with study medication score, and a weekly average of diary pain score</td>
<td>Pain intensity: 11-point pain scale (0=no pain and 10=worst pain you can imagine); rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Yes (Purdue Pharma)</td>
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<td>Peloso et al. 2000 (54)</td>
<td>103 participants with hip or knee OA requiring acetaminophen, NSAIDs or opioids for the previous 3 months, who experienced a flare during the washout period. Mean age: 60.1 (11.4) years in the opioid group and 63.0 (10.9) years in the placebo group.</td>
<td>Controlled release codeine 100 - 400 mg/day (n=51) or placebo (n=52). Mean daily opioid dose: 317.8 mg</td>
<td>4 weeks</td>
<td>Primary outcomes: WOMAC pain VAS and daily overall Pain Intensity scores over the previous week. Secondary outcomes: WOMAC stiffness and physical sub scales, daily VAS average pain scale, 7 item questionnaire on sleep, Drug Liking Index</td>
<td>Pain intensity: Weekly pain intensity - VAS (0-100); Disability: WOMAC physical function subscale (0-1700); rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Unclear</td>
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<td>Roth, 1998 (35)</td>
<td>42 participants on stable NSAIDs therapy who experienced breakthrough musculoskeletal pain attributed to OA. Mean age: 67 years in the opioid group and 65.9 in the placebo group.</td>
<td>Tramadol HCl 50 - 400 mg/day (n=21) or placebo (n=21)</td>
<td>2 weeks</td>
<td>Primary outcome: time to exit from the study because of therapeutic failure. Secondary outcome: severity of pain at rest, severity of pain on motion, severity of current pain, patient’s ability to perform activity of daily living and patient's overall assessment of therapy</td>
<td>Pain intensity on motion: 4-point severity of pain score (0=none and 3=severe); Disability: ADL score (0-3); discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Yes (Ortho-McNeil)</td>
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<td>Roth et al. 2000 (55)</td>
<td>133 participants with moderate-to-severe OA-</td>
<td>Controlled-release oxycodone 10 mg</td>
<td>2 weeks</td>
<td>Primary outcome: daily mean pain intensity. Secondary</td>
<td>Pain intensity: 4-point pain intensity scale</td>
<td>Unclear</td>
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<td>Study</td>
<td>Participants</td>
<td>Intervention</td>
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<td>Related pain. Mean age: 62 (2) and 63 (2) years in the opioid groups and 62 (2) in the placebo group.</td>
<td>240 participants with pain due to knee OA in use of naproxen. Mean study age: 61.4 years</td>
<td>Tramadol 200 mg/day (n=117) or placebo (n=123)</td>
<td>8 weeks</td>
<td>Primary outcome: Minimal effective naproxen dose (MEND)</td>
<td>Discontinuation due to adverse events</td>
<td>Among participants stratified as naproxen responders, the MEND was significantly lower in patients receiving tramadol than in patients receiving placebo.</td>
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<td>Schnitzer et al., 1999 (56)</td>
<td>308 participants with symptomatic OA of the hip or knee who had been experiencing OA flare pain for 2 to 5 days on use of stable doses of NSAIDs or coxibs. Mean population age: 60 (9.74) years in the opioid group and 60.4 (10.12) in the placebo group.</td>
<td>Tramadol-paracetamol (Ultracet) 150 - 300 mg/day (n=197) or placebo (n=111)</td>
<td>10 days</td>
<td>Primary outcome: average daily pain scores, average pain relief scores for days 1 to 5. Secondary outcomes: dose response (SPRID), patient's and investigator's overall assessments, WOMAC scores</td>
<td>Pain intensity: WOMAC pain subscale (0-10); Disability: WOMAC physical function subscale (0-12.5); rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: tramadol superior to placebo (p=0.004) Disability: tramadol superior to placebo (p=0.013)</td>
<td></td>
</tr>
<tr>
<td>Silverfield et al., 2002 (57)</td>
<td>100 participants with symptomatic hip or knee OA, on acetaminophen, NSAIDs or combination opioid and non-opioid analgesics for at least 3 months and at least moderate pain at the time of enrolment. Mean age of 61 (10.3) years.</td>
<td>Controlled-release tramadol 150 to 400 mg/day (n=50), or placebo (n=50). Mean daily opioid dose: 340.3 (90.7) mg</td>
<td>8 weeks - 4 weeks each for period of treatment</td>
<td>Primary outcome: VAS pain intensity from the patients' daily diaries averaged over the last week of treatment. Secondary outcomes: WOMAC scores, PDI, Pain and Sleep Questionnaire, SF-36, treatment effectiveness and treatment preference</td>
<td>Pain intensity: VAS (0-100); Disability: WOMAC physical function subscale (0-1700); Quality of life: SF-36 - PCS and MCS scores; rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: tramadol superior to placebo (p=0.0009) Disability: tramadol superior to placebo (p=0.0205) SF-36 PCS: tramadol superior to placebo (p=0.0002) SF-36 MCS: NS</td>
<td></td>
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<tr>
<td>Thorne et al., 2008 (33)</td>
<td>100 participants with symptomatic hip or knee OA, on acetaminophen, NSAIDs or combination opioid and non-opioid analgesics for at least 3 months and at least moderate pain at the time of enrolment. Mean age of 61 (10.3) years.</td>
<td>BID (n=44), 20 mg BID (n=44) or placebo (n=45)</td>
<td>outcomes: quality of sleep, BPI, interference of pain and ability to perform 8 daily activities</td>
<td>(0=None and 3=severe); Disability: 4-point ADL score (1=without any difficulty to 4=unable to do); discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>significantly superior to placebo Disability: no significant differences between oxycodone 10 or 20 mg BID and placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schnitzer et al., 1999 (56)</td>
<td>240 participants with pain due to knee OA in use of naproxen. Mean study age: 61.4 years</td>
<td>Tramadol 200 mg/day (n=117) or placebo (n=123)</td>
<td>8 weeks</td>
<td>Primary outcome: Minimal effective naproxen dose (MEND)</td>
<td>Discontinuation due to adverse events</td>
<td>Among participants stratified as naproxen responders, the MEND was significantly lower in patients receiving tramadol than in patients receiving placebo.</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Mean Age</td>
<td>Study Duration</td>
<td>Primary Outcome</td>
<td>Secondary Outcomes</td>
<td>Insufficient Statistical Power</td>
<td>Conclusion</td>
</tr>
<tr>
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</tr>
<tr>
<td>Vorsanger et al., 2013 (58)</td>
<td>108 participants with symptomatic vertebral compression fractures. Mean study age: 69.8 (12.28) years in the tapentadol group, 69.3 (13.26) years in the oxycodone group and 69.6 (12.36) years in the placebo group</td>
<td>69.8 (12.28)</td>
<td>10 days</td>
<td>Sum of pain intensity difference (SPID) over 72 hours. Secondary outcomes: total pain relief (TOTPAR) and sum of pain relief and intensity differences (SPRID)</td>
<td>Pain intensity: SPID (0-10); rate of AE; discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Insufficient statistical power for comparative efficacy analysis – trial was stopped due to slow enrolment</td>
<td>Yes (Janssen)</td>
</tr>
<tr>
<td>Zautra et al., 2005 (59)</td>
<td>107 participants with OA (defined by the ACR) and moderate-to-severe pain. Mean population age: 62.6 years in the opioid group and 63.9 years in the placebo group</td>
<td>62.6</td>
<td>90 days</td>
<td>Average daily pain intensity, changes in positive and negative affect scales, Vanderbilt Multidimensional Pain Coping Inventory, coping efficacy and arthritis helpless</td>
<td>Pain intensity: average 24h pain - 0-10 (0=no pain to 10=pain as bad as you can imagine); discontinuation due to AE; discontinuation due to lack of efficacy</td>
<td>Pain intensity: oxycodone superior to placebo (p&lt;0.001)</td>
<td>Yes (Purdue Pharma)</td>
</tr>
</tbody>
</table>

a Osteoarthritis  
b Low back pain  
c Visual Analog Scale  
d Brief Pain Inventory Short Form  
e Short Form  
f Physical Component Summary  
g Mental Component Summary  
h Adverse events  
i Non significant  
j Western Ontario and McMaster Universities Osteoarthritis Index  
k Chronic Pain Sleep Inventory  
l Nonsteroidal anti-inflammatory drugs  
m Pain intensity – Numerical Rating Scale  
n Area under the curve  
o Patient Generated Index  
p Roland-Morris Disability Questionnaire  
q American College of Rheumatology
Figure 1. Summary of the search process.

13,381 records identified through database searching

MEDLINE: 3365
EMBASE: 3351
Cochrane Library: 3412
Web of Science: 2182
CINHAL: 1010
AMED: 39
Lilacs: 22

9,940 records after duplicates removed

9,648 records excluded: not relevant to topic

172 studies excluded
- Duplicates not previously identified: 89
- Study population mean age < 60 years: 7
- Ineligible study design: 38
- Ineligible outcome: 4
- Ineligible intervention: 1
- Incomplete report: 32
- Other: 3

292 studies identified for abstract review

95 full-text articles excluded
- Study population mean age < 60 years: 68
- Ineligible study design: 17
- Ineligible outcome: 8
- Intravenous opioid: 2

120 full-text articles assessed for eligibility

25 of studies included in qualitative analysis

2 studies excluded from meta-analysis
- Cross-over studies: 02

23 studies included in quantitative synthesis (meta-analysis) as follow:
- Pain intensity: 16
- Discontinuation due to lack of efficacy: 21
- Functionality: 9
- Quality of life – PCS: 6
- Quality of life – MCS: 5
- Rate of adverse events: 14
- Discontinuation due to adverse events: 22
Figure 2. Effect of opioid on pain intensity according to the site of pain: back pain or hip or knee osteoarthritis

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<tr>
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<tbody>
<tr>
<td>Hurka Lee 2010</td>
<td>-2.27</td>
<td>1.69</td>
<td>85</td>
<td>-1.6</td>
<td>1.69</td>
<td>90</td>
<td>4.3%</td>
<td>-0.39 [-0.69, -0.10]</td>
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<tr>
<td>Vorsanger 2013 (1)</td>
<td>-42.9</td>
<td>382.76</td>
<td>43</td>
<td>-389.9</td>
<td>343.31</td>
<td>10</td>
<td>0.9%</td>
<td>-0.09 [-0.77, 0.60]</td>
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<tr>
<td>Vorsanger 2013 (2)</td>
<td>-505</td>
<td>173</td>
<td>44</td>
<td>-389.9</td>
<td>343.31</td>
<td>11</td>
<td>1.9%</td>
<td>-0.41 [-0.97, 0.17]</td>
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</tr>
<tr>
<td><strong>Subtotal (95%) CI</strong></td>
<td><strong>172</strong></td>
<td></td>
<td></td>
<td><strong>111</strong></td>
<td></td>
<td></td>
<td><strong>6.1%</strong></td>
<td><strong>-0.34 [-0.59, -0.09]</strong></td>
<td><strong>-0.34 [-0.59, -0.09]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity $I^2 = 0.00; Ch^2 = 0.60; df = 2; P = 0.72; I^2 = 0$

Test for overall effect: $Z = 2.63; P = 0.008$

1.3.2 Hip or knee OA

Badal 2004  
-0.54  29.1  124  -17.7  29.1  122  5.7%  -0.42 [-0.68, -0.17]

Bennet 2010  
-3.2  3.8  95  -2.3  3.7  99  4.7%  -0.24 [-0.52, 0.04]

Burton 2007  
-5.01  2.12  193  -2.29  1.97  196  10.0%  -0.36 [-0.53, -0.18]

Caldwell 2002 (3)  
-22.2  16.5  123  -14.6  16.9  124  2.0%  -0.26 [-0.47, 0.01]

Caldwell 2002 (5)  
-36.7  29.9  73  -14.6  29.9  84  2.2%  -0.40 [-0.76, 0.06]

Devlin 2001 (6)  
-66.4  125.5  199  -94.9  125.8  167  4.9%  0.64 [-0.25, 1.13]

Djuric 2013 (7)  
-82.5  126.8  201  -94.9  125.8  167  4.9%  0.10 [-0.18, 0.37]

Djuric 2012 (8)  
-117.8  125.5  199  -94.9  125.8  167  4.9%  -0.18 [-0.46, 0.10]

Firth 2007 (9)  
-42.8  46.4  107  -32.3  42.8  107  7.5%  -0.22 [-0.52, 0.07]

Firth 2007 (10)  
-42.8  46.4  107  -32.3  42.8  107  7.5%  -0.22 [-0.52, 0.07]

Firth 2007 (11)  
-41.6  50.2  103  -52.3  46.2  75  4.1%  -0.19 [-0.49, 0.11]

Firth 2007 (12)  
-111  50  92  -37  29  93  2.3%  -0.15 [-0.57, 0.27]

Knee 2006 (13)  
-46.1  29.9  265  -1.7  174  264  1.7%  -0.15 [-0.38, 0.00]

Knee 2006 (14)  
-46.1  29.9  265  -1.7  174  264  1.7%  -0.15 [-0.38, 0.00]

Lambell 2006  
-12.0  25.1  202  -17.2  26.6  207  0.1%  -0.22 [-0.42, 0.00]

Libert 2004  
-44.3  23.5  85  -15.5  23.5  112  4.6%  -0.37 [-0.66, -0.09]

Mumtaz 2005  
-1.7  1.24  56  -6.6  2.855  51  2.7%  -0.41 [-0.83, -0.04]

Mumtaz 2005 (6)  
-26.5  58.0  114  -17.5  28.0  114  4.0%  -0.32 [-0.68, 0.04]

Mumtaz 2005 (6)  
-26.5  58.0  114  -17.5  28.0  114  4.0%  -0.32 [-0.68, 0.04]

Mumtaz 2005 (6)  
-26.5  58.0  114  -17.5  28.0  114  4.0%  -0.32 [-0.68, 0.04]

Mumtaz 2005 (6)  
-26.5  58.0  114  -17.5  28.0  114  4.0%  -0.32 [-0.68, 0.04]

Munoz 2020  
-1.04  2.69  149  -1.4  0.72  102  6.9%  -0.16 [-0.49, 0.17]

Peterson 2006  
-16.6  27.6  31  -8.9  22.2  31  1.6%  -1.10 [-1.60, -0.60]

**Subtotal (95%) CI**  
2888  
1677  93.6%  -0.26 [-0.33, -0.19]

Heterogeneity $I^2 = 0.00; Ch^2 = 0.67; df = 22; P = 0.19; I^2 = 12$

Test for overall effect: $Z = 7.85; P < 0.0001$  

Test for subgroup differences: $I^2 = 0.00; df = 1; P = 0.56; I^2 = 0$

**Composites**  
(1) Oxycodone 20-60 mg/day  
(2) Tapentadol 200-450 mg/day  
(3) Morphine (MS Contin) 30 mg/day  
(4) Morphine (Amitz) 30 mg CPM  
(5) Morphine (Amitz) 30 mg IVAM  
(6) Tramadol 200 mg/day  
(7) Tramadol 100 mg/day  
(8) Tramadol 300 mg/day  
(9) Tramadol 200 mg/day  
(10) Tramadol 300 mg/day  
(11) Tramadol 100 mg/day  
(12) Oxycodone 10 mg ED  
(13) Oxycodone 40 mg ED  
(14) Oxycodone 50 mg ED  
(15) Oxycodone 40 mg ED  
(16) Oxycodone 20 mg ED  
(17) Oxycodone 20 mg BED  

Total 95% CI  
1788  100.0%  -0.27 [-0.35, -0.20]

Heterogeneity $I^2 = 0.00; Ch^2 = 0.67; df = 22; P = 0.20; I^2 = 12$

Test for overall effect: $Z = 7.85; P < 0.0001$

Test for subgroup differences: $I^2 = 0.00; df = 1; P = 0.56; I^2 = 0$
Figure 3. Effect of opioid on function according to the site of pain: back pain or hip or knee osteoarthritis

### Table

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Houpaye 2013</td>
<td>-11.26</td>
<td>83</td>
<td>-7.178</td>
<td>13.879</td>
<td>87</td>
<td>-0.31</td>
<td>-0.61</td>
<td>-0.01</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>F = 0.01 (P = 0.94)</td>
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</table>

**1.3.2 Hip or Knee OA**

<table>
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<tr>
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<th>Total</th>
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<tr>
<td>Rabit 2004</td>
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<td>121</td>
<td>121</td>
<td>-0.69</td>
<td>95</td>
<td>-0.39</td>
<td>-0.62</td>
<td>-0.27</td>
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<td>Ekbert 2010</td>
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<td>0.35</td>
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<td>Cadwell 2002 (1)</td>
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<td>523</td>
<td>523</td>
<td>-0.76</td>
<td>25</td>
<td>-0.68</td>
<td>-0.94</td>
<td>-0.33</td>
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<tr>
<td>Cadwell 2002 (2)</td>
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<td>-0.94</td>
<td>-0.33</td>
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<tr>
<td>Cadwell 2002 (3)</td>
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<td>523</td>
<td>523</td>
<td>-0.76</td>
<td>25</td>
<td>-0.68</td>
<td>-0.94</td>
<td>-0.33</td>
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<tr>
<td>Dalies 2001 (4)</td>
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<td>159</td>
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<td>-0.94</td>
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<td>-0.94</td>
<td>-0.33</td>
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<td>-0.68</td>
<td>-0.94</td>
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<td>Larchet 2006</td>
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<td>Matsusono 2005 (1)</td>
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<td>Matsusono 2005 (2)</td>
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<td>Pfeifer 2006</td>
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<td>Subtotal (95% CI)</td>
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<td>F = 0.01 (P = 0.94)</td>
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<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Heterogeneity**

- Tau² = 0.01
- CH² = 20.31, df = 15 (P = 0.16), I² = 26\%

**Total (95% CI)**

<table>
<thead>
<tr>
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<td>95</td>
<td>-0.39</td>
<td>-0.62</td>
<td>-0.27</td>
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</tbody>
</table>

**Favours (Experimental)**

**Favours (Control)**

- Tau² = 0.01
- CH² = 20.32, df = 16 (P = 0.21), I² = 21\%

**Total (95% CI)**

<table>
<thead>
<tr>
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**Favours (Experimental)**

**Favours (Control)**

- Tau² = 0.01
- CH² = 20.32, df = 16 (P = 0.21), I² = 21\%

**Total (95% CI)**

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<td>-0.39</td>
<td>-0.62</td>
<td>-0.27</td>
</tr>
</tbody>
</table>

**Favours (Experimental)**

**Favours (Control)**

- Tau² = 0.01
- CH² = 20.32, df = 16 (P = 0.21), I² = 21\%
### Figure 4. Risk of adverse events – opioid vs. placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Total Exposed</th>
<th>Weight</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
<th>Odds Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arai 2015</td>
<td>50</td>
<td>73</td>
<td>123</td>
<td>77</td>
<td>3.05</td>
<td>2.48 [1.27, 4.82]</td>
<td></td>
</tr>
<tr>
<td>Basu 2004</td>
<td>98</td>
<td>124</td>
<td>222</td>
<td>122</td>
<td>5.66</td>
<td>2.13 [1.20, 3.76]</td>
<td></td>
</tr>
<tr>
<td>Breivik 2010</td>
<td>92</td>
<td>106</td>
<td>202</td>
<td>99</td>
<td>5.96</td>
<td>4.93 [1.75, 9.58]</td>
<td></td>
</tr>
<tr>
<td>Dallemes 2011 (1)</td>
<td>197</td>
<td>202</td>
<td>400</td>
<td>66</td>
<td>6.5</td>
<td>1.12 [0.65, 1.97]</td>
<td></td>
</tr>
<tr>
<td>Dallemes 2011 (2)</td>
<td>144</td>
<td>199</td>
<td>340</td>
<td>67</td>
<td>5.5</td>
<td>1.77 [0.98, 3.25]</td>
<td></td>
</tr>
<tr>
<td>Dallemes 2011 (3)</td>
<td>149</td>
<td>199</td>
<td>340</td>
<td>67</td>
<td>5.5</td>
<td>2.01 [1.12, 3.51]</td>
<td></td>
</tr>
<tr>
<td>Fishman 2007 (4)</td>
<td>62</td>
<td>106</td>
<td>168</td>
<td>76</td>
<td>5.4</td>
<td>1.34 [0.74, 2.42]</td>
<td></td>
</tr>
<tr>
<td>Fishman 2007 (5)</td>
<td>74</td>
<td>111</td>
<td>185</td>
<td>76</td>
<td>5.4</td>
<td>1.90 [1.04, 3.45]</td>
<td></td>
</tr>
<tr>
<td>Fishman 2007 (6)</td>
<td>81</td>
<td>108</td>
<td>189</td>
<td>75</td>
<td>5.2</td>
<td>2.92 [1.56, 5.47]</td>
<td></td>
</tr>
<tr>
<td>Hupu Lee 2013</td>
<td>104</td>
<td>125</td>
<td>229</td>
<td>120</td>
<td>5.4</td>
<td>4.19 [2.32, 7.46]</td>
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</tr>
<tr>
<td>Langford 2006</td>
<td>169</td>
<td>216</td>
<td>385</td>
<td>200</td>
<td>6.5</td>
<td>3.32 [2.30, 5.49]</td>
<td></td>
</tr>
<tr>
<td>Malamie 2004</td>
<td>90</td>
<td>111</td>
<td>201</td>
<td>139</td>
<td>5.4</td>
<td>3.42 [1.90, 6.17]</td>
<td></td>
</tr>
<tr>
<td>Markenson 2005</td>
<td>52</td>
<td>56</td>
<td>115</td>
<td>51</td>
<td>2.6</td>
<td>10.68 [3.36, 33.96]</td>
<td></td>
</tr>
<tr>
<td>Matsunome 2005 (7)</td>
<td>110</td>
<td>121</td>
<td>231</td>
<td>43</td>
<td>3.9</td>
<td>7.83 [3.26, 18.76]</td>
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</tr>
<tr>
<td>Matsunome 2005 (8)</td>
<td>113</td>
<td>119</td>
<td>232</td>
<td>43</td>
<td>3.2</td>
<td>13.34 [4.76, 37.36]</td>
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<tr>
<td>Matsunome 2005 (9)</td>
<td>110</td>
<td>125</td>
<td>235</td>
<td>42</td>
<td>3.2</td>
<td>5.50 [2.42, 12.43]</td>
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<tr>
<td>Munera 2010</td>
<td>108</td>
<td>152</td>
<td>260</td>
<td>163</td>
<td>6.3</td>
<td>2.06 [1.30, 3.28]</td>
<td></td>
</tr>
<tr>
<td>Pellet 2000</td>
<td>42</td>
<td>51</td>
<td>95</td>
<td>52</td>
<td>3.7</td>
<td>3.42 [1.36, 8.47]</td>
<td></td>
</tr>
<tr>
<td>Silverman 2002</td>
<td>88</td>
<td>197</td>
<td>285</td>
<td>111</td>
<td>5.9</td>
<td>2.64 [1.57, 4.45]</td>
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</tr>
<tr>
<td>Vorsanger 2013 (10)</td>
<td>23</td>
<td>44</td>
<td>67</td>
<td>21</td>
<td>2.5</td>
<td>2.74 [0.90, 8.16]</td>
<td></td>
</tr>
<tr>
<td>Vorsanger 2013 (11)</td>
<td>31</td>
<td>43</td>
<td>74</td>
<td>21</td>
<td>2.5</td>
<td>6.46 [2.03, 20.56]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>2580</strong></td>
<td><strong>1707</strong></td>
<td><strong>4287</strong></td>
<td><strong>100.0%</strong></td>
<td><strong>2.94</strong> [<strong>2.35</strong>, <strong>3.72</strong>]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 1375

Heterogeneity: Tau² = 0.17, Chi² = 52.46, df = 20 (p = 0.0001); I² = 62%

Test for overall effect: Z = 8.93 (p < 0.00001)

Footnotes:
(1) Tramadol 100 mg/day
(2) Tramadol 200 mg/day
(3) Tramadol 300 mg/day
(4) Tramadol 100 mg/day
(5) Tramadol 200 mg/day
(6) Tramadol 300 mg/day
(7) Oxycodone 40 mg BID
(8) Oxycodone 20 mg BID
(9) Oxycodone 20 mg BID
(10) Tapentadol 200-450 mg/day
(11) Oxycodone 20-60 mg/day

109
Table 2. Summary of findings: opioid analgesics compared with placebo for older adults with musculoskeletal pain

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain intensity (follow-up) - Immediate-term</td>
<td>4998 (16 studies)</td>
<td>⊕⊕⊕⊕ moderate</td>
<td>SMD -0.27 (-0.33 to -0.2)</td>
</tr>
<tr>
<td></td>
<td>Different scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up: 10-168 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain intensity (source of pain) - Low back pain</td>
<td>283 (2 studies)</td>
<td>⊕⊕⊕ low</td>
<td>SMD -0.34 (-0.59 to -0.09)</td>
</tr>
<tr>
<td></td>
<td>Different scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up: 10-29 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain intensity (source of pain) - Hip or knee OA</td>
<td>4565 (13 studies)</td>
<td>⊕⊕⊕ moderate</td>
<td>SMD -0.26 (-0.33 to -0.19)</td>
</tr>
<tr>
<td></td>
<td>Different scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up: 14-168 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function (follow-up) - Immediate-term</td>
<td>2989 (9 studies)</td>
<td>⊕⊕⊕ moderate</td>
<td>SMD -0.27 (-0.36 to -0.18)</td>
</tr>
<tr>
<td></td>
<td>Different scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up: 14-168 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function (source of pain) - Low back pain</td>
<td>170 (1 study)</td>
<td>⊕⊕⊕ very low</td>
<td>SMD -0.31 (-0.61 to -0.01)</td>
</tr>
<tr>
<td></td>
<td>Oswestry</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up: 29 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Function (source of pain) - Hip or knee OA</td>
<td>2819 (8 studies)</td>
<td>⊕⊕⊕ moderate</td>
<td>SMD -0.27 (-0.36 to -0.17)</td>
</tr>
<tr>
<td></td>
<td>Different scales</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up: 14-168 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QoL - Physical Component Summary (follow-up) - Immediate-term</td>
<td>2478 (6 studies)</td>
<td>⊕⊕⊕ low</td>
<td>MD -1.49 (-2.27 to -0.72)</td>
</tr>
<tr>
<td></td>
<td>SF-36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up: 14-90 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>QoL - Mental Component Summary (follow-up) - Immediate-term</td>
<td>2123 (5 studies)</td>
<td>⊕⊕⊕ very low</td>
<td>MD 0.59 (-0.31 to 1.49)</td>
</tr>
<tr>
<td></td>
<td>SF-36</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Follow-up: 28-90 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rate of adverse events</td>
<td>4288 (14 studies)</td>
<td>⊕⊕⊕ very low</td>
<td>OR 2.94 (2.33 to 3.72)</td>
</tr>
<tr>
<td></td>
<td>Follow-up: 10-168 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation due to AE</td>
<td>6368 (22 studies)</td>
<td>⊕⊕⊕ moderate</td>
<td>OR 4.04 (3.1 to 5.25)</td>
</tr>
<tr>
<td></td>
<td>Follow-up: 10-168 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuation - lack of efficacy</td>
<td>5803 (20 studies)</td>
<td>⊕⊕⊕ low</td>
<td>OR 0.37 (0.29 to 0.47)</td>
</tr>
<tr>
<td></td>
<td>Follow-up: 10-168 days</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Serious study limitations
2 Imprecision
3 Very serious study limitations
4 Publication bias
5 Inconsistency of results ($I^2 > 50\%$)

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.
References


CHAPTER FIVE

Conclusion
5.1 Overview of principal findings

The main aim of this thesis was to contribute to the current knowledge of how age-related conditions such as multimorbidity and frailty interact with musculoskeletal pain and its management. In order to achieve this aim, the thesis has focused on investigating the association between frailty and chronic musculoskeletal pain, and the role and effectiveness of pain medication for musculoskeletal conditions in this specific population.

While previous studies have found that chronic pain is a significant risk factor for disability (1-7), depressive symptoms (8) and decreased quality of life (9), its association with the risk of developing the frailty phenotype still needed to be elucidated. Therefore, the first aim of this thesis was to investigate whether musculoskeletal pain was an independent risk factor for the development of frailty in older men. Chapter Two demonstrated that chronic pain, i.e. daily pain for at least three months, was associated with an increased risk of developing the physical frailty phenotype, assessed using the CHS criteria, over 5 years. This finding suggests an important potential role for effective pain management in the prevention of further decline in physical function among older people. While randomized controlled trials have shown that nutritional supplementation, cognitive training and physical exercises intervention may prevent or reduce frailty (10-12), no trials have been conducted assessing the effects of pain management on frailty development. Likewise, current trials of pain management for older people have failed to include frailty as an outcome measure and therefore there is paucity of evidence on the impact of pain management on frailty.
The second aim of this thesis was to investigate whether frailty status was an independent risk factor for developing pain. Chapter Two has confirmed that pre-frail and frail older men were not at an increased risk of developing chronic or intrusive pain. Frailty has been associated with brain pathology, including macroinfarcts, senile plaques, neurofibrillary tangles and nigral neuronal loss (13), which might result in impaired descendent inhibitory pain modulation (14). This link provides a reasonable rationale for investigating whether frailty leads to pain of longer duration or greater severity. Although frailty was found to be associated with future intrusive pain in the CHAMP study, this association was confounded by other clinical features, particularly age, BMI, number of comorbidities and depression. The pathophysiology of pain is multifactorial and not completely understood, and our findings suggest that the relationship between frailty and pain cannot be solely attributed to frailty-related changes of the brain. For instance, there is accumulated evidence that late-life depression and frailty are interrelated concepts that might share the same underlying pathology (15-17) and that may be the case for other commonly observed comorbidities in this age group.

Although frailty has not proved to be a risk factor for developing pain, pain is still very prevalent among older adults (18-22). Unfortunately, evidence on the effectiveness of musculoskeletal pain management interventions in older people is scarce. As a result, clinicians need to rely on their own judgement and past experience to treat this condition. Therefore, the third aim of this thesis was to describe aspects of the current management of musculoskeletal pain in older adults in Australia. Chapter Three describes primary care management of vertebral compression fracture, a common and painful musculoskeletal
condition typically seen in older patients. The results confirm that primary care clinicians rely mostly on opioid analgesics, usually in low doses, to treat pain associated with vertebral fractures. Interestingly, prescriptions for “strong” opioid analgesics, i.e. opioid analgesics used for moderate-to-severe pain according to the World Health Organization three-step analgesic ladder (23), were more frequent in follow-ups than in first encounters for vertebral compression fractures, suggesting that the need for opioids did not decrease over time, as would be expected. This practice is problematic as many older adults with vertebral compression fractures remain on opioid analgesics long after an episode of acute pain typically resolves, increasing the risks of opioid-related side effects such as constipation, sedation, falls and physical dependence (24). The findings of the study reported in Chapter Three also suggest that referrals to allied health care have been unusual in general practice management of vertebral compression fractures. Although the evidence on the effectiveness of non-pharmacological treatment for this condition is scarce (25), a multidisciplinary team approach could contribute to pain management.

A similar pattern of opioid analgesic prescription was also found in the United States, where a study showed that around 15% of older patients admitted to hospital are prescribed a new opioid analgesic before being discharged and around 40% of them are still in use of opioid analgesics 90 days later (26). This practice is likely reflective of the American Geriatric Society recommendations for the management of older patients with moderate to severe persistent pain (27). However, these recommendations do not seem to be derived from high quality evidence and it is currently still unknown whether the benefits of opioid analgesics outweigh their risks of adverse events, particularly in older patients. Therefore, the fourth and final aim
of this thesis was to systematically review and appraise the literature on the efficacy and safety of opioid analgesics for older adults with musculoskeletal pain. Chapter Four showed that regular use of opioid analgesics for musculoskeletal pain, at daily doses varying from 10 to 300 mg of oral morphine equivalents, results in only a small benefit in terms of pain and function among older adults. In addition, the effect of opioid analgesics in these patients is not influenced by dosage or treatment duration. The risk of any adverse event, however, is three times higher in the opioid analgesics group, compared to placebo. This finding suggests that recommendations on prescription of opioid analgesics for musculoskeletal pain in older people should be re-evaluated, given that their modest effect on pain and function is probably not outweighed by their risks. Moreover, it reinforces the need for non-pharmacological strategies in chronic pain managements since even opioid analgesics alone have only a small benefit in chronic musculoskeletal conditions. Improving and promoting non-pharmacological pain management strategies may contribute in controlling the opioid epidemic that also affects older adults.

5.2 Implications and directions for future research

5.2.1 Pain and frailty

The cohort study presented in Chapter Two reinforces the association between pain and frailty, and represents a step forward in understanding this association. It seems that chronic pain is a risk factor for developing frailty but frailty on its own is not a risk factor for developing chronic or intrusive pain in older men. Only one longitudinal study has previously assessed the association between chronic pain and frailty and they have also included data from a cohort of aged men (28). Therefore, to date, the longitudinal association between chronic
pain and frailty in women is still unknown, even though there is reason to believe that relationship would differ according to gender. For instance, frailty has been shown to be more prevalent among women, when compared to men (29), and this is partly because they have reduced lean mass and strength compared to age-matched men (30). Women also are at greater risk of developing a number of clinical pain conditions, including osteoarthritis and fibromyalgia, (31) that may lead to muscle wasting and disuse atrophy (32). Future studies should investigate the role of chronic pain as a risk factor for frailty across both genders.

In addition, most older adults who experience chronic pain are long-term users of analgesic drugs. However, the role of analgesic drugs use on the risk of developing frailty remains unclear. A cross-sectional population-based study found that the use of analgesics was positively associated with the severity of frailty, even after adjusting for presence of pain (33). Although it was suggested that pain management could be a potential strategy to prevent frailty, excessive opioid analgesics consumption could have an opposite effect. Future studies should investigate the relationship between analgesics consumption and risks of frailty in order to determine which pain management strategies could be beneficial and which of them could cause additional harm in older adults with musculoskeletal pain.

The role of depressive symptoms and physical comorbidities in the association between frailty and the risk of intrusive pain is also a question that needs to be elucidated in the future. Pain usually co-occurs with core elements of the frailty phenotype, i.e. weight loss, exhaustion, weakness, slowness and low energy expenditure (34). It is possible that pain may result in, or be the result of, each one of the frailty criteria. There are, however, many clinical variables
that could be underlying such association. For instance, depressive symptoms, that are usually associated with chronic pain, are also associated with the CHS frailty criteria (15-17) and it is possible that depressive symptoms as well as other clinical conditions act as mediators in that relationship. Future studies should consider carrying out mediation analysis in order to identify and explain mechanisms underlying pain and frailty association.

5.2.2 Pain management in older adults

Chapters Three and Four are concerned with the management of older adults with musculoskeletal pain. Chapter Three concludes that primary care clinicians have become opioid-centred in treating vertebral compression fractures in older adults. Concerns around the rise in the prescription of opioids analgesics (35, 36) must be viewed in the context of global ageing and increased prevalence of chronic pain conditions. Clinicians have to deal with an increasing number of older patients with chronic pain who seek care with unrealistic expectations regarding the effectiveness of pharmacological treatments (37). Chronic musculoskeletal pain is a multidimensional condition (38) and it is unlikely that the use of analgesics alone will address all dimensions of this condition, particularly psychosocial and functional dimensions (39-41). Rather, the combination of analgesics with non-pharmacological approaches might result in better pain relief and improvement of function. Future clinical trials should assess the efficacy of multi-modal pain treatments including patient education, physical rehabilitative and psychological approaches, occupational therapy, analgesic drugs and regional anaesthesia, in older adults with musculoskeletal pain, particularly in those with chronic pain conditions.
Opioid analgesics have only a small effect on pain relief and disability as shown in Chapter Four, despite their growing popularity for the management of musculoskeletal pain in older adults. Opioids are also three times more likely to cause side effects, compared to placebo in this population. In general, however, the participants included in the identified trials were younger-old adults (i.e. those between 65 and 75 years old) and less likely to present with comorbidities, including frailty. Although older adults are now being enrolled in clinical trials, it seems that there remains a preference to include the young old. Possible reasons for not including older-old adults are challenges in gaining informed consent, risk of polypharmacy, challenges in compliances with the trial procedures and the belief that this subgroup will not respond to treatment (42). Unfortunately, exclusion and under-recruitment of older adults in clinical trials implies that many treatments currently in use by clinicians who deal with older and frail patients have not been appropriately evaluated. Clinical trials involving frail older patients are urgently needed as extrapolating results from trials including only robust individuals to an aged population might result in potentially harmful practices.

The finding that opioid analgesics have only a small benefit in older populations with musculoskeletal pain is consistent across clinical trials using different opioid analgesics, in different doses, and for different musculoskeletal conditions. Although opioid analgesics could be a good option for selected patients, arguably they should not be the first line treatment for older adults in pain. Because older patients are at higher risk of adverse drug reactions, clinicians should start with non-opioid medications in combination with non-pharmacological therapies, leaving time-limited use of opioid analgesics to those who did not achieve adequate pain relief with this first approach. While addiction is the main concern in
younger adults who are on opioid analgesics, in older adults the main concern is the risk of adverse events, that impose great harm for these patients. The best way to manage individuals with musculoskeletal pain who do not respond to non-opioid medications is still unclear. At this moment it is not possible to suggest a safer and more effective alternative to opioid analgesics. Non-pharmacological treatment, however, might be an interesting approach, particularly for patients with persistent pain.

As it was shown in Chapter Three, allied health services are underused in the management of painful vertebral compression fracture in older adults and they could be a good alternative to avoiding indiscriminate use of opioids. While this thesis reinforces the importance of better pain treatment in older people, it shows that relying exclusively on analgesics and excluding non-pharmacological approaches is not ideal. Comprehensive assessment, multi-modal therapy and multidisciplinary approach have always been an important part of the geriatric care and it would not be different when dealing with musculoskeletal pain.

5.3 Concluding remarks

a) Chronic musculoskeletal pain is an independent risk factor for the development of the CHS frailty phenotype;

b) Frailty does not increase the risk of developing chronic or intrusive pain. Although frailty may be associated with risk of intrusive pain, this association seems to be confounded by age, body mass index, comorbidities and depression;

c) In the last decade, general practitioners in Australia have been treating pain related to vertebral compression fractures with opioid analgesics in low doses;
d) Allied health care services have been underused as part of a pain management strategy in Australian older adults with vertebral compression fractures;

e) Opioid analgesics offer only small effects over placebo on pain and function for older people with musculoskeletal conditions. The risk of adverse events is considerably higher;

f) In older populations, the effect of opioid analgesics in chronic musculoskeletal conditions is not influenced by dosage (in daily doses varying from 10 to 300 mg morphine equivalents) or treatment duration.
5.4 References


APPENDIX A

Supplementary material for the Chapter Three: Management of vertebral compression fracture in general practice: BEACH program
Calculating the “National annual estimated encounters”

The “National annual estimated encounters” gives the estimated number of encounters in a year for general practice across Australia, at which vertebral compression fractures (VCF) is managed. It is calculated as \[
\frac{\text{average annual number of encounters with at least one specified condition managed (n)}}{\text{average annual number of recorded encounters within the specified study period}} \times \text{average annual number of general practice consultations claimed from Medicare in the specified year.}
\]

The table below lists the number of BEACH encounters for each year.

<table>
<thead>
<tr>
<th>BEACH Year</th>
<th>Number of encounters Raw (weighted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 2005-March 2006</td>
<td>101,700 (101,993.0)</td>
</tr>
<tr>
<td>April 2006-March 2007</td>
<td>93,000 (91,804.7)</td>
</tr>
<tr>
<td>April 2007-March 2008</td>
<td>95,300 (95,897.7)</td>
</tr>
<tr>
<td>April 2008-March 2009</td>
<td>101,100 (96,687.7)</td>
</tr>
<tr>
<td>April 2009-March 2010</td>
<td>98,800 (101,349.0)</td>
</tr>
<tr>
<td>April 2010-March 2011</td>
<td>95,800 (95,839.0)</td>
</tr>
<tr>
<td>April 2011-March 2012</td>
<td>98,400 (99,030.0)</td>
</tr>
<tr>
<td>April 2012-March 2013</td>
<td>97,800 (98,563.9)</td>
</tr>
<tr>
<td>April 2013-March 2014</td>
<td>95,900 (95,879.0)</td>
</tr>
<tr>
<td>April 2014-March 2015</td>
<td>99,500 (98,728.4)</td>
</tr>
</tbody>
</table>
The table below lists the number of non-specialist GP Medicare services for each financial year (July-June). These numbers are used for each specified BEACH year (April-March).

<table>
<thead>
<tr>
<th>BEACH year</th>
<th>Annual GP consultations^</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005–06</td>
<td>101,100,000</td>
</tr>
<tr>
<td>2006–07</td>
<td>103,400,000</td>
</tr>
<tr>
<td>2007–08</td>
<td>109,500,000</td>
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<tr>
<td>2008–09</td>
<td>113,000,000</td>
</tr>
<tr>
<td>2009–10</td>
<td>116,600,000</td>
</tr>
<tr>
<td>2010–11</td>
<td>119,200,000</td>
</tr>
<tr>
<td>2011–12</td>
<td>123,900,000</td>
</tr>
<tr>
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<td>128,700,000</td>
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<td>2013–14</td>
<td>134,200,000</td>
</tr>
<tr>
<td>2014-15</td>
<td>139,400,000</td>
</tr>
</tbody>
</table>

^Annual GP consultations are rounded to the nearest 100,000.


Therefore, the “National annual estimated encounters” were calculated as follows:

\[
(21.1 / 97,300) \times 118,900,000 = 25,670, \text{ rounded to } 26,000 (22,000-29,000)
\]
APPENDIX B

Supplementary material for the Chapter Four: Efficacy and safety of oral and transdermal opioid analgesics for musculoskeletal pain in older adults: a systematic review of randomized, placebo-controlled trials
Search strategy:
Ovid MEDLINE, Ovid EMBASE and Ovid AMED

Search terms for design
randomized controlled trial.pt. or controlled clinical trial.pt. or comparative study.pt. or clinical trial.pt. or randomized.ab. or placebo.ab,ti. or randomly.ab,ti. (animals not (humans and animals)).sh.

1 not 2

Search terms for musculoskeletal pain
exp osteoarthritis/ or osteoarthriti$.ti,ab. or osteoarthro$.ti,ab. or gonarthriti$.ti,ab. or gonarthro$.ti,ab. or coxarthriti$.ti,ab. or coxarthro$.ti,ab. or arthros$.ti,ab. or arthrot$.ti,ab. or
((knee$ or hip$ or joint$) adj3 (pain$ or ach$ or discomfort$)).ti,ab. or ((knee$ or hip$ or joint$) adj3 stiff$).ti,ab. or Arthritis, Psoriatic/ or Arthritis, Rheumatoid/ or Arthritis/ or Arthritis, Gouty/ or arthritis,ti,ab. or gout,ti,ab or dorsalgia,ti,ab. or exp Back Pain/ or backache,ti,ab. or exp Low Back Pain/ or (lumbar adj pain).ti,ab. or coccyx,ti,ab. or coccydynia,ti,ab. or sciatica,ti,ab. or sciatic neuopathy/ or spondylolisthesis,ti,ab. or lumbago,ti,ab. or back disorder$.ti,ab. or neck muscles.sh. or exp Neck/ or exp neck pain/ or whiplash injuries.sh. or neck,ti,ab. or exp Spine/ or discitis,ti,ab. or exp Spinal Diseases/ or (disc adj degeneration).ti,ab. or (disc adj prolapse).ti,ab. or (disc adj herniation).ti,ab. or spinal fusion.sh. or (facet adj joints).ti,ab. or intervertebral disc.sh. or Intervertebral Disc or Displacement.sh. or spinal stenosis or canal stenosis or (spin* adj3 stenosis) or (lumbar adj3 stenosis) or (lateral adj3 stenosis) or (central adj3 stenosis) or (foramin* adj3 stenosis or neurogenic claudication or radiculopathy or radicular pain or lumbar radicular pain or spondylolysis or (lumb* adj5 spondyl*) or spondylolisthesis).mp. or spinal fractures/ or (Vertebr$ adj3 fracture$).ti,ab or vertebral compression fracture$.ti,ab or (Osteopor$ adj3 fracture$).ti,ab or (Osteopor$ adj3 compress$).ti,ab or (verteb$ adj3 fracture$).ti,ab or (spin$ adj3 fracture$).ti,ab or (lumbar adj3 fracture$).ti,ab or (thoracic adj3 fracture$).ti,ab or (compress$ adj3 fracture$).ti,ab or Shoulder Pain/ or Shoulder Impingement Syndrome/ or Rotator Cuff/ or exp Bursitis/ or ((should$ or rotator cuff ) adj5 (bursitis or adhesive capsulitis or arthritis$ or frozen or impinge$ or tend*nitis or pain$)).ti,ab or rotator cuff.mp or adhesive capsulitis.mp or Musculoskeletal Pain/ or Chronic Pain/ or Fibromyalgia.mp. or Fibromyalgia/ or (skelet* adj3 pain).mp. or (muscul* adj3 pain).mp. or (chronic adj3 pain).mp or Myofascial Pain Syndromes/ or myofascial pain.ti,ab.

Search terms for opioids
exp Analgesics, Opioid/ or exp Narcotics/ or acetyl dihydrocodeine.ti. or alfentanil.ti. or allylprodine.ti. or alphamethylfentanyl.ti. or alphaprodine.ti. or benzylmorphine.ti. or betaprodine.ti. or buprenorphine.ti. or butorphanol. ti. or bremazocine.ti. or codeine.ti. or contin.ti. or dextromoramidade.ti. or dextropropoxyphene.ti. or dezocine.ti. or diacetylmorphine.ti. or diamorphine.ti. or dihydrocodeine.ti. or dihydromorphine.ti. or dihydromorphone.ti. or diphenoxylate.ti. or dipipanone.ti. or enadoline.ti. or ethylketazocine.ti. or ethylmorphine.ti. or etonitazene.ti. or etorphine.ti. or fentanyl.ti. or heroin.ti. or hydrocodone.ti. or hydromorphin$.ti. or hydromorphone.ti. or ketazocine.ti. or ketobemidone.ti. or lefetamine.ti. or levomethadon.ti. or levomethadyl.ti. or levomethorphan$.ti. or levorphanol. ti. or loperamide.ti. or meperidine.ti. or meptazinol.ti. or methadone.ti. or methadyl.ti. or
methylmorphine.tw. or morphin$.tw. or nalbuphine.tw. or narcotic$.tw. or nicocodeine.tw.
or nicomorphine.tw. or normorphine.tw. or noscapin$.tw. or ohmefentanyl.tw. or opiate$.tw. or opioid$.tw. or opium.tw. or oripavine.tw. or oxycodone.tw. or oxycontin.tw. or oxymorphone.tw. or papaveretum.tw. or papaverin.tw. or pentazocine.tw. or percocet.tw. or peronine.tw. or pethidine.tw. or phenazocine.tw. or phencyclidine.tw. or pholcodine.tw. or piritramid$.tw. or prodine.tw. or promedol.tw. or propoxyphene.tw. or remifentanil.tw. or sufentanil.tw. or tapentadol.tw. or thebaine.tw. or tilidine.tw.

**Cochrane Library via Wiley**

**Search terms for musculoskeletal pain**

MeSH descriptor Arthritis explode all trees OR arthritis OR MeSH descriptor Osteoarthritis explode all trees OR osteoarthritis* OR osteoarthro* OR gonarthriti* OR gonarthro* OR coxarthriti* OR coxarthro* OR arthros* OR arthrot* OR (knee* OR hip* OR joint*) near/3 (pain* OR ach* OR discomfort*) OR (knee* OR hip* OR joint*) near/3 (stiff*) OR MeSH descriptor Gout explode all trees or gout or MeSH descriptor Back Pain explode all trees OR dorsalgia OR backache OR MeSH descriptor Low Back Pain explode all trees OR (lumbar next pain) or coccyx or coccydynia or sciatica or spondylosis OR MeSH descriptor Spine explode all trees OR MeSH descriptor Spinal Diseases explode all trees OR (lumbago or discitis or (disc near degeneration) or (disc near prolapse) or (disc near herniation) OR facet joints OR MeSH descriptor Intervertebral Disk explode all trees OR MeSH descriptor Cauda Equina explode all trees OR lumbar near vertebra* OR spinal near stenosis OR slipped near (disc* or disk*) OR degenerat* near (disc* or disk*) OR stenosis near (spine or root or spinal) OR displace* near (disc* or disk*) OR prolap* near (disc* or disk*) OR MeSH descriptor Sciatic Neuropathy explode all trees OR sciatic* OR back disorder* OR back near pain OR MeSH descriptor Neck, this term only OR MeSH descriptor Neck Pain explode all trees OR MeSH descriptor Neck Muscles explode all trees OR MeSH descriptor Neck Injuries explode all trees OR MeSH descriptor Whiplash Injuries explode all trees OR whiplash OR neck pain OR neck disorder* OR cervical near vertebra* OR neck near pain or spinal stenosis or canal stenosis or (spin* adj3 stenosis) or (lumbar adj3 stenosis) or (lateral adj3 stenosis) or (central adj3 stenosis) or (foramin* adj3 stenosis) or neurogenic claudication or radiculopathy or radicular pain or lumbar radicular pain or spondylothesis or (lumb* adj5 spondyl*) or spondylisis or MeSH descriptor Fractures, Compression explode all trees OR MeSH descriptor Spinal Cord Compression explode all trees OR MeSH descriptor Spinal Fractures explode all trees OR vertebral near compression or fracture OR thoracic or lumbar or spin* near fracture* OR compression near fracture OR (thoracic or lumbar or spin*) near compression OR “fractured vertebrae” or MeSH descriptor Shoulder pain explode all trees OR MeSH descriptor Shoulder Impingement Syndrome explode all trees OR MeSH descriptor Rotator Cuff explodes all trees OR MeSH descriptor Bursitis explode all trees or ((should$ or rotator cuff) adj5 (bursitis or adhesive capsulitis or arthriti$ or frozen or impinge$ or tend?nitis or pain$)) or rotator cuff or adhesive capsulitis or MeSH descriptor Fibromyalgia explode all trees OR MeSH descriptor Myofascial Pain Syndromes explode all trees OR MeSH descriptor Chronic pain explode all trees OR MeSH descriptor Musculoskeletal pain explode all trees OR MeSH descriptor Artralgia explode all trees in Clinical Trials

**Search terms for Opioids**

MeSH descriptor Analgesics, Opioid explode all trees OR MeSH descriptor Narcotics explode all trees OR (acetyldihydrocodeine OR alfentanil OR allylprodine OR alphamethylfentanyl OR alphaprodine OR benzylmorphine OR betaprodine OR bezitriamide OR buprenorphine OR
butorphanol OR bremazocine OR carfentanil OR codeine OR contin OR dextromoramide OR dextropropoxyphene OR dezocine OR diacetylmorphine OR diamorphine OR dihydrocodeine OR dihydromorphine OR hydromorphone OR diphenoxylate OR dipipanone OR enadoline OR ethylketazocine OR ethylmorphine OR etonitazene OR etorphine OR fentanyl OR heroin OR hydrocodone OR hydromorphin OR ketazocine OR ketobemidone OR lefetamine OR levomethadon OR levomethadyl OR levomethorphan* OR levorphanol OR loperamide OR meperidine OR metapertun OR methadone OR methadyl OR methylmorphine OR morphine* OR nalbuphine OR narcotic* OR nicocodeine OR nicomorphine OR normorphine OR noscapine OR oxymorphone OR papaverine OR pentazocine OR percocet OR peronine OR pethidine OR phencyclidine OR pholcodine OR piritramide OR prodine OR promedol OR propoxyphene OR ramsay OR sufentanil OR tapentadol OR thebaine OR tilidine) in Clinical Trials

CINAHL via EBSCO

Search terms for design
MH "Clinical Trials" or MH "Random Assignment" or MH "Double-Blind Studies" or MH "Single-Blind Studies" or TX (clin$ n25 trial$) or TX (sing$ n25 blind$) or TX (sing$ n25 mask$) or TX (doub$l n25 blind$) or TX (doub$l n25 mask$) or TX (trebl$l n25 blind$) or TX (trebl$l n25 mask$) or TX (trip$l n25 blind$) or TX (trip$l n25 mask$) or MH "Placebos" or TX placebo$ or TX (placebo$ or MH "Study Design" or MH "Comparative Studies" or MH "Evaluation Research" or MH "Prospective Studies" or TX (control$ or prospectiv$ or volunteer$)

Search terms for musculoskeletal pain
MH "Arthritis" or OR MH "Rheumatoid arthritis" or OR MH "Gout" OR TX gout OR MH "Arthritis, Psoriatic" OR MH "Spondylarthritis" or TX osteoarthriti$ or MH "Osteoarthritis" or TX arthritis or TX osteoarthro$ or TX gonarthriti$ or TX gonarthro$ or TX coxarthriti$ or TX coxarthro$ or TX arthrosis$ or TX arthrot$ or TX (knee$ n3 pain$) or TX (hip$ n3 pain$) or TX (joint$ n3 pain$) or TX (knee$ n3 ach$) or TX (hip$ n3 ach$) or TX (joint$ n3 ach$) or TX (knee$ n3 discomfort$) or TX (hip$ n3 discomfort$) or TX (joint$ n3 discomfort$) or TX (knee$ n3 stiffness) or TX (hip$ n3 stiffness) or TX (joint$ n3 stiffness) or TX lumbago or MH "Spondylolisthesis" or MH "Spondylisis" or MH "Thoracic vertebrae" or TX (lumbar n2 vertebral) or MH "Lumbar vertebral" or TX coccodynia or TX (back disorder$) or TX coccyx or TX sciatica or MH "Sciatica" or MH "Coccyx" or TX (lumbar n5 pain) or TX (lumbar w1 pain) or TX backache or (MH "low back pain" or MH "Back pain") or (MH "Back pain$") or TX dorsalgia or MH "Whiplash Injuries" or MH "Cervical Vertebrae" or MH "Neck Pain" or MH "Neck" or "neck muscles" or MH "Neck Muscles" or TX (disc w5 herniation) or TX (disc w5 prolapse) or TX (disc w5 degeneration) or MH "Spinal Diseases" or MH "Intervertebral Disk" or MH "Spine$" or MH "Spinal Stenosis" or TX (spinal stenosis$) or TX (spin$ stenosis) or TX (canal stenosis) or TX (lumbar stenosis) or TX (lateral stenosis) or TX (central stenosis) or TX (foramin$ stenosis) or MH "Intervertebral Claudication" or TX (neurogenic claudication) or MH "Radiculopathy" or TX radiculopathy or TX (radicular pain) or TX (lumbar radicular pain) or MH "FRACTURES, VERTEBRAL COMPRESSION" or MH "FRACTURES, COMPRESSION" or MH "SPINAL FRACTURES" or MH "OSTEOPOROSIS/COMPLICATIONS" or MH "OSTEOPOROSIS/POSTMENOPAUSALCOMPLICATIONS" or TX lumbar vertebral or TX (verteb$ compression) or TX (verteb$ fracture$) or TX (osteopor$ fracture$) or TX (osteopor$ vertebral) or TX (compress$ or adj$ fracture$) or TX (spinal
compress*) or TX(vertebra* adj3 compression adj3 fracture*) or TX(spinal fracture*) or MH "Shoulder Pain" or MH "Shoulder Impingement Syndrome" or MH "Rotator Cuff" or MH "Bursitis" or TX(should$ or rotator cuff ) adj5 (bursitis or adhesive capsulitis or arthritis or frozen or impinge$ or tend$initis or pain$)) or TX (rotator cuff) or TX(adhesive capsulitis) or MH "Musculoskeletal Pain" or MH "Chronic Pain" or TX fibromyalgia or MH "Fibromyalgia" or TX (skelet* adj3 pain) or TX (muscul* adj3 pain) or TX (chronic adj3 pain) or MH "Myofascial Pain Syndromes*" OR (myofascial pain)

**Search terms for Opioids**
MH “Analgesics, Opioid” or MH “Narcotics” or TX acetyldihydrocodeine or TX alfentanil or TX allylprodine or TX alphanemethylfentanyl or TX alphaprodine or TX benzylmorphine or TX betaprodine or TX bezitriamide or TX buprenorphine or TX butorphanol or TX bremazone or TX carfentan$ or TX codeine or TX contin or TX dextromoramide or TX dextropropoxyphene or TX dezocine or TX diacetylormorphine or TX diamorphine or TX dicyclomine or TX dihydromorphine or TX diphenoxyllate or TX dipipanone or TX enadoline or TX ethylketazocine or TX ethylmorphine or TX etonitazene or TX etorphine or TX fentanyl or TX heroin or TX hydrocodeone or TX hydromorphin$ or TX hydromorphone or TX ketocaine or TX ketobemidone or TX lefentamine or TX levomethadon or TX levomethadyl or TX levomethorphan$ or TX levorphanol or TX loperamide or TX meperidine or TX metazolin or TX methadone or TX methadyl or TX methylmorphine or TX morphin$ or TX nalbuphine or TX narcotic$ or TX nicocodeine or TX nicomorphine or TX normorphine or TX noscapin$ or TX opiate$ or TX opium or TX opipavine or TX oxycodeone or TX oxycontin or TX oxymorphone or TX papaveretum or TX papaverin or TX pentazocine or TX Percocet or TX peronine or TX pethidine or TX phenazocine or TX phencyclidine or TX piritramid$ or TX prodine or TX promedol or TX propoxyphene or TX remifentaniol or TX sufentanil or TX tapentadol or TX thebaine or TX tilidine

**Web of Science**

**Search terms for design**
randomized controlled trial or controlled clinical trial or comparative study or clinical trial or randomized or placebo or randomly

**Search terms for musculoskeletal pain**
osteoarthritis or osteoarthro$ or gonarthriti$ or gonarthro$ or coxarthriti$ or coxarthro$ or arthros$ or arthrot$ or psoriatic arthritis or rheumatoid arthritis or arthritis or gouty arthritis or gout or dorsalgiaor back Pain or backache or coccydynia,ti,ab. or sciatica or spondylitis or lumbago or neck muscles or neck pain or whiplash injuries or spine or discitis or disc degeneration or facet joints or intervertebral disc or spinal stenosis or canal stenosis or neurogenic claudication or radiculopathy or radicular pain or lumbar radicular pain or spondylolisthesis or spinal fractures or vertebral compression fracture$ or osteoporotic fracture or vertebral fracture or spinal fracture or shoulder pain or shoulder Impingement or rotator cuff or bursitis or adhesive capsulitis or frozen or tend$initis or musculoskeletal pain or chronic pain or fibromyalgia or myofascial pain

**Search terms for Opioids**
opioid or narcotics or acetyldihydrocodeine or alfentanil or allylprodine or alphanemethylfentanyl or alphaprodine or benzylmorphine or betaprodine or buprenorphine or butorphanol or bremazone or codeine or contin or dextromoramide or dextropropoxyphene or dezocine or diacetylormorphine or diamorphine or dihydrocodeine or
dihydromorphine or dihydromorphone or diphenoxylate or dipipanone or enadoline or ethylketazocine or ethylmorphine or etonitazene or etorphine or fentanyl or heroin or hydrocodone or hydromorphin$ or hydromorphone or ketazocine or ketobemidone or lefetamine or levomethadon or levomethadyl or levomethorphan$ or levorphanol or loperamide or meperidine or meptazinol or methadone or methadyl or methylmorphine or morphin$ or nalbuphine or narcotic$ or nicocodeine or nicomorphine or normorphine or noscapin$ or ohmefentanyl or opiate$ or opioid$ or opium or oripavine or oxycodone or oxocontin or oxymorphone or papaveretum or papaverin or pentazocine or percocet or peronine or pethidine or phanenzine or phencyclidine or pholcodine or piritramid$ or prodine or promedol or propoxyphene or remifentanil or sufentanil or tapentadol or thebaine or tilidine

LILACS via BVS

(PT randomized controlled trial OR PT controlled clinical trial OR PT multicenter study OR MH randomized controlled trials as topic OR MH controlled clinical trials as topic OR MH multicenter studies as topic OR MH random allocation OR MH double-blind method OR MH single-blind method) OR (trial$ AND placebo OR control$ OR random$) AND NOT (MH animals OR MH rabbits OR MH rats OR MH primates OR MH dogs OR MH cats OR MH swine OR PT in vitro) AND (osteoarthritis or osteoarthro$ or gonarthriti$ or gonarthro$ or coxarthriti$ or coxarthro$ or arthros$ or arthrot$ or psoriatic arthritis or rheumatoid arthritis or arthritis or gouty arthritis or gout or dorsalgiar back Pain or backache or coccydynia.ti,ab. or sciatica or spondylosis or lumbago or neck muscles or neck pain or whiplash injuries or spine or discitis or disc degeneration or facet joints or intervertebral disc or spinal stenosis or canal stenosis or neurogenic claudication or radiculopathy or radicular pain or lumbar radicular pain or spondylolisthesis or spinal fractures or vertebral compression fracture$ or osteoporotic fracture or vertebral fracture or spinal fracture or shoulder pain or shoulder Impingement or rotator cuff or bursitis or adhesive capsulitis or frozen or tendSnitis or musculoskeletal pain or chronic pain or fibromyalgia or myofascial pain ) AND (opioid or narcotics or acetyldihydrocodeine or alfentanil or allylprodine or alphamethylfentanyl or alphaprodine or benzylmorphine or betaprodine or buprenorphine or butorphanol or bremazocine or codeine or contin or dextromoramide or dextropropoxyphene or dezocine or diacetyl morphine or diamorphine or dihydrocodeine or dihydromorphine or dihydromorphone or diphenoxylate or dipipanone or enadoline or ethylketazocine or ethylmorphine or etonitazene or etorphine or fentanyl or heroin or hydrocodone or hydromorphin$ or hydromorphone or ketazocine or ketobemidone or lefetamine or levomethadon or levomethadyl or levomethorphan$ or levorphanol or loperamide or meperidine or meptazinol or methadone or methadyl or methylmorphine or morphin$ or nalbuphine or narcotic$ or nicocodeine or nicomorphine or normorphine or noscapin$ or ohmefentanyl or opiate$ or opioid$ or opium or oripavine or oxycodone or ozycontin or oxymorphone or papaveretum or papaverin or pentazocine or percocet or peronine or pethidine or phanenzine or phencyclidine or pholcodine or piritramid$ or prodine or promedol or propoxyphene or remifentanil or sufentanil or tapentadol or thebaine or tilidine)
Figure S1. Study level risk of bias summary table

<table>
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<tr>
<th>Study (Year)</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
</table>
Figure S2. Risk of bias graph

- Random sequence generation (selection bias)
- Allocation concealment (selection bias)
- Blinding of participants and personnel (performance bias)
- Blinding of outcome assessment (detection bias)
- Incomplete outcome data (attrition bias)
- Selective reporting (reporting bias)
- Other bias

Legend:
- Green: Low risk of bias
- Yellow: Unclear risk of bias
- Red: High risk of bias
Figure S3. Effect of opioid on pain intensity in the immediate-term follow-up

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std. Mean Difference IV</th>
<th>Random</th>
<th>95% CI</th>
<th>Std. Mean Difference IV</th>
<th>Random</th>
<th>95% CI</th>
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<td>1.9</td>
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<td>-94.9</td>
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<td>86</td>
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<tr>
<td>Delant 2011 (6)</td>
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<td>-94.9</td>
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<td>86</td>
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<td>Vorsanger 2013 (37)</td>
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<td>382</td>
<td>47</td>
<td>-389.9</td>
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<tr>
<td>Overall 95% CI</td>
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<td>1.333</td>
<td>1.333</td>
<td>-0.27</td>
<td>-0.33</td>
<td>0.26</td>
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</table>

**Heterogeneity: Tau² = 0.00; df = 26; I² = 10%**

Test for overall effect: Z = 8.22 (p < 0.0001)

Total 95% CI: 1.333 to 1.333

**Heterogeneity: Tau² = 0.00; df = 26; I² = 10%**

Test for overall effect: Z = 8.22 (p < 0.0001)

Test for subgroup differences: not applicable

Footnotes:
(1) Amline (morphine) QAM
(2) Amline (morphine) QPM
(3) MS Centin (morphine)
(4) Tramadol 200 mg
(5) Tramadol 100 mg
(6) Tramadol 300 mg
(7) Tramadol 50 mg
(8) Tramadol 40 mg
(9) Tramadol 40 mg
(10) Oxymorphone 0.1 mg
(11) Oxymorphone 0.5 mg
(12) Oxymorphone 0.1 mg
(13) Oxymorphone 0.5 mg
(14) Oxycodone 20 mg
(15) Oxycodone 20 mg
(16) Tapentadol
(17) Oxycodone
Figure S4. Effect of opioid on function in the immediate-term follow-up

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<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
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<td>Eskil 2004</td>
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<td>124</td>
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<td>0.24</td>
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<tr>
<td>Erikk 2010</td>
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<td>0.16</td>
<td>96</td>
<td>-0.03 [-0.05, -0.02]</td>
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<tr>
<td>Caldwel 2002 (1)</td>
<td>-0.18</td>
<td>0.38</td>
<td>76</td>
<td>-0.07</td>
<td>0.24</td>
<td>76</td>
<td>-0.06 [-0.10, -0.03]</td>
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<tr>
<td>Caldwel 2002 (2)</td>
<td>-0.20</td>
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<td>73</td>
<td>-0.35</td>
<td>0.25</td>
<td>73</td>
<td>-0.05 [-0.10, 0.00]</td>
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</tr>
<tr>
<td>Caldwel 2002 (3)</td>
<td>-0.04</td>
<td>0.24</td>
<td>70</td>
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<td>0.24</td>
<td>70</td>
<td>-0.03 [-0.06, -0.00]</td>
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<tr>
<td>Delamor 2011 (4)</td>
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<td>0.15</td>
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<td>0.15</td>
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<td>-1.01 [-1.06, -0.96]</td>
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<td>Delamor 2011 (5)</td>
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<td>199</td>
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<td>199</td>
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<td>0.15</td>
<td>199</td>
<td>-0.97 [-0.92, -0.02]</td>
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</tr>
<tr>
<td>Hooch 2013</td>
<td>-1.10</td>
<td>0.86</td>
<td>83</td>
<td>-1.37</td>
<td>0.89</td>
<td>83</td>
<td>-0.26 [-0.31, -0.21]</td>
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<tr>
<td>Hooch 2006 (7)</td>
<td>-2.30</td>
<td>1.99</td>
<td>29</td>
<td>-2.30</td>
<td>1.99</td>
<td>29</td>
<td>-0.08 [-0.14, -0.02]</td>
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<td>Hooch 2006 (8)</td>
<td>-2.63</td>
<td>2.11</td>
<td>29</td>
<td>-2.63</td>
<td>2.11</td>
<td>29</td>
<td>-0.08 [-0.14, -0.02]</td>
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<td>0.86</td>
<td>83</td>
<td>-1.37</td>
<td>0.89</td>
<td>83</td>
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<td>Langford 2013</td>
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<td>0.86</td>
<td>83</td>
<td>-1.37</td>
<td>0.89</td>
<td>83</td>
<td>-0.26 [-0.31, -0.21]</td>
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<tr>
<td>Martinson 2005 (10)</td>
<td>-3.10</td>
<td>1.78</td>
<td>126</td>
<td>-1.09</td>
<td>0.78</td>
<td>126</td>
<td>-1.97 [-2.27, -1.68]</td>
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<tr>
<td>Martinson 2005 (11)</td>
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<td>1.82</td>
<td>114</td>
<td>-1.09</td>
<td>0.78</td>
<td>114</td>
<td>-1.97 [-2.27, -1.68]</td>
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<tr>
<td>Martinson 2005 (12)</td>
<td>-3.10</td>
<td>1.82</td>
<td>114</td>
<td>-1.09</td>
<td>0.78</td>
<td>114</td>
<td>-1.97 [-2.27, -1.68]</td>
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<tr>
<td>Petsis 2000</td>
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<td>4.00</td>
<td>35</td>
<td>-4.44</td>
<td>4.00</td>
<td>35</td>
<td>-0.86 [-1.53, -0.20]</td>
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Subtotal (95% CI) 1973: 1.016 100.0% -0.37 [-0.36, -0.18]  

Heterogeneity Tau^2 = 0.01; CHi^2 = 20.32, df = 16, p = 0.211; F = 21%
Test for overall effect: Z = 5.75 (p = 0.00031)

Test for subgroup differences: Not applicable

Endnotes:
(1) MS Contin (morphine) 30 mg/day
(2) Ameza (morphine) 30 mg QAM
(3) Ameza (morphine) 30 mg QAM
(4) Tramadol 100 mg/day
(5) Tramadol 200 mg/day
(6) Tramadol 100 mg/day
(7) Oxymorphone 10 mg BD
(8) Oxymorphone 10 mg BD
(9) Oxymorphone 50 mg BD
(10) Oxycodone CR 20 mg BD
(11) Oxymorphine 20 mg BD
(12) Oxymorphone 40 mg BD

NHQ shoots: 100%
Figure S5. Effect of opioid on quality of life (SF-36 physical and mental component summary) in the immediate-term follow-up

<table>
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<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
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<th>Mean Difference IV, Random, 95% CI</th>
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<td>-1.80 [-6.73, 3.13]</td>
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<tr>
<td>Delimos 2011 (1)</td>
<td>-3.5</td>
<td>8.464</td>
<td>190</td>
<td>-3.4853</td>
<td>66</td>
<td>9.6%</td>
<td>-0.50 [-2.86, 1.85]</td>
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<td>Delimos 2012 (1)</td>
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<td>294</td>
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<td>9.7%</td>
<td>-0.20 [-2.15, 2.55]</td>
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<td>-3.1</td>
<td>8.464</td>
<td>190</td>
<td>-3.4853</td>
<td>67</td>
<td>9.7%</td>
<td>-0.10 [-2.45, 2.25]</td>
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<td>7.999</td>
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<td>9.277</td>
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<td>-3.70 [-6.76, -0.64]</td>
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<td>40</td>
<td>6.4%</td>
<td>-2.70 [-5.65, 0.25]</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1645</td>
<td>833</td>
<td>100.0%</td>
<td>-1.49 [-2.27, -0.72]</td>
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Footnotes:
1. tramadol 300 mg/day
2. tramadol 100 mg/day
3. tramadol 200 mg/day
4. oxycodone 10 mg BD
5. oxycodone 40 mg BD
6. oxycodone 50 mg BD
7. oxymorphone 20 mg BD
8. oxymorphone 20 mg BD
9. oxymorphone 40 mg BD

<table>
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<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
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<td>190</td>
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<td>8.4853</td>
<td>67</td>
<td>14.7%</td>
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<td>8.4853</td>
<td>67</td>
<td>14.7%</td>
<td>-0.60 [-2.95, 2.75]</td>
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<td>10.9</td>
<td>153</td>
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<td>11.02</td>
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<td>-3.5</td>
<td>16.4471</td>
<td>114</td>
<td>-2.2</td>
<td>9.8176</td>
<td>49</td>
<td>6.4%</td>
<td>0.70 [-1.92, 3.32]</td>
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</tr>
<tr>
<td>Maitreanice 2005 (5)</td>
<td>-2.6</td>
<td>3.853</td>
<td>120</td>
<td>-2.2</td>
<td>9.8176</td>
<td>39</td>
<td>6.4%</td>
<td>-3.00 [-6.55, 6.55]</td>
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<tr>
<td>Maitreanice 2005 (6)</td>
<td>-3.4</td>
<td>11.7448</td>
<td>114</td>
<td>-2.2</td>
<td>9.8176</td>
<td>40</td>
<td>5.8%</td>
<td>2.60 [-1.13, 6.31]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>1375</td>
<td>748</td>
<td>100.0%</td>
<td>0.59 [-0.31, 1.49]</td>
<td></td>
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<td></td>
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<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1375</td>
<td>748</td>
<td>100.0%</td>
<td>0.59 [-0.31, 1.49]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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</table>

Footnotes:
1. tramadol 200 mg/day
2. tramadol 100 mg/day
3. tramadol 200 mg/day
4. oxycodone 20 mg BD
5. oxymorphone 20 mg BD
6. oxymorphone 40 mg BD

Test for overall effect: 2 = 3.76 (P = 0.052)
Test for overall effect: 2 = 3.76 (P = 0.052)
Test for overall effect: 2 = 1.28 (P = 0.26)
Test for overall effect: 2 = 1.28 (P = 0.26)
Test for subgroup differences: Not applicable
Test for subgroup differences: Not applicable
Figure S6. Risk of discontinuation due to adverse events – opioid vs. placebo

<table>
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<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boston 2004</td>
<td>22</td>
<td>124</td>
<td>9</td>
<td>122</td>
<td>4.4%</td>
<td>4.55 (2.07, 10.00)</td>
<td></td>
</tr>
<tr>
<td>Brubek 2010</td>
<td>21</td>
<td>100</td>
<td>2</td>
<td>98</td>
<td>2.3%</td>
<td>21.79 (5.05, 94.00)</td>
<td></td>
</tr>
<tr>
<td>Erbal 2007</td>
<td>44</td>
<td>421</td>
<td>11</td>
<td>214</td>
<td>4.9%</td>
<td>2.10 (1.06, 4.25)</td>
<td></td>
</tr>
<tr>
<td>Caldwell 2002 (1)</td>
<td>12</td>
<td>73</td>
<td>2</td>
<td>71</td>
<td>2.1%</td>
<td>3.60 (0.77, 16.82)</td>
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</tr>
<tr>
<td>Caldwell 2002 (2)</td>
<td>13</td>
<td>73</td>
<td>1</td>
<td>72</td>
<td>1.2%</td>
<td>6.08 (0.28, 55.58)</td>
<td></td>
</tr>
<tr>
<td>Caldwell 2002 (3)</td>
<td>10</td>
<td>76</td>
<td>2</td>
<td>74</td>
<td>2.1%</td>
<td>2.57 (0.77, 8.62)</td>
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<tr>
<td>DeLancey 2011 (4)</td>
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<td>201</td>
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<td>67</td>
<td>3.6%</td>
<td>1.76 (0.65, 4.60)</td>
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<td>199</td>
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<td>3.7%</td>
<td>3.72 (1.41, 9.81)</td>
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<td>3.60 (1.44, 9.45)</td>
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<td>108</td>
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<td>6.71 (2.49, 18.11)</td>
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<td>4.0%</td>
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<td>4.51 (1.77, 11.49)</td>
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<td>3.15 (0.88, 11.32)</td>
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<td>93</td>
<td>2.7%</td>
<td>10.93 (1.10, 38.56)</td>
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<td>91</td>
<td>3</td>
<td>90</td>
<td>2.7%</td>
<td>9.61 (2.72, 33.95)</td>
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<tr>
<td>Langford 2006</td>
<td>58</td>
<td>202</td>
<td>20</td>
<td>182</td>
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<td>5.23 (1.85, 15.64)</td>
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<tr>
<td>MacIntyre 2004</td>
<td>24</td>
<td>111</td>
<td>2</td>
<td>109</td>
<td>2.2%</td>
<td>16.14 (3.71, 70.11)</td>
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<tr>
<td>Markenson 2005</td>
<td>20</td>
<td>56</td>
<td>2</td>
<td>54</td>
<td>2.1%</td>
<td>13.61 (2.99, 61.98)</td>
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<tr>
<td>Matsumoto 2005 (11)</td>
<td>57</td>
<td>121</td>
<td>2</td>
<td>119</td>
<td>2.3%</td>
<td>17.81 (4.12, 77.04)</td>
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<td>2</td>
<td>119</td>
<td>2.2%</td>
<td>13.66 (2.76, 67.90)</td>
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<td>125</td>
<td>2</td>
<td>123</td>
<td>2.2%</td>
<td>6.43 (1.47, 28.10)</td>
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<tr>
<td>Muscera 2010</td>
<td>36</td>
<td>152</td>
<td>18</td>
<td>162</td>
<td>5.3%</td>
<td>2.50 (1.35, 4.63)</td>
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</tr>
<tr>
<td>Pelle 2000</td>
<td>15</td>
<td>51</td>
<td>4</td>
<td>47</td>
<td>3.0%</td>
<td>5.00 (1.55, 16.15)</td>
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<tr>
<td>Pelle 2000</td>
<td>12</td>
<td>44</td>
<td>1</td>
<td>43</td>
<td>1.3%</td>
<td>7.08 (0.95, 55.15)</td>
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<td>15</td>
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<td>47</td>
<td>3.0%</td>
<td>5.00 (1.55, 16.15)</td>
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<td>43</td>
<td>1.3%</td>
<td>10.27 (1.25, 84.01)</td>
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<td>137</td>
<td>16</td>
<td>123</td>
<td>4.9%</td>
<td>1.91 (0.37, 7.95)</td>
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<td>2.54 (1.01, 6.40)</td>
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<td>43</td>
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<td>1</td>
<td>43</td>
<td>1.0%</td>
<td>8.40 (0.04, 57.70)</td>
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<tr>
<td>Zafrin 2005</td>
<td>20</td>
<td>56</td>
<td>2</td>
<td>51</td>
<td>2.1%</td>
<td>13.61 (2.99, 61.98)</td>
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<tr>
<td>Total (95% CI)</td>
<td>3925</td>
<td>2443</td>
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<td>100%</td>
<td>4.04</td>
<td>[3.10, 5.25]</td>
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Heterogeneity: $I^2 = 50.34$%

Test for overall effect: $Z = 10.37, P < 0.00001$

Footnotes:
(1) Azura (morphine) 30 mg QPM
(2) Azura (morphine) 30 mg QAM
(3) MS Contin (morphine) 30 mg/d
(4) Tramadol 100 mg/day
(5) Tramadol 200 mg/day
(6) Tramadol 300 mg/day
(7) Tramadol 400 mg/day
(8) Tramadol 500 mg/day
(9) Tramadol 600 mg/day
(10) Oxycodone 10 mg BID
(11) Oxycodone 40 mg BID
(12) Oxycodone 50 mg BID
(13) Oxycodone 80 mg BID
(14) Oxycodone 10 mg BID
(15) Oxycodone 20 mg BID
(16) Oxycodone 30 mg BID
(17) Oxycodone 40 mg BID
(18) Oxycodone 50 mg BID
(19) Tapered 200-430 mg/day
Figure S7. Risk of discontinuation due to lack of efficacy – opioid vs. placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
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<tr>
<td>Arai 2015</td>
<td>21</td>
<td>72</td>
<td>28</td>
<td>77</td>
<td>4.3%</td>
<td>0.67 (0.44, 1.01)</td>
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<tr>
<td>Eskal 2004</td>
<td>19</td>
<td>124</td>
<td>45</td>
<td>122</td>
<td>4.7%</td>
<td>0.21 (0.17, 0.57)</td>
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<tr>
<td>Erickhi 2010</td>
<td>7</td>
<td>100</td>
<td>12</td>
<td>99</td>
<td>3.1%</td>
<td>0.55 (0.21, 1.46)</td>
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<td>Eutix 2007</td>
<td>34</td>
<td>431</td>
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<td>214</td>
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<td>Caldwell 2002 (1)</td>
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<td>76</td>
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<td>2.2%</td>
<td>0.59 (0.16, 2.15)</td>
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<td>Caldwell 2002 (2)</td>
<td>12</td>
<td>73</td>
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<td>25</td>
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<td>0.79 (0.35, 1.75)</td>
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<td>0.52 (0.16, 1.70)</td>
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<td>0.41 (0.22, 0.77)</td>
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<td>22</td>
<td>67</td>
<td>4.7%</td>
<td>0.70 (0.33, 1.47)</td>
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<td>22</td>
<td>199</td>
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<td>0.27 (0.13, 0.53)</td>
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<td>153</td>
<td>26</td>
<td>153</td>
<td>4.2%</td>
<td>0.45 (0.22, 0.90)</td>
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<tr>
<td>Fishman 2007 (7)</td>
<td>21</td>
<td>106</td>
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<td>4.1%</td>
<td>0.93 (0.45, 1.92)</td>
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<td>Fishman 2007 (8)</td>
<td>11</td>
<td>108</td>
<td>15</td>
<td>75</td>
<td>3.6%</td>
<td>0.45 (0.20, 0.95)</td>
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<tr>
<td>Fishman 2007 (9)</td>
<td>11</td>
<td>111</td>
<td>16</td>
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<td>3.7%</td>
<td>0.41 (0.18, 0.95)</td>
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<td>0.38 (0.18, 0.77)</td>
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<td>95</td>
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<td>31</td>
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<td>0.41 (0.12, 1.41)</td>
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<td>91</td>
<td>5</td>
<td>30</td>
<td>2.6%</td>
<td>0.23 (0.06, 0.92)</td>
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<tr>
<td>Langford 2005</td>
<td>13</td>
<td>202</td>
<td>64</td>
<td>197</td>
<td>4.7%</td>
<td>0.17 (0.09, 0.31)</td>
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<tr>
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<td>56</td>
<td>5</td>
<td>51</td>
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<td>0.10 (0.04, 0.24)</td>
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<td>121</td>
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<td>3.2%</td>
<td>0.20 (0.08, 0.52)</td>
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<td>41</td>
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<td>0.12 (0.04, 0.36)</td>
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<td>0.12 (0.03, 0.49)</td>
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<td>Munera 2010</td>
<td>42</td>
<td>152</td>
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<td>162</td>
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<td>0.72 (0.45, 1.18)</td>
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<td>20</td>
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<td>28</td>
<td>1.8%</td>
<td>0.24 (0.06, 1.00)</td>
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<td>44</td>
<td>11</td>
<td>22</td>
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<td>0.18 (0.02, 0.86)</td>
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<td>0.14 (0.04, 0.48)</td>
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<td>197</td>
<td>6</td>
<td>111</td>
<td>0.5%</td>
<td>1.70 (0.07, 42.24)</td>
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<tr>
<td>Versapmer 2018 (18)</td>
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<td>43</td>
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<td>10</td>
<td>0.5%</td>
<td>1.27 (0.06, 28.10)</td>
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<tr>
<td>Versapmer 2018 (19)</td>
<td>0</td>
<td>44</td>
<td>1</td>
<td>11</td>
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<td>0.08 (0.00, 2.07)</td>
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<tr>
<td>Zitara 2005</td>
<td>9</td>
<td>56</td>
<td>34</td>
<td>51</td>
<td>3.3%</td>
<td>0.10 (0.04, 0.24)</td>
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**Total (95% CI):**

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<tr>
<th>Total events</th>
<th>3645</th>
<th>2158</th>
<th>100.0%</th>
<th>0.37 (0.29, 0.47)</th>
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Heterogeneity: Tau² = 0.22, Q(df = 38) = 118.7 (p = 0.00001); I² = 51%

Test for overall effect: Z = 3.27 (p < 0.00001)

Favours [experimental] Favours [control]

Footnotes:

1. MS Conte (morphine) 30 mg/day
2. Aza 20 mg (morphine 30 mg QPM)
3. Aza (morphine) 30 mg QAM
4. Tramadol 200 mg/day
5. Tramadol 100 mg/day
6. Tramadol 300 mg/day
7. Tramadol 100 mg/day
8. Tramadol 300 mg/day
9. Tramadol 200 mg/day
10. Oxycodeine ER 40 mg BID
11. Oxycodeine ER 10 mg BID
12. Oxycodeine ER 50 mg BID
13. Oxycodeine 40 mg BID
14. Oxycodeine 20 mg BID
15. Oxycodeine 20 mg BID
16. Oxycodeine 10 mg BID
17. Oxycodeine 20 mg BID
18. Oxycodeine 20–60 mg/day
19. Tapertadol 200–450 mg/day

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