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Pharmaceutical opioid use and cognitive and behavioural harms among people who experience chronic non-cancer pain

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The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian Government's Office of the Gene Technology Regulator, and the rulings of the Safety, Ethics and Institutional Biosafety Committees of the University. Ethics approval numbers: #H0016554, #H0016303, and #H0016430 (Tasmanian Health and Medical Human Research Ethics Committee); #H0018009 (Tasmanian Social Sciences Human Research Ethics Committee); #A17/9586 (Department of Police, Fire and Emergency Management).

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CHAPTER 5: KNOWLEDGE OF IMPAIRMENT AND SIDE EFFECTS, DRIVING BEHAVIOURS, AND RISK PERCEPTIONS OF OPIOIDS AND DRIVING IN PEOPLE WITH CHRONIC NON-CANCER PAIN

Abstract

In Australia, pharmaceutical opioids are widely used for the treatment of chronic non-cancer pain (CNCP). However, opioids are typically not recommended for chronic use given the limited evidence of long-term analgesic efficacy and the potential for adverse side effects. In particular, people who are prescribed opioids for CNCP may experience impairments in key cognitive functions (e.g., concentration, memory) that are drawn upon for activities of daily living. This may subsequently impact driving-related abilities and increase the risk of physical injury (e.g., via falls, motor vehicle collisions). At the population level, increased opioid prescribing may also be associated with increasing rates of opioid-related motor vehicle collisions.

Concern around the chronic effects of opioids on cognitive function stems from the known effects following acute administration of opioids in healthy people. However, these studies fail to capture the complexities of real-world opioid use among CNCP cohorts. In particular, little is known about the long term (>12 months) effects of opioids on cognition, and how both duration of use and opioid dose may be related to cognitive complaints and physical injuries in naturalistic settings. Related to this, there is a dearth of research examining consumer perceptions of risk of driving-related harms and opioid side effects. Finally, within Australia, relatively little is known about the relationship between increased opioid prescribing and population-level behavioural harms, particularly motor vehicle collisions.

In light of the gaps identified above, the aim of the present thesis was to explore the association between chronic use of opioids for CNCP and cognitive and related behavioural harms. This included an examination of consumer perceptions of risk and opioid side effects. The research was guided by five aims: i) to examine objective cognitive performance in people who take opioids for CNCP; ii) to explore the relationship between duration of opioid use and cognition in people with CNCP; iii) to assess the association between opioid dose and related harms (e.g., cognitive dysfunction) in people who take opioids for CNCP; iv) to assess awareness of opioid-related driving impairment and associated factors in people with CNCP and; v) to assess whether opioid-related vehicle collisions have increased with increased prescribing.

To assess these aims, five studies were undertaken: i) a systematic review and meta-analysis of studies (n=17) that examined objective cognitive task performance in people taking opioids for CNCP, compared with opioid-free groups (healthy or with CNCP) and over the course of opioid therapy; ii) a longitudinal study examining cognitive performance among people with chronic use of opioids for CNCP (n=14; use duration ≥3 months) and comparable opioid-free controls (n=12) at baseline and three months; iii) a cross-sectional, self-report online survey that examined how variations in opioid dose and use duration was associated with the frequency of cognitive complaints and physical injuries among people prescribed opioids for CNCP (n=226); iv) a cross-sectional, self-report online survey that examined the relationship between opioid use (including non-use) and perceptions of risk related to driving under the influence of opioids, knowledge of opioid side effects, and factors associated with risk perceptions among people with CNCP (n=218); and v) a population-level analysis of changes in the rate of opioid-related motor vehicle collisions per 100,000 opioid script dispensations from 2008–2016 in an Australian jurisdiction (Tasmania) with high rates of opioid prescribing.

Study 1 indicated that people prescribed opioids for CNCP performed more poorly than did healthy controls on key functions (attention, memory). However, the magnitude of these effects was only moderate. Further, the study found small magnitude, non-significant differences in performance between people prescribed opioids for CNCP and opioid-free controls with CNCP. Finally, this study found relatively consistent improvements in key cognitive domains with continued opioid use (i.e., at follow-up compared with opioid-free baseline). Broadly, these findings indicate: i) factors that are common to both CNCP groups (e.g., pain, mental health conditions) may affect functioning to a greater degree than does opioid use, and ii) people who take opioids for CNCP did not experience cognitive worsening with continued use. Similarly, *Study 2* found limited evidence of cognitive impairment in the opioid group compared to opioid-free CNCP controls, with only two attention outcomes robustly affected. Additionally, this study did not find continued cognitive decline in the opioid group across time.

Following on from the first two studies, *Study 3* found no clear relationship between opioid dose or use duration and cognitive complaints. However, the findings did highlight the role of key co-morbid factors that were commonly reported by participants. Cognitive complaints were common, and were positively associated with pain, psychological distress, and the experience of physical injuries.

Study 4 aimed to explore perceptions of risk (e.g., driving-related harms) and knowledge of opioid side effects among people with CNCP with varying chronicity of opioid use (including non-use). The study found that most people with CNCP perceived alcohol to be more 'risky' than pharmaceutical opioids, and current opioid consumers had lower risk perceptions for opioid than did ex- or never-consumers. Factors associated with risk perceptions included previous opioid DUI and risk ratings for alcohol, as well as knowledge of side effects and cognitive function for risk of motor vehicle collision. *Study 5*, which examined the relationship between community-level opioid utilisation and opioid-related motor vehicle collisions (MVC), found that the rate of opioid-related MVC per 100,000 dispensations has remained stable across time. This adds to the conclusions of *Study 1, Study 2,* and *Study 3*, suggesting that opioids are not uniquely related to driving-related cognitive impairments, at least at the doses examined here.

Broadly, the present thesis found that people who take opioids for CNCP frequently experience specific cognitive and behavioural harms, but these are not clearly associated with opioid use. Both subjective and objective cognitive function were impaired to some extent in people with CNCP compared to healthy populations. However, the experience of objective cognitive dysfunction was similar among people with CNCP regardless of whether they used opioids or not. Similarly, self-reported cognitive complaints did not vary according to opioid dose or use duration. At the population level, increased opioid prescribing was not associated with increasing rates of opioid-related MVC. However, characteristics that are common among this cohort (e.g., poorly controlled pain, psychological distress) were related to cognitive complaints and related harms (e.g., injuries). This may have implications in clinical settings, where practitioners can identify and educate people about risk factors for harms.

CHAPTER 1: INTRODUCTION TO PHARMACEUTICAL OPIOIDS AND CHRONIC NON-

CANCER PAIN IN THE AUSTRALIAN CONTEXT

Chronic non-cancer pain

Prevalence and harms

Chronic non-cancer pain (CNCP) is classed as pain persisting longer than three months and which is not related to cancer [1]. CNCP is a leading cause of disability worldwide [2]. Estimates from the 2017 Global Burden of Disease (GBD) study suggest that 1.3 billion (18.1% of the global population) reported recurrent migraines, 580 million (7.8%) experienced low back pain, and 290 million (3.9%) were affected by neck pain [3]. These figures are reflected in Australian data. The 2017–18 National Health survey found that, at the time of the survey, 16.4% of Australians experienced chronic back problems, 15.3% had arthritis, and 6.2% experienced migraines [4]. Similarly, a 2011 meta-analysis estimated that past-month community rates of CNCP across multiple European countries was 19.0% [5]. These data indicate CNCP is prevalent across Western countries, affecting around one-fifth of the population.

For the one in five people who are affected, CNCP can substantially impact quality of life [6, 7]. In each GBD survey conducted between 1990 and 2017, low back pain was the leading cause of years lived with disability (YLD) globally. In 2017, it contributed 64,947 YLDs [2, 3]. CNCP is associated with negative health outcomes including reduced mobility and physical strength, altered sleeping and eating patterns, poor mental health outcomes, and cognitive impairment [8, 9]. Chronic pain is also associated with high rates of unemployment. In a sample of 1,514 Australians with CNCP, 44.8% reported that they were currently unemployed [8]. Among working-age participants (n=623; age 19-54 years), this figure increased to two-thirds (66.3%) [8]. Given this, effective and affordable treatments for chronic pain are essential.

Neurobiology and pathophysiology of pain

Acute pain. Chronic pain conditions can be debilitating. However, the normal (acute) pain experience is both adaptive and protective [10, 11]. Pain is a form of negatively experienced somatic sensation, in which actual or perceived tissue damage triggers a range of

protective biological responses [10, 11]. Pain alerts people to the presence of potentially damaging stimuli (e.g., a hot surface) so that they can appropriately respond (e.g., by withdrawing their hand), minimising tissue damage.

Pain is perceived and modulated through ascending and descending pathways that link the injury site and the central nervous system (CNS) via the spinal cord [10, 12]. This process begins with the acute sensation of pain in the peripheral nervous system (PNS). Here, specialised pain receptors (nociceptors) are activated by rapid and dramatic changes in temperature, pressure, or chemical composition in tissue [10]. Before nociceptors will activate, stimulation must reach an intensity that indicates potential injury [12]. Once activated, nociceptors carry pain signals from the target organ (e.g., the dermis) to the spinal cord. These signals are transmitted to the brainstem and thalamus via multiple pathways, including the spinothalamic and spinoreticular tracts [12, 13].

In the CNS, there is no one region responsible for sensing and responding to pain. Rather, activation of multiple regions produces experiences including autonomic and motor responses (reticular system), pain perception and interpretation (somatosensory cortex), and emotional and behavioural responses (limbic system) [10, 12]. Modulation of pain occurs via descending pathways that release inhibitory neurotransmitters to block or reduce the sensation of pain. In particular, the periaqueductal grey (PAG) and nucleus raphe magnus (NRM) play a critical role in the body's response to pain [13]. When pain reaches a sufficient level, the PAG and NRM release multiple neurotransmitters including endogenous opioids (e.g., endorphin, enkephalins), noradrenaline, and 5-hydroxytryptamine (5-HT) [13]. These neurotransmitters suppress or reduce pain transmission in the CNS or spinal tract. For example, endogenous opioids bind to opioid receptors in the CNS to produce analgesia [13]. Together, ascending and descending pain pathways produce a comprehensive response to pain that begins with perception and results in numerous behavioural, emotional, motor, and neuronal responses.

Chronic pain. A key characteristic of acute pain is that it dissipates once a noxious stimulus has been removed or damaged tissue has healed. In contrast, pain that persists beyond

normal tissue healing time (approximately three months) is no longer useful and generally reflects the presence of an underlying disease or condition [14]. According to the central sensitisation theory, the progression from acute to chronic pain is primarily driven by repeated or prolonged stimulation of nociceptors. This causes increased neural signalling and reduced inhibition in the spinal cord and CNS [15]. Increased signalling can produce a range of conditions. For example, hyperalgesia occurs when a person becomes hyper-sensitive to painful stimuli [13, 15]. Allodynia occurs when inoffensive stimuli produce pain sensations as a result of mechanoreceptors responding to non-noxious stimuli and activating pain circuits [15].

Increased signalling in the CNS can also result in broader structural changes. Affected regions are typically those that play some role in pain modulation, including the medial prefrontal cortex, amygdala, hippocampus, and periaqueductal grey [16]. These regions are also implicated in functions aside from pain detection and modulation, including autonomic function, emotional regulation, and cognitive ability (e.g., decision making) [16]. Neuroplasticity in these areas can cause a range of issues including negative affective disorders, cognitive impairment, and poor impulse control [16]. In sum, chronic pain affects a range of brain regions and functions, resulting in diffuse impacts.

Pain in clinical practice

Chronic pain classifications. Chronic pain conditions are often described according to pathophysiology as nociceptive, neuropathic, or nociplastic. Nociceptive pain is caused by activation of nociceptors due to non-neural tissue damage (e.g., a broken bone) [17]. It can be somatic (e.g., involving skin or tendons) or visceral (i.e., involving internal organs). Neuropathic pain stems from damaged or dysfunctional neural pathways or nerves, either in the PNS or CNS. For example, nerve damage in the spinal cord can produce pain in the lower limbs [17]. More recently, the International Association for the Study of Pain (IASP) has recognised nociplastic pain as a separate classification [18]. This pain arises when nociceptive pathways in the CNS or PNS are altered, leading to hypersensitivity in the absence of actual or potential tissue damage,

disease, or lesions [17-19]. Nociplastic pain includes non-specific conditions such as fibromyalgia [17].

Notably, all chronic pain shares key symptomatology regardless of classification. Indeed, in clinical practice, it is not always useful to describe pain according to traditional neurobiological definitions. Many individuals experience a mixture of pain types (e.g., nociceptive with neuropathic). Some pain academics argue that pure nociceptive pain is rare, and typically becomes a mixture of nociceptive and neuropathic pain as central sensitisation occurs [20]. In recognition of the overlap between pain classifications, pain practitioners increasingly use the term 'mixed pain' [21]. Treatment of pain also does not necessarily differ depending on aetiology, particularly for neuropathic and nociplastic pain. Given this, it is not always necessary or appropriate to classify pain in this way.

An alternative way to classify chronic pain is by clinical outcomes and treatment practices. This is particularly relevant when comparing chronic cancer pain (CCP) to non-cancer pain (CNCP), where there are noted differences in demographic characteristics, comorbidities, treatments, and outcomes between populations [11]. Perhaps most importantly, treatment goals often differ between the two [11]. CNCP conditions are frequently life-long but not terminal. As such, treatment goals focus on improving quality of life and functionality, and treatments with lesser potential for adverse side effects (e.g., physiotherapy) are preferred over pharmacotherapy (e.g., opioids) [11]. In contrast, the Royal Australasian College of General Practitioners (RACGP) guidelines recommend opioid therapy as a first-line approach to management of CCP [22]. Reflecting these distinctions, two separate bodies of literature have assessed CCP and CNCP. For parsimony, the remainder of this chapter will discuss CNCP only, as this is the population of interest for the present thesis.

Biopsychosocial treatment models. To reflect the effects of chronic pain beyond physical sensation, academics have described the biopsychosocial (BPS) model of pain. This model posits that chronic pain comprises an interaction of biological, psychological, and social factors [23]. In line with the BPS model of pain, the core treatment goals for CNCP are to reduce

pain and improve functional outcomes (e.g., mobility). Reflecting the complex nature of CNCP and the considerable heterogeneity between individual pain conditions, pain management options are diverse. The most commonly-used pain treatments include pharmacological, surgical, behavioural, psychological, and complementary and alternative medicine therapies (CAMs) such as acupuncture [24].

Prescribing guidelines recommend non-drug therapies as a first-line treatment for CNCP [25]. Pharmacological therapies (primarily opioids) are no longer recommended for initial use. This is due to a lack of evidence for the long-term (>3 months) analgesic efficacy of pain medicines and the risk of adverse outcomes such as dependence and cognitive impairment [26, 27]. CAM therapies are also not recommended due to a lack of evidence for the analgesic efficacy of these treatments [28, 29]. Another important recommendation is the use of multi-disciplinary pain treatments, which target all aspects of pain [30]. Numerous reviews have highlighted that approaches that use physical rehabilitation and psychological therapy are more effective than unimodal treatments such as rehabilitation only [30]. In sum, prescribing guidelines generally favour non-pharmacological, multi-disciplinary approaches that encompass both physical and psychological approaches to pain management.

Pain treatment in clinical practice does not always reflect guidelines. Use of opioids, antidepressants, and anticonvulsants is common among CNCP groups [24]. In a general European population sample (n=46,394), two-thirds of respondents used prescription medicines (Non-Steroidal Anti Inflammatory Drugs [NSAIDs]: 44%; weak opioids: 23%; paracetamol: 18%; cyclooxygenase-2 [COX-2] inhibitors: 1-36%; strong opioids: 5%) and almost half used non-prescription medicines [31]. This may reflect treatment barriers such as high costs and lack of availability of multi-disciplinary services [32]. Conversely, medicines are typically cheap and accessible. Additionally, the benefits obtained from best-practice pain management may be relatively low. A recent review concluded that pharmacological, surgical, behavioural, psychological, complementary and CAMs therapies failed to completely eliminate pain in any included study. Even the most effective treatment (physical rehabilitation) only

reduced pain by around 30% for around half of participants [23]. Similarly, 40% of people with chronic pain surveyed in a European population study reported their pain management was inadequate [31].

Broadly, it is important to examine the impacts of commonly-used pain therapies as well as 'best practice' treatments. It is also critical to understand person-related factors that predict the effectiveness of and adherence to treatments, such as pain self-efficacy and coping styles [33]. A focus on opioids is important as these medicines are commonly used and the potential for harm is greater than for non-drug treatments.

Key points

Acute pain protects organisms from tissue damage. By contrast, chronic pain is a disease state that can be debilitating and affects many parts of life. Treatment goals for CNCP include improving quality of life and functional outcomes. Multi-disciplinary, non-pharmacological treatments are preferable over medicines, but high costs and lack of service availability may prevent people from accessing these therapies. Use of medicines (namely opioids) is common among individuals with CNCP.

Opioid pharmacology and use in clinical practice

Opioids have an important role in pain management, and are used to treat a range of pain conditions (acute, chronic, and palliative) and as opioid pharmacotherapy [34-36]. The World Health Organization lists morphine and codeine as drugs of choice for the treatment of chronic and severe cancer pain [34]. These medicines are also implicated clinically as a treatment for acute pain (e.g., post-operative), and palliative pain [1]. Buprenorphine and methadone are also often used as opioid substitution therapy (OST) for opioid use disorders [1, 37]. At present, the use of opioids for CNCP remains controversial. This is largely due to a lack of evidence that opioids significantly improve chronic pain or physical function compared to placebo or other analgesics (e.g., NSAIDs), and the link between chronic opioid use and harms (e.g., dependence and overdose) [35, 38]. Rates of sleep and mood disorders and unemployment are also high among people who take opioids for CNCP [6-8].

In Australia, numerous opioid preparations are subsidised by the federal government under the Pharmaceutical Benefits Scheme (PBS) for Australian citizens and permanent visitors (Table 1.1) [39]. Due to their strong addictive potential and psychoactive effects, access to opioids is restricted in Australia. Opioid medicines are assigned an indication (i.e., approved uses) by the Therapeutic Goods Association (TGA). They are also given a classification of Schedule 4 (Prescription-Only Medicine) or 8 (Controlled Drug). Both Schedule 4 and 8 drugs require a prescription from a medical practitioner, with Schedule 8 drugs being more heavily restricted than Schedule 4 in terms of storage and administration. There are currently no over-the-counter (OTC; Schedule 3) opioid preparations available in Australia, after codeine was re-scheduled from Schedule 3 to Schedule 4 in February 2018.

Table 1.1. *PBS-listed opioid medicines, including TGA indication and Schedule*

Generic name	Common trade names	Preparations	Clinical indication/s	Schedule
Codeine	Nurofen Plus, Panadeine Forte	Oral, parenteral	Severe pain	4
Tramadol	Tramal, Zydol	Oral, parenteral	Severe pain	4
Buprenorphine	Suboxone, Subutex	Sublingual, transdermal	Chronic severe pain or OST	8
Fentanyl	Denpax, Durogesic, Fenpatch	Buccal/oral, transdermal	Chronic severe disabling pain or cancer pain	8
Hydromorphone	Dilaudid	Oral, parenteral	Severe pain	8
Methadone	Biodone Forte	Oral, parenteral	Chronic severe disabling pain or OST [a]	8
Morphine	MS Contin, Ordine	Oral, parenteral	Severe pain	8
Oxycodone	OxyContin, OxyNorm	Oral, parenteral	Severe pain	8
Tapentadol	Palexia	Oral	Chronic severe pain	8

[a] Opioid substitution therapy.

Note. Adapted from the Pharmaceutical Benefits Scheme website [39].

Opioid pharmacokinetics & pharmacodynamics

Both the analgesic properties of opioids and their adverse effects arise from complex interactions within the human body. Endogenous opioids are produced as part of the normal pain response [13]. Exogenous opioids are compounds that are produced externally to the body and bind to endogenous opioid receptors at a cellular level [38]. Largely due to their analgesic and sedative effects, exogenous opioids have been used recreationally and medicinally (e.g., to treat pain) for centuries [40]. Initially, naturally-occurring opioids were isolated from the opium poppy (*Papaver somniferum*) and used medicinally. More recently, various semi-synthetic and synthetic opiate-derivatives have been developed for clinical use [40, 41]. Semi-synthetic opioids are modified versions of natural opiates, while synthetic opioids, developed later, are fully synthesized from precursor compounds [41].

Opioid pharmacokinetics. Most exogenous opioids are absorbed via the gastrointestinal tract and are readily bioavailable following oral administration [42]. The exceptions to this are fentanyl and sufentanil, which demonstrate low oral bioavailability. These drugs are commonly administered via parenteral or transdermal routes (e.g., patches) [42].

Following absorption, opioids are distributed widely throughout the body [42]. In humans, opioid-type receptors have been located in the spinal cord, knee, gastrointestinal tract, cardiovascular system, immune system, and vas deferens [40]. In rats, distribution of opioid receptors in the CNS is broad, with dense population in areas including the nucleus accumbens (NAcc), thalamus, amygdala, and cerebral cortex [43]. In humans, dense populations of μ-agonist receptors have been noted in the basal ganglia, thalamus, and frontal cortex [44].

Opioids are primarily metabolised in the liver, producing both active and inactive metabolites (Table 1.2) [45-47]. In some cases, the active metabolites are more potent than the parent drug: for example, codeine is metabolised to morphine [42]. The half-life of most prescription oral opioid medicines ranges from 2–6 hours. Methadone and buprenorphine, commonly used in OST, evidence somewhat longer half-lives [45]. The relatively short half-life of most opioids means that plasma concentrations can fluctuate substantially unless regular dosing is achieved. For this reason, some medical practitioners prefer to prescribe sustained-release (SR) opioid formulations, which slow absorption and prolong the drug half-life [45]. Most SR formulations require dosing every 12–24 hours [45].

Table 1.2. *Pharmacokinetics of common pharmaceutical opioids and their active metabolites*

Opioid type	Oral bioavailability	Half-life (hrs) [a]	Metabolism	Major metabolites
Codeine	60%	3	Hepatic	C6G [b], morphine, hydrocodone
Tramadol	70%	6	Hepatic	Trans-*O*-desmethyltramadol
Buprenorphine	30%	35	Hepatic	B3G [c], N3G [d]
Fentanyl	50%	3	Hepatic	--
Hydromorphone	30%	2.5	Hepatic, renal	H3G [e]
Methadone	40-90%	15-60	Hepatic	--
Morphine	30%	3	Hepatic, renal	Hydromorphone, M3G [f] M6G [g]
Oxycodone	70%	2.5	Hepatic, renal	Oxymorphone
Tapentadol	32%	4.3	Renal	Tapentadol-*O*-glucuronide, N-desmethyl tapentadol, hydroxyl tapentadol

[a] For immediate release formulations. [b] Codeine-6-glucuronide. [c] Buprenorphine-3-glucuronide. [c] Norbuprenorphine-3-glucuronide. [e] Hydromorphone-3-glucuronide. [f] Morphine-3-glucuronide. [g] Morphine-6-glucuronide.

Note. Adapted from [45-49].

Opioid metabolism is subject to substantial inter-individual variation, which can lead to heterogeneity in analgesia and side effects. Most opioids are not subject to sex differences in metabolism. However, some opioids (e.g., oxycodone, hydromorphone) evidence higher plasma concentrations in females compared to males [46]. Genetic variation in the activity of metabolic enzymes such as CYP2D6 (codeine) and CYP2B6 (tramadol) can also impact the rate at which certain opioids are metabolised [42]. Up to 10% of the Caucasian population have limited CYP2D6 activity, meaning they metabolise codeine slowly and experience poor analgesia [42]. Conversely, a minority (1–7%) of Caucasian individuals experience hyper-metabolism of codeine, which can lead to toxicity at relatively low doses [46]. There is also some evidence of age-based variation in opioid clearance and plasma concentrations, with several pharmaceutical opioids evidencing higher concentrations in individuals ≥65 years [46]. For this reason, opioids should be used with caution among older CNCP patients, and dose closely monitored.

Opioid pharmacodynamics. Acute administration of opioids has been shown to produce a range of effects including analgesia, sedation, constipation, and respiratory depression [38]. The effects vary according to neurotransmitter affinity and mechanism of action, and are typically dose-dependent. Broadly, the analgesic effects of opioids can be attributed to the activation of specific opioid receptors that inhibit transmission of pain signals in the ascending and descending pain pathways [45]. Activation of these receptors is also responsible for many of the side effects associated with opioid use (e.g., constipation, respiratory depression) [45]. Some opioids also act on non-opioid receptors (e.g., serotonin, noradrenaline), either aiding with analgesia or producing other effects (e.g., increased risk of cardiac arrhythmia) [45]. However, most effects are produced via excitation of opioid receptors within the CNS.

Researchers have identified three primary opioid receptors, all of which are G-protein coupled: μ- (mu), κ- (kappa), and δ- (delta) [38]. These receptors are sometimes classified as MOP-R, KOP-R, and DOP-R, respectively [40]. Among these, μ-type receptors produce the strongest analgesic and euphoric effects, and are also responsible for many of the adverse side

effects of opioids, including constipation and respiratory depression (Table 1.3) [41]. Activation of κ-receptors produces moderate analgesic effects, as well as sedative and diuretic effects; δ-receptors produce weak analgesic effects [50]. Activation of δ-receptors also contributes to opioid tolerance by degrading μ-receptors, rending them less responsive to the acute analgesic effects of opioids [50]. Most pharmaceutical opioids act primarily at μ-receptors; certain opioids (e.g., methadone, morphine, fentanyl) also activate κ-receptors, while activation of δ-receptors is relatively uncommon [51]. Some opioids also interact with other chemical systems; for example, tramadol and tapentadol act as noradrenaline reuptake inhibitors, and tramadol also inhibits serotonin re-uptake [45].

Table 1.3. *Opioid receptors and their effects*

Effect	Mu		Delta		Kappa	
	Systemic	Peripheral	Systemic	Peripheral	Systemic	Peripheral
Analgesia	✓	✓	✓	✓	✓	✓
Euphoria	✓	--	--	--	--	--
Dysphoria	--	--	--	--	✓	--
Constipation	--	✓	--	✓	--	--
Diuresis	--	--	--	--	✓	--
Anxiolysis/sedation	--	--	✓	--	--	--
Reduced inflammation	--	✓	--	--	--	✓
Convulsions	--	--	✓	--	--	--
Respiratory depression	✓	--	--	--	--	--

Note. Adapted from [38].

The effects of exogenous opioids differ by affinity, and they are classed as agonists (full, partial, mixed) or antagonists accordingly (Table 1.4) [40]. In clinical practice, formulations used as pain management are primarily μ-agonists, which produce the strongest analgesic effects. Full opioid agonists bind to receptors to produce a maximal response. For example, morphine binds to μ-receptors to produce strong analgesic effects [40]. Partial agonists also bind to receptors to excite a response, but this is not maximal. This is particularly noticeable at higher doses: full agonists will typically produce stronger analgesia as dose increases, whereas partial agonists have a threshold beyond which dose increase may not improve analgesia [37].

Table 1.4. *Common pharmaceutical opioids classified by affinity and synthesis*

Agonists			Antagonists	Partial agonists
Natural	Semi-synthetic	Synthetic		
Codeine Morphine	Hydromorphone Oxycodone	Fentanyl Methadone Tapentadol Tramadol	Naloxone Naltrexone	Buprenorphine

Note. Adapted from [40].

In contrast to agonists, opioid antagonists have inhibitory effects, preventing opioid agonists from binding to a receptor while producing no notable pharmacological effects of their own [40]. For example, naloxone prevents heroin or morphine from binding to opioid receptors, but does not produce any analgesic or euphoric effects itself [40]. Antagonists are commonly used to reverse opioid toxicity or prevent individuals with an opioid use disorder or at risk of dependence from experiencing euphoric effects (i.e. the 'high') following consumption of opioids [40]. In Australia, some agonists are formulated in combination with an antagonist to reduce the potential for extra-medical use (e.g., oxycodone with naloxone). Notably, buprenorphine is pharmacologically unique in that it acts as a partial μ-agonist and δ- and κ-antagonist [37]. This is why buprenorphine is primarily used as OST rather than for the management of pain, with the exception of buprenorphine patches such as Norspan.

Tolerance and dependence

Tolerance and dependence to opioids are a key concern in the field of pain management, for both consumers and prescribers. Tolerance occurs when the effects of a drug become diminished with repeated administration and the individual requires larger or more frequent dosing to achieve the desired effect [52]. In the context of pain management, opioid tolerance is generally conceptualised in terms of analgesic efficacy, but also applies to other side effects such as respiratory depression [52]. In comparison with other drugs, tolerance to opioids develops rapidly; sometimes within hours, depending on initial dose and route of administration [52]. Tolerance is particularly concerning for chronic consumers as it necessitates dose escalation,

which is linked to subsequent opioid-induced hyperalgesia (i.e., increased pain sensitivity) [52]. This can perpetuate a cycle that leads to poor long-term pain management outcomes.

Tolerance is one symptom of opioid dependence, which develops when the body adapts to the presence of opioids and cannot function properly in their absence [53]. Dependence is also often characterised by the experience of withdrawal accompanying opioid cessation, including both physiological (e.g., vomiting, muscle spasms) and psychological (e.g., cravings) symptoms [53]. Dependence, tolerance, and withdrawal are key features of opioid use disorders (OUD), though the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) states that people taking opioid medicines exactly as prescribed do not meet criteria for tolerance or withdrawal [53]. Nonetheless, certain safeguards have been introduced in Australia to reduce the risk of dependence and subsequent OUD in people who take opioids for chronic pain. In June 2020 the TGA introduced a range of measures, including reducing the size of prescription opioid packets and requiring individuals who are prescribed opioids for more than 12 months to undergo a review by a pain specialist or alternative clinician [54]. These changes highlight the degree of concern around opioid dependence in Australia.

Guidelines for opioid prescribing

Given the potential for dependence and other adverse side effects related to opioid use [38], health organisations such as the Centre for Disease Control (CDC) have developed prescribing guidelines to assist clinicians [25]. These guidelines generally provide a broad overview of opioid prescribing, rather than recommendations for specific medications. This is because, despite the known pharmacological differences between opioids, analgesic efficacy and side effects do not appear to vary according to opioid type at the population-level [42]. However, as responses can vary substantially, individuals may need to trial several different classes of opioids in order to achieve maximal analgesia and minimal side effects [42].

Clinical guidelines, including those outlined by the Royal Australasian College of General Practitioners, recommend initially prescribing the lowest dose for adequate analgesia. This is

because the risk of adverse effects increases with higher opioid doses [17, 25]. The CDC suggests an initial dose of <20mg oral morphine equivalent (OME)/day. While recommendations have changed over time, the most recent guidelines suggest that dose titration to ≥50mg OME/day should only occur after appropriate assessment of risks and benefits for each patient, while titration to ≥90mg OME/day requires clear justification [25]. These guidelines are based primarily on the risk of overdose: doses of 50-100mg OME/day can increase overdose risk by factors of 1.9–4.6, while individuals taking >100mg OME are 2.0–8.9 times more likely to experience overdose than people on doses of 1–<20mg OME/day [25].

In addition to dose, clinicians and consumers need to consider opioid formulation. Most opioid medicines are available in immediate- (IR) and sustained-release (SR) formulations. These are also sometimes referred to as long- (LAOs) and short-acting opioids (SAOs), respectively [55]. IR opioids generally have a 2–6 hour half-life, meaning that plasma opioid concentrations can quickly oscillate unless frequent and regular dosing occurs to achieve steady-state [55]. As such, IR formulations are generally preferential for acute or intermittent pain, though they can be useful for persistent pain if regular dosing is achievable [55]. In contrast to IR formulations, SR preparations have a long duration of action; in some cases, up to 35 hours [45]. This means the burden on consumers (e.g., remembering to take frequent doses) is considerably less with SR formulations than IR formulations. There is some disagreement regarding which form is preferential for CNCP, however, the CDC does not recommend use of SR formulations [25]. This is primarily because they do not appear to be any more efficacious than IR opioids used on an 'as needed' basis, and may be associated with a higher risk of overdose upon initiation [25].

Finally, prescribing guidelines consider duration of opioid prescribing as a key factor for risk of harm. As mentioned, the CDC does not endorse opioid medicines as a first-line treatment for CNCP [25]. In specific cases, opioid treatment may be deemed appropriate. If this is the case, it is strongly recommended that use is closely monitored for the first month of therapy, when the risk of adverse effects is high [25]. If appropriate analgesia has not been achieved after one

month, the CDC recommends rotating to a different opioid or non-opioid treatment. In cases where analgesia is appropriate, clinicians should review treatment every three months [25].

Key points

Pharmaceutical opioids are implicated in pain management due to their strong analgesic effects. Opioids produce numerous side effects (e.g., sedation), and may also be used extra-medically for their euphoric effects. There is also a risk of developing tolerance and dependence to opioid drug effects with repeat dosing.

Key bodies such as the RACGP have developed clinical guidelines to help reduce the harms of opioid use. Broadly, these guidelines recommend using low doses in immediate-release formulations, and, where possible, for short durations. Additionally, guidelines recommend conducting regular clinical reviews to ensure the functional benefit of opioid prescribing for each patient.

Prevalence and characteristics of opioid use in Australia

Measuring prescribed use of opioids

Data sources. Estimation of pharmaceutical opioid use rates in Australia typically uses data from the Pharmaceutical Benefits (PBS) and Repatriation Pharmaceutical Benefits (R-PBS) Schemes. Through these schemes, the Australian government subsidises the cost of many medicines [36]. All PBS-subsidised medicines are allocated a unique item code with details of brand, dose, form, quantity, and indication. The frequency of dispensing for each item code is recorded in a central database, categorised by state and calendar year [36]. The PBS database is publicly available, providing a detailed, accessible source of dispensing information. However, the database has certain caveats. For example, PBS data does not capture all prescription drug use (e.g., drugs that are not subsidised or that have been prescribed for a non-TGA approved indication) [36]. For this reason, PBS data tends to under-estimate total opioid utilisation. In 2014, it failed to account for 25.4% of the total opioid dispensing for that year [56]. Despite this, the PBS database remains the most comprehensive, publicly accessible research tool for estimating population-level medicine use. Options for researchers also include sales data and a 10% representative sample of PBS dispensing [57, 58].

Units of measurement. Pharmaceutical opioid utilisation data are generally expressed as defined daily doses (DDDs) or oral morphine equivalents (OMEs). DDDs were developed as an international metric for calculating population-level medicine use [59]. A DDD represents the average maintenance dose per day of a given drug, when used by adults and for the primary indication of that drug (e.g., pain) [59]. DDDs provide a standardised measure to help overcome difficulties in calculating usage due to differences in drug type and dose [59]. However, use of DDDs is somewhat problematic for opioids, where real-world use differs from clinical guidelines and dosages vary greatly by opioid type [58]. A recent study examining doses among Australians prescribed opioids for CNCP (*n*=1,101) found that DDDs for oxycodone and buprenorphine were 2–7 times higher than actual doses reported by the sample [59]. This suggests that DDDs over-estimate opioid use among people with CNCP.

Oral morphine equivalents (OMEs) offer a more precise method of estimating population-level opioid utilisation than DDDs. OMEs are based on the principle of equi-analgesic dosing, whereby different types of opioids can produce similar analgesic effects when administered in 'equivalent' doses [60]. For example, a lower dose of a strong-acting opioid (e.g., oxycodone) may be equivalent to a higher dose of a weak-acting opioid (e.g., codeine). This also applies to different routes of administration, with more direct routes producing stronger effects [60]. Health professionals and researchers have developed a range of OME conversion charts, with morphine as a baseline comparator (i.e., 1:1 ratio for morphine OME) for other types of opioids (Table 1.5) [60]. Notably, OME was developed as a research tool and is not recommended for use in clinical practice.

Table 1.5. *Oral morphine equivalents for oral preparations of common opioids*

Trade name	Dosing	Common Australian brand names	Conversion factor [a]
Codeine	Mg/day	Panadeine Forte, Mersyndol	0.13
Tramadol	Mg/day	Tramal	0.2
Buprenorphine [b]	Mcg/day	Subutex, Suboxone	37.5
Dextropropoxyphene	Mg/day	Di-Gesic, Doloxene	0.1
Fentanyl [b]	Mcg/day	Abstral, Duragesic	0.1
Hydromorphone	Mg/day	Dilaudid	5.0
Methadone	Mg/day	Aspen	4.7
Morphine	Mg/day	MS Contin, Kapanol	1.0
Oxycodone	Mg/day	Endone, OxyContin	1.5
Tapentadol	Mg/day	Palexia	0.4

[a] As reported by [61]. [b] Sublingual/buccal.

Prevalence of prescribed opioid use in Australia

General population use of opioids. Pharmaceutical opioid prescribing is commonplace in Australia. The 1990s and 2000s saw substantial and consistent increases in the rate of opioid prescribing: from 1990–2014, opioid dispensing rates increased from 4.6 DDDs/1000

population/day to 17.4 DDDs/1000 population/day [62]. More recently, a large study examined the incidence and prevalence of opioid use in Australia by reviewing data from a 10% random sample of Australian adults prescribed opioids [63]. According to these data, over 3 million individuals were currently prescribed opioid medicines as at June 2017, representing 16.0% of the total adult population at that time [63]. However, the study reported that there was a slight decrease (2.3%) in overall opioid initiation each year from June 2014, with approximately 1.9 million adults (10.0%) initiating use of opioids each financial year [63]. Additionally, total OME amounts dispensed each year remained relatively stable across the period [63]. These data suggest that, since 2013, the incidence of opioid initiation has slightly decreased while prevalence of use has remained stable.

Prevalence of opioid use for CNCP. Despite prescribing guidelines, most people who are prescribed opioids do not have cancer. In 2016–17, individuals without cancer comprised 98.2% of the total number of individuals who initiated opioid use and 95.3% of the total number of people who consumed opioids that year in Australia [63]. This figure remained relatively stable from 2013–14 to 2016–17 [63]. Additionally, pharmaceutical opioid use among individuals with CNCP is common and has increased over time. There is a lack of available data examining use of opioids for CNCP in Australia. However, a recent systematic review and meta-analysis of 42 studies (n=5,059,098 participants) assessed opioid use among people with CNCP. The authors reported that almost one-third (30.7%) of participants were prescribed an opioid, and that this figure did not substantially vary by geographic location [64]. Notably, prescribing was positively correlated with year of sampling (i.e., prescribing has increased over time) [64]. These data broadly indicate that most individuals who are prescribed opioids do not have cancer and use of opioids is both common and increasing among people with CNCP.

Demographic characteristics of people who take opioids for CNCP

People who take opioids for CNCP are predominantly female and aged in their 50s and over. For example, among people prescribed opioids for CNCP in the POINT study, over half (55.6%) were female [8]. This likely reflects the higher prevalence of CNCP among females compared to males [65]. Additionally, almost one-third (32.3%) of POINT participants were aged 65 and over, and a further 26.6% were aged 55-64 [8]. This is likely due to a higher rate of many CNCP conditions (e.g., arthritis) in older people compared to younger people. Notably, however, certain harms can disproportionately affect younger people with CNCP. For example, working-age people (aged 19-64) in the POINT study were more likely to report being unemployed than those in older age groups [8]. Notably, pain was also more likely to affect employment in younger participants: 78.0% of people aged 19-54 and 74.6% of those aged 55-94 reported a change in their employment because of pain [8]. For this reason, it is also important to examine outcomes for younger people who take opioids for CNCP.

Risk factors relating to opioid use among people with CNCP

While use of opioids for CNCP is not recommended in general, certain additional factors can further increase the risk of harm. In particular, high doses and chronic use are risk factors for hospitalisation and injury.

Use of strong opioids. In the systematic review of 42 studies described in the paragraph above, the authors classified weak opioids (e.g., codeine, tramadol) as OME <50mg/day and strong opioids (e.g., oxycodone, tapentadol, morphine) as ≥50mg/day [64]. This study found that more participants were prescribed strong (18.4%) than weak (8.5%) opioids [64]. Notably, many people were also prescribed combination opioids (11.0% for weak combinations and 24.1% for strong combinations). However, Australian data indicate that use of weak opioids may be somewhat higher than reported in this meta-analysis. Two studies have reported that 24.4–55.1% people with CNCP are prescribed codeine and paracetamol combination medicines, compared with 23.4–61.3% for oxycodone [8, 63]. Notably, this research was conducted prior to the re-scheduling of codeine in 2018 and may not reflect

current consumption patterns. In sum, a substantial proportion of people with CNCP appear to be prescribed a strong opioid, but estimates of use vary.

Use of high opioid doses. In Australia, a substantial minority of people with CNCP are prescribed high doses (>100mg OME). In a random 10% sample of Australians with CNCP who were prescribed opioids under the PBS from 2013–14 to 2016–17, almost one-third (30.2%) were prescribed 100–249mg/day [63]. Around 10% of these individuals reported that their current opioid dose exceeded 250mg OME [63, 66]. A similar figure (8.9%) was reported in a large-scale Australian prospective cohort study, the Pain and Opioids in Treatment (POINT) study, which examined treatment outcomes for individuals prescribed opioids for CNCP [8].

Chronic opioid use. Rates of extra-medical opioid use and opioid use disorders are typically low among people with CNCP [67]. However, many people who are prescribed opioids for CNCP use these medicines chronically. For example, participants in the POINT study reported a median opioid treatment duration of four years at entry to the cohort. This is considerably longer than the CDC's recommended three months and may elevate the risk of harms such as physical injury and overdose [8, 25].

Key points

Use of prescribed pharmaceutical opioids is commonplace in Australia, though the incidence of use has declined somewhat since 2013. Despite WHO guidelines, over 9 in 10 people who receive an opioid prescription have CNCP. Extra-medical opioid use is relatively uncommon in this cohort, but some people are prescribed strong opioids or high doses, and many take opioids chronically. This may place people at risk of harms such as physical injury.

Opioid-related harms

While opioid medicines have an important place in pain management, these drugs also contribute to population-level harms such as opioid use disorders, poisoning, and premature death. In 2011, opioids accounted for 0.9% of the total burden of disease in Australia [68]. Of this, just under two-thirds (63%) of the burden was related to accidental poisoning [68]. A further 29% was related to opioid dependence [69].

The burden of disease related to opioid use is primarily associated with use of pharmaceutical opioids. Notably, many of these harms (e.g., drug-induced deaths) often relate to illicit or extra-medical use of opioids, and are not specific to prescribed use. Indeed, people with CNCP who use opioids as prescribed are more commonly affected by harms like driving-related impairment and increased risk of involvement in motor vehicle collisions [70], experience of falls and physical injuries [71], and cognitive impairment [72]. Given this, the present thesis focuses primarily on cognitive functioning and driving-related risks (related to cognitive function). As such, the sections below provide a brief overview of population-level harms, falls and physical injuries, with a more detailed review of driving-related harms and cognition.

Hospitalisations and deaths in Australia

Hospitalisations. In Australia, most opioid-related hospitalisations arise from opioid poisoning. In 2016–17, there were 4,232 emergency department presentations and 9,636 hospital admissions involving opioid poisoning. Around 44% (4,234) of all hospital admissions listing opioid poisoning as the principal diagnosis [73]. This translates to a rate of 11.6 opioid-related ED presentations and 26 hospital admissions per day [73]. Australian Institute of Health and Welfare (AIHW) data have shown that hospitalisations with a principal diagnosis of opioid poisoning increased from 14.1 admissions per 100,000 population in 2007–08 to 17.6 in 2016–17 [73]. This is despite increased awareness of, and legislation to reduce, the harms associated with opioid use.

Opioid-induced deaths. In 2018, 1,123 deaths were directly attributable to opioid use. This represents 64.5% of all recorded drug-induced deaths that year [74]. This figure has increased over the past decade, following a long-term decline since the 1990s. From 2009 to 2018, opioid-induced deaths increased from 4.0 to 4.6 deaths/100,000 population [74].

Despite a recent increase in the proportion of deaths related to the use of illegal opioids (e.g., heroin), prescription opioids continue to account for most deaths. Analysis of the National Mortality Dataset showed that pharmaceutical opioids were present in 71% of opioid-induced deaths in 2018 [74]. These data indicate that pharmaceutical opioids continue to be a key driver of drug-induced deaths in Australia.

Extra-medical opioid use and use disorders

Extra-medical opioid use. Recent data from the National Drug Strategy Household Survey (NDSHS) indicated that extra-medical use of pharmaceutical opioids is relatively uncommon. From 2016 to 2019, the proportion of the Australian population who had recently used an opioid for non-medical reasons halved, falling from 3.0% to 1.5% [75]. This was largely driven by a reduction in extra-medical use of codeine, following the up-scheduling of this drug to a prescription-only medicine in February 2018 [75].

Opioid use disorders. Compared with extra-medical pharmaceutical opioid use, estimating the prevalence of opioid use disorders (OUD) in Australia is somewhat more difficult. This is primarily due to the large proportion of people with substance use disorders who do not seek treatment. Data from the 2016 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) provide an estimate of OUD within the region of Australasia, but do not provide estimates for Australia specifically. Nonetheless, these data indicate that 123,500 people in Australasia experienced an opioid use disorder (OUD) in 2016 [76]. After adjusting for age, this translates to a rate of 414.7 (95%CI: 358.6, 479.4) people per 100,000 population [76]. The rate of OUD in the community can also be assessed via proxy measures, such as the number of treatment services provided to people seeking treatment for opioid use. In 2018–19, 3% of all treatment

episodes provided by publicly-funded alcohol and other drug (AOD) treatment agencies were for pharmaceutical opioids [77]. This was slightly less than treatment episodes provided for heroin (5%), but represented 55% of all episodes for pharmaceutical drugs [77]. The proportion of episodes for individual opioid types has fluctuated across time, with opioids overall remaining relatively stable over time.

Falls and physical injuries

Falls and related injuries are a key concern for people prescribed opioids for CNCP, due to the typical age of opioid consumers and the outcomes of falls in these age groups. Specifically, people who take opioids chronically are frequently those in older age groups (65 and over) [78]. A recent study examined the predictors of persistent prescription opioid use among a 10% sample of Australians prescribed opioids via the PBS (*n*=431,963) [78]. This study reported that people aged 75 and over were 2.5 (95%CI [2.3–2.6]) times as likely as those aged 18–44 to evidence persistent opioid use [78]. This is problematic given the outcomes of falls for older adults. In 2016–17, three-quarters (75.5%) of all injury-related hospitalisations among people aged 65 and over were the result of a fall [79]. More than half of these hospitalisations related to fractures [79]. The experience of falls is also associated with negative outcomes such as the fear of falling, which is in turn a predictor of poorer quality of life and subsequent falls [80].

The association between use of psychotropic medicines and an increased risk of falls and physical injuries (e.g., fractures) is well documented [81]. While researchers have primarily focused on non-opioid drugs such as benzodiazepines and antidepressants, there is growing evidence that opioids are also linked with falls [71]. A recent meta-analysis examined use of prescription opioid medicines and the risk of falls, fractures, and other fall-related injuries among older people (aged ≥65) [71]. This study (*n*=30 studies) found a small magnitude positive effect for use of opioids and the incidence of falls (log-transformed effect size: 0.15, 95%CI [0.02, 0.27]), but large magnitude effects for the incidence of fall-related injuries (ES: 0.40, 95%CI [0.24, 0.56]) and fractures (ES: 0.71, 95%CI [0.45, 0.97]) [71]. This finding is

supported by several previous meta-analyses that have reported an increased risk of fractures among people who are prescribed opioids, with relative risks of 1.54–1.88 [82, 83].

Notably, falls are typically studied in the context of older cohorts and people living in residential care settings [71]. Given this, the present thesis assesses falls in a limited capacity only. This is primarily because this thesis programme aimed to assess cognitive functioning and related behavioural outcomes (such as driving) in community-dwelling adults, who are likely to be younger than the cohorts examined in opioid-related falls data.

Driving-related harms

The sedating effects of opioids may substantially impair the ability to safely operate a motor vehicle, and use of certain prescription opioids has been associated with an increased risk of involvement in motor vehicle collisions (MVC) [84]. This is pertinent for many individuals who use strong opioids to manage CNCP, where driving is crucial for maintaining independence [85]. Additionally, the risk of adverse effects may be heightened by high doses [8, 25, 63]. However, driving impairment is typically greatest in the weeks following opioid initiation or dose increase, with relatively consistent evidence that people on stable opioid doses can safely operate a motor vehicle [86]. To reflect this, pharmaceutical opioids in Australia typically carry warning labels regarding the potential impairing effects of opioids, but driving under the influence (DUI) of opioids is unregulated and the decision to drive is primarily left to consumers. Due to ongoing debate around the safety of this practice, there is a growing body of research examining the chronic effects of opioids on driving performance and the risk of MVC-involvement among people who are prescribed opioids. These topics are described below.

Driving simulators and on-road driving tests. Objective cognitive tasks can detect specific impairments (e.g., slow reaction time) that may reduce driving ability, but these deficits do not necessarily translate to real-world driving impairment. To overcome this, numerous studies have examined the effects of chronic, prescribed opioid use on actual and simulated driving ability [85, 87]. The increased risk of MVC among pharmaceutical opioid consumers

relates to opioid-induced impairments in the ability to safely handle a motor vehicle. Driving is a complex activity that comprises multiple underlying cognitive abilities (e.g., reaction speed, attention), many of which are susceptible to the impairing effects of psychotropic drugs [88]. Currently, the most accurate way to assess driving performance is via on-road driving tests, in which participants are required to drive under normal traffic conditions in various scenarios (e.g., highway driving, urban driving), or in closed 'obstacle' courses (e.g., manoeuvring around cones) [89, 90]. However, such tests are seldom used in research settings as they are expensive, time-consuming to administer, and pose an ethical challenge (i.e., administering substances that may impair driving ability) [89]. Driving performance is more often studied via simulators, which mimic in situ driving scenarios [91]. Driving simulators display good external validity (i.e., correlation with real-world driving) and are sensitive to drug-induced impairments in driving ability [91]. The sections below describe the effects of long-term opioid use on driving ability. Acute opioid effects are not examined here, as this is not a core question of the current thesis programme and the acute effects of opioids on cognitive performance have been described in detail.

Despite concern about the effects of opioid use on driving ability, very few studies have examined the effects of long-term prescription opioid use on driving ability. A recent systematic review examined driving performance among individuals with CNCP who were prescribed opioid agonists long-term, but located only three studies matching inclusion criteria [89]. These studies comprised a case-control [85], a cross-sectional [87], and a pre- and post-test study [92], and included individuals (*n*=59) prescribed opioids (codeine, fentanyl, or mixed opioid-agonists) for CNCP. All studies reported no effect of chronic opioid use on driving performance, with the authors of the review concluding that stable doses of opioid agonists do not appear to impair driving ability [89]. However, they noted the paucity of literature available and the lack of studies examining the effects of extended-release, low-dose opioids and recommended further research investigating driving ability among this group. The analysis was also limited by small sample sizes in the included studies.

Opioid DUI and motor vehicle collisions. While research on the effects of opioid use on driving remains relatively scarce, there is a substantial body of research demonstrating that pharmaceutical opioids are typically among the most commonly-detected drugs in biological samples (blood, urine) taken from crash-involved drivers. In a seminal meta-analysis on the prevalence of drug detections among MVC-involved drivers in Australia, opioids were reportedly the sixth most commonly detected drug in crashes that occurred from 1991–2000 [93]. Opioids were detected in 3–5% of MVC-involved drivers, following cannabis (2–32%), benzodiazepines (2–15%), cocaine (4–11%), and amphetamines (2–6%) [93]. More recently, a study examining use of prescription drugs among fatally injured drivers (n=2,638) in the Australian jurisdiction of Victoria reported that 6.6% of drivers tested positive for opioids from 2000–2013 [94]. This was somewhat lower than alcohol (24.8%), but comparable to detections of benzodiazepines (7.0%) [94]. Credible estimates of prescription opioid use among the Australian driving population are limited. However, one study on a 10% sample of PBS data found that 16.0% of the total adult population were prescribed an opioid as at June 2017, a slightly higher proportion than for opioid detections in fatally injured drivers [63]. Together, these data indicate that opioids are detected in a small but substantial proportion of crash-involved drivers relatively consistently from the early 1990s until the mid-2010s.

The data described above provide a broad overview of opioid DUI, but do not specifically examine prescribed opioid use (i.e., may include extra-medical or illicit use; that is, use of illicit opioids or use of pharmaceutical opioids other than prescribed). The impact of prescribed opioids has become a key research focus in recent years amid concerns that increased opioid dispensing may be reflected in MVC data [70]. Specifically, community utilisation of specific drugs may be predictive of harms [95, 96]. For example, recent data from Maryland, USA noted increasing opioid detections among blood samples from crash-involved motorists that correlated with rising prescribing rates in the region [70]. Such data do not exist in Australia; while the data described in the previous paragraph indicate relative stability in the rate of opioid detections in Australia from the 1990s, despite increased opioid prescribing [62,

78], the specific relationship between community utilisation of opioids and related MVC has not been examined.

The relative frequency with which opioids are detected among crash-involved motorists may indicate a greater risk of MVC for opioid consumers versus non-consumers. However, while there is mounting evidence that use of prescribed opioids is linked to increased risk of MVC, findings remain inconsistent overall. For example, a 2013 meta-analysis examining studies (n=7) on the risk of MVC involvement for senior drivers (age ≥55 years) who were opioid consumers or non-consumers revealed weak evidence of an increased risk of crashes for the former group (pooled Odds Ratio [OR]=1.20, 95%CI: 1.08, 1.32) [97]. However, a more recent systematic review assessing 15 published studies concluded that use of opioid medications more than doubled the risk of MVC involvement (OR=2.29, 95%CI: 1.51, 3.48; see Table 1.6) [98]. These findings may reflect the differential effects of opioids according to type; a 2016 meta-analysis (n=27 studies) reported heterogeneity in crash risk depending on opioid type (increased risk: buprenorphine, dihydrocodeine, and methadone; mixed findings: codeine, tramadol; no increased risk: morphine) [84]. Together, these data tentatively indicate that use of prescription opioids may increase crash risk, but that this effect is differential depending on opioid type. Crash risk also likely differs according to population characteristics, given known differences in opioid pharmacokinetics and pharmacodynamics based on person-level factors such as age [42, 46].

In addition to crash risk, there is some indication that individuals who are prescribed opioids are at greater risk of being culpable (i.e., at fault) for initiation of serious and fatal MVC. For example, a recent study examining two-vehicle fatal MVC (n=18,321) in the USA found that individuals who tested positive for prescription opioids were more than twice as likely to initiate crashes than were those who tested negative (OR=2.18, 95%CI: 1.91, 2.48) [99]. Similarly, the aforementioned review noted a pooled odds ratio of 1.47 (95%CI: 1.01, 2.13) for crash culpability for prescription opioid consumers versus non-consumers, indicating that the opioid group was at a higher risk for crash culpability than were non-consumers [98]. However,

crash culpability studies should generally be interpreted with caution as they may fail to
account for extraneous factors (e.g., weather conditions, fatigue) that also contribute to crash
initiation [100].

Table 1.6. *Studies included in Chihuri & Li 2017's meta-analysis examining prescription opioids and risk of MVC involvement*

Study	Country	Design	Time period	Participants	Opioid use	Data	No. MVC-involved	Opioid use %	No. not MVC-involved	Opioid use, %	OR
Bernhoft, 2012	European countries	Case-control	2007-2009	Licensed drivers, 18+	Morphine, codeine, methadone, tramadol	Whole blood, oral fluid test	3392	2.1	48436	0.4	5.32
Dussault, 2002	Canada	Case-control	1999-2011	Licensed drivers	Prescription opioids	Whole blood, urine test	354	1.4	5931	1.2	1.18
Gjerde, 2011	Norway	Case-control	2003-2008	Licensed drivers	Morphine, codeine, methadone	Whole blood, oral fluid test	204	3.4	10540	0.9	4.09
Gomes, 2013	Canada	Case-control, nested	2003-2011	Members of the Ontario Provincial Public Drug Program, 18-64	Codeine, morphine sulfate, oxycodone, hydromorphone hydrochloride, transdermal fentanyl (oral, dispensed within past year)	Ontario Drug Benefit database (prescription medications for all Ontario residents)	2428	79.4	2428	74.9	1.30
Leveille, 1994	USA	Case-control	1987-1988	Licensed drivers, 65+ years, health organisation members	Codeine, propoxyphene, oxycodone (dispensed within past 6 months)	Group Health Cooperative database (prescription medications for all Puget Sound residents)	234	19.7	447	15.0	1.39
Meuleners, 2011	Australia	Case-crossover	2002-2008	Licensed drivers, 60+	Codeine, detropropoxyphene, fentanyl, hydromorphone hydrochloride, morphine, oxycodone, pethidine, tramadol (prescribed past 6 months)	Pharmaceutical Benefits Scheme database (all Australians with access to government prescriptions)	616	46.1	616	36.2	1.51
Monarrez-Espino, 2016	Sweden	Case-control	2005-2009	Licensed drivers, 50-80	Morphine, opium, hydromorphone, nicomorphine, oxycodone, papaveretum, morphine combinations, oxycodone combinations, dihydrocodeine combinations, codeine combinations (dispensed within previous 180 days)	Swedish Prescribed Data Register (all medications dispensed in all pharmacies throughout Sweden)	4445	6.8	17780	2.0	3.58
Movig, 2004	Netherlands	Case-control	2000-2001	Licensed drivers, 18+	Morphine, codeine, 6-monoacetylmorphine	Serum, urine test	110	7.3	816	2.6	3.12
Mura, 2003	France	Case-control	2000-2001	Licensed drivers, 18+	Morphine, codeine, codethyline	Whole blood test	900	2.7	900	0.3	8.19
Romano, 2014	USA	Case-control	2006-2008	Licensed drivers, 16+	Codeine, morphine, hydrocodone, hydromorphine, oxycodone, methadone, oxymorphine, meperidine, propoxyphene	Whole blood, urine, oral fluid test	1766	3.1	3424	2.9	1.15

Note. Adapted from [98].

Perceptions of driving-related risks. Data examining the prevalence of and attitudes towards DUI of prescribed opioids among the general population are relatively limited in Australia and internationally. One study has examined perceptions of DUI of pharmaceutical analgesics among a community sample (*n*=2,257) of people who use analgesics, reporting that almost two-thirds (31.9%) of respondents elected not to drive after the last time they had consumed an analgesic [101]. Notably, this study was published more than a decade ago. It is likely that community perceptions of and attitudes towards DUI have changed in this time, for example due to changes to medicine warning labels [102]. As such, perceptions of risk among people with CNCP, as well as associated population-level harms, are relatively poorly understood.

Key points

Use of pharmaceutical opioids is related to a range of harms. At the population level, opioid-related hospitalisations, deaths, and use disorders remain a key concern, and are often related to pharmaceutical opioids rather than heroin.

People who are prescribed opioids for CNCP may be less likely to experience these more severe harms, but are at risk of experiencing poor outcomes related to falls and injuries, driving-related impairment, and involvement in MVC.

Despite this, little is known about how patients perceive these risks (e.g., driving impairment), how often they drive after taking opioids, and how aware they are of opioid side effects. Additionally, it is not known whether opioid-related MVC have changed across time with changes in opioid prescribing.

Understanding real-world harms and consumer risk awareness would allow researchers and policy-makers to identify where there is a need for improved consumer education and devise programs to address this need (e.g., by introducing short clinical interventions).

Opioid-related cognitive impairment

Many of the behavioural harms associated with opioid use (e.g., driving ability) relate to the cognitive effects of opioids. Cognition refers to the processes through which an individual acquires, stores, manipulates, and retrieves information via the central nervous system (CNS) [103]. Cognition is generally thought to include numerous discrete functions including psychomotor speed, attention, memory, and executive function [103], and are best assessed via objective tasks (see Table 1.7).

Table 1.7. *Examples of cognitive tasks used to assess specific domains and functions*

Domain	Function	Example tasks
Motor performance	Manual dexterity & co-ordination	Grooved Pegboard Test Finger Tapping Test
Attention	Information processing speed	Digit Symbol Substitution Test Trail Making Test A
	Sustained attention	Stress Tolerance test (DT) Continuous Performance Test
Executive functions	Inhibitory control	Stop Signal Task
	Decision making	Iowa Gambling Task
Learning & memory	Working memory	Trail Making Test B *n*-Back task
	Verbal recall & recognition	Rey's Auditory Verbal Learning Test

Note. Adapted from [103].

Acute cognitive effects in healthy people

Acute administration of opioids has been shown to impair performance on a range of cognitive tasks in healthy, opioid-naïve individuals. Effects are differential according to opioid dose, type, route of administration, and time since dosing occurred [72, 104]. For example, a recent double-blind randomised controlled study noted impaired task performance on the Digit Symbol Substitution Task (DSST) at lower OME doses of buprenorphine (15.5mg OME) compared to methadone (47mg OME) [104]. The effects of acute opioid administration in healthy volunteers on key areas of cognitive function are described below.

Motor performance. Motor performance encompasses a range of basic motor skills including manual dexterity, co-ordination, and speed of motor responses [103]. In the pain and

opioid literature, motor performance is often examined via manual tasks that measure the speed and accuracy of motor responses (e.g., the Grooved Pegboard Task). While sometimes not considered a cognitive function, many tasks assessing motor performance involve a cognitive component; for example, the Grooved Pegboard Task requires attentional capacity. Additionally, motor performance can be a sensitive indicator of broader cognitive impairment attention [103].

Several studies have examined the effect of acute administration of opioids on motor performance in healthy, naïve individuals. In a seminal review, the author noted impairment for specific tasks (e.g., finger tapping tasks), particularly at higher opioid doses and with non-opioid agonists [72]. Since this review, relatively few studies have examined motor performance in naïve individuals. Those studies (including reviews) that do exist have not found consistent effects of opioids on simple motor performance at therapeutic doses [105, 106]. Given this, it seems likely that opioids do not produce consistent or large impairments in motor performance even in healthy, opioid-naive individuals.

Attention. Attention encompasses a range of processes, including information processing (IP) speed (i.e., the rate at which an individual can perform cognitive processes), focused attention (i.e., vigilance), and divided attention [103]. Numerous attention tasks exist, many of which also assess other functions such as working memory and psychomotor speed [103]. Attention tasks are generally visual or auditory, and typically involve participants eliciting a response to one stimulus or critical combinations of stimuli; for example, by pressing a button in response to a specific number displayed on screen. However, attention tasks do not always use this mode of assessment; for example, span tasks such as the Digit Span Task (forwards trials) require participants to listen to a verbally delivered list and then repeat it back to an examiner [103, 107].

Several studies examining the effects of opioids on attentional processes have noted impairments in task performance at therapeutic doses (7.8–47mg OME) and for a range of opioid types and ROAs (Table 1.8). Several randomised controlled trials have reported

performance deficits on IP speed tasks in healthy individuals following acute administration of opioids, including: methadone, hydrocodone, oxycodone, and morphine (oral); buprenorphine (sublingual); and morphine, butorphanol, and nalbuphine (intravenous) [104]. Notably, there was considerable variance between studies in terms of the dosage administered before effects were noted (10–47mg OME). This may point to differential effects according to opioid type and route of administration (ROA). However, the range of OME doses fall within the recommended therapeutic dose range (i.e., <50mg OME), highlighting the importance of understanding the potential cognitive effects of longer-term opioid use.

Table 1.8. *The dose-dependent effects of opioids on tasks assessing attention in healthy, naïve individuals*

Authors	N	Design	Blinding	Task	DV [a]	ROA [b]	Opioid type	Opioid dose	OME [c] (mg)	Score vs. placebo/baseline
Cherrier, 2009 [108]	35 [d]	Case-crossover, placebo, pre-post	Double blind	SRT [e]	Sustained attention	Oral	Oxycodone	10mg	15	↓ at 1hr; = at 5 hrs post-administration
				CRT [f]	Sustained attention	Oral	Oxycodone	10mg	15	↓ at 1hr; = at 5 hrs post-administration
				SDMT [g]	Sustained attention	Oral	Oxycodone	10mg	15	↓ at 1hr, 5hrs post-administration
				SAT [h]	Sustained attention	Oral	Oxycodone	10mg	15	=
Comer, 2010 [109]	18	Case-crossover, placebo	Double blind	DSST [i]	IP speed [j]	Intramuscular	Morphine	5mg/70kg	5	=
								10mg/70kg	10	↓
				RVIP [k]	IP speed [j]	Intramuscular	Morphine	5mg/70kg	5	=
								10mg/70kg	10	↓ (females); = (males)
				DAT [l]	Divided attention	Intramuscular	Morphine	5mg/70kg	5	=
								10mg/70kg	10	↓
Friswell, 2008 [110]	18	Case-crossover, RCT [m]	Double blind	DS, forwards [n]	Sustained attention	Oral	Morphine	10mg	10	=
							Oxycodone	5mg	7.5	=
				TMT A [o]	IP speed [j]	Oral	Morphine	10mg	10	=
							Oxycodone	5mg	7.5	=
O'Neill, 2000 [111]	8	Case-crossover, RCT [m]	Double blind	SRT [e]	Sustained attention	Oral	Dextropropoxyphene napsylate	100mg	10	=
							Morphine sulphate	10mg	10	= (↓ at 36h)
				CRT [f]	Sustained attention	Oral	Dextropropoxyphene napsylate	100mg	10	↓ (4h, 8h, 12h, 26h, 36h)
							Morphine sulphate	10mg	10	↑ (accuracy)
				Number vigilance	Sustained attention	Oral	Dextropropoxyphene napsylate	100mg	10	=
							Morphine sulphate	10mg	10	=
				CFFT [p]	Visual IP speed [j]	Oral	Dextropropoxyphene napsylate	100mg	10	=
							Morphine sulphate	10mg	10	= (↓ at 26h, 30h)

Authors	N	Design	Blinding	Task	DV [a]	ROA [b]	Opioid type	Opioid dose	OME [c] (mg)	Score vs. placebo/baseline
Strand, 2019 [104]	22	Case-crossover, RCT [d]	Double blind	DSST [i]	IP speed [j]	Oral	Methadone	5mg	23.5	=
								10mg	47	↓
						Sublingual	Buprenorphine	0.2mg	7.8	=
								0.4mg	15.5	↓
				PVT [q]	Sustained attention	Oral	Methadone	5mg	23.5	=
								10mg	47	↓
						Sublingual	Buprenorphine	0.2mg	7.8	↓
								0.4mg	15.5	↓
				DAT [l]	Divided attention	Oral	Methadone	5mg	23.5	=
								10mg	47	↓
						Sublingual	Buprenorphine	0.2mg	7.8	↓
								0.4mg	15.5	↓
				UFOV [r]	Divided & selective attention	Oral	Methadone	5mg	23.5	=
								10mg	47	↓
						Sublingual	Buprenorphine	0.2mg	7.8	=
								0.4mg	15.5	↓
				DT [f]	Sustained attention, resilience	Oral	Methadone	5mg	23.5	=
								10mg	47	↓
						Sublingual	Buprenorphine	0.2mg	7.8	=
								0.4mg	15.5	↓
Walker, 2001 [112]	15	Case-crossover, RCT [m]	Double blind	DSST [i]	IP speed [j]	Intravenous	Morphine	2.5mg/70kg	7.5	=
								5mg/70kg	15	=
								10mg/70kg	30	↓
							Butorphanol	0.5mg/70kg	7.5	=
								1mg/70kg	15	↓
								2mg/70kg	30	↓
							Nalbuphine	2.5mg/70kg	7.5	=
								5mg/70kg	15	=
								10mg/70kg	30	↓
Zacny, 2007 [113]	16	Case-crossover, RCT [m]	Double blind	DSST [i]	IP speed [j]	Oral	Hydrocodone + acetaminophen	5mg	6	=
								10mg	12	↓
							Oxycodone + acetaminophen	5mg	7.5	=
								10mg	15	↓

[a] Dependent variable. [b] Route of administration. [c] Oral morphine equivalent units, calculated using Nielsen et al.'s conversion scale [61]. [d] Study included 2 groups (middle-aged, older adults); results for the middle-aged group (18-55 years) are summarised here. [e] Simple reaction time. [f] Choice reaction time. [g] Symbol Digit Modalities Test. [h] Sustained Attention Test. [i] Digit Symbol Substitution Task. [j] Information processing speed. [k] Rapid Visual Information Processing task. [l] Divided Attention Test. [m] Randomised controlled trial. [n] Digit Span test. [o] Trail Making Test, version A. [p] Critical Flicker Fusion Task. [q] Psychomotor Vigilance Task. [r] Useful Field of View test.

Executive functions. Executive functions (EF) are high-level cognitive abilities that underlie complex cognitive, social, and emotional processes [103]. EF comprise four components, which are volition, planning and decision-making, purposive action, and effective performance [103]. Together, these components enable individuals to self-identify needs, develop goals, formulate and enact plans, and efficiently complete steps in these plans. Volition relies on self-awareness and motivation, and describes intentional behaviours such as formulating goals to achieve self-identified needs [103]. The second component, planning and decision-making, involves identifying steps and materials required to achieve goals, pre-empting difficulties and developing contingencies [103]. Planning is often assessed via tower tests (e.g., the Tower of London) that involve planning sequences of moves, while decision-making can be measured via risk-taking tasks (e.g., the Iowa Gambling Task) [103, 107]. The third EF component, purposive action, is the ability to translate plans into activities via initiation and maintenance of complex behaviours [103]. Finally, effective performance is the ability to monitor and adapt behaviour to achieve goals efficiently [103]. In the pain and opioids literature, most EF tasks assess planning and decision-making, while volition, purposive action, and effective performance are seldom, if ever, assessed.

Compared with other cognitive functions, relatively few studies have examined the acute effects of opioids on tasks of executive functions in humans (Table 1.9). One study, which examined the effects of acute administration of oxycodone on tasks assessing risk-taking and inhibitory control in healthy, opioid-naïve individuals (n=12), reported no impairing effects from 70–120 minutes post-consumption [114]. This was true even after administration of oxycodone at relatively high doses (30mg OME) [114].

Table 1.9. *The dose-dependent effects of opioids on tasks assessing executive functions in healthy, naive individuals*

Authors	N	Design	Blinding	Task	DV [a]	ROA [b]	Opioid type	Opioid dose	OME [c] (mg)	Score vs. placebo
Zacny, 2009 [114]	12	Case-crossover, RCT [d]	Double blind	DPD [e]	Risk-taking	Oral	Oxycodone	5mg	7.5	=
								10mg	15	=
								20mg	30	=
				BART [f]	Risk-taking	Oral	Oxycodone	5mg	7.5	=
								10mg	15	=
								20mg	30	=
				Go/No-Go Task	Inhibitory control	Oral	Oxycodone	5mg	7.5	=
								10mg	15	=
								20mg	30	=
				Stop Task	Inhibitory control	Oral	Oxycodone	5mg	7.5	=
								10mg	15	=
								20mg	30	=

[a] Dependent variable. [b] Route of administration. [c] Oral morphine equivalent units, calculated using Nielsen et al.'s conversion scale [61]. [d] Randomised controlled trial. [e] Delay and Probability Discounting task. [f] Balloon Analogue Risk Task.

Working memory and memory. Memory refers to the short- or long-term ability to store and retrieve information. It is generally thought to comprise at least three domains: working memory, recognition, and episodic memory. Working memory refers to the ability to 'hold' information while manipulating it (e.g., remembering a telephone number while you dial it), recognition refers to the ability to recognise pre-learned information, and episodic memory relates to the ability to associate a particular event or memory with a specific place and time [103, 107]. Working memory (WM) is arguably distinct from other aspects of memory function. It is closely linked to attention and is often assessed via attention tasks (e.g., backwards trials in the Digit Span Test) [103, 107].

Acute administration of opioids has not been found to reliably predict performance deficits for tasks assessing working memory and memory, even at relatively high doses (Tables 1.10 & 1.11). Broadly, tasks assessing working memory (WM) function are more consistently impaired than recall and recognition tasks, indicating that opioids may affect information manipulation rather than storage and retrieval processes [110].

Table 1.10. *The dose-dependent effects of opioids on tasks assessing working memory in healthy, naive individuals*

Authors	N	Design	Blinding	Task	DV [a]	ROA [b]	Opioid type	Opioid dose	OME [c] (mg)	Score vs. placebo
Cherrier, 2009 [108]	35 [d]	Case-crossover, placebo, pre-post	Double blind	Alphabet and Number Sequencing	WM [e]	Oral	Oxycodone	10mg	15	=
Friswell, 2008 [110]	18	Case-crossover, RCT [f]	Double blind	DS, backwards trials [g]	WM [e]	Oral	Morphine	10mg	10	=a
							Oxycodone	5mg	7.5	=a
				TMT B [h]	WM [e]	Oral	Morphine	10mg	10	=
							Oxycodone	5mg	7.5	=

[a] Dependent variable. [b] Route of administration. [c] Oral morphine equivalent units, calculated using Nielsen et al.'s conversion scale [61]. [d] Study included 2 groups (middle-aged, older adults) – this summarises results for the middle-aged group (18-55 years). [e] Working memory. [f] Randomised controlled trial. [g] Digit Span test. [g] Trail Making Test, version B.

Table 1.11. *The dose-dependent effects of opioids on tasks assessing memory in healthy, naive individuals*

Authors	N	Design	Blinding	Task	DV [a]	ROA [b]	Opioid type	Opioid dose	OME [c] (mg)	Score vs. placebo
Cherrier, 2009 [108]	35 [d]	Case-crossover, placebo, pre-post	Double blind	Word List Test [e]	Immediate & delayed verbal recall	Oral	Oxycodone	10mg	15	↓ (delayed recall); = (intrusions)
Friswell, 2008 [110]	18	Case-crossover, RCT [f]	Double blind	Verbal prose recall [g]	Immediate & delayed recall	Oral	Morphine	10mg	10	=
							Oxycodone	5mg	7.5	=
				Complex figure recall	Immediate & delayed visual recall	Oral	Morphine	10mg	10	=
							Oxycodone	5mg	7.5	=
				Source memory	Episodic memory	Oral	Morphine	10mg	10	=
							Oxycodone	5mg	7.5	=
O'Neill, 2000 [111]	8	Crossover RCT [f]	Double blind	Word recall	Immediate & delayed verbal recall	Oral	Dextropropoxyphene napsylate	100mg	10	=
							Morphine sulphate	10mg	10	↑ (4h, 16h, 30h)
				Word recognition	Delayed verbal recognition	Oral	Dextropropoxyphene napsylate	100mg	10	=
							Morphine sulphate	10mg	10	=
				Picture recognition	Delayed visual recognition	Oral	Dextropropoxyphene napsylate	100mg	10	↓ (12h, 26h, 30h, 36h)
							Morphine sulphate	10mg	10	=
				Memory scanning	WM [h] retrieval	Oral	Dextropropoxyphene napsylate	100mg	10	=
							Morphine sulphate	10mg	10	= (↓ at 12h, 16h)

[a] Dependent variable. [b] Route of administration. [c] Oral morphine equivalent units, calculated using Nielsen et al.'s conversion scale [61]. [d] After co-varying weight. [e] Based on the Rey's Auditory Verbal Learning Test and the Hopkins Verbal Learning Test. [f] Randomised controlled trial. [g] Prose recall sub-test of the Rivermead Behavioural Memory Test. [h] Working memory.

Chronic opioid effects in the context of CNCP

Understanding the cognitive effects of opioids in healthy individuals may help to elucidate drug effects. However, it largely ignores complexities that surround real-world use. In Australia, even weak opioids (e.g., codeine) must be prescribed by a doctor. As such, their use is largely limited to people with chronic health conditions, who may be affected by co-morbid factors (e.g., pain, mood disorders) that are also known to impact cognitive function. For this reason, it is important to examine the effects of opioid use specifically within the context of chronic use for CNCP. As the present thesis is focused on the effects of opioids on cognitive function in those with CNCP rather than CCP, the literature on cognitive function in people who are prescribed opioids for CCP will not be reviewed here.

Methodologies for assessing cognitive function in people with CNCP. Numerous methodologies have been used to assess cognitive function in people who take opioids for CNCP long-term. Case-control studies have been used to compare cognitive performance between a group of people who take opioids for CNCP and a control group, generally comprised of healthy people or opioid-free people with CNCP (i.e., comparable controls) [115, 116]. Case-control studies may recruit people who already take opioids, or may include participants who have initiated opioid therapy as part of the study. By contrast, case-crossover studies generally compare cognitive performance in the same individuals with CNCP under different opioid regimes (e.g., IR- versus SR-formulations). Finally, relatively few studies have used longitudinal and cohort designs to compare cognitive performance in the same individuals across time [117-119]. These studies assessed changes in cognitive function from opioid-free baseline to multiple follow-up time points, to determine whether performance changes with chronic opioid therapy.

In addition to study design, the pain and opioids literature has multiple different modes for assessing cognitive function. Most studies assess cognitive performance via objective cognitive tasks that assess one or more dimension of cognition (e.g., attention, working memory). However, some studies also include subjective measures of cognition, such as the Mini Mental State Exam. In the context of a laboratory-type study, these measures are not

considered to be as accurate as objective cognitive tasks, but may be useful in certain situations. Specifically, they are generally quick to administer, portable, and can provide a broad indication of real-world cognitive function. Newer scales, such as the Patient Reported Outcome Measurement Information System (PROMIS) battery of cognitive function scales, may be particularly useful in study designs that aim to examine multiple clinical characteristics of a large sample of people with CNCP, including studies that are administered online.

Objective cognitive task performance. Chapter 3 (Study 1) comprises a systematic review and meta-analysis of the available data on objective cognitive task performance in individuals prescribed opioids for CNCP. Given this, a detailed description of objective cognitive task performance for specific domains will not be provided here. To briefly review, several cross-sectional and case-control studies have reported performance deficits on tasks assessing IP speed and complex attention for individuals on stable opioid doses for CNCP, compared with healthy controls [115, 116]. In the same populations, consistent impairments have not been noted for executive functions or memory. When compared with 'pain' controls (i.e., individuals who experience pain but do not use opioids), people with CNCP who are prescribed strong opioids have not evidenced consistent deficits across tasks assessing attention, executive functions, and memory [115, 116]. Together, these results indicate that opioids may produce impairment in specific cognitive functions (i.e., attention and information manipulation), but that this effect appears to dissipate with chronic use. Cognitive impairment noted in individuals with CNCP may be related to frequently co-morbid factors (e.g., pain, mood disorders), explaining the lack of consistent evidence for opioid-related impairment between CNCP groups.

While case-control and cross-sectional studies offer some insight into the effects of opioids on cognitive function, longitudinal studies (e.g., pre-post studies) can better account for inter-individual variables that may affect cognitive function. However, there are surprisingly few studies assessing cognitive performance in people with CNCP before commencement of opioid therapy and after dose stabilisation [92, 117-121]. Of these, even fewer studies have assessed cognitive performance more than two months' post-treatment commencement [117-

119], when opioid dose is stabilised and tolerance effects are more likely to have developed. These studies have reported no impairment across time from baseline to 3-, 6-, or 12-month follow-up, with either stable or improved performance for tasks assessing IP speed, attention, executive functions, working memory, verbal fluency, and verbal recall [117-119]. These results bolster arguments that opioid-induced impairments dissipate with chronic, stable dosing, and that cognitive impairments in CNCP cohorts likely relate to other co-morbid factors. Improved task performance is thought to relate either to indirect effects of opioids (e.g., reductions in pain), but may relate to practice effects (i.e., due to task familiarity upon repeat administrations of the same task) [117-119].

Cognitive effects of co-morbid factors in CNCP

Understanding the unique effects of opioids on cognitive and behavioural outcomes is complicated by the range of comorbid factors that also impact functioning. Firstly, pain itself is known to impair cognition, with numerous chronic pain conditions linked to performance deficits on tasks assessing working memory, attention, and executive functions [122-124]. Other factors can also predict performance deficits (e.g., sleep and mood disorders, concomitant medications) [125-127] in individuals with CNCP. Key co-morbidities and their inter-related effects on functioning are reviewed below.

Chronic pain. Cognitive impairment is a common complaint among people who experience chronic pain. The presence of objective deficits is now well established in scientific literature. In quasi-experimental research, CNCP patients have been shown to display poorer performance compared with healthy controls on a range of tasks assessing attention, executive function, working memory, and recall [122-124, 128, 129]. While this effect is not consistent across all cognitive domains (e.g., mental flexibility appears to be unaffected) [129], cognitive impairment appears to be common across specific pain conditions (e.g., migraine, fibromyalgia) [123, 128, 130] and pain types (e.g., neuropathic pain, regardless of aetiology) [131]. Taken

together, these results indicate that the experience of pain, rather than specific underlying conditions, has the potential to broadly impair cognitive function.

The neural bases for the cognitive effects of pain are complex, reflecting both structural changes in the CNS and competing demands for limited cognitive resources. While this is a relatively new field of research, there is growing evidence that many chronic pain conditions are associated with structural changes in the CNS [132]. In particular, chronic pain affects areas that modulate pain, including the prefrontal cortex and amygdala [132]. In addition to these structural changes, perceptual load theories argue that pain has a strong cognitive-affective component and requires considerable neural resources (i.e., attention) to process and respond to pain [133-135]. This hypothesis may explain the results of the studies outlined in the paragraph above. Additionally, this phenomenon is supported by the findings of several functional imaging studies that have noted decreased activation of pain-related brain regions (e.g., the affective region of the anterior cingulate cortex) when individuals are distracted from pain via cognitive tasks (e.g., the Stroop task) [136].

Fibromyalgia and cognitive function. Fibromyalgia is a nociplastic pain condition characterised by widespread musculoskeletal pain, fatigue, and stiffness [137]. Memory impairments, also known as "fibro-fog", are very common among people with fibromyalgia [138]. Notably, while chronic pain itself is linked to cognitive dysfunction, impaired cognition appears to be more prevalent among people with fibromyalgia than those with other CNCP conditions [139]. For example, a seminal study examined cognitive complaints among people with rheumatism with (*n*=57) and without (n=57) [139]. The authors reported that people with fibromyalgia were more likely to report problems with memory, speech, and mental confusion than those without fibromyalgia [139]. The mechanism behind this effect is not clearly understood, but likely reflects fibromyalgia-related structural changes in the CNS (e.g., reduced grey matter volume) [140, 141].

Mental health conditions. Many people with a CNCP condition also experience mental health conditions or high levels of psychological distress [8, 142]. This likely relates to

structural changes in the CNS. Specifically, many of the cortical regions that are associated with pain modulation are also linked to emotional processing, and changes in these areas may produce negative affective states [132, 142]. Mental health conditions may also relate to the physical limitations that often come alongside chronic non-cancer pain, as well as related factors such as loss of employment and mobility [8, 142]. Notably, depression and pain appear to have a reciprocal relationship [142]. Specifically, the experience of pain can predict the onset of depression, while depression can in turn worsen or extend the duration of pain symptoms [142].

Mental health conditions are associated with cognitive complaints and objective impairments. For example, a seminal study examined the relationships between chronic pain, co-morbid factors and cognitive complaints Over half (54%) of participants reported experiencing any cognitive difficulties (e.g., forgetfulness). Both depression and pain-related anxiety had moderate, positive correlations with cognitive complaints, and depression explained a large and unique proportion of variance in the experience of cognitive failures [143]. Similarly, numerous studies have shown that people with depression perform more poorly than people without these conditions on objective cognitive tasks assessing information processing, working memory, and attention [144, 145]. A recent study found that these deficits endured even with treatment with antidepressants [145].

Concomitant use of medicines and other drugs. People who take opioids for CNCP may also use other substances. These include medical and extra-medical use of pharmaceuticals, alcohol, tobacco, and illicit drugs (e.g., cannabis) [8]. Some of these substances are psychoactive, and can produce independent and synergistic cognitive effects that are often similar to those of opioids (e.g., sedation, mental 'cloudiness') [146, 147]. Psychoactive medicines are of particular concern as these are often prescribed for adjunct pain relief (e.g., gabapentinoids) or to help manage co-morbidities like mental health conditions (e.g., benzodiazepines, anti-depressants).

Key points

Cognitive impairment underlies many of the behavioural harms (e.g. impaired driving ability) related to chronic opioid use in people with CNCP. In healthy people, acute administration of opioids is associated with impairment in numerous key functions. The cognitive effects of opioids may dissipate as drug tolerance occurs, but the intermediate (4 weeks–12 months) and long-term (>12 months) effects of opioids are relatively poorly understood.

People with CNCP commonly experience co-morbid factors (e.g., mood disorders) that can also impact cognition. Currently, not enough is known about the unique effects of opioids and the synergistic effects of opioids and comorbid factors. Understanding the prevalence of cognitive impairment and the role of co-morbid factors has implications for clinical practice. In particular, if long-term opioid use is associated with cognitive impairment, clinicians may consider adding routine cognitive screening to routine medication reviews. Additionally, understanding relevant co-morbid factors would help clinicians to identify patients at risk of cognitive impairment in the early stages of treatment.

Thesis programme and rationale

Since the 1990s, prescribing of pharmaceutical opioids for chronic non-cancer pain (CNCP) conditions has substantially increased. While opioids have an important clinical role for pain management, their use for CNCP pain remains controversial. Academics and healthcare professionals have expressed concern that increased prescribing may be associated with a rise in opioid-related harms. Notably, many of these harms (e.g., involvement in motor vehicle collisions, experience of physical injuries) relate to the cognitive effects of opioids. These cognitive and behavioural harms are relatively poorly understood among people who take opioids chronically for CNCP, with a dearth of literature examining factors such as duration of use and dose on cognitive outcomes. To this end, the present thesis examined cognitive deficits and behavioural outcomes (e.g., physical injuries) associated with the use of pharmaceutical opioids, with a focus on chronic use among people with chronic non-cancer pain (CNCP).

Research questions

The thesis was guided by five key research questions relating to pharmaceutical opioid use and risk of cognitive and behavioural harms, including objective cognitive performance, cognitive complaints, physical injuries, perceptions of driving impairment and driving-related behaviours, and population-level harms. The research questions were:

1. Do people who take opioids for CNCP evidence objective performance deficits on cognitive tasks, compared with opioid-free controls (healthy or with CNCP) or opioid-free baseline?

2. What is the relationship between duration of opioid use and cognitive function among people with CNCP? Does cognition continue to change over time with chronic use?

3. Among people who take opioids for CNCP, is opioid dose positively correlated with harms such as cognitive dysfunction and physical injuries?

4. Are people with CNCP aware of opioid-related driving risks and what are their real-world driving behaviours? What factors are associated with risk perceptions?

a. To what extent are people with CNCP aware of driving-related risks and other side effects, and does this differ by opioid use status? Where do people source this information?

b. Do people take precautions when driving with regards to opioid use?

c. Do people with CNCP perceive DUI of opioids to be less risky than for alcohol (over the limit), and does this differ by opioid use status?

d. What factors are associated with perceived risks of opioid DUI?

5. At the population level, is increased prescribing of opioids associated with a higher rate of opioid-related motor vehicle collisions?

Thesis structure

The thesis begins with an introductory chapter (Chapter 1) outlining: the prevalence, aetiology, and treatment of CNCP; opioid pharmacology and the use of opioids for CNCP in the Australian context; harms associated with opioid use, including overdose, physical injuries, and driving-related harms; the acute and chronic effects of opioids on cognitive performance; and relevant co-morbid factors that may predict poor outcomes in people with CNCP.

Chapter 2 outlines the results of a systematic review and meta-analysis (*Study 1*) that examined objective cognitive performance in people prescribed opioids for CNCP (Table 1.12). The study had two primary aims: i) to determine whether people with chronic use of opioids for CNCP evidence objective cognitive deficits compared with people who are opioid-free (healthy or with CNCP), and ii) to examine changes in cognitive function from opioid-free baseline to follow-up (*Research Question 1*). A secondary aim was to examine the effects of opioid dose on cognitive function (*Research Question 3*), via a series of meta-regressions. Chapter 3 complements the findings of Chapter 2. It presents a longitudinal study (*Study 2*) that assessed cognition in people who take opioids for CNCP compared to opioid-free controls with CNCP and over time. The study aimed to examine the main and interactive effects of Time (baseline, 3 months) and Group on objective cognitive performance (*Research Questions 1* and *2*).

Table 1.12. *Thesis research questions, topic overview, and relevant chapters*

Research question	Topic	Relevant chapters
1	Objective cognitive performance in people taking opioids for CNCP versus opioid-free controls	2, 3
2	Association between duration of use and cognitive performance in people taking opioids for CNCP [a]	2, 3, 4
3	Relationship between opioid dose and cognitive and behavioural harms in people with CNCP	2, 4
4	Knowledge of driving-related risks and other side effects, sources of information, driving behaviours, and factors associated with perceived risks of driving after taking opioids among people with CNCP	5
5	Prevalence of opioid-related motor vehicle collisions with increased opioid prescribing	6

[a] This includes pre-post (i.e., opioid-free baseline versus follow-up) and longitudinal designs, and designs comparing intermediate- versus long-term consumers.

Chapter 4 presents the results of a cross-sectional survey (Study 3) that examined the associations between opioid dose and cognitive complaints and physical injuries among people with CNCP. The study aimed to: i) explore the association between opioid dose and frequency of cognitive complaints and physical injuries (*Research Question 3*), ii) compare the frequency of cognitive complaints between intermediate- and long-term consumers (*Research Question 1*), and iii) explore the association between cognitive complaints and physical injuries.

Chapter 5 details a cross-sectional survey (*Study 4*) that aimed to examine knowledge of driving-related impairment and other side effects, real-world driving behaviours (including safety precautions), and perceptions of risk for driving after taking opioids (including associated factors) among people with CNCP (*Research Question 4*). The study described in Chapter 6 (*Study* 5) aimed to determine whether opioid-related motor vehicle collisions (MVC) have increased alongside increased prescribing (*Research Question 5*). The study examined rates of opioid detections in samples from Tasmanians involved in serious MVC from 2008–2016.

Chapter 7 presents a general discussion that synthesises the findings from each included study and summarises the thesis strengths and limitations. This chapter also outlines recommendations for future research programs based on the findings of the present thesis.

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CHAPTER 2: A SYSTEMATIC REVIEW AND META-ANALYSIS OF COGNITIVE PERFORMANCE AMONG PEOPLE WITH CHRONIC USE OF OPIOIDS FOR CHRONIC NON-CANCER PAIN

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Preface

This chapter presents the findings of a systematic review and meta-analysis examining the cognitive effects of prescription opioid use in people with chronic non-cancer pain (*Study 1*). The study aimed to examine objective cognitive task performance in people who were taking opioids for CNCP, compared with opioid-free controls (*Research Question 1*) or opioid-free baseline (i.e., pre-post) (*Research Question 2*). The purpose of this study was to provide an updated review on this topic. A similar review had not been conducted within the past five years, during which time interest in the potential harmful effects of prescription opioid use has increased substantially. The study also expanded on previous reviews by including realistic inclusion criteria (e.g., by permitting studies in which concomitant medicine use was reported) and multiple comparator groups (healthy controls, opioid-free controls with CNCP), meaning the conclusions drawn here may be more generalizable to real-world opioid use than that of previous studies where, for example, only healthy controls have been included. Finally, the study included an examination of the effect of opioid dose on cognitive performance.

Abstract

Objective

Opioids, often prescribed for chronic non-cancer pain, may adversely affect cognition. Research has not been synthesised in recent years, during which time academic interest has increased. This study presents meta-analyses on cognitive performance in people taking opioids for CNCP.

Methods

We ran systematic literature searches in EMBASE, Medline, and PsycINFO. Eligible studies included people taking opioids for CNCP and an opioid-free group (i.e., case-control) or session (e.g., pre-post), and objective cognitive assessments. Using random-effects meta-analyses, we computed pooled effect sizes for differential task performance for each study design across five domains (motor performance, attention, working memory, executive functions, memory).

Results

Seventeen studies were included. Case-control studies covered 3 control types (healthy, CNCP, taper-off). Pre-post studies were grouped into 5 follow-ups (4–6 and 6–9 weeks; 3, 6, and 12 months). Effect sizes ranged from 0.02–0.62. Cases showed small magnitude impairments in attention and memory compared with healthy controls. Although limited by small sample sizes, there was no clear evidence of impairment in cases compared with opioid-free controls with CNCP. Cases showed some cognitive improvements from opioid-free baseline to follow-up. Effects were strongest for attention and working memory, and were apparent from 4 weeks to 6 months follow-up. Other effects were small and non-significant.

Conclusions

Opioid therapy for CNCP did not worsen cognitive performance and improved it for some domains. People who take opioids for CNCP may evidence deficits in attention and memory, but this is unlikely to translate to global impairment and likely relates to pain more so than opioids.

Introduction

Pharmaceutical opioids, which are among the most commonly-used medicines worldwide, are often prescribed to people who experience chronic non-cancer pain (CNCP) [1, 2]. However, medical professionals have cautioned against the prolonged use of opioid medicines given limited evidence for their long-term analgesic efficacy and the potential for pain escalation or dependence [3-5]. In addition, health professionals and academics have expressed concern about the potential long-term effects of pharmaceutical opioids on cognition.

Concern around the effects of chronic pharmaceutical opioid use on cognitive functioning arises from the known impairing effects following acute administration of opioids in healthy people. Several acute dosing studies have revealed impaired performance for tasks assessing attention (e.g., Divided Attention Test) and information processing (e.g., Digit Symbol Substitution Task) following opioid administration [6, 7]. However, such studies have also highlighted the variability of opioid effects according to factors related to both opioid use (e.g., dose, type, route of administration) and cognition (e.g., domain, task)[6]. A minority of studies have also provided evidence of cognitive enhancement following opioid administration in healthy people [8], potentially reflecting known inter-individual variability in opioid effects [9].

Understanding the cognitive effects of pharmaceutical opioids becomes further complicated when assessing chronic use, particularly as pain itself can interfere with cognitive functioning [10]. Numerous cross-sectional studies have reported impaired performance among individuals prescribed opioids for CNCP, compared with pain-free controls, on tasks assessing attention (e.g., Paced Auditory Serial Addition Test), executive functions (e.g., Trail Making Test – B), and working memory (e.g., Spatial Span test, backwards) [11-13]. However, similar studies have demonstrated no differences between groups on tasks assessing the same functions [14-17]. When noted, impairments are not always unique to people who are prescribed opioids: in several studies, people with CNCP performed more poorly than healthy controls on tasks assessing functions such as attention and working memory, irrespective of their use of opioids [12, 18]. Further, several longitudinal pre-post studies (i.e., before and during opioid therapy)

have noted stable or improved cognitive task performance in people with CNCP at follow-up [8, 19, 20]. These findings align with the results of a systematic review that reported impairing effects were most apparent in opioid-naïve individuals and patients who had recently initiated therapy or changed dose (i.e., in the past few days) [21].

While this research area has received increased interest in recent years, current understandings of the effects of chronic opioid use on cognitive performance among people with CNCP are currently limited. One recent review compared cognitive outcomes among people with CNCP, all treated with opioid or non-opioid medicines only [22]. However, this review excluded studies that used healthy, opioid-free controls. A hand search of key databases (e.g., PubMed) located several more recent studies that were not included in this review, likely for this reason [12, 23, 24]. As pain itself can impair cognitive function, it is important to assess cognitive performance among people who use opioids for CNCP compared to controls who are both pain- and opioid-free (i.e., healthy). This would help to differentiate the effects of pain from those of opioids. Given this, as well as an increase in academic and prescriber interest in this topic in recent years, an updated review is timely.

This study aimed to compare objective cognitive task performance for i) people who report chronic pharmaceutical opioid use (daily or near-daily use for ≥2 weeks) and two opioid-free control groups, with and without CNCP, respectively; and iii) people with CNCP before and after tapering off chronic opioid therapy. We also aimed to determine whether deficits differed according to cognitive domains and opioid dose. Cognitive domains of interest were motor performance, attention, working memory, executive functions, and memory.

Methods

Study protocol

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, which can be found in Supplementary Table 2.1 [25]. The protocol was registered with PROSPERO (#CRD42018118170).

Eligibility criteria

Study inclusion and exclusion criteria were developed in accordance with the PICOS (Participant, Intervention, Comparator, Outcome, Study design) model. Studies were eligible for inclusion if they met the following criteria: 1) used a case-control, case-crossover, cohort (≥ 2 time points), or randomised control trial design; 2) included a group of individuals taking opioid medicines for CNCP for ≥ 2 weeks; 3) included a control group or assessment when cases were opioid-free (post-taper or pre-therapy) or on low opioid doses used as needed (i.e., pro re nata, or p.r.n.); 4) where included, the control group was i) healthy controls or ii) people who experienced CNCP but were opioid-free (including people who tapered off opioids during the study); 5) included outcome measures for an objective test of at least one cognitive domain of interest; 6) provided sufficient details to calculate effect sizes for cognitive outcomes (e.g., mean, standard deviation, or values for F or p); 7) reported dose in oral morphine equivalence (OME) or included sufficient details to calculate OME dose; 8) included details of timelines for follow-up sessions; and 9) reported sampling method details.

Studies were excluded if they met any of the following criteria: 1) comprised a review article, editorial, or abstract-only articles; 2) the case group included people with cancer pain; 3) a control group or low/no-opioid assessment was absent or inappropriate (e.g., cognitively impaired); 4) cognitive outcomes were subjective (e.g., self- or clinician-reported measures); 5) the control group included people prescribed opioids (i.e., cases were not distinct from opioid-free controls); 6) non-medical opioid use was included; 7) the case group included people with

or being treated for an opioid use disorder; 8) the study was published prior to 2000; 9) the study assessed paediatric populations (i.e., <18 years); 10) the case group comprised people with a significant neurological disorder or known cognitive impairment; 11) the study included non-human subjects. There were no exclusion criteria regarding concomitant use of psychoactive medicines (e.g., antidepressants), as polypharmacy is common among people with CNCP [26]. Articles in a language other than English were screened for suitability after translation via Google Translate.

Search strategy and data extraction

Relevant articles were identified via a comprehensive literature search of three databases, with the last search conducted on 7 January 2019 via the OVID platform: EMBASE, Medline, and PsycINFO. Text words and MeSH (Medline, PsycINFO) and Emtree (EMBASE) terms were used for each database (see Supplementary Table 2.2 for the example search strategy). Terms related to three concepts of interest: 1) chronic non-cancer pain; 2) pharmaceutical opioids; 3) cognitive function, combined using the 'and' operator. A manual search of the reference lists of review articles identified via the literature search was conducted to identify additional studies. Duplicates were removed prior to abstract screening. One reviewer (JA) conducted a title and abstract screening of all citations using Covidence systematic review software [27]. A second reviewer (RB) conducted a screen of 10% of those articles rejected based on title and abstract. Two reviewers (JA, RB) independently reviewed full texts. Disagreements were resolved via discussion and consultation with a third reviewer (AP).

Two reviewers (JA, ML) extracted data from eligible studies, including participant demographics (age, sex, intelligence, education), information on pain (duration, condition) and opioid use (duration, frequency, dose, type, duration of action), substance use (e.g., alcohol), cognitive tasks and outcomes, and key findings (Supplementary Table 2.3). Cognitive tasks were grouped according to domain as motor performance, attention, working memory, executive functions, and memory (Table 2.1), in accordance with Lezak et al.'s classification of

neuropsychological tasks [28]. Some attention tasks assess multiple domains, and may be classified differently across studies. For example, some previous studies have classified the Digit Symbol Substitution Test and reaction time tests as measures of processing speed [29, 30]. We included tasks as attentional where the outcome reported in the original work most closely aligns with measuring attention.

Table 2.1. *Cognitive tasks used in included studies, with abbreviations, by cognitive domain*

Domain	Task	Abbreviation
Motor performance	Grooved Pegboard Test	GPT
	Test for Motor Co-Ordination (2-Hand)	2-Hand
	9 Peg Hole Test	9 Peg
	Finger Tapping Test	FTT
Attention	Trail Making Test A	TMT A
	Conner's Continuous Performance Test-II	CCPT-II
	Test of Variables of Attention	TOVA
	Digit Symbol Substitution Test	DSST
	Test for Reaction Time Under Pressure [a]	DT
	Attention Test [a]	COG
	Test for Visual Orientation, Tachitoscopic Perception [a]	TAVT
	Vigilance Test [a]	VIG
	Digit Span Test, forwards	DST, forwards
	Choice Reaction Time	Choice RT
	Paced Auditory Serial Addition Test	PASAT
	Reaction Time	RT
	Stroop task [b]	Stroop
	In-town driving	–
	Highway destination driving	–
	Evasive action RT	–
	D2 Test of Attention	D2
	Rural driving test	–
	Urban driving test	–
	Corsi's Block Tapping/Spatial Span test, forwards	CBT/SST, forwards
	Useful Field of View [a]	UFOV
Working memory	Corsi's Block Tapping/Spatial Span test, backwards	CBT/ SST, backwards
	Digit Span Test, backwards	DST, backwards
	Wechsler Adult Intelligence Scale-III A/B (number forwards & backwards)	WAIS-III B
	Wechsler Adult Intelligence Scale-III C (letter-number-combination)	WAIS-III C
Executive functions	Cambridge Gambling Task	CGT
	Go/NoGo	–
	Stockings of Cambridge/FAS Test	SOC/FAS
	Verbal Fluency Test	VFT
	Trail Making Test B	TMT B
	Wisconsin Card Sorting Test	WCST
Memory	Delayed Matching to Sample	DMS
	Paired Associate Learning	PAL
	Pattern Recognition Memory	PRM
	Spatial Recognition Memory	SRM
	California Verbal Learning Test-II	CVLT-II
	Rey's Auditory Verbal Learning Test	RAVLT
	Hopkins Verbal Learning Test	HVLT
	Free and Cued Delayed Selective Reminding Test	FCDSRT
	Rey Complex Figure Test	RCFT

[a] These tests are available from the Schuhfried Vienna Test System [31]. [b] The Stroop task comprised the word, colour, and interference sub-tests; see Tassain et al. [8]. [c] The Rey Complex Figure Test comprised immediate and delayed recall sub-tests and a recognition sub-test; see Menefee et al. [32].

Risk of bias

Risk of bias assessment was conducted by one reviewer (JA) via three scales for differing study designs. Case-control and cohort studies were assessed via two adapted versions of the Newcastle-Ottawa scale [33], while case-crossover studies were examined via a revised version of the Cochrane risk-of-bias tool for randomized trials (RoB 2) [34].

Statistical analyses

We ran univariate meta-analyses for each of the five cognitive domains within each design (case-control: healthy, pain, taper-off controls; pre-post: 4–6 and 6–9 weeks, and 3, 6, and 12 months follow-up). Where longitudinal studies included a control group, data were included in both pre-post (case group) and cross-sectional (case and control groups) analyses. For two studies with multiple follow-up sessions, the follow-up session closest to 9–12 weeks was selected for inclusion in case-control analyses. See Supplementary Table 4 for more information. Where one study in a given analysis reported multiple outcomes, the mean effect size was calculated in Comprehensive Meta-Analysis (CMA) version 3.3.070 [35]. See Supplementary Tables 5 and 6 for individual effect sizes for each study.

Analyses were conducted in CMA using a random-effects model [35]. Pooled effect sizes were calculated as Hedges' g, and forest plots were obtained. Moderate magnitude effects (≥0.40) were considered meaningful and interpreted. Publication bias was assessed via a funnel plot. Study heterogeneity was assessed via Cochran's Q and I^2 statistics. I^2 values were interpreted as low (25%), moderate (50%), and high (75%) heterogeneity [36].
In addition to meta-analyses, we planned meta-regressions for each cognitive domain to examine the effect of opioid dose on task performance. Dose was calculated according to study design. For case-control analyses with opioid-free controls, raw doses for the opioid group were extracted. In one study where controls were a taper-off group [37], dose was calculated as the difference between doses in the case and control groups. For longitudinal analyses with a baseline opioid dose of 0mg (i.e., opioid-free) [8, 17, 19, 20, 38], dose at follow-up was carried

forward. Finally, two longitudinal studies had the primary aim of examining performance before and after transition from one opioid to another (e.g., immediate- to sustained-release) [32, 39]. Dose did not substantially change at follow-up (<10mg OME change) and was carried forward as dose at follow-up. However, due to the small number of studies in each analysis, meta-regressions could only be conducted for cross-sectional studies with i) healthy controls (motor performance, attention), and ii) opioid-free controls with CNCP (attention).

Results

Study characteristics

After excluding duplicates, 2,669 articles were retrieved. 18 papers across 17 studies were included in analyses (Figure 2.1). Most studies were conducted in continental Europe (*n*=9), the United States (*n*=7), and Scotland (*n*=1; Table 2.2). The most common design was case-control (*n*=9; five cross-sectional, four prospective; four used matched pairs), with fewer studies using cohort (*n*=5; four prospective, one retrospective), case-crossover (*n*=2; both prospective), and randomised control (*n*=1) designs. Prospective and retrospective studies reported intervals of 1–12 months between sessions, and 1–12 months from first to last session. Most studies assessed attention (*n*=16; Table 2.1), with fewer studies assessing executive functions (*n*=9 studies), motor performance (*n*=9 studies), memory (*n*=8), and working memory (*n*=3).

Figure 2.1. *PRISMA flow chart for study screening and inclusion*
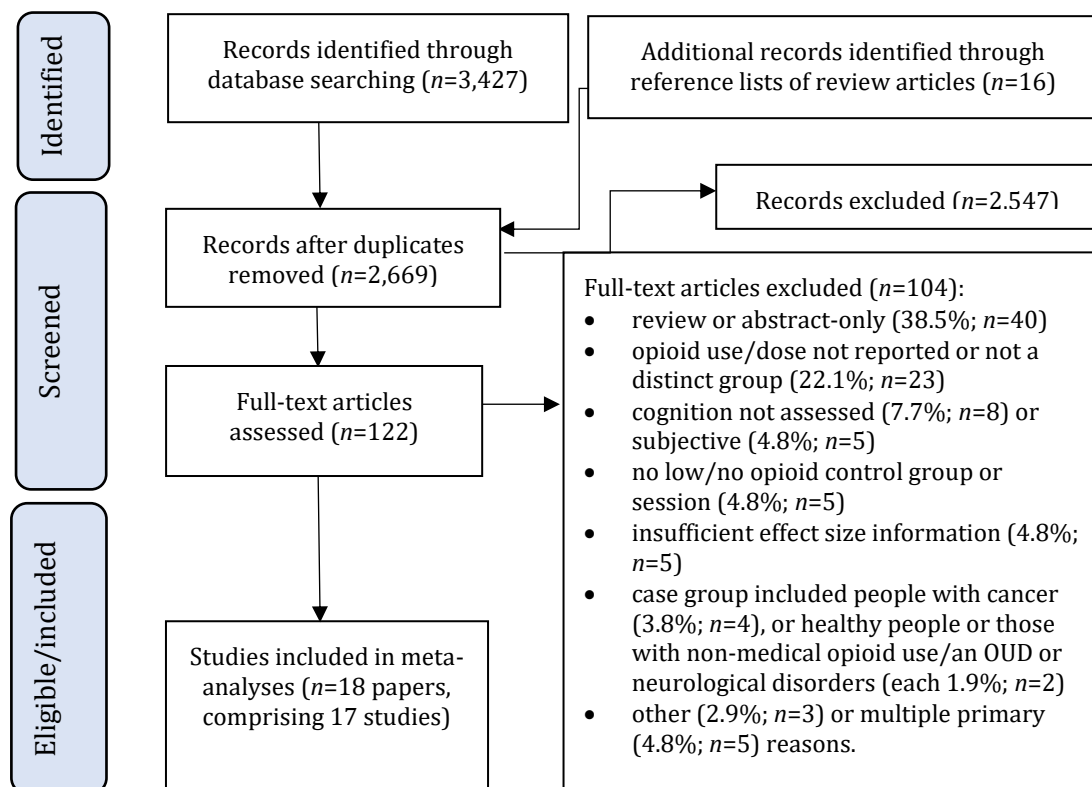
Case and control group sample sizes. The final sample (n=1,266) comprised mostly cases (n=639; n=631 after exclusion of intent-to-treat participants) and healthy controls (n=487, eight studies), with relatively fewer opioid-free controls with CNCP (n=125, five studies) and controls who tapered off opioids (n=15, one study). Sample sizes ranged from 21– 144 participants, including 18–144 cases, 20–90 healthy controls, 10–33 opioid-free controls with CNCP, and 15 taper-off controls.

Assessment of opioid use. The studies assessed 11 opioid drugs, including immediate- and sustained-release formulations (Tables 2.2–2.4). Most studies (n=10) reported inter- individual variation in opioid type or use of multiple opioids by individual participants, and most (n=14) included details of opioid dose and type. The remaining studies expressed opioid doses in OME milligrams, and did not specify opioid dose or type. Opioid-treated individuals reported mean opioid doses of 16–345.8mg OME/day, and treatment duration ranged from approximately 4 weeks to 6.6 years.

Assessment of pain severity and duration. Pain duration (mean or median) was reported for 10 studies, and, among studies that included a range (n=7), ranged from 2 months to 57 years. Reporting of pain severity was somewhat better than for pain duration, with 16 out of 17 studies describing recent pain for at least one group or time point. Included studies reported pain (mean or median) via numerical rating scales (0–10, n=9 studies), visual analogue scales (0–10, n=1; 0–100, n=4; 15cm, n=1), and the Brief Pain Inventory (0–10, n=1). Most studies reported current (n=8 studies) or past 24 hour pain (n=3), with fewer studies reporting past week or 'usual' pain (n=1 each). Three studies did not report the time period for pain ratings. Due to substantial variation in the assessment of pain severity, pain ratings are not reported here.

Table 2.2. *Characteristics of included case-control studies*

Study	Country	Design overview	Session times	Control type and n (% Female)	Case n (% Female)	Pain type	Pain duration	Opioid type/s	ROA	Mean OME/day	Frequency of use	Opioid use duration
Baldacchino 2015, Baldacchino 2018	Scotland	Cross-sectional; male Ps with CNCP on a stable opioid regimen were compared with healthy controls at one time	N.A.	HC=28 (0.0%)	28 (0.0%)	CNCP	Not reported	Tramadol, codeine, tramadol + codeine	Oral	59.1mg	Not reported	Mean: 5 years
Block 2014	U.S.A.	Cross-sectional; Ps with CNCP on a stable opioid regimen were compared with Ps with CNCP and no opioid use and healthy controls at one time	N.A.	P/NO=30 (63.3%); HC=30 (56.7%)	30 (76.7%)	Nociceptive or musculoskeletal	6mnths-1yr=3.3%; 1-3yrs=20.0%; 3-5yrs=3.3%; 5-10yrs=30.0%; >10yrs=43.3%	Hydrocodone, oxycodone, morphine sulfate, tapentadol, tramadol (all IR)	Oral	66.7mg	Not reported	Mean: 48.1 months
Byas-Smith 2005	U.S.A.	Prospective; Ps on stable opioid regimen were compared with healthy controls at one time	N.A.	P/NO=11 (54.5%); HC=50 (54.0%)	21 (52.4%)	Not reported	Not reported	Hydromorphone, methadone, morphine SR, oxycodone, propoxyphene, hydrocodone, tramadol, codeine	Not reported	118.0mg	Not reported	Not reported
Dagtekin 2007	Germany	Prospective, matched pairs; Ps with CNCP on stable doses of transdermal buprenorphine compared with healthy matched controls at one time	N.A.	HC=90 (37.0%)	27 (ITT=30, 37.0%)	Low back pain, neuropathic pain, other (n=5)	Median 62 months (range: 2.0-400.0)	Buprenorphine	T/derm	99.0mg[a]	Not reported	Mean: 52 days (range: 14-271)
Gaertner 2006	Germany	Prospective, matched pairs; Ps with CNCP who were on stable doses of SR oxycodone were compared with healthy matched controls at one time	N.A.	HC=90 (23.0%)	25 (ITT=30, 23.0%)	Low back pain, neuropathic pain, miscellaneous (n=5)	Mean 93 months (median 65, range: 5-360)	SR oxycodone	Not reported	114.0mg[b]	Daily	Mean: 62 days (range: 14-990)
Kurita 2018	Denmark	Prospective RCT; as part of an RCT, Ps who were stabilised on opioids were compared with Ps who tapered off	Baseline, ~3wk, 5-6wk, 7-9wk	T-O=15 (40.0%)	20 (75.0%)	Neuropathic +/- nociceptive somatic/visceral, nociceptive somatic/visceral	Mean 11.4 years (median 11, range: 2-25)	Not reported	Oral	Baseline: 220.8; ~3wk: 321.8;	Not reported	Mean: 6.6 years (median 5, range: 1-16)

Study	Country	Design overview	Session times	Control type and n (% Female)	Case n (% Female)	Pain type	Pain duration	Opioid type/s	ROA	Mean OME/day	Frequency of use	Opioid use duration
		their stable opioid dose at baseline (pre-taper) and three follow-ups (post-taper)								5-6wk: 345.8; 7-9wk: 300.8		
Nilsen 2011	Norway	Cross-sectional; Ps with CNCP on stable codeine therapy were compared with CNCP patients who were not using opioids at one time	N.A.	P/NO=20 (65.0%); HC=20 (60.0%)	20 (50.0%)	Musculoskeletal pain, neuropathic pain, abdominal pain, chronic headache	Not reported	IR codeine	Oral	18.0mg[c]	Daily	Not reported
Sabatowski 2003	Germany	Prospective; Ps with CNCP on stable (min. 2 weeks) doses of transdermal fentanyl were compared with healthy matched controls at one time	N.A.	HC=90 (37.0%)	30 (40.0%)	Low back pain, neuropathic pain, other (n=6)	Median 36 months (range: 2-216)	Fentanyl	T/derm	135.0mg[d]	Not reported	Median: 44 days (range: 30-1530)
Schiltenwolf 2014	Germany	Prospective cross-sectional; Ps with chronic back pain on long-term opioid therapy were compared with Ps with chronic back pain not on opioid therapy and healthy controls at one time	N.A.	P/NO=33 (40.0%); HC=25 (75.8%)	37 (59.5%)	Low back pain	Mean 10.3 years	Not reported	Not reported	100.2mg	Daily	Mean: 19.8 months
Sjogren 2005	Denmark	Cross-sectional, matched pairs; Ps with CNCP on long-term oral opioid treatment were compared with CNCP patients without opioids at one time	N.A.	P/NO=21 (76.2%); HC=64 (54.7%)	19 (76.2%)	Somatic, neuropathic, and visceral pain	Median 7 years (range: 0.5-57)	Not reported	Not reported	60.0mg	Not reported	Not reported

P/NO=Controls with chronic pain but no opioids; HC=Healthy controls; T-O=taper-off group (i.e., a group of individuals initially prescribed opioids for chronic pain, who then tapered off their dose); IR=immediate release (i.e., short-acting); SR=sustained release (i.e., long-acting); ITT='intent to treat'. [a] Converted from reported mean of 45.0mcg/hr transdermal buprenorphine using Nielsen et al's guide [40]. [b] Converted from reported mean of 76.0mg/day oxycodone (assumed oral). [c] Converted from reported mean of 180.0mg/day oral codeine. [d] Converted from reported mean of 50.0ug/hr transdermal fentanyl.

Table 2.3. *Characteristics of included cohort studies (pre–post)*

Study	Location	Design	Cohort n (% Female)	N sessions	Session times	Pain type	Pain duration	Opioid type/s	ROA	Mean OME/day	Frequency of use
Francis 2000	U.S.A.	Prospective cohort; Ps were eligible for opioid therapy at baseline, with opioid use not restricted; dose was then stabilised by follow-up	Baseline: 50 (52.0%) ~4wk: 40 (55.0%)	2	Baseline, ~4wk; (M=159.5 days)	Nociceptive, neuropathic, mixed	Mean 7.8 years (range: 0.5-35)	Not reported	Not reported	Baseline: 39.5mg; 4wk: 90.2	Not reported
Freo 2018	Italy	Retrospective cohort; Ps were tested at opioid-free baseline and again after stabilisation on SR tapentadol	21 (47.6%)	3	Baseline, 3m, 6m	Parkinson's Disease-related pain	Not reported	SR tapentadol	Not reported	Baseline: 0mg 3m: 76.5; 6m: 82.5[a]	Daily
Menefee 2004	U.S.A.	Prospective cohort, pre-test post-test; Ps taking <15mg/day oral oxycodone were tested at baseline and after 8 weeks of stable transdermal fentanyl therapy	23 (74.0%)	2	Baseline, 8wk	Degenerative spinal conditions, neuropathic pain	Not reported	Baseline: oxycodone, 8wk: oxycodone, fentanyl	Oral (oxycodone), transdermal (fentanyl)	Baseline: 18mg; 8wk: 16[b]	Not reported
Panjabi 2008	U.S.A.	Prospective cohort; Ps with CNCP 'inadequately' controlled with IR opioids were tested at baseline (no restriction on opioid use) and 4 weeks after initiation of treatment with SR morphine sulfate	84 (51.2%)	2	Baseline, 4wk	Not reported	<1yr (8.3%), 1-5yr (59.6%), >5yr (32.1%)	Baseline: codeine, hydrocodone, methadone, IR morphine sulfate, fentanyl citrate, oxycodone, propoxyphene, tramadol (all IR); 4wk: SR morphine	Oral	Baseline: 52.3mg; 4wk: 59.1	Not reported
Tassain 2003	France	Prospective cohort; Ps with CNCP who stayed on stable morphine doses compared with a sub-set of Ps who dropped out of morphine treatment at baseline (pre-opioid), and 3-, 6-, and 12-months post-morphine commencement	28 (Case n=18, 44.4%); Control n=10, 90.0%)	4	Baseline, 3m, 6m, 12m	Low back pain, spinal cord injury, osteoarthritis, cervicobrachial neuralgia, post-surgical nerve lesion, multiple sclerosis, CRPS, pachypleuritis	Mean 10.1 years (7)range: 1.5-45)	SR morphine	Oral	Baseline: 0mg; 3m: 62.0; 6m: 65.0; 12m: 72.0	Daily

CRPS=Chronic Regional Pain Syndrome. [a] Converted from reported means of 191.3mg/day tapentadol (presumed oral) at 3 months, and 206.3mg/day at 6 months.

[b] Converted from reported means of 12mg/day oral oxycodone at baseline, and 11mg/day oral oxycodone equivalent at 8 weeks.

Table 2.4. *Characteristics of included case-crossover studies*

Study	Country	Design overview	Case n	N sessions	Session times	Pain type	Pain duration	Opioid type/s	ROA	Mean OME dose (mg/day)	Frequency of use
Jamison 2003	U.S.A.	Randomised case-crossover (but data analyses as cohort); Ps with CNCP were tested at opioid-free baseline and then after 90 days on either oxycodone or fentanyl; they were then crossed over between oxycodone and fentanyl and tested after another 90 days	144 (39.6%)	3	Baseline, 90 days, 180 days	Low back pain	Not reported	Oxycodone, fentanyl	Oral (oxycodone), transdermal (fentanyl)	Baseline: 0; 90 days: 99.6 180 days: 104.7	Daily
Raja 2002	U.S.A.	Prospective case-crossover; Ps were tested at baseline and after ~8 weeks on opioids or placebo (& anti-tricyclic anti-depressants), then crossed over to other condition after 1 week washout	Randomised: 76 (53.3%); Period 1: 71; Period 2: 60; Period 3: 50	6	Baseline, 6wk, 9wk (baseline), 15wk, 18wk (baseline), 26wk	Post-herpetic neuralgia	Not reported	Morphine, methadone (all SR)	Oral	Baseline: 0; 6wk/15wk/26wk: 91 (morphine), 70.5 (methadone)[a]	Daily

[a] Converted from reported mean of 15mg/day oral morphine.

Risk of bias assessment

Risk of bias assessment incorporated factors such as the quality of cognitive tasks and study design (Supplementary Tables 2.7–2.9). All studies reported using valid and reliable cognitive assessments and appropriate statistical analyses (e.g., ANOVA). Most studies (15 out of 17) were randomised, used matched pairs, or statistically controlled for ≥1 key covariate (e.g., age). Most studies (11 out of 17) scored poorly on sample size criteria (i.e., did not justify sample size or sample size was not adequately powered to detect a difference). Ascertainment of opioid exposure (e.g., blood or urine analysis, self-report) was generally poor: only six studies described how opioid use was assessed.

Cognitive outcomes

Case-control studies. Effect sizes for case-control meta-analyses varied between control types and across cognitive domains (Table 2.5 and Supplementary Figures 2.1–2.14).

Healthy controls. Cases performed significantly more poorly than controls on attention (k=8, g=-0.29, 95%CI [-0.52,-0.06], I^2=39.90%) and memory (k=3, g=-0.37, 95%CI [-0.66, -0.07], I^2=0.00%) tasks, though these effects were small magnitude. All other effects were small and non-significant (gs≤0.39).

Pain controls. Effects for motor performance, attention, working memory, executive functions, and memory were all small magnitude and non-significant for cases versus opioid-free controls with CNCP (gs≤0.25).

Taper-off controls. There were non-significant, moderate magnitude performance differences between cases and taper-off controls. Cases performed more poorly than controls on motor performance, attention, and working memory, and better than controls for executive functions (gs≥0.42). There was no assessment of memory in this group. These comparisons included only one study, and should be interpreted with caution.

Table 2.5. *Effect sizes for studies included in case-control analyses, by control type and cognitive domain*

Control type and cognitive domain	k [a]	Case n	Control n	Hedges' g	p	95%CI Lower limit	95%CI Upper limit	Heterogeneity I^2	Heterogeneity Q
Healthy controls									
Motor performance	5	119	364	0.06	.826	-0.46	0.58	82.77%	23.21
Attention	8	198	459	-0.29	.013*	-0.52	-0.06	39.90%	11.65
Working memory	1	37	25	-0.39	.137	-0.89	0.12	–	–
Executive functions	3	95	83	-0.39	.065	-0.80	0.02	48.14%	3.86
Memory	3	95	83	-0.37	.015*	-0.66	-0.07	0.00%	0.69
Pain controls									
Motor performance	2	93	95	0.02	.907	-0.27	0.30	0.00%	0.47
Attention	7	187	169	-0.09	.375	-0.30	0.11	0.00%	2.35
Working memory	2	53	43	-0.04	.907	-0.65	0.58	48.76%	1.95
Executive functions	3	83	73	-0.25	.179	-0.62	0.12	23.80%	2.63
Memory	4	127	117	0.04	.820	-0.33	0.41	50.20%	6.02
Taper-off controls									
Motor performance	1	18	12	**-0.42**	.252	-1.14	0.30	–	–
Attention	1	18	11	**-0.55**	.147	-1.29	0.19	–	–
Working memory	1	18	11	**-0.43**	.254	-1.17	0.31	–	–
Executive functions	1	18	12	**0.47**	.206	-0.26	1.19	–	–
Memory	–	–	–	–	–	–	–	–	–

* $p<.050$.

[a] Comparisons that include only one study should be interpreted with caution.

Note. Hedges' $g \geq 0.40$ indicated in **bold.**

Cohort (pre–post) studies. Effect sizes for meta-analyses comparing cognition before and during opioid therapy varied by domain and treatment duration in cohort (pre-post) studies (Table 2.6). Relatively few studies included follow-up times beyond 3 months, and several comparisons for 6 and 12 months comprised only one study. These comparisons should be interpreted with caution. See Supplementary Table 2.10 for a summary of all meta-analyses (including case-control and cohort designs) by cognitive domain.

Motor performance. There was no evidence of changes in motor performance from baseline to follow-up at 4-6 weeks, 6-9 weeks, 3 months, or 6 months (gs≤0.21).

Attention. Performance significantly improved from baseline to 4–6 weeks (k=3, g=0.27, 95%CI [0.10, 0.43], I^2=0.50%), 3 months (k=3, g=0.30, 95%CI [0.15, 0.45], I^2=0.00%), and 6 months (k=3, g=0.33, 95%CI [0.16, 0.51], I^2=0.00%), though these effects were small magnitude. Effects for 6–9 weeks and 12 months were small magnitude and non-significant (gs≤0.16).

Working memory. Significant improvements in working memory were noted at 4–6 weeks (k=3, g=0.29, 95%CI [0.12, 0.45], I^2=0.00%), 3 months (k=2, g=0.38, 95%CI [0.07, 0.69], I^2=0.00%), and 6 months (k=2, g=0.60, 95%CI [0.27, 0.94], I^2=0.00%), but not at 6–9 weeks (g=0.19). There was a non-significant, moderate magnitude effect for improved working memory performance at 12 months (k=1, g=0.47, 95%CI [-0.11, 1.04], I^2=0.00%), though this comparison included only one study and should be interpreted with caution.

Executive functions. Performance on tasks assessing executive functions improved at 4–6 weeks (k=2, g=0.28, 95%CI [0.02, 0.53], I^2=0.00%) and 6–9 weeks (k=2, g=0.55, 95%CI [0.23, 0.87], I^2=0.00%), but not at 3, 6, or 12 months (gs≤0.22).

Memory. Comparisons for memory performance were limited by the small number of included studies (k=1) at 4–6 weeks, 3 months, and 12 months. Tentatively, memory performance improved at 12 months (k=1, g=0.62, 95%CI [0.01, 1.23], I^2=0.00%), but not any other time (gs≤0.38).

Table 2.6. *Effect sizes for studies included in cohort analyses, by cognitive domain and follow-up time*

Domain & follow-up time	k [a]	Cohort n	Hedges' g	p	95%CI		Heterogeneity	
					Lower limit	*Upper limit*	I^2	Q
Motor performance								
Pre-post: 4-6wks	2	59	0.21	.106	-0.04	0.46	0.00%	0.10
Pre-post: 6-9wks	2	62	0.03	.792	-0.21	0.28	0.00%	0.16
Pre-post: 3 months	1	21	0.20	.345	-0.22	0.62	–	–
Pre-post: 6 months	1	21	0.16	.459	-0.26	0.57	–	–
Attention								
Pre-post: 4-6wks	3	143	0.27	.002*	0.10	0.43	0.50%	2.01
Pre-post: 6-9wks	3	85	0.16	.144	-0.05	0.37	0.00%	0.08
Pre-post: 3 months	3	176	0.30	<.001**	0.15	0.45	0.00%	1.06
Pre-post: 6 months	3	136	0.33	<.001**	0.16	0.51	0.00%	1.78
Pre-post: 12 months	1	11	0.12	.667	-0.43	0.68	–	–
Working memory								
Pre-post: 4-6wks	3	143	0.29	.001*	0.12	0.45	0.00%	1.79
Pre-post: 6-9wks	2	41	0.19	.207	-0.11	0.49	0.00%	0.74
Pre-post: 3 months	2	39	0.38	.017*	0.07	0.69	0.00%	0.00
Pre-post: 6 months	2	37	**0.60**	<.001**	0.27	0.94	0.00%	0.00
Pre-post: 12 months	1	11	**0.47**	.115	-0.11	1.04	–	–
Executive functions								
Pre-post: 4-6wks	2	59	0.28	.033*	0.02	0.53	0.00%	0.18
Pre-post: 6-9wks	2	41	**0.55**	.001*	0.23	0.87	0.00%	0.11
Pre-post: 3 months	3	168	0.22	.051	-0.00	0.45	31.71%	2.93
Pre-post: 6 months	3	131	0.21	.106	-0.04	0.46	37.35%	3.19
Pre-post: 12 months	1	11	0.14	.630	-0.42	0.69	–	–
Memory								
Pre-post: 4-6wks	1	40	0.31	.065	-0.02	0.63	–	–
Pre-post: 6-9wks	2	67	0.38	.051	-0.00	0.76	53.20%	2.14
Pre-post: 3 months	1	21	0.22	.293	-0.19	0.64	–	–
Pre-post: 6 months	2	37	0.36	.198	-0.19	0.90	62.43%	2.66
Pre-post: 12 months	1	11	**0.62**	.048*	0.01	1.23	–	–

* p<.050. ** p<.001.

[a] Comparisons that include only one study should be interpreted with caution.

Note. Hedges' g ≥0.40 indicated in **bold.**

Opioid dose and cognitive performance. Meta-regression is not recommended for analyses involving <10 studies [41]. However, we ran exploratory meta-regressions for three comparisons with ≥5 studies: motor performance for cases versus healthy controls (k=5), and attention for cases versus healthy (k=8) and pain controls (k=7). Opioid dose did not significantly improve model fit for cases (n=119) versus healthy controls (n=364) on motor performance (p=.798; Table 7). Opioid dose also did not improve model fit for attention for cases (n=187) versus pain controls (n=169; p=.802), but improved fit for cases (n=198) versus healthy controls (n=459; p=.001).

Table 2.7. *Meta-regressions examining the effect of opioid dose on cognitive performance*

Domain & control group type	Coefficient	SE	p	95%CI Lower limit	Upper limit	T^2	T	R^2 analog	Heterogeneity I^2	Q
Motor performance										
Healthy controls	<0.01	0.01	.798	-0.01	0.02	0.27	0.52	0.00	80.27%	25.34
Attention										
Healthy controls	0.01	<0.01	.006*	<0.01	0.01	0.00	0.00	1.00	0.00%	4.18
Pain controls	<-0.01	0.00	.802	-0.01	0.01	0.00	0.00	0.00	0.00%	0.97

* $p<.050$.

Publication bias

A publication bias funnel plot showed asymmetry, with most studies reporting a negative effect (Figure 2.2). However, this should not be overstated given the use of random effects meta-analyses that accounted for heterogeneity between studies, the inclusion of meta-regressions assessing the effects of opioid dose, and that the plot was skewed in favour of studies reporting a negative effect (i.e., opioids impaired cognition). The latter is expected given robust evidence of impaired cognitive performance in people with CNCP [10, 23].

Figure 2.2. *Funnel plot of publication bias (Hedges' g) for included studies*
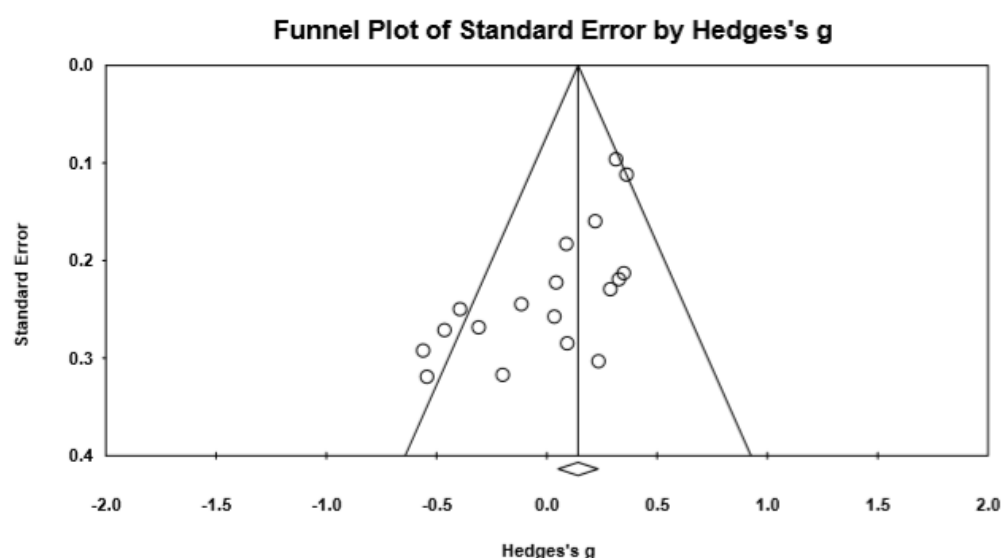
Discussion

This review examined objective cognitive performance in people taking pharmaceutical opioids for CNCP, compared with opioid-free groups and across time. People who used opioids for CNCP evidenced impairments in attention and memory function, but not other domains, compared with healthy controls. A meta-regression indicated a role of opioid dose in attentional impairment. However, there were no significant differences in task performance between people who took opioids for CNCP and people with CNCP who were not taking opioids (including taper-off controls). Finally, compared with opioid-free baseline, people with CNCP showed fairly consistent, significant improvements in attention and working memory ≥4 weeks after opioid initiation. These effects were consistent at 3 and 6 months. Some improvements were also noted for executive functions and memory, though these were less robust and evident only at certain time points. Notably, meta-analyses for some comparisons and domains were limited by small numbers of included studies. With this in mind, the present findings indicate that cognitive impairment effects may be driven by pain rather than opioids and may be reversible with appropriate pain management, at least at the range of doses examined here.

Cases versus healthy controls

The present findings suggest that people who are prescribed opioids for CNCP may experience specific cognitive deficits when compared with healthy individuals. Notably, robust cognitive deficits were apparent only for tasks assessing attention and memory; simple motor performance and tasks assessing executive functions and working memory were not affected. Similarly, meta-regressions indicated an effect of opioid dose on attention, but not motor performance; meta-regressions could not be conducted for other domains due to small study numbers. Together, these findings may indicate that opioids impair attention in a dose-dependent manner, with no noticeable effect on motor performance regardless of dose.

This finding broadly aligns with numerous cross-sectional studies, in which acute administration of opioids in healthy individuals has produced dose-dependent impairments in

attentional processes (information processing speed, complex attention) but not executive functions [6, 7, 42, 43]. Interestingly, these findings are at odds with similar research where impairments have been noted for working memory performance, but not longer-term memory (e.g., delayed recall) [43]. This may relate to greater sensitivity due to the larger sample size used here, but may also indicate a cognitive effect arising from comorbidities. For example, pain and psychological distress can affect memory regardless of medicine use [44]. Further, we were not able to control for frequency or duration of opioid use. Potentially, individuals taking higher opioid doses may have been prescribed opioids for a longer duration.

Cases versus pain controls

In this study, people with CNCP displayed similar cognitive abilities regardless of their use of opioid medicines. When contrasted with the deficits noted for people who take opioids compared with healthy controls, this suggests that pain itself may affect cognition to a greater degree than chronic use of opioid medicines. This finding broadly aligns with past studies, in which researchers have concluded that both acute and chronic pain appear to affect attentional processes (e.g., information processing speed, complex attention) more so than other functions [10, 45, 46]. The effect of pain on attention may relate to numerous factors, including structural changes in the central nervous system and the demands of pain on cognitive resources [10]. Specifically, pain is thought to compete for cognitive resources such that the experience of pain limits the capacity to perform cognitive tasks and, conversely, sufficiently engaging tasks can lead to reduced activity in CNS regions associated with pain [47, 48].

The present review also included analysis of one study comparing cognitive performance between cases and people who had tapered off opioids for CNCP [37]. No significant differences were found between the two groups for any cognitive outcome. However, there were moderate magnitude effects whereby cases (i.e., people taking opioids) performed more poorly than controls for tasks assessing motor performance, attention, and working memory, and better than controls for executive functions. Given that only one study was

included and these results were non-significant, this finding should not be overstated. Tentatively, this may indicate that discontinuation of opioid medicines does not impact cognitive performance, and that any effects that do exist are likely reversible. However, given the magnitude of the effects for these comparisons and the small sample size, carry over effects of opioids after cessation may be a valuable avenue for future research.

Pre-post studies

In addition to highlighting the role of pain in cognitive impairment, the present findings offer some insight into cognitive trajectories for people with CNCP who use opioids chronically. Performance improvements in tasks assessing attention, working memory, and executive functions were present from relatively early in treatment (4–9 weeks), and were still apparent up to 6 months after opioid initiation for both attention and working memory. There was also some indication that memory improved at 12 months, though this analysis included only one study and should be interpreted cautiously. Overall, these findings are positive, suggesting that opioid therapies may help some individuals with chronic non-cancer pain to improve their cognitive performance across multiple domains. The mechanism driving this effect is not absolutely clear, but is likely related to the pain-relieving effects of pharmaceutical opioids [8]. Additionally, in at least one study, the control group comprised individuals who ceased using opioids due primarily to side effects. This indicates that individuals who do continue using opioids presumably do so because they experience tolerable side effects, if any, and likely some analgesic benefit.

Implications and future research directions

This review suggests that chronic opioid use may not impair cognition more so than pain itself. In some cases, opioids may actually attenuate cognitive deficits caused by pain. This may potentially reflect at least a proportion of people who benefit from opioid use. However, few studies included detailed analysis of the sample's clinical characteristics (e.g., experience of

side effects, analgesic efficacy), so the distinct effects of pain and opioids could not be individually examined. Given the known inter-individual variability in opioid metabolism and analgesic efficacy [49, 50], this is a promising avenue for future research.

Other key questions raised by the present review relate to the effects of opioid type, carry-over effects after opioid discontinuation, and inter-individual variability in opioid effects and the choice to commence, continue, or discontinue use. To date, only one study has examined the residual effects of opioids on cognitive functioning within CNCP populations. This study found moderate magnitude effects, whereby opioid-free taper controls evidenced superior cognitive performance than people currently taking opioids for pain [33]. It may also be useful to compare the effects of full- versus partial-agonists to determine whether impairment can be overcome by switching drug type. This could be examined either by comparing groups, or using a case-crossover study to examine the effects of each type of agonist within the same person.

The present review also highlights the need for greater consistency with regards to the assessment of cognitive function in this field. Our review included outcomes from 44 different measures of cognition, almost half (n=21) of which were categorised as attention tasks. Coupled with the paucity of research in this field, this represents a substantial weakness in the current body of literature. For example, in the present review, we classified tasks relatively broadly (e.g., measures of on-road driving ability were included as 'attention', but involve other abilities as well) as more specific categorisation would have further reduced the number of studies included in each comparison. Even with our broad classifications, several comparisons included only 1 or 2 studies. This impacts the specificity of our findings, and makes it difficult to determine the exact aspects of cognition that are impaired (e.g., are memory problems related to coding, or retrieval?). The implementation of a standardised cognitive test battery for use in pain and opioid research would help to overcome these issues and would improve the comparability of studies. Several such batteries already exist and could be adapted for use in the pain and opioid field. For example, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) and the Addictions Neuroclinical Assessment (ANA)

tools were developed to assess cognitive function in people undergoing drug-based treatment for schizophrenia and people with substance use disorders, respectively [51, 52]. Future research activities should endeavour to adapt a battery for use in this field. This would greatly improve the generalisability of findings.

Strengths and limitations

The relatively broad inclusion criteria in this systematic review allowed us to examine the chronic cognitive effects of opioids in multiple contexts. In particular, the inclusion of different study designs and methodologies (e.g., different control groups, cross-sectional and pre-post designs) and the examination of the effects of opioid dose on task performance are strengths of this study. Together, these factors allowed for a comprehensive and nuanced interpretation of the findings that accounted for numerous factors, not least the role of pain itself on cognitive performance. This is particularly important given the complexity of this field, where numerous comorbidities can affect cognition (e.g., concomitant medication use, pain intensity).

The present review has several key limitations, including the potential for publication bias and the small number of studies included in some analyses. While random-effects models were used for all meta-analyses, there was some skew in the funnel plot as well as high heterogeneity for several analyses (I^2 up to 82.77%). This may reflect the substantial variation between studies in terms of cognitive assessments used, research design (e.g., inclusion/exclusion criteria), type of control group, and timing of follow-up sessions. Additionally, the search strategy used here may have failed to detect studies that were not in the three included databases, or studies that were not in English. While our search did return several articles in non-English languages, it is possible that others were missed.

Another key limitation of the present study is the inability to assess comorbidities. Meta-regressions to assess the effect of opioid dose on cognition were only conducted for three comparisons due to the small number of studies for other comparisons. Given that one of these

comparisons indicated that opioid dose affected cognitive performance, this is a clear limitation.

Additionally, the small number of eligible studies and inter-study variation in the assessment of

comorbidities meant that we were not able to control for even key comorbid factors such as

pain itself. Pain and other common comorbid factors (e.g., the experience of depression) can

substantially impact upon cognitive functioning, but were poorly controlled for across studies.

Conclusions

The present review aimed to examine cognitive performance in individuals who are prescribed opioids as a long-term pain therapy. Broadly, this review suggests that chronic opioid use may not impair cognition more so than pain itself. The results suggest that people who are prescribed opioids for CNCP evidence specific cognitive deficits compared to healthy people, namely for attention and memory. While these domains are crucial for a range of cognitive processes, these effects were small magnitude and were not apparent for other key skills (e.g., working memory, executive functions). For this reason, it is unlikely that these impairments significantly impact real-world abilities to engage in ordinary activities, like driving. Additionally, although the sample size was small, there was some evidence of practically equivalent functioning between people with CNCP regardless of opioid use. Finally, the review revealed some evidence that use of opioids may actually improve cognitive function in some people, with effects apparent as early as four weeks after opioid initiation and lasting up to six months. The present results also highlight several key limitations in the current body of literature on opioid use and cognition, including small sample sizes and methodological heterogeneity across studies. Inconsistent assessment of cognitive function (including differences in the classification of domains as well as tasks used) are particularly important to address in future research.

Conflict of Interest

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CHAPTER 3: COGNITIVE PERFORMANCE IN PEOPLE WITH CHRONIC OPIOID USE FOR NON-CANCER PAIN, ACROSS TIME AND COMPARED WITH OPIOID-FREE CONTROLS

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Preface

As outlined in Chapter 2, people with CNCP can and do evidence improvements in their objective cognitive performance after commencing long-term opioid therapy, compared with opioid-free baseline. However, it is not well understood what happens to cognition with prolonged use (e.g., >6 months), despite the fact that a substantial proportion of people who take opioids for CNCP will continue to use these medicines for years. Additionally, it is unclear as to what is driving these improvement effects: this could be related to reductions in pain or unique drug effects, or may be due to the presence of practice effects.

Given this, the following paper (*Study 2*) presents the findings of a longitudinal study that aimed to examine objective cognitive performance in people who were taking opioids for CNCP, compared with opioid-free controls with CNCP and across time. The study is unique in that it included naturalistic inclusion criteria (e.g., use of a comparable control group, concomitant medications permitted) and specifically aimed to examine cognitive trajectories in people who were taking opioids chronically.

Abstract

Introduction

There is concern that opioid use may impair cognition. However, several studies have reported improved cognition after opioid initiation. The mechanism of action is poorly understood and it is unclear what happens with long-term use. This study examined cognition in people taking opioids for CNCP, across time and compared with opioid-free controls.

Methods

In this 2(Group: Opioid, Controls) x2(Time: baseline, 3 months) prospective study, participants with CNCP reported details of pain, opioid use, and other relevant factors. They completed tasks assessing attention, working memory, executive functions, and memory. Mixed models analyses for repeated measures and Bayesian sensitivity analyses were used to examine main and interactive effects of Group and Time on task performance, controlling for premorbid IQ and pain. Tests of simple effects of Time were used to examine practice effects in each group.

Results

There were no significant Group differences for any cognitive outcome, with several significant main effects of Time for tasks assessing attention, executive functions, and memory. Significant Group*Time interactive effects for 2 measures (Determination Test, Arrow Flankers) indicated that performance improved in Controls but not the Opioid group. Tests of simple effects of Time at each level of group revealed inconsistent effects within domains.

Conclusions

Chronic opioid use was not associated with impaired performance, though opioid-free people evidenced greater improvements in 2 measures of attention and executive function. This may indicate differential practice effects due to subtle opioid impairing effects. Clinicians may use this information to brief patients on cognitive impacts and identify those at risk of impairment.

Introduction

Pharmaceutical opioids are commonly prescribed to individuals with chronic non-cancer pain (CNCP), as a relatively affordable and accessible long-term pain therapy [1, 2]. However, pharmaceutical opioids can produce a range of adverse effects, and chronic use is typically not recommended for CNCP due to limited evidence of long-term analgesic efficacy, the potential for opioid use to worsen pain, and risks relating to dependence and overdose [3-6]. Opioids also have strong psychoactive effects (e.g., sedation) and chronic use may produce impairments in cognitive function [7, 8], potentially affecting activities of daily living.

The acute impairing effects of opioids on cognitive performance are well documented [9, 10]. Following acute administration, opioid-naïve individuals have shown impairments in performance on tasks assessing information processing speed (e.g., Digit Symbol Substitution Test) and complex attention (e.g., Divided Attention Test) compared with opioid-free baseline, though these deficits vary by opioid dose and type [9, 10]. Similarly, people who take opioids for CNCP have shown impaired performance compared with healthy controls on tasks assessing information processing speed [7] and complex attention [11]. These deficits are most pronounced soon after opioid initiation or dose increase [12]. However, people who report chronic opioid use and comparable non-consumers (i.e., both with CNCP) have evidenced similar cognitive performance in cross-sectional studies [7, 11, 12]. These data suggest that cognitive deficits in people who use opioids for CNCP may relate to co-morbid factors (e.g., mood disorders, pain) [13, 14], rather than opioid use specifically.

To overcome potential issues regarding the cognitive effects of confounds and inter-individual variables, several studies have used longitudinal designs to assess cognitive function pre- and post-commencement of long-term opioid therapy for CNCP. In contrast with the findings of cross-sectional studies, these data have relatively consistently revealed that cognitive function in CNCP cohorts does not deteriorate after initiation of opioid therapy [15, 16]. While most studies have only examined these effects in the shorter term (i.e., less than three months), three studies assessing cognitive task performance 3–12 months after initiation

of opioid therapy have reported stability or moderate improvements in tasks assessing information processing, complex attention, and working memory from opioid-free baseline [15, 17, 18]. These researchers concluded that improved task performance may have been related to practice effects (excluding Tassain et al., who ruled this out as improvements were not noted in the control group), reductions in pain, psychological distress, and functional impairments noted over the same period, rather than being related to opioids [15].

Practice effects are of particular interest given their potential to impact cognition. These effects have been found to improve performance on key cognitive tasks (e.g., Trail Making Test, Digit Symbol Substitution Test) even after 6–12 months [19]. While this may be viewed as a limitation, practice effects also offer an opportunity to infer cognitive performance. If they are of smaller magnitude for opioid-treated versus opioid-free individuals, this may indicate the presence of subtle, deleterious cognitive effects related to opioid use. Practice effects have not been well addressed in the present literature. Two of the longitudinal studies described above noted that practice effects could not be discounted due to the lack of a control group [17, 18]. The third study, which included an opioid-free CNCP group, noted improved performance for opioid consumers but not controls [15]. This finding may indicate that improved performance is related to opioid-induced pain reductions rather than being the product of learning effects. However, this study is yet to be replicated.

Given the lack of research on long-term cognitive effects of opioids, and in particular the role of practice effects, the primary aim of the present study was to examine objective cognitive performance in people prescribed opioids for CNCP versus comparable opioid-free controls and over time. The control group enabled examination of the magnitude of change likely related to practice effects, building upon Tassain et al.'s earlier study [15]. Understanding the longer-term cognitive effects of opioids (accounting for practice effects) could have clinical and policy implications. For example, if cognition worsens with long-term use, it may be appropriate to include a brief cognitive screener in existing routine 12-month clinical reviews of patients who are using opioid medicines. Cognitive interventions could then be implemented as appropriate.

Methods

Participants

Participants with CNCP, aged 18–65 and residing in the Australian jurisdiction of Tasmania, were recruited from April 2018–May 2019 via social media and advertisements at pain clinics and pharmacies. Eligibility was determined via an online survey. Inclusion criteria were English as a first language and normal or corrected-to-normal vision. Additional criteria for the Opioid group included current CNCP (≥3 months) and daily or near-daily prescription opioid use (duration ≥2 months; this excluded codeine-only medicines which were over-the-counter at the time of study design and approval). There was no minimum daily OME dose required, given codeine was excluded and participants were long-term, frequent opioid consumers. Exclusion criteria were current cancer diagnosis, use of opioids for treatment of an opioid use disorder, alcohol dependence (>16 on the Alcohol Use Disorders Identification Test) [20], frequent (>1 occasion) use of illicit drugs in the past 6 months, significant intellectual disability (≤70 on the Weschler Test of Adult Reading) [21], and neurological disorders. Participants aged 66 and over were excluded as cognitive function naturally declines with age, potentially confounding results. Control participants were included if they experienced regular pain in the past 3 months, and excluded if they reported frequent (≥weekly) use of opioid medicines. Participants in the opioid group were excluded if they had used opioids as part of an alternative treatment regimen in the 3 months prior to their current treatment.

Procedure

This prospective study used a 2(Group: Opioid, Control) x 2(Time: baseline, 3 months) mixed design to compare cognitive outcomes for participants with CNCP who were i) prescribed opioids or ii) opioid-free across two sessions (baseline, three months). Participants completed all measures in each session, and were reimbursed AUD$40 per session. Ethics approval was granted by the Tasmanian Health and Medical Human Research Ethics Committee (#H0016554).

Materials

Opioid and concomitant medication use. Using a timeline follow-back method [22], participants reported past-week medication use (brand, dose, days used). Average daily doses were calculated for opioid and benzodiazepine medications via conversion to oral morphine equivalents (OME; mg) [23] and oral diazepam equivalents (ODE; mg) [24], respectively.

Brief Pain Inventory. Participants described past 24-hour pain severity and interference via the Brief Pain Inventory [25]. This scale has good construct validity in people with low back pain and arthritis (*n*=250), with a strong relationship to other measures of pain (r≥0.57) and sensitivity to changes in pain over time [26]. The severity scale comprises four items on an 11-point Likert scale (anchors: 0 'no pain'–10 'pain as bad as you can imagine'). The interference scale comprises seven items about the degree to which pain interferes with ordinary activities, rated on an 11-point Likert scale (anchors: 0 'does not interfere'–10 'completely interferes'). Mean scores were calculated for each sub-scale (range: 0–10), with higher scores indicating higher levels of pain severity or interference.

Kessler Psychological Distress Scale (K10). The K10 is a 10-item scale assessing symptoms of psychological distress during the past 30 days [27]. The K10 has demonstrated good validity. For example, in a large Australian community sample (National Survey of Mental Health and Well-Being; *n*=1,401), K10 scores were positively correlated with a World Health Organisation Composite International Diagnostic Interview diagnosis of anxiety or affective disorder as well as number of recent (past 12 months) mental health consultations [28]. In the present study, participants used a 5-point Likert scale (anchors: 1 'none of the time'–5 'all of the time') to indicate the frequency of symptoms. Items were summed to provide a total score (range: 10–50), with higher scores indicating greater distress. Scores are classified as low (<20), mild (20–24), moderate (25–29), or severe (≥30) distress [28].

Wechsler Test of Adult Reading (WTAR). The WTAR was used to assess premorbid intellectual functioning. The WTAR has been strongly correlated with scores on the Wechsler Adult Intelligence Scale (WAIS-III) in an Australian community sample (*n*=93), indicating

validity as a measure of intelligence [29]. The WTAR comprises a 50-item English word list, which participants read aloud. They are scored on number of correctly pronounced words. Raw scores (range: 0–50) were converted to age-standardised scores [21], with higher scores indicating higher intellectual functioning.

Alcohol Use Disorders Identification Test. The Alcohol Use Disorders Identification Test was used to assess risky alcohol use. This measure is a brief screening tool developed by the World Health Organization for use in clinical settings. It is a valid marker of current alcohol use disorder [30, 31], and has predictive validity for alcohol-related harms [32]. Participants reported frequency and quantity of alcohol use and related harms recently (past year) and in their lifetime. Scores ≥16 may indicate the presence of an alcohol use disorder [20].

Opioid Severity of Dependence Scale. The Severity of Dependence Scale is a 5-item scale assessing psychological symptoms of drug dependence [33]. In a study of Norwegian hospital inpatients (*n*=246), this scale was a valid indicator of DSM-IV criteria for use disorders relating to opioid medicines, with an optimal cut-off of 5.5 [34]. In this study, participants in the Opioid group reported past 6-month symptoms (e.g., "Do you worry about your use of opioids?") for opioid medicines via a 4-point Likert scale (anchors: 0 'never or almost never/not at all difficult'–3 'always or nearly always/impossible'). Scores ≥5 indicate opioid dependence [34].

Table 3.1. *Cognitive tasks, domains, and outcomes assessed*

Task	Cognitive domain	Outcomes
Attention		
Inspection Time Task	Information processing speed	Mean inspection time
Trail Making Test A	Information processing speed	Completion time
Reaction Time test [a]	Choice reaction time	Motor speed, reaction time
Reaction Time test [a]	Choice reaction time	Motor speed, reaction speed
Determination Test [a]	Stress tolerance	Number of correct responses
Rapid Visual Information Processing Test [b]	Sustained attention, visual information processing speed	Number of correct responses, reaction time (correct responses), false positives
Working memory		
2-Back, 3-Back [b]	Working memory	Number of correct responses, reaction time (correct responses), false positives
Executive functions		
Trail Making Test B	Executive functions	Time
Arrow Flanker Task [b]	Inhibitory control, attention	False positives, reaction time (correct responses), number of errors
Stop Signal Task [b]	Inhibitory control	Stop signal reaction time
Memory		
Rey's Auditory Verbal Learning Test	Verbal learning and memory	Total (sum of Trials A1-A5), immediate recall (Trial A1), retroactive interference (Trial A6), delayed recall
Royal Prince Alfred Prospective Memory test	Prospective memory	Total score

[a] Assessed via the Schuhfried Vienna Test System DRIVEPLS Fitness to Drive Plus test battery. [b] Assessed via the PenScreenSix test battery.

Note. Reaction times reported in milliseconds.

Inspection Time task. The Inspection Time task was used to assess information processing speed (Table 3.1) [35]. Participants were seated 50cm from a computer monitor on which a white fixation point was presented on screen (500ms), followed by a target symbol for a variable stimulus onset asynchrony (SOA) dependent on task performance. The target, representing two legs of unequal length, appeared on-screen before presentation of a backward-mask (a target with 'lightning-bolt' legs) for 290ms. Participants used a mouse click (left or right) to indicate the shorter leg, with no constraints on response time. Presentation time was adjusted using a staircase procedure, with correct responses followed by decreased target presentation (i.e., increased difficulty). Three correct responses at a given SOA triggered a reduction of 18ms for subsequent SOAs, and one incorrect response triggered an increase of 18ms. Participants were scored on mean Inspection Time (ms), calculated as the minimum target presentation time required for reliably correct identification (80% of trials) over eight reversals of the staircase. Lower scores indicate faster information processing speed.

Trail Making Test A & B (TMT A & B). The TMT A and B were used to assess information processing speed and executive functions, respectively [36]. In the TMT A, 25 consecutive numbers were displayed in scattered positions on a sheet of paper. Participants were instructed to connect the numbers in ascending order (e.g., 1-2-3) by drawing lines between numbers until they reached the final number. In the TMT B, the 25 target stimuli comprised both letters and numbers and participants were required to alternate between letters and numbers when sequencing stimuli (e.g., 1-A-2-B-3-C). Scores were calculated as the time taken to complete the task, with higher scores indicating poorer task performance. A different, matched form was used at baseline (Form A) and three months (Form B).

Schuhfried Vienna Test System DRIVEPLS Fitness to Drive Plus test battery. Two tests from the DRIVEPLS cognitive test battery were used to assess choice reaction time and stress tolerance, respectively [37]. Participants were seated 30cm from a computer monitor, wearing headphones. In addition to raw scores, both tasks provide age-normed percentile ranks based on the general population, with a higher percentile rank indicating better performance.

Reaction Time test. Choice reaction time, comprising decision speed and physical motor speed, was assessed via the Reaction Time test [37]. Visual (yellow and red circles) and acoustic (auditory tone) stimuli were presented on-screen and via headphones. Participants responded to a critical combination of acoustic and visual stimuli (i.e., a yellow circle and a tone) via button press, resting their finger on a keypad between responses. Scores reflected mean motor speed (speed of movement in planned action sequences) and reaction speed (decision speed in response to relevant stimuli). Lower scores indicated faster reaction times.

Determination Test. The Determination Test is a multi-stimuli task assessing reactive stress tolerance [37]. Acoustic (high and low tones) and visual (light-up, coloured circular and rectangular boxes) stimuli were presented on-screen and via headphones. Participants responded to stimuli using corresponding buttons (via a keypad) and foot pedals. Stimuli were presented continuously, with presentation frequency increasing (i.e., becoming more difficult) following correct responses and decreasing following incorrect responses, using a

psychophysical staircasing procedure. Scores reflected number of correct reactions, with higher scores indicating better performance.

PenScreenSix test battery. Four tests were completed on an Android® tablet via the PenScreenSix [38]. For all tasks, participants were seated 30cm from the tablet and responded to visual stimuli via a button or buttons displayed on-screen.

Rapid Visual Information Processing test. The Rapid Visual Information Processing test assesses sustained attention and visual information processing speed [39]. Visual stimuli (numbers; N=300 trials) were displayed consecutively on screen at a rate of one digit per 600ms. Participants responded to sequences of three consecutive odd or even numbers (e.g., 3-9-5, 2-8-4) via button press, with a total of 24 targets. Scores reflect number of correct responses, reaction time, and number of false positives.

n-back. The 2- and 3-back were used to assess working memory [40]. Participants were presented with a consecutive sequence of individual numbers (N=75 trials), and responded via button press when a stimulus matched the number preceding it by either two (2-back) or three (3-back) digits. In the sequence "A-B-C-**B**-**C**-A", target stimuli were indicated in bold. Scores reflect number of correct responses, reaction time, and number of false positives.

Arrow Flanker Task. The Arrow Flanker Task assesses selective attention and inhibitory control [41]. For the selective attention task, a target stimulus (arrow, pointing left or right) was presented on screen, flanked by two identical symbols on either side. Symbols were i) congruent (arrows corresponding to target direction), ii) incongruent (arrows opposing target direction), or iii) neutral (squares). Participants indicated target direction by pressing the corresponding response button (left or right). Flankers appeared in random order; congruent, incongruent, and neutral trials each comprised 25% of total trials (N=94), with the inhibitory control task representing the remaining 25%. For this task, participants were asked to inhibit responses (i.e., not respond) when the arrow was flanked by crosses. Scores reflect number of false positives, mean reaction time for correct responses, and number of errors.

Stop Signal Task. The Stop Signal Task assesses response inhibition [42]. Participants responded to the appearance of two visual targets using two buttons (cross: left; circle: right). On 25% of trials (total *N*=96), a stop signal (two horizontal red lines) was superimposed over the target stimulus, initially after a 250ms delay, with participants required to inhibit their response for these trials. The stop signal delay increased by 50ms each time a participant responded to a stop signal (i.e., making the task easier) and decreased by 50ms each time they correctly inhibited their response. Participants were scored on stop signal reaction time (i.e., RT for incorrect responses to stop signals), with slower Stop Signal RT indicating superior inhibitory control.

Rey's Auditory Verbal Learning Test (RAVLT). The RAVLT assesses verbal learning and memory [43]. Participants were required to recall words from a verbally presented, 15-item word list (List A). List A was repeated five times, with a recall trial immediately after each repetition. A distractor list (List B) was then delivered, followed by a recall trial each for List B and List A, respectively. Following a 20-minute interval, participants were tested on free recall and word recognition for List A. Scores reflected the total (sum of words recalled across the five trials), immediate recall (Trial A1), retroactive interference (Trial A6), and delayed recall, with higher scores indicating superior performance. To reduce potential learning effects, two different versions of the RAVLT, matched for difficulty, were used: Form A was used at baseline, and Form B at three months.

Royal Prince Alfred Prospective Memory test (RPA Pro-Mem). The RPA Pro-Mem was used to assess prospective (future) memory [44]. Participants were instructed to perform an action (e.g., "ask for a glass of water") following a pre-determined trigger across four scenarios that were combinations of short- and long-term (e.g., '10 minutes' versus 'one week') and event- and time-based (e.g., 'when the alarm rings' versus 'when this clock shows 11:45AM'). Participants were scored from 0–3 for each scenario, with sub-scales summed to provide a total score (range: 0–12). Higher scores indicate better memory performance. Similar

to the RAVLT, the RPA Pro-Mem is available in multiple versions; Form 1 was used at baseline

and Form 2 at three months.

Statistical analysis

Power analysis was conducted using G*Power 3.1.9.2, with a proposed sample size of 28

after accounting for a 20% drop-out rate due to opioid discontinuation. This was based on

power analysis yielding a moderate magnitude effect (g=0.5 or f=0.25), assessing either a

within-between factor (Group*Time, assuming participants discontinue opioid treatment) or a

solely within group design (assuming no discontinuation of treatment), whereby n=24 was

sufficient (power=0.80) to identify either effect as statistically significant at alpha=0.05.

Differences between groups and over time for cognitive outcomes. Data were

analysed in General Analyses for the Linear Model in jamovi (GAMLj), using mixed models for

repeated measures [45]. Variables that were significantly different between the Opioid and

Control groups at baseline were included as covariates. Pain severity was included to control for

variation in pain between participants and across time. Group, Time, premorbid IQ, and pain

severity and interference were entered as covariates, and participant number was included as a

random effect, to account for performance variation between people. Bayesian mixed models

analyses were conducted for each cognitive outcome, as sensitivity analyses. These analyses

compared the fit of the null model with that of the alternative (i.e., that Time, Group, and

Group*Time affected task performance). Given this, we report BF_{01} (i.e., the strength of evidence

in favour of the null hypothesis). In each analysis, the null model included participant number

and baseline scores for the WTAR and BPI (severity, interference) scales. Bayes factors are

interpreted as anecdotal (1–3), substantial (3–10), strong (10–30), very strong (30–100), and

decisive (>100).

In addition to mixed models analyses, independent samples t-tests were used to identify

main effects of Group (Opioid, Control) and Time (baseline, three months) for all cognitive

outcomes, as well as the Group*Time interaction effect. As this study examined differential

practice effects between groups from baseline to follow-up, tests of simple effects of Time at each level of Group were conducted regardless of statistical significance. All moderate magnitude effects (Hedges' $g \geq 0.40$) were considered meaningful and interpreted.

Cognitive outcomes compared to population norms. A series of one-sample *t*-tests were conducted to compare standardised scores on the Schuhfried (Reaction Time test, Determination Test) and Rey's Auditory Verbal Learning Test (RAVLT) with data from the general population. For the Schuhfried tasks, test output included a percentile rank based on scores from a European general population (*M*=50, *SD*=10) [37]. For the RAVLT, raw scores for each participant were converted to z-scores (*M*=0, *SD*=1) using the formula z=(χ- μ)/σ, where χ=sample score, μ=mean, and σ=standard deviation. Means (and standard deviations) for total recall, immediate and best learning, retrospective interference, and recognition were based on predicted scores by age, as described by Mitrushina et al. in their meta-analysis of RAVLT scores from a healthy population [46]. As scores for prospective interference and delayed recall were not included in the meta-analysis, means for these outcomes were calculated based on normative data from an Australian sample aged 18–34 (*n*=98); separate norms were provided for males and females [47]. For all tasks (Reaction Time test, Determination Test, RAVLT), standardised scores (percentile ranks and z-scores) were compared with normative means via one-sample *t*-tests for each outcome.

Missing data. Due to technological and methodological issues, baseline data were missing for some members of the Opioid group for the Rapid Visual Information Processing (RVIP) test (*n*=3) and K10 (*n*=10). This was addressed by using a linear mixed models analysis, which has the ability to overcome missing data. This missing data is not expected to impact results, given that the K10 was not a core measure and, in the case of the RVIP, the study included numerous other measures of attention.

Results

Participant characteristics

Participants (*n*=26) comprised 14 opioid-treated individuals and 12 controls. Chronic back or neck pain, arthritis/rheumatism, and frequent headaches were common among both groups (Table 3.2). The Opioid group had a mean age of 43 years and was predominantly female (71.4%). Median opioid treatment duration was 17 months (IQR: 16.5). Commonly-used opioids included oxycodone, tramadol, and tapentadol.

Controls evidenced a significantly higher baseline mean Wechsler Test of Adult Reading score (*p*=.024, Hedges' *g*=0.92) and lower pain interference score (*p*=.017, *g*=1.07) than the Opioid group. There were also moderate magnitude, non-significant differences whereby Controls had a lower mean age (*p*=.144, *g*=0.60) and lower mean pain severity score (*p*=.113, *g*=0.70) than the Opioid group. In the Opioid group, OME did not significantly differ from baseline (*M*=57.2, *SD*=54.4) to follow-up (*M*=60.0, *SD*=67.8), *p*=.738, *g*=0.04. There were no significant differences in pain severity or interference from baseline to follow-up for the Opioid group (*p*s≥.460, *g*s≤0.25). However, pain severity was significantly lower (i.e., improved) for Controls at follow-up (*M*=2.4, *SD*=1.6), compared with baseline (*M*=3.6, *SD*=1.7) *p*=.028, *g*= 0.70. There was also a moderate magnitude effect where pain interference was lower at follow-up (*M*=2.25, *SD*=2.25) than baseline (*M*=3.58 *SD*=2.26), *p*=.053, *g*=0.55. These effects were controlled for in the mixed models analyses, as pain severity and interference were included as covariates.

Table 3.2. *Sample characteristics for the Opioid and Control groups at baseline*

	Opioid (*n*=14)	Control (*n*=12)
Demographic characteristics		
Mean age (SD)	42.6 (12.6)	34.4 (14.7)
% Male	28.6	8.3
Education		
% Completed grade 12%	42.9	41.7
% Completed further education [a]	35.7	58.3
Mean Wechsler Test of Adult Reading score *(SD)*	104.9 (11.0)*	113.7 (7.5)*
% Current pain condition		
Arthritis/rheumatism	14.3	16.7
Chronic back or neck pain	50.0	16.7
Complex Regional Pain Syndrome	7.1	0.0
Frequent or severe headaches	14.3	16.7
Fibromyalgia	14.3	16.7
Other [b]	28.6	66.7
% Multiple pain conditions	28.6	33.3
Current pain level		
Mean pain severity score (SD)	4.5 (0.8)	3.6 (1.7)
Mean pain interference score (SD)	5.6 (1.4)*	3.6 (2.3)*
Median opioid use duration, months (range)	15.3 (3.0–30.0)	n..a
Median average daily opioid dose (OME; mg), past week (range)	40.0 (8.6–180.0)	n.a.
% Opioid type, past week		
Codeine	21.4	n.a.
Oxycodone	28.6	n.a.
Tapentadol	35.7	n.a.
Tramadol	42.9	n.a.
% Opioid formulation, past week		
Sustained-release	85.7	n.a.
Immediate-release	64.3	n.a.
% Multiple opioids, past week	64.3	n.a.
Opioid dependence, past 6 months		
Mean Severity of Dependence Scale score (SD)	3.4 (2.0)	n.a.
% with Severity of Dependence Scale score >3	64.3	n.a.
% Other medicines, past week		
Antidepressants	71.4	8.3
Antipsychotics	7.1	0.0
Benzodiazepines	7.1	0.0
Gabapentinoids	50.0	8.3
Other prescription medicines	85.7	75.0
Median average daily benzodiazepine dose (ODE; mg), past week [c]	15.0	n.a.
% Used multiple non-opioid medications, past week [d]	71.4	54.5
Mean AUDIT score *(SD)*	3.8 (3.8)	5.0 (5.6)
Psychological distress, past 30 days		
Mean K10 score (SD)	22.4 (3.4) [e]	23.0 (7.1)
% with K10 score <20	20.0	33.3
% with K10 score 20-24	60.0	0.0
% with K10 score 25-29	20.0	58.3
% with K10 score ≥30	0.0	8.3

*p<.050.

[a] Comprise trade and/or university qualifications beyond Grade 12. [b] Includes endometriosis, tendon pain, repetitive strain injury, degenerative and connective tissue disorders, and other/undiagnosed. [c] Among participants who reported past-week benzodiazepine use (*n*=1).

[d] Of those who reported past-week use of psychoactive medicines other than opioids. [e] Due to missing data at baseline, *n*=5.

1. OME: 'Oral morphine equivalent'.

2. K10: Kessler Psychological Distress scale. Higher scores denote higher levels of distress.

Cognitive performance between groups and across time

Descriptive statistics for each cognitive outcome, including mean scores, are outlined in Table 3.3. Main and interaction effects of Group and Time for each cognitive outcome are described in Table 3.4.

Inspection Time task. All main and interactive effects were non-significant ($ps \geq .078$; Table 3.4). Tests of simple effects of Time at each level of Group revealed a non-significant, moderate magnitude reduction in information processing speed at three months for Controls, but not the Opioid group (Table 3.3). Bayesian models provided anecdotal evidence in favour of there being no main effect of Group or Time on IP speed ($BF_{01}s \geq 1.53$) and substantial evidence in favour of no Group*Time interaction effect ($BF_{01}=5.10$; Table 3.4).

Trail Making Test (TMT).

TMT A. The effects of Group and Group*Time were non-significant ($ps \geq .383$), but there was a significant main effect of Time ($p=.026$). Tests of simple effects of Time revealed a significant, moderate magnitude reduction in completion time at three months for the Opioid group, but not Controls (Table 3.3). Bayesian sensitivity analyses provided only weak evidence for the null for the effects of Time, Group, and Group*Time ($BF_{01}s \leq 0.56$; Table 3.4).

TMT B. All main and interactive effects were non-significant effects ($ps \geq .081$; Table 3.4). Tests of simple effects of Time revealed a significant, moderate magnitude reduction (i.e., improvement) in completion time at three months for the Opioid group, but not Controls. Bayesian analyses revealed anecdotal support for the null (i.e., no effect) for a main effect of Group ($BF_{01}=1.58$), but only weak support for no effect of Time or Group*Time ($BF_{01}s \leq 0.71$).

Table 3.3. *Cognitive test scores (M and SD) at baseline and 3 months, and tests of simple main effects of Time on cognitive task performance (p and Hedges' g) for Opioid and Control groups*

	Opioid Group				Control Group			
	Baseline M (SD)	3 months M (SD)	p	g	Baseline M (SD)	3 months M (SD)	p	g
IT task Mean IT	n=14 43.50 (19.00)	n=14 42.44 (16.49)	.621	0.13	n=12 43.55 (12.13)	n=12 38.13 (11.15)	.057	**0.57**
TMT TMT A TMT B	n=14 27.84 (11.30) 63.91 (33.38)	n=14 24.98 (9.41) 55.12 (30.49)	.016* .023*	**0.70** **0.65**	n=12 24.96 (8.16) 52.39 (15.10)	n=12 22.55 (6.00) 50.28 (9.68)	.341 .705	0.27 0.10
RT Motor Reaction	n=14 211.64 (83.90) 474.71 (144.59)	n=14 210.21 (77.42) 457.14 (98.19)	.765 .281	0.08 0.28	n=12 191.75 (61.06) 447.33 (93.34)	n=12 168.17 (46.36) 447.67 (68.76)	.379 .647	0.25 0.13
DT N. correct	n=14 226.86 (35.58)	n=14 232.64 (36.45)	.208	0.33	n=12 231.25 (33.42)	n=12 247.25 (36.88)	<.001*	**1.19**
RVIP N. correct RT correct N. FP	n=11 11.73 (5.29) 563.73 (85.41) 9.18 (11.89)	n=14 10.14 (5.25) 550.46 (68.83) 5.71 (5.24)	.884 .492 .107	0.04 0.20 **0.49**	n=12 7.17 (2.33) 588.67 (91.11) 7.08 (6.45)	n=12 9.17 (2.59) 577.83 (72.55) 7.58 (7.51)	.186 .720 .973	0.38 0.10 0.01
2-back N. correct RT correct N. FP	n=14 10.50 (2.93) 664.79 (82.51) 1.93 (1.33)	n=14 11.07 (3.73) 683.23 (65.99) 1.29 (1.27)	.321 .444 .080	0.26 0.20 **0.48**	n=12 11.33 (1.87) 668.08 (57.23) 1.67 (1.83)	n=12 10.00 (2.56) 679.25 (68.94) 1.42 (1.83)	.106 .434 .619	**0.47** 0.22 0.14
3-back N. correct RT correct N. FP	n=14 7.07 (3.05) 690.86 (93.77) 2.57 (2.21)	n=14 7.64 (3.46) 629.69 (105.17) 2.43 (1.74)	.498 .096 .939	0.18 **0.48** 0.02	n=12 6.25 (3.05) 681.08 (94.33) 3.17 (2.12)	n=12 6.58 (3.23) 672.00 (75.75) 2.08 (1.31)	.635 .571 .262	0.13 0.16 0.32
AFT N. FP RT correct N. errors	n=14 1.64 (1.08) 650.64 (122.80) 1.71 (3.56)	n=14 1.57 (1.55) 618.43 (60.99) 1.21 (1.58)	.788 .031* .350	0.07 **0.61** 0.24	n=12 3.42 (1.51) 606.67 (86.83) 0.58 (1.16)	n=12 1.67 (1.50) 590.33 (61.06) 0.50 (1.24)	<.001* .794 .992	**1.19** 0.07 <0.01
SST SSRT	n=14 467.79 (93.86)	n=14 509.07 (122.59)	.216	0.33	n=12 411.17 (108.38)	n=12 453.08 (144.64)	.085	**0.51**
RAVLT[b] Total Trial A1 Trial A6 Delayed	n=14 49.64 (8.45) 5.79 (0.97) 10.43 (2.65) 9.29 (3.00)	n=14 51.71 (6.47) 6.29 (0.91) 10.21 (3.21) 9.14 (3.70)	.200 .095 .649 .672	0.34 **0.45** 0.12 0.11	n=12 55.67 (5.82) 7.17 (1.53) 11.42 (1.62) 12.08 (2.07)	n=12 59.25 (6.17) 7.58 (1.98) 12.33 (1.56) 11.67 (1.83)	.117 .563 .176 .413	**0.46** 0.16 0.39 0.23
ProMem Total	n=14 10.79 (2.19)	n=14 9.71 (3.07)	.177	0.36	n=12 9.92 (2.50)	n=12 10.50 (1.45)	.169	**0.40**

*p<.050.

a Percentile ranks based on normative data from the general population. b For the RAVLT, Total: Sum of scores for trials A1-A5; Trial A1: immediate learning; Trial A6: retroactive interference.; Delayed: Delayed recall.

Notes.

1. Hedges' g s≥0.40 are shown in **bold**.

2. IT task: Inspection Time task. TMT: Trail Making Test. RT: Reaction Time test. DT: Determination Test. RVIP: Rapid Visual Information Processing test. AFT: Arrow Flanker Task. SST: Stop Signal Task. SSRT: Stop Signal RT. RAVLT: Rey's Auditory Verbal Learning Test. ProMem: Royal Prince Alfred Prospective Memory test.

Schuhfried Vienna Test System DRIVEPLS Fitness to Drive Plus test battery.

Reaction Time test. All main and interactive effects were non-significant for both

reaction and motor speed ($ps\geq.296$; Table 3.4). Tests of simple effects for Time were small and

non-significant (Table 3.3). Bayesian analyses provided anecdotal evidence in favour of no main

effect of Group or Time ($BF_{01}s\geq1.14$), and substantial evidence in favour of no Group*Time

interaction ($BF_{01}s\geq3.21$) for both outcomes.

Determination Test. There was a non-significant effect of Group on correct responses

($p=.504$), but significant Time and Group*Time effects ($ps\leq.043$). Tests of simple effects of Time

revealed a significant, large magnitude improvement in the number of correct responses at

three months for Controls, but not the Opioid group (Table 3.3). Bayesian analyses provided

anecdotal evidence in favour of there being no effect of Group ($BF_{01}=0.75$) but only weak

evidence in favour of the null for the effects of Time and Time*Group ($BF_{01}s\geq0.05$; Table 3.4).

This supports the finding of differential changes over time for the two groups.

Rapid Visual Information Processing test. All main and interactive effects were non-

significant for all outcomes ($ps\geq.180$; Table 3.4). Tests of simple effects revealed a non-

significant, moderate magnitude reduction in false positives at three months for the Opioid

group, but not Controls (Table 3.3). All other effects were small and non-significant. Bayesian

analyses provided anecdotal-strong support in favour of no Time effect on any outcome

($BF_{01}s\geq0.38$), and no Group ($BF_{01}s\geq1.75$) or Group*Time ($BF_{01}\geq6.33$) effect on RT or number of

false positives. There was no clear evidence favouring the null for Group ($BF_{01}=0.38$) or

Group*Time ($BF_{01}=0.76$) for number of correct responses, indicating a possible effect.

Table 3.4. *Main and interaction effects of Group and Time on cognitive outcomes*

	Group		Time		Group*Time	
	Analysis	BF_{01}	Analysis	BF_{01}	Analysis	BF_{01}
IT task						
Mean IT	$F_{1,24.9}=0.33, p=.571$	1.84	$F_{1,23.9}=3.40, p=.078$	1.53	$F_{1,23.4}=1.51, p=.232$	5.10
TMT						
TMT A	$F_{1,24.6}=0.52, p=.479$	0.56	$\mathbf{F_{1,23.4}=5.61, p=.026*}$	**0.12**	$F_{1,23.1}=0.79, p=.383$	0.37
TMT B	$F_{1,24.8}=0.91, p=.350$	1.58	$F_{1,23.7}=3.32, p=.081$	0.63	$F_{1,23.3}=1.58, p=.222$	0.71
RT						
Motor	$F_{1,25.4}=0.60, p=.445$	1.14	$F_{1,24.3}=0.77, p=.389$	1.78	$F_{1,23.9}=0.26, p=.618$	3.21
Reaction	$F_{1,25.0}<0.01, p=.994$	1.66	$F_{1,23.9}=0.12, p=.736$	1.88	$F_{1,23.4}=1.14, p=.296$	10.85
DT						
N. correct	$F_{1,24.1}=0.46, p=.504$	0.75	$\mathbf{F_{1,22.9}=13.83, p=.001*}$	**0.03**	$\mathbf{F_{1,22.7}=4.62, p=.043*}$	**0.05**
RVIP						
N. correct	$F_{1,23.6}=0.94, p=.341$	0.38	$F_{1,20.8}=0.82, p=.377$	1.32	$F_{1,20.0}=1.22, p=.283$	0.76
RT correct	$F_{1,23.4}=1.91, p=.180$	1.75	$F_{1,22.0}=0.05, p=.834$	3.25	$F_{1,21.3}=0.55, p=.465$	15.87
N. FP	$F_{1,26.3}=0.02, p=.882$	1.93	$F_{1,23.5}=1.24, p=.276$	2.40	$F_{1,22.7}=1.36, p=.256$	6.33
2-back						
N. correct	$F_{1,25.7}=0.19, p=.665$	2.05	$F_{1,25.3}=0.39, p=.540$	3.25	$F_{1,24.6}=3.78, p=.063$	4.43
RT correct	$F_{1,26.2}=0.02, p=.903$	2.16	$F_{1,25.2}=1.22, p=.280$	1.91	$F_{1,24.5}=0.01, p=.932$	11.10
N. FP	$F_{1,21.5}=0.20, p=.659$	2.17	$F_{1,21.0}=2.46, p=.131$	1.11	$F_{1,20.4}=0.66, p=.426$	5.24
3-back						
N. correct	$F_{1,25.5}=0.03, p=.869$	2.10	$F_{1,25.3}=0.65, p=.427$	2.83	$F_{1,24.7}=0.01, p=.936$	15.43
RT correct	$F_{1,23.2}=0.02, p=.891$	2.35	$F_{1,23.7}=2.52, p=.126$	1.49	$F_{1,23.2}=0.54, p=.468$	5.34
N. FP	$F_{1,25.5}=1.14, p=.296$	2.07	$F_{1,25.9}=0.83, p=.370$	1.66	$F_{1,25.4}=0.67, p=.422$	5.45
AFT						
N. FP	$F_{1,25.5}=1.95, p=.174$	1.26	$\mathbf{F_{1,24.9}=10.19, p=.004*}$	**0.12**	$\mathbf{F_{1,24.3}=8.27, p=.008*}$	**0.01**
RT correct	$F_{1,24.7}=0.72, p=.406$	2.09	$F_{1,23.9}=2.78, p=.109$	2.11	$F_{1,23.3}=1.64, p=.214$	11.73
N. errors	$F_{1,25.4}=3.08, p=.091$	0.83	$F_{1,25.5}=0.39, p=.536$	3.14	$F_{1,24.9}=0.38, p=.544$	6.14
SST						
SSRT	$F_{1,25.2}=0.27, p=.608$	1.60	$\mathbf{F_{1,25.6}=4.74, p=.039*}$	**1.19**	$F_{1,25.0}=0.27, p=.607$	5.37
RAVLT[a]						
Total	$F_{1,25.2}=4.01, p=.056$	0.23	$\mathbf{F_{1,24.9}=4.32, p=.048*}$	**0.54**	$F_{1,24.2}=0.15, p=.702$	0.30
Trial A1	$F_{1,24.2}=3.05, p=.093$	0.38	$F_{1,23.8}=2.46, p=.130$	1.11	$F_{1,23.1}=0.47, p=.501$	1.26
Trial A6	$F_{1,25.5}=1.38, p=.251$	0.67	$F_{1,25.0}=0.58, p=.453$	2.74	$F_{1,24.3}=1.87, p=.184$	2.82
Delayed	$F_{1,25.4}=1.77, p=.195$	0.33	$F_{1,25.0}=0.82, p=.373$	3.18	$F_{1,24.4}=0.13, p=.722$	2.82
ProMem						
Total score	$F_{1,25.6}=0.53, p=.474$	2.49	$F_{1,25.8}=0.03, p=.872$	3.31	$F_{1,25.2}=3.95, p=.058$	7.88

*$p<.050$.

[a] For the RAVLT, Total: Sum of scores for trails A1-A5; Trial A1: immediate learning; Trial A6: retroactive interference; Delayed: Delayed free recall.

Notes:

1. Significant results that are supported by Bayesian analysis are indicated in **bold**.

2. BF_{01} describes the likelihood of scores being observed under the null hypothesis (i.e., no effect). Bayes factors are interpreted as anecdotal (1–3), substantial (3–10), strong (10–30), very strong (30–100), and decisive (>100).

3. IT task: Inspection Time task. TMT: Trail Making Test. RT: Reaction Time test. DT: Determination Test. RVIP: Rapid Visual Information Processing test. AFT: Arrow Flanker Task. SST: Stop Signal Task. SSRT: Stop Signal RT. RAVLT: Rey's Auditory Verbal Learning Test. ProMem: Royal Prince Alfred Prospective Memory test.

N-Back.

2-back. All main and interactive effects were non-significant for all outcomes ($ps \geq .063$; Table 3.4). However, tests of simple effects showed a non-significant, moderate magnitude reduction in false positives at three months for the Opioid group, but not Controls (Table 3.3). There was also a moderate magnitude reduction in correct responses for Controls, but not the Opioid group. All other effects were small and non-significant. Bayesian analyses provided anecdotal-substantial evidence in favour of no Group or Time effect ($BF_{01}s \geq 1.11$) and substantial-strong evidence for no Group*Time interaction for all outcomes ($BF_{01}s \geq 4.43$).

3-back. All main and interactive effects were non-significant for all 3-back outcomes ($ps \geq .126$; Table 3.4). Tests of simple effects for Time indicated a non-significant, moderate magnitude decrease in RT from baseline to follow-up in the Opioid group, but not Controls (Table 3.3). All other effects were small and non-significant. Bayesian analyses provided anecdotal-strong evidence in favour of the null for all outcomes across all effects ($BF_{01}s \geq 1.49$).

Arrow Flanker Task. A significant main effect of Time was subsumed by a significant Group*Time effect for number of false positives ($ps \leq .008$; Table 3.4). Tests of simple effects of Time revealed a significant, large magnitude reduction in number of false positives for Controls, but not the Opioid group (Table 3.3). Bayesian analyses revealed no clear evidence for the null for the effects of Time and Group*Time ($BF_{01}s \leq 0.12$), supporting the finding of differential changes over time for the two groups.

Tests of simple effects of Time revealed that mean RT for correct reactions was significantly faster at three months for the Opioid group, but not Controls (Table 3.3). However, Bayesian analyses provided anecdotal evidence in favour of the null for the main effects of Group and Time on RT ($BF_{01}s \geq 2.09$), and strong evidence favouring the null for the effect of Group*Time ($BF_{01} = 11.73$). All other main and interactive effects were small and non-significant ($ps \geq .091$, $BF_{01}s \geq 0.83$).

Stop Signal Task. The effects of Group and Group*Time on Stop Signal RT were non-significant ($ps \geq .607$), but there was a significant Time main effect ($p = .039$; Table 3.4). Tests of

simple effects revealed a moderate magnitude increase in Stop Signal RT (i.e., improved inhibition) at three months relative to baseline for Controls, but not the Opioid group (Table 3.3). Bayesian analyses revealed anecdotal evidence favouring the null for the effects of Group and Time on SSRT (BF_{01}s≥1.19; Table 3.4), and substantial evidence favouring the null for the effect of Group*Time (BF_{01}=5.37).

Rey's Auditory Verbal Learning Test. There was a significant main effect of Time on total number correct (p=.048), with both groups improving at follow-up. No other effects for other outcomes achieved significance (ps≥.056). Tests of simple effects revealed a moderate magnitude improvement in immediate recall (Trial A1) at three months relative to baseline for the Opioid group, but not Controls (Table 3.3). There was also a moderate magnitude improvement for total number correct (sum of Trials 1–5) at 3 months for Controls, but not the Opioid group. Bayesian analyses provided anecdotal-strong evidence favouring the null for the effect of Group, Time, and Group*Time on retroactive interference (Trial A6) (BF_{01}s≥1.67), and Time and Group*Time on immediate and delayed recall (BF_{01}s≥2.74).

Royal Prince Alfred Prospective Memory test. There were no significant main or interaction effects for total score (ps≥.058; Table 3.4). Tests of simple effects revealed a non-significant, moderate magnitude improvement in total score at three months for Controls, but not the Opioid group. Bayesian analyses provided anecdotal-strong evidence in favour of the null for all effects (BF_{01}s≥2.49).

Cognitive outcomes compared to a healthy population

Schuhfried Vienna Test System DRIVEPLS Fitness to Drive Plus test battery.

Determination Test. Mean percentile ranks for number of correct responses did not significantly differ from the general population for both groups at both times (ps≥.175; Table 3.5). Bayesian t-tests supported this, providing anecdotal-substantial evidence for the null (BF_{01}s≥1.50).

Reaction Time test. There were no significant differences in percentile ranks between normative data and either group for mean motor speed or reaction speed ($ps \geq .091$). Bayesian one-sample *t*-tests revealed anecdotal-substantial support for the null ($BF_{01}s \geq 1.00$).

Rey's Auditory Verbal Learning Test. The Opioid group performed significantly more poorly than the general population for immediate recall (Trial A1) and delayed recall at baseline and three months ($ps \leq .044$, $BF_{01}s \leq 0.58$); this was non-significant for Controls ($ps \geq .193$, $BF_{01}s \geq 1.60$). Conversely, total recall (sum of Trials A1-A5) was significantly better compared with the general population at three months for Controls ($ps \leq .010$, $BF_{01}s \leq 0.17$), but not the Opioid group ($ps \geq .381$, $BF_{01}s \geq 2.60$). This is consistent with the finding of differential practice effects. All other effects were non-significant ($ps \geq .095$, $BF_{01}s \geq 0.98$).

Table 3.5. *Standardised scores for Reaction Time test, Determination Test, and Rey's Auditory Verbal Learning Test, and* t-*test results for the sample scores compared to scores from a normative sample*

	Opioid group		Control group	
	Baseline	3 months	Baseline	3 months
Reaction Time test, motor speed	*n*=14	*n*=14	*n*=12	*n*=12
Percentile rank, M (SD)	37.14 (29.12)	35.43 (29.85)	43.50 (27.43)	52.75 (24.31)
p-*value*	.122	.091	.429	.703
BF_{01}	1.24	1.00	2.61	3.26
Reaction Time test, reaction speed	*n*=14	*n*=14	*n*=12	*n*=12
Percentile rank, M (SD)	45.21 (27.95)	46.07 (26.29)	48.00 (32.07)	43.92 (27.71)
p-*value*	.533	.586	.833	.463
BF_{01}	3.10	3.23	3.41	2.72
Determination Test, number correct	*n*=14	*n*=14	*n*=12	*n*=12
Percentile rank, M (SD)	48.79 (20.35)	52.64 (23.16)	50.00 (24.46)	61.17 (26.69)
p-*value*	.827	.676	>.999	.175
BF_{01}	3.62	2.87	3.48	1.50
RAVLT, total [a]	*n*=14	*n*=14	*n*=12	*n*=12
z-score, M (SD)	-0.41 (0.88)	-0.16 (0.68)	0.19 (0.69)	0.62 (0.69)
p-*value*	.108	.381	.362	**.010***
BF_{01}	1.13	2.60	2.18	**0.17**
RAVLT, Trial A1 **[a,b]**	*n*=14	*n*=14	*n*=12	*n*=12
z-score, M (SD)	-0.58 (0.58)	-0.29 (0.48)	0.15 (0.91)	0.40 (1.15)
p-*value*	**.002***	**.044***	.574	.256
BF_{01}	**0.05**	**0.58**	3.04	1.93
RAVLT, Trial A6 [a,c]	*n*=14	*n*=14	*n*=12	*n*=12
z-score, M (SD)	-0.26 (0.81)	-0.32 (1.06)	-0.12 (0.70)	0.30 (0.58)
p-*value*	.257	.278	.575	.095
BF_{01}	2.05	2.16	3.48	0.98
RAVLT, delayed recall [d]	*n*=14	*n*=14	*n*=12	*n*=12
z-score, M (SD)	-1.19 (1.17)	-1.27 (1.55)	-0.16 (0.93)	-0.32 (0.79)
p-*value*	**.002***	**.009***	.559	.193
BF_{01}	**0.05**	**0.17**	2.98	1.60

*p<.050.

[a] Based on age-stratified predicted scores for healthy people from Mitrushina et al.'s meta-analysis (2005) [46]. [b] Immediate recall. [c] Retroactive interference. [d] Based on sex-adjusted norms for healthy Australians aged 18–34 retrieved from Carstairs et al. (2013) [47].

Notes:

1. Estimates where traditional significance testing and Bayesian analyses suggest there is a difference are indicated in **bold**.

2. Sample scores for the RT and DT were compared with mean of 50 (*SD*=10), while z-scores for the RAVLT were compared with a mean of 0 (*SD*=1).

3. RAVLT: Rey's Auditory Verbal Learning Test.

Discussion

This study examined cognitive outcomes in people prescribed opioids for CNCP across time, focussing on differential practice effects compared with opioid non-consumers. Cognitive performance on tasks assessing attention, executive functions, and memory was largely similar for chronic opioid consumers and non-consumers at baseline and after three months.

While there was an overall practice effect across numerous tasks (i.e., significant main effect of Time), significant Group*Time interaction effects were only apparent on two outcomes. Both these outcomes were attention tasks (Determination Test: number correct; Arrow Flanker Task: number of false positives), and related to task accuracy rather than response speed. However, when we examined the simple effects of Time for opioid consumers versus non-consumers, we detected a range of effects whereby one group improved at follow-up and the other did not (Table 3.6). Notably, these effects did not follow a clear pattern within domains or between groups.

Finally, performance on attention tasks with available normative data (Reaction Time task, Determination Test) was similar for both groups compared to the general population. While there was some indication of impairment for opioid consumers compared with healthy Australians on two memory measures (Rey's Auditory Verbal Learning Test immediate and delayed recall), this effect did not worsen over time. Delayed recall scores may also reflect the older age of the Opioid group (43 years) compared to the normative sample (18–34 years).

Table 3.6. *Summary of cognitive performance at baseline versus three months for the Opioid and Control groups, based on effect sizes (Hedges' g) for the simple effects of Time*

Cognitive domain, task, & outcome		Performance at 3 months vs. baseline	
		Opioid group	Control group
Attention			
Inspection Time task	Mean inspection time	-	↑
Trail Making Test A	Time	↑	-
Reaction Time test	Motor speed	-	-
	Reaction speed	-	-
Determination Test	N. correct	-	↑
Rapid Visual Information Processing test	N. correct	-	-
	RT	-	-
	N. false positives	↑	-
Working memory			
2-Back	N. correct	-	↓
	RT	-	-
	N. false positives	↑	-
3-Back	N. correct	-	-
	RT	-	-
	N. false positives	↑	-
Executive functions			
Trail Making Test B	Time	↑	-
Arrow Flanker Task	N. false positives	-	↑
	RT	↑	-
	N. errors	-	-
Stop Signal Task	SSRT	-	↑
Memory			
Rey's Auditory Verbal Learning Test	Total recall (Trials A1-A5)	-	↑
	Trial A1 (immediate learning)	↑	-
	Trial A6 (interference)	-	-
	Delayed recall	-	-
RPA Pro-Mem	Total score	-	↑

Note. ↑ denotes improved task performance (Hedges' $g \geq 0.40$), ↓ denotes worsened performance ($g \geq 0.40$), and - denotes insufficient evidence for any change in performance from baseline to three months ($g < 0.40$).

Attention and working memory tasks

Performance on attention and working memory tasks demonstrated some subtle impairment effects related to chronic opioid use, though these were inconsistent across tasks. Accuracy on the Determination Test (number correct) yielded a significant interaction effect, with opioid-free people showing a greater improvement in task performance at three months than opioid consumers. Pairwise tests for the effect of Time indicated differential effects between groups across a range of tasks (Table 3.6), though not all achieved significance. Finally,

there were practice effects for the Trail Making Test A and Determination Test, whereby both groups improved at follow-up. These findings are similar to previously-noted improvements in people with CNCP on the Trail Making Test A at three and six months post-initiation of stable opioid therapy, compared to baseline [17].

However, the present findings regarding improvement on the Trail Making Test A and Determination Test are mixed: while there was a significant main effect of Time, tests of simple effects indicated differential performance whereby one group improved and the other did not. However, these effects were not consistent (Table 3.6) and potentially reflect the small sample size. Tentatively, these improvements may reflect practice effects rather than genuine improvement. Specifically, both opioid consumers and non-consumers improved at follow-up, suggesting that both groups improved due to learning. Further, while overall task performance was similar between the groups, opioid consumers may improve to a lesser degree than opioid-free controls.

Executive functions tasks

Compared with the effects noted for attention tasks, the present study revealed few differences between groups for executive functions. While several outcomes for the two executive function tasks (Arrow Flanker Task: false positive; Stop Signal Task: Stop Signal RT) were susceptible to practice effects (i.e., a main effect of Time), only Arrow Flanker Task false positives evidenced differential practice effects (i.e., a significant interaction effect). For this task, Controls evidenced a greater magnitude of improvement than the Opioid group (Table 3.6). However, when compared with normative data, neither opioid consumers nor non-consumers performed significantly more poorly than did the general population. This suggests that the effects noted here were subtle, and unlikely to affect real-world attentional abilities.

Memory tasks

The present results indicated that opioids may impair some aspects of memory, with opioid consumers performing more poorly than both opioid-free pain patients and healthy people. Within the sample, there was a significant main effect of group for Rey's Auditory Verbal Learning Test total recall, with opioid-free participants recalling a significantly higher number of words across all immediate recall trials. By contrast, initial immediate and delayed free recall (RAVLT) performance was similar between groups and remained stable across time. Broadly, these results align with Tassain et al.'s findings, whereby verbal recall was similar for morphine-treated and opioid-free individuals with CNCP and did not differ at baseline and after three, six, and 12 months of stable opioid treatment [15]. However, when compared with data from healthy samples, opioid consumers performed significantly more poorly on both immediate and delayed free recall; for immediate recall, this effect remained after accounting for the effects of age. Notably, this effect was consistent across time, indicating that memory performance did not further deteriorate with continued opioid use. This finding is somewhat inconsistent with cross-sectional research demonstrating similar visuospatial memory performance for CNCP patients on stable opioid doses and healthy controls [48], but potentially indicates specific impairments related to auditory memory.

Present findings in the context of previous research

The present results add to a growing body of literature on cognitive and prescription opioids and are particularly important when synthesised with findings from the only previous study with a comparable research design. In that study, individuals on stable morphine doses (n=18) evidenced significantly improved performance on two cognitive outcomes 6–12 months after opioid initiation [15]. This effect was non-significant for comparable opioid-free controls (n=10), with the authors noting that improved task performance for the opioid group was related to reductions in pain and better mood and subjective well-being at follow-up [15].

Given that the control group comprised individuals who ceased opioid therapy due to intolerable side effects or insufficient pain relief, opioids may improve cognitive function when individuals experience reduced pain and improved quality of life, likely in the early stages of opioid use. However, while the groups were matched for pain intensity, pain was considered an outcome variable rather than a covariate in that study. In the present study, the lack of opioid-related improvement on tasks may be explained by the relatively longer duration of opioid use (median 17 months), at which point pain is unlikely to continue improving and individuals experiencing severe side effects have likely ceased treatment. This is supported by the finding that pain (severity, interference) and opioid dose remained stable from baseline to follow-up for participants who were taking opioids. Together, this indicates that cognitive impairment related to opioids' psychoactive effects may dissipate with chronic use due in part to tolerance, but also the effects of opioids on pain and quality of life.

Limitations and future research directions

This study had a small sample size and included a large number of cognitive outcomes. Multiple hypothesis testing may have inflated the risk of a Type I error (that is, detecting a false effect). Future endeavours may seek to include larger samples and fewer outcome measures. Participants also evidenced substantial inter-individual variability in terms of pain aetiology, opioid dose and duration of use, and comorbid factors (e.g., distress). In particular, a substantial proportion of participants in the Opioid group used atypical opioids. Additionally, a higher proportion of people in the Opioid group used anti-depressants and gabapentinoids, compared to Controls. These drugs may have unique effects on cognitive function that were unable to be explored here due to the small sample size. Future research may seek to explore the effect of opioid type on cognition, and the effects of gabapentinoids both separately and in combination with opioids.

Participants in this study also typically consumed opioids in lower doses and for a shorter duration than that noted in larger studies of long-term opioid consumers [49, 50]. In the

Australian Pain and Opioids in Treatment study, participants (n=1,514) prescribed opioids for CNCP reported a median opioid use duration of four years at study commencement [50]. Assessment of functioning in people reporting longer-term use may help determine whether opioid duration (e.g., medium- versus long-term use) impacts cognition in a manner not detected here. Finally, it may be useful to include subjective ratings of cognitive complaints (e.g., the degree to which cognitive impairment interferes with activities of daily living) to determine whether people prescribed opioids for CNCP experience broader real-world difficulties not captured via specific cognitive tasks.

Conclusions

Our results support the hypothesis that opioid-induced cognitive impairment may dissipate as tolerance occurs [15, 17, 18], and, where it persists, is subtle and affects attention to a greater degree than executive functions and memory [7, 51]. Conversely, pre-existing cognitive impairments may be ameliorated in some individuals if opioids substantially reduce pain and improve mood. Our data also suggest that previously-noted impairments in task performance among individuals with CNCP may relate to co-morbid factors, rather being a unique opioid effect. Both in previous literature and in the current study, CNCP cohorts demonstrate frequent co-morbidities that may negatively affect cognitive abilities, including pain [14, 18, 52], sleep and mood disorders [13, 53] and concomitant medication use [54]. Identifying and treating these co-morbidities may help to improve cognitive outcomes.

Conflict of Interest

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CHAPTER 4: COGNITIVE FUNCTION AND INJURIES AMONG PEOPLE WHO USE PHARMACEUTICAL OPIOIDS FOR CHRONIC NON-CANCER PAIN: A CROSS-SECTIONAL, SELF-REPORT SURVEY

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Preface

Laboratory-based studies, such as that outlined in Chapter 3, offer a controlled environment in which to examine objective cognitive performance. However, they have several caveats. Firstly, objective cognitive performance does not necessarily predict real-world impairment. Additionally, the mode of delivery may prevent some people (e.g., those with limited mobility) from participating. This may result in smaller and less representative samples, with limited generalisability.

Given this, the following chapter (*Study 3*) presents the findings of a cross-sectional survey study that aimed to examine self-reported cognitive complaints and associated real-world harms (physical injuries) in a community sample of people who were taking opioids for CNCP. The study built upon the findings of Chapter 3 by examining factors that are associated with real-world impairment, including opioid dose and duration of use. Additionally, the study included an examination of behavioural harms and how these relate to cognitive impairment. A considerable strength of the study was the use of an online mode of delivery. This made it accessible to participants with limited mobility and also enabled us to recruit a larger cohort.

Abstract

Introduction

Opioids, often prescribed for chronic non-cancer pain (CNCP), may impair cognition and predict poor health outcomes. This study examined associations between individual-level opioid use factors (e.g., dose) and cognitive complaints, and cognitive complaints and physical injuries.

Methods

In this cross-sectional study, a convenience sample of people with CNCP was recruited via social media from November 2017 to February 2018. Participants completed an online survey where they reported opioid dose and use duration, recent injuries, and cognitive complaints via the Patient Reported Outcomes Measurement Information System (PROMIS) Cognitive Function v2.0 and Prospective-Retrospective Memory Questionnaire (PRMQ). Covariates included psychological distress, pain severity and interference, and concomitant medicines.

Results

Participants (*n*=226; median age=46; 85% female) reported a median pain duration of eight years and opioid treatment duration of 4 years. Cognitive complaints were common. 60% described symptoms consistent with moderate to severe psychological distress, and 40% reported recent experience of a major injury. Opioid dose and treatment duration were not significantly related to PROMIS and PRMQ scores, but pain interference and distress were linked to cognitive complaints. Injuries were uniquely associated with cognitive complaints.

Conclusions

While not related to opioid use, cognitive complaints were common among participants and were associated with psychological distress and physical injuries. In clinical practice, screening for cognitive impairment may help to identify patients at risk of adverse health events.

Introduction

Chronic non-cancer pain (CNCP), which affects several billion people worldwide, is associated with negative health outcomes and poses a considerable economic burden [1, 2]. Opioids are commonly prescribed for pain management, with many individuals continuing use for multiple years [3]. Chronic opioid use in CNCP remains controversial given the risk of dependence and potential psychoactive effects (e.g., sedation) [4-6]. Chronic use is also associated with impairment in cognitive domains including attention and impulsivity [7-9]. Such deficits may substantially impair the ability to engage in activities of daily living (ADLs), impacting functional outcomes [3]. Additionally, cognitive impairment has been linked to subsequent injuries [10], though this relationship is poorly understood in CNCP.

Past research on cognitive deficits and chronic opioid use in CNCP has typically comprised small, laboratory-based studies, with most using quasi-experimental designs to compare cognitive outcomes for opioid-treated individuals with opioid-free controls [8, 9]. While useful, this research is limited by its inability to assess cognitive outcomes for chronic opioid consumers compared to the general population. Additionally, this research does not fully account for potential inter-individual variations in cognitive outcomes based on opioid use factors (e.g., dose) and co-morbidities. For example, pain [11], mood disorders [12, 13], and concomitant medications (e.g., benzodiazepines) [1, 14] are associated with cognitive deficits. Additionally, demographic variables (age, gender) may also be linked to cognition; for example, cognitive performance is typically poorer among older CNCP cohorts [11].

Given the lack of understanding of individual-level variation in cognitive function, this study had three main aims: i) examine associations between subjective cognitive complaints, opioid use (e.g., dose), and co-morbid factors in people with CNCP; ii) to compare the frequency of cognitive complaints among intermediate- (<12 months) and long-term consumers; and iii) to examine the association between cognitive complaints and physical injuries.

Methods

Participants

From November 2017–February 2018, participants residing in Australia were recruited

via advertisements on social media and pain organisation websites, and in Tasmanian

newspapers, pharmacies, and doctors' surgeries. Inclusion criteria included age 18–65,

experience of chronic non-cancer pain (≥3 months), current use of minimum one prescription-

only opioid (restricted access; as at January 2018), and English as a first language. Exclusion

criteria were self-reported opioid use disorder, current use of opioids as opioid substitution

therapy, current cancer diagnosis, and use of codeine-only medications, as low-dose (<30mg per

dosage unit) codeine products were available without a prescription at that time. Participants

aged 66 and over were excluded as cognitive function naturally declines with age, potentially

confounding results.

Procedure

Participants completed a 15-minute online questionnaire administered via LimeSurvey.

Informed consent was obtained at the beginning of the survey, and participants could enter the

draw to win an AUD$50 voucher. Survey responses were anonymous. Ethics approval was

granted by the Tasmanian Health and Medical Human Research Ethics Committee

(#H0016303).

Materials

Key measures are described below. The full survey is described in detail in Appendix B.

Measures of opioid and concomitant medicine use. Participants reported past-week

use of opioid and benzodiazepine medications (brand, days used, daily dose), using a timeline

follow-back method [15]. Participants were prompted with a list of drug (opioid,

benzodiazepine) types and examples of common brand names (e.g., Palexia as an example of

tapentadol), and were asked to report the number of days they had used each opioid and their usual daily dose. Participants could select multiple drug types as applicable.

Average daily opioid dose was calculated by converting opioid medications to oral morphine equivalents (OME; mg) [16]. Where participants indicated use of multiple opioids, OMEs for each medication were summed to provide a total daily OME. Similarly, benzodiazepines were converted to oral diazepam equivalents (ODE; mg) [17].

Brief Pain Inventory. Past 24-hour pain was detailed via the Brief Pain Inventory, an 11-item questionnaire comprising two sub-scales assessing pain severity (4 items) and interference (7 items) [18]. Respondents rated pain severity on an 11-point Likert scale (anchors: 0 'no pain'–10 'pain as bad as you can imagine') and reported the degree to which pain interferes with activities of daily living via a second 11-point Likert scale (anchors: 0 'does not interfere'–10 'completely interferes'). Mean scores were calculated for each sub-scale (range: 0–10), with higher scores indicating greater levels of severity or interference.

Kessler Psychological Distress Scale (K10). The K10 assesses the frequency of symptoms of psychological distress over the past 30 days [19], comprising 10 items (e.g., "How often have you felt worthless?") rated via a 5-point Likert scale (anchors: 1 'none of the time'–5 'all of the time'). Items were summed to provide a total score (range: 10–50), with higher scores indicating greater levels of distress. Respondents were classified as having low (<20), mild (20–24), moderate (25–29), or severe (≥30) distress [20].

Prospective-Retrospective Memory Questionnaire. The Prospective-Retrospecitve Memory Questionnaire is a 16-item scale comprising two sub-scales assessing the frequency of memory failures for future (i.e., prospective) and past (i.e., retrospective) events [21]. Participants responded to each item via a 5-point Likert scale (1 'never'–5 'very often'). Scores reflected the mean of prospective and retrospective items, with higher scores indicating more frequent memory complaints. The PRMQ has adequate concurrent and predictive validity [22, 23], evidencing small-moderate positive correlations with objective memory performance measures [24, 25].

Patient Reported Outcomes Management Information System (PROMIS) Item Bank v2.0 Cognitive Function. A modified, 23-item version of the PROMIS Item Bank v2.0 Cognitive Function scale assessed the frequency of past-week cognitive failures [26]. Responses were rated on a 5-point Likert scale (anchors: 1 'never'–5 'very often'); items were summed to provide a total score, with higher scores indicating more frequent cognitive complaints. The PROMIS scale is an update of the PROMIS Applied Cognition-Abilities (PROMIS AC-A), which has adequate concurrent validity, evidencing strong positive correlations with existing gold-standard measures of cognitive function including the Mini-Mental State Exam and the Saint Louis University Mental Status test [27]. Further, the PROMIS AC-A is strongly correlated with scores on the Instrumentals of Activities of Daily Living Scale, indicating an association with real-world outcomes [27].

Scale of Perceived Occupational Stress. Injuries were assessed via items 10 and 11 from the Scale of Perceived Occupational Stress [28]. Participants reported the frequency of minor (no medical attention required) and major (medical attention required) injuries over the past 12 months, during and outside of work (response options: 'none', '1–2', '3–4', '5–6', '>6', 'N/A-do not work').

Statistical analysis

Power analysis was conducted using G*Power 3.1.9.2, with a proposed target sample size of 150 based on power analysis yielding a small-moderate effect size (Cohen's f^2=.07). That is, this sample size is sufficient to detect a small to moderate effect of opioid dose on cognitive complaints. Survey responses were exported from LimeSurvey to IBM SPSS Statistics 24.

Missing values. Individual missing items for the K10, Brief Pain Inventory, and Prospective-Retrospective Memory Questionnaire (PRMQ) were imputed via PRELIS 2.80, which uses response pattern scoring, to determine values for missing items based on identical response patterns from other participants [29]. PROMIS scales were scored via HealthMeasures, using response pattern scoring [30]. For the PROMIS and PRMQ scales, raw scores were

converted to *t*-scores (*M*=50, *SD*=10), which are standardised scores derived from a reference group. Reference groups were the U.S. general population (PROMIS), and a large non-clinical sample in the U.K. (PRMQ) [22, 31]. PROMIS *t*-scores were included as HealthMeasures output, while PRMQ scores were standardised using PRMQSCOR software [22]. Higher *t*-scores indicate fewer cognitive failures.

Factors associated with cognitive function in people prescribed opioids for CNCP. To assess the association between opioid use, co-morbid factors, and cognitive outcomes, we conducted three hierarchical multiple regression analyses (one for each cognitive scale). Analyses were guided by theory, with opioid variables entered in Steps 1 (average daily OME) and 2 (treatment duration) to determine if these predictors uniquely accounted for variance in cognitive complaints. Average daily ODE (Step 3), pain severity and interference (Step 4), pain duration (Step 5), age and gender (Step 6), and K10 scores (Step 7) were then added to the model. Data were also examined in JASP, using Bayesian Information Criteria to estimate Bayes factors [32]. For each cognitive outcome, this analysis compared the fit of the null model with that of the alternative (i.e., average daily OME was related to cognitive complaints). For covariate-adjusted models, covariates (treatment duration, ODE, pain severity, interference, and duration, age, and K10 score) were treated as a null model.

Cognitive function and duration of opioid use. To examine differences in cognitive scores between intermediate- (≤1 year) and long-term (>1 year) opioid consumers, we conducted an independent samples *t*-test comparing the two groups.

Cognitive function and frequency of physical injuries. We conducted three binary logistic regressions to assess the relationship between cognitive predictors and injury frequency. PROMIS scores were entered at Step 1, and PRMQ retrospective and prospective scores in Step 2. Step 3 included all covariates used in the main analyses.

Results

Of 524 participants who commenced the survey, 226 were included after excluding incomplete responses (*n*=228; identified as incomplete if cognitive scales had not been attempted), ineligible participants (*n*=48; reasons included current cancer diagnosis, use of codeine-only medicines, and pain duration <3 months), and responses missing data for opioid type and dose (*n*=21). After imputation, 226 and 224 complete responses remained for the PROMIS and Prospective-Retrospective Memory Questionnaire scales, respectively.

Participant characteristics

Included participants *(n*=226) had a median age of 46 years and were predominantly female (*n*=198; Table 4.1). Participants reported a median pain duration of 8 years, and median opioid treatment duration of 4 years. Commonly-reported pain conditions were chronic back/neck pain, arthritis or rheumatism, and frequent/severe headaches. Oxycodone, codeine, and tramadol were the most widely reported opioids. Demographic information for ineligible participants was not gathered, meaning comparison of eligible and ineligible participants was not possible. There is potential for completion bias to have influenced results, although the participant characteristics observed here (i.e., predominantly female, middle-aged) broadly align with other data sources on demographic characteristics of people with CNCP [3].

Cognitive dysfunction, psychological distress, and physical injuries were common among participants (Table 4.1). One-sample *t*-tests indicated that mean *t*-scores were significantly lower than referent populations from the U.K. and U.S. for the PRMQ prospective and retrospective memory scales and the PROMIS scale, respectively (*p*s<.001) [22, 31]. The mean K10 score was 28, indicating moderate psychological distress. Additionally, 2 in 5 (43%) of participants recorded a K10 score in the severe distress range (≥30). Finally, 9 in 10 participants reported experiencing a minor injury outside of work in the past 12 months, and 40% said they had experienced a major injury outside of work.

Table 4.1. *Characteristics of people prescribed opioids for CNCP (n=226)*

Characteristic	Estimate
Median age	46.0 (Range: 18.0–65.0)
% Male	14.6
Median pain duration, years	8.0 (Range: 0.40–55.0)
% Current pain condition	
Chronic back or neck pain	77.9
Arthritis/rheumatism	56.2
Frequent or severe headaches	49.6
Fibromyalgia	38.1
Visceral pain	24.8
Complex Regional Pain Syndrome	12.4
Shingles pain	3.5
Other	45.1
% Multiple pain conditions	85.4
Current pain level	
Mean BPI [a] severity score (n=195)	5.0 (*SD*=1.2)
Mean BPI [a] interference score (n=199)	7.0 (*SD*=2.0)
Median opioid treatment duration, years	4.0 (Range: 0.40–40.0)
Median opioid dose (OME [b]; mg), past week	
Median weekly dose	280.0 (Range: 12.4–2926.0)
Median average daily dose	40.0 (Range: 1.8–418.0)
% Opioid type, past week	
Oxycodone, tablets	52.7
Codeine, tablets	48.7
Tramadol, tablets	20.4
Tapentadol, tablets	15.0
Buprenorphine, patches	9.7
Fentanyl, patches	8.4
Morphine, tablets	4.9
Hydromorphone, tablets	2.7
Methadone, tablets	1.3
Buprenorphine, tablets	0.9
Dextropropoxyphene, tablets	0.9
% Multiple opioids, past week	51.8
% Other medicines, past week	
Antidepressants	50.9
Antipsychotics	7.8
Benzodiazepines	28.3
Other prescription medicines	76.1
Median past week benzodiazepine dose (ODE [c]; mg) [d]	
Median weekly dose	17.9 (Range: 0.3–315.0)
Median average daily dose	3.6 (Range: 0.3–45.0)
% Used multiple other medications, past week	65.0
Psychological distress, past 30 days	
Mean K10 score (n=193) [e]	27.9
% with K10 score <20 [f]	18.7
% with K10 score 20–24 [f]	21.8
% with K10 score 25–29 [f]	16.6
% with K10 score ≥30 [f]	43.0
Mean t-score, cognitive scales	
PROMIS	42.7 (*SD*=9.5)
PRMQ prospective memory	41.9 (*SD*=15.7)
PRMQ retrospective memory	46.6 (*SD*=13.8)
Injuries, past 12 months	
% minor injury, at work (n=144) [g]	60.1
% minor injury, outside of work	92.0
% major injury, at work (n=145) [g]	25.5
% major injury, outside of work	39.8

[a] Brief Pain Inventory. [b] Oral morphine equivalent. [c] Oral diazepam equivalent. [d] Among those who had used benzodiazepines. [e] Kessler Scale of Psychological Distress. [f] Scores <20: low distress; 20–24: mild; 25–29: moderate; ≥30: severe. [g] Among those who had worked.

Factors associated with cognitive complaints

Cognitive complaints were not significantly associated with opioid use, but were significantly associated with psychological distress (K10 scores) and pain interference and severity (BPI scores; Table 4.2). All three cognitive measures evidenced significant negative correlations with K10 scores (i.e., higher distress corresponded with more frequent cognitive complaints). Prospective and retrospective memory scores also had significant negative correlations with pain interference, indicating poorer memory performance as pain levels increased. Prospective memory was also negatively correlated with pain severity.

Table 4.2. *Associations between cognitive function, opioid use, and related factors*

	Average daily OME	Treatment duration	Average daily ODE	BPI severity	BPI interference	Pain duration	Age	Gender	K10
Average daily OME	--								
Treatment duration	0.03	--							
Average daily ODE	0.03	0.23**	--						
BPI severity	0.01	0.01	0.08	--					
BPI interference	-0.03	0.01	0.13	0.53**	--				
Pain duration	0.04	0.65**	0.14*	-0.05	-0.02	--			
Age	0.01	0.27**	0.16*	0.02	0.05	0.20**	--		
Gender	0.04	0.07	0.04	-0.06	-0.06	-0.03	-0.07	--	
K10	0.11	-0.01	0.15*	0.08	0.15*	-0.08	-0.14*	0.06	--
PROMIS	-0.12	0.12	0.02	-0.07	-0.06	0.11	0.13	0.12	-0.54**
PRMQ prospective memory	-0.05	0.09	-0.04	-0.08	-0.24*	0.09	0.10	-0.06	-0.26**
PRMQ retrospective memory	-0.02	0.09	-0.02	-0.19*	-0.29**	0.10	0.07	-0.02	-0.28**

* p<.050; ** p<.001

Note. PROMIS and PRMQ scales were converted to *t*-scores.

Factors associated with PROMIS scale scores. Opioid dose and treatment duration were not significantly associated with PROMIS scores in any model. In Step 1, these variables together explained just 2.9% of variance in PROMIS scores (Table 4.3). The final model accounted for 33.3% of variance in PROMIS scores, but only K10 score and gender were

significantly associated with PROMIS scores in this model. Specifically, people who identified as female or who had higher levels of psychological distress demonstrated poorer cognition. An estimated Bayes factor indicated that this finding was 1.4 times as likely to be observed under the null as the alternative hypothesis (i.e., that daily OME was related to cognitive function). After accounting for covariates, this was still 1.2 times as likely. This provides anecdotal evidence in favour of the null hypothesis (i.e., opioid dose is not related to cognitive complaints).

Factors associated with PRMQ prospective memory scores. Opioid dose and treatment duration were not significantly associated with prospective memory scores in any model. Together, they accounted for 1.0% of score variance for PRMQ prospective memory in Step 1 (Table 4.3). The final model explained a significant 12.7% of score variance, with pain interference and psychological distress being significantly and positively correlated with PRMQ score (i.e., higher levels were associated with more frequent memory complaints). An estimated Bayes factor showed that this result was 5.2 times as likely to be observed under the null hypothesis (i.e., OME was not related to cognition). This was still 1.9 times as likely after accounting for covariates.

Factors associated with PRMQ retrospective memory scores. Opioid dose and treatment duration were not associated with retrospective memory scores. Together, they accounted for only 0.9% of retrospective memory score variance in Step 1 (Table 4.3). The final model accounted for a significant 15.3% of variance in memory scores, but again, only pain interference and K10 scores significantly and uniquely explained score variance. Higher levels of each were linked to more frequent memory complaints. An estimated Bayes factor showed that this result was 6.5 times as likely to be observed under the null as the alternative hypothesis (i.e., that OME was related to cognition); after accounting for covariates, this was still 1.9 times as likely.

Table 4.3. *Factors associated with PROMIS and PRMQ prospective and retrospective memory scale t-scores (hierarchical regression analyses)*

Step	Variables added	$\beta_{Step\ 1}$ (95% CI)	$\beta_{Step\ 2}$ (95% CI)	$\beta_{Step\ 3}$ (95% CI)	$\beta_{Step\ 4}$ (95% CI)	$\beta_{Step\ 5}$ (95% CI)	$\beta_{Step\ 6}$ (95% CI)	$\beta_{Step\ 7}$ (95% CI)
				Factors associated with PROMIS scale *t*-scores				
1	Average daily OME	-0.02 (-0.04, 0.01)	-0.02 (-0.04, 0.01)	-0.02 (-0.04, 0.01)	-0.02 (-0.04, 0.01)	-0.02 (-0.04, 0.01)	-0.02 (-0.04, 0.00)	-0.01 (-0.03, 0.01)
2	Treatment duration	–	0.18 (-0.04, 0.40)	0.18 (-0.05, 0.41)	0.18 (-0.05, 0.41)	0.13 (-0.17, 0.43)	0.08 (-0.23, 0.38)	0.14 (-0.12, 0.40)
3	Average daily ODE	–	–	-0.01 (-0.31, 0.30)	0.01 (-0.30, 0.32)	0.01 (-0.30, 0.32)	-0.01 (-0.32, 0.30)	0.15 (-0.11, 0.42)
4	BPI severity	–	–	–	-0.39 (-1.87, 1.09)	-0.37 (-1.84, 1.12)	-0.32 (-1.79, 1.16)	-0.38 (-1.62, 0.87)
	BPI interference	–	–	–	-0.21 (-1.08, 0.66)	-0.21 (-1.08, 0.66)	-0.21 (-1.08, 0.65)	0.19 (-0.55, 0.93)
5	Pain duration	–	–	–	–	0.05 (-0.16, 0.27)	0.06 (-0.15, 0.28)	-0.01 (-0.19, 0.17)
6	Age	–	–	–	–	–	0.08 (-0.05, 0.21)	-0.00 (-0.11, 0.11)
	Gender: *Female – Male*	–	–	–	–	–	2.78 (-1.14, 6.69)	3.59 (0.28, 6.91)*
7	Psychological distress	–	–	–	–	–	–	-0.63 (-0.78, -0.47)**
	ΔR^2	0.01	0.02	0.00	0.01	0.00	0.02	0.27
	ΔF	2.30	2.57	0.00	0.53	0.23	1.84	63.99**
	Adjusted model R^2	0.01	0.02	0.01	0.01	0.00	0.01	0.29
	Model F	2.30	2.45	1.62	1.18	1.02	1.23	8.64**
				Factors associated with PRMQ prospective memory scores				
1	Average daily OME	-0.01 (-0.05, 0.03)	-0.01 (-0.05, 0.03)	-0.01 (-0.05, 0.03)	-0.01 (-0.05, 0.02)	-0.01 (-0.05, 0.02)	-0.01 (-0.05, 0.02)	-0.01 (-0.04, 0.03)
2	Treatment duration	–	0.21 (-0.16, 0.58)	0.24 (-0.14, 0.62)	0.23 (-0.14, 0.60)	0.13 (-0.36, 0.62)	0.010 (-0.39, 0.60)	0.14 (-0.35, 0.63)
3	Average daily ODE	–	–	-0.20 (-0.71, 0.31)	-0.10 (-0.61, 0.40)	-0.10 (-0.60, 0.40)	-0.13 (-0.63, 0.38)	-0.03 (-0.53, 0.47)
4	BPI severity	–	–	–	0.95 (-1.45, 3.35)	1.00 (-1.41, 3.41)	0.96 (-1.44, 3.37)	0.93 (-1.44, 3.29)
	BPI interference	–	–	–	-2.18 (-3.59, -0.77)*	-2.18 (-3.59, -0.77)*	-2.24 (-3.66, -0.83)*	-2.00 (-3.40, -0.60)*
5	Pain duration	–	–	–	–	0.11 (-0.24, 0.46)	0.08 (-0.27, 0.43)	0.04 (-0.31, 0.38)
6	Age	–	–	–	–	–	0.14 (-0.07, 0.36)	0.10 (-0.12, 0.31)
	Gender: *Female – Male*	–	–	–	–	–	-3.42 (-9.80, 2.97)	-2.92 (-9.21, 3.37)
7	Psychological distress	–	–	–	–	–	–	-0.38 (-0.67, -0.09)*
	ΔR^2	0.00	0.01	0.00	0.06	0.00	0.02	0.04
	ΔF	0.35	1.22	0.60	5.13*	0.38	1.37	6.48*
	Adjusted model R^2	-0.00	-0.00	-0.01	0.04	0.04	0.04	0.08
	Model F	0.35	0.78	0.72	2.51*	2.15	1.96	2.52*
				Factors associated with PRMQ retrospective memory scores				
1	Average daily OME	-0.01 (-0.04, 0.03)	-0.01 (-0.04, 0.03)	-0.01 (-0.04, 0.03)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.02)	-0.01 (-0.04, 0.03)	-0.00 (-0.03, 0.03)
2	Treatment duration	–	0.19 (-0.13, 0.52)	0.21 (-0.12, 0.55)	0.20 (-0.12, 0.52)	0.11 (-0.31, 0.54)	0.10 (-0.34, 0.53)	0.13 (-0.29, 0.56)
3	Average daily ODE	–	–	-0.13 (-0.58, 0.31)	-0.02 (-0.46, 0.41)	-0.02 (-0.45, 0.41)	-0.04 (-0.47, 0.40)	0.07 (-0.37, 0.50)
4	BPI severity	–	–	–	-0.55 (-2.63, 1.52)	-0.51 (-2.59, 1.57)	-0.52 (-2.61, 1.57)	-0.56 (-2.60, 1.48)
	BPI interference	–	–	–	-1.84 (-3.06, -0.62)*	-1.84 (-3.06, -0.62)*	-1.88 (-3.10, -0.65)*	-1.63 (-2.84, -0.42)*
5	Pain duration	–	–	–	–	0.10 (-0.20, 0.40)	0.08 (-0.22, 0.39)	0.04 (-0.26, 0.34)
6	Age	–	–	–	–	–	0.09 (-0.10, 0.27)	0.04 (-0.15, 0.22)
	Gender: *Female – Male*	–	–	–	–	–	-1.70 (-7.25, 3.84)	-1.20 (-6.62, 4.22)
7	Psychological distress	–	–	–	–	–	–	-0.38 (-0.64, -0.13)*
	ΔR^2	0.00	0.01	0.00	0.09	0.00	0.01	0.05
	ΔF	0.10	1.35	0.34	**7.52***	0.40	0.56	**8.97***
	Adjusted model R^2	-0.01	-0.00	-0.01	0.07	0.06	0.10	0.10
	Model F	0.10	0.73	0.60	**3.39***	**2.88***	**2.29***	**3.14***

* p<.050. ** p<.001.

Cognitive function and duration of opioid use

Cognitive function was poorer among intermediate- than long-term opioid consumers for PROMIS and retrospective memory scores, but not prospective memory (Figure 4.1). Independent samples *t*-tests revealed that mean PROMIS *t*-scores were lower in intermediate- (*n*=27; *M*=38.2, *SD*=8.2) than long-term opioid consumers (*n*=198; *M*=43.4, *SD*=9.4), *t*(223)=-2.85, *p*=.005, *d*=0.58. Mean *t*-scores for retrospective memory were significantly lower for intermediate- (*M*=41.9, *SD*=14.8) than long-term consumers (*M*=47.4, *SD*=13.5), *t*(221)=-2.11, *p*=.036, *d*=0.43. There were no differences for prospective memory (intermediate: *M*=40.3, *SD*=15.4; long-term: *M*=42.4, *SD*=15.8), *t*(222)=-0.77, *p*=.442, *d*=0.25).

Co-morbid factors. Cognitive impairment remained after controlling for co-morbid factors. A univariate ANOVA showed significantly lower PROMIS scores in intermediate-term consumers after accounting for K10 score and BPI interference, *F*(1, 167)=4.29, *p*=.040, *d*=0.47. Bayesian analyses provided anecdotal support for this effect, BF_{10}=1.65. There was also a moderate magnitude effect whereby intermediate consumers had poorer PRMQ retrospective memory than long-term consumers (*F*(1, 166)=3.73, *p*=.055, *d*=0.43), with limited support for this effect, BF_{10}=1.26. There remained no significant difference between consumption groups on prospective memory scores in these covariate analyses, *F*(1, 166)=0.237, *p*=.627, *d*=0.11, with moderate evidence in support of no effect of duration, BF_{01}=3.49.

Figure 4.1. *Mean t-scores (with 95%CIs) for the PROMIS, PRMQ prospective memory, and PRMQ retrospective memory, and results of independent sample t-tests for differences between intermediate- (n=27) and long-term (n=198) opioid consumers*
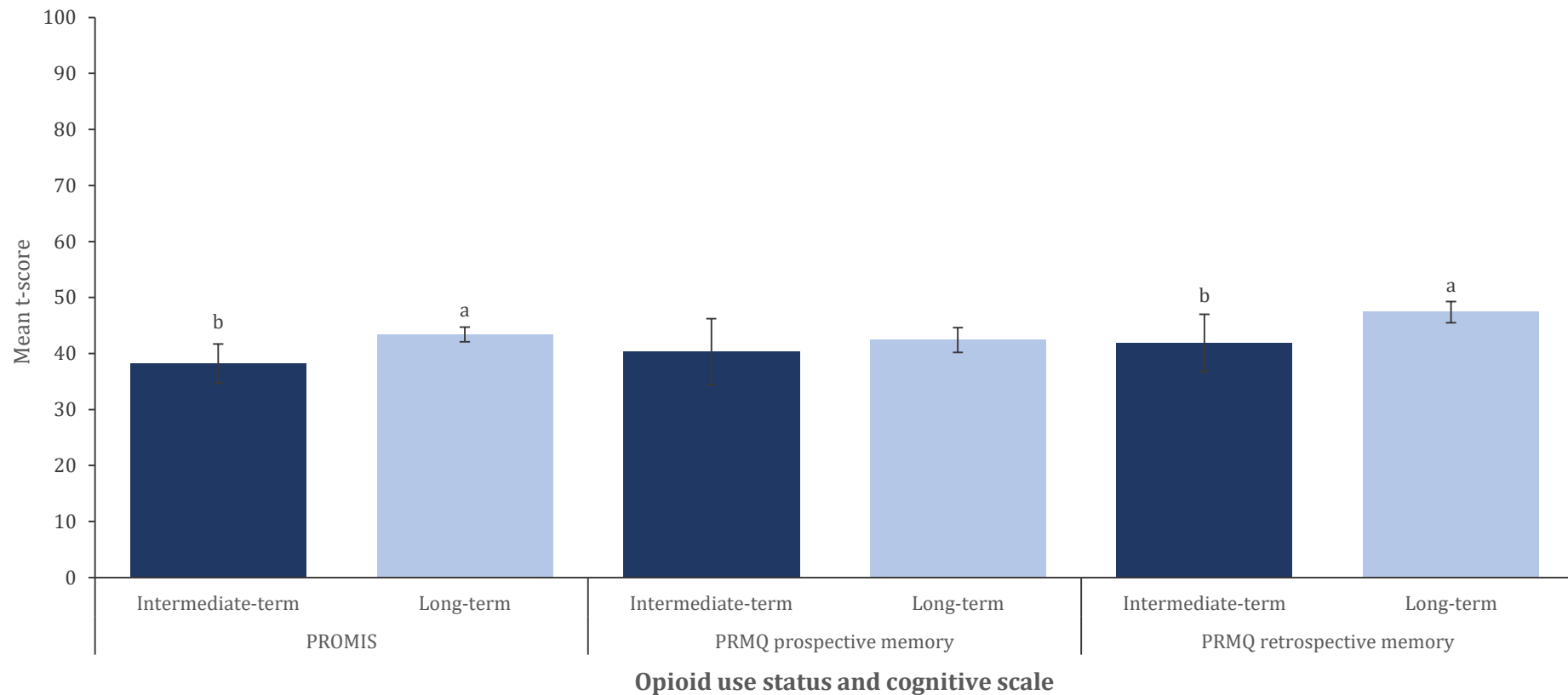
[a] Significantly different to intermediate-term opioid consumers, *p*<.050. [b] Significantly different to long-term opioid consumers, *p*<.050.

Note. t-scores are based on norms from reference groups from the U.S. (PROMIS scale) and U.K. (PRMQ scales) general population. All scores have a mean of 50 and standard deviation of 10 in these reference groups.

Association between cognitive complaints and physical injuries

PROMIS score accounted for significant variance in the likelihood of experiencing minor (10.6% of variance) or major (5.6%) non-workplace injuries (Table 4.4). This remained significant after controlling for covariates, suggesting a unique association between cognition and injuries. PROMIS score was not associated with frequency of workplace injuries, while PRMQ scores were not associated with any injury type. BPI interference had a significant, unique association with minor workplace injuries only.

Table 4.4. *Factors associated with the experience of physical injuries (hierarchical logistical regression analyses)*

Step	Variables in model	Minor injury, work		Minor injury, other		Major injury, work		Major injury, other	
		B	Adjusted OR (95%CI) [a]	B	Adjusted OR (95%CI) [a]	B	Adjusted OR (95%CI) [a]	B	Adjusted OR (95%CI) [a]
1	PROMIS score	-0.03	0.97 (0.93, 1.02)	-0.09	0.91 (0.85, 0.98)*	-0.03	0.97 (0.93, 1.02)	-0.05	0.95 (0.92, 0.99)*
2	PROMIS score	-0.03	0.97 (0.92, 1.01)	-0.09	0.91 (0.85, 0.99)*	-0.03	0.97 (0.93, 1.02)	-0.05	0.95 (0.92, 0.99)*
	PRMQ retrospective	-0.04	0.96 (0.97, 1.07)	0.02	1.02 (0.86, 1.21)	-0.02	0.98 (0.87, 1.10)	0.06	1.06 (0.98, 1.15)
	PRMQ prospective	0.00	1.00 (0.90, 1.12)	-0.02	0.98 (0.82, 1.17)	0.03	1.04 (0.91, 1.18)	-0.09	0.92 (0.84, 1.01)
3	PROMIS score	0.00	1.00 (0.94, 1.06)	-0.15	0.87 (0.77, 0.97)*	-0.02	0.98 (0.92, 1.04)	-0.05	0.95 (0.91, 1.00)*
	PRMQ retrospective	-0.01	0.99 (0.87, 1.13)	-0.02	0.98 (0.79, 1.23)	-0.01	0.92 (0.87, 1.14)	0.05	1.05 (0.97, 1.15)
	PRMQ prospective	-0.00	1.00 (0.88, 1.14)	0.04	1.05 (0.82, 1.34)	0.03	1.03 (0.89, 1.19)	-0.08	0.92 (0.83, 1.01)
	Age	-0.01	1.00 (0.95, 1.03)	0.05	1.05 (0.98, 1.12)	-0.01	0.99 (0.94, 1.04)	-0.02	0.99 (0.96, 1.02)
	Pain duration	-0.01	1.00 (0.94, 1.05)	0.08	1.08 (0.92, 1.26)	-0.01	0.99 (0.94, 1.05)	0.00	1.00 (0.96, 1.05)
	BPI severity	0.22	1.25 (0.81, 1.94)	-0.24	0.79 (0.36, 1.73)	0.24	1.27 (0.76, 2.11)	0.05	1.05 (0.74, 1.50)
	BPI interference	-0.34	0.71 (0.52, 0.97)*	-0.15	0.86 (0.56, 1.32)	-0.08	0.92 (0.66, 1.30)	-0.04	0.96 (0.78, 1.18)
	Opioid use duration	0.06	1.06 (0.96, 1.17)	0.39	1.47 (0.99, 2.19)	0.07	1.07 (0.96, 1.19)	0.03	1.03 (0.96, 1.11)
	Average daily OME	0.00	1.00 (1.00, 1.01)	-0.00	1.00 (0.98, 1.01)	0.01	1.01 (1.00, 1.01)	0.00	1.00 (0.99, 1.01)
	Average daily ODE	-0.13	0.88 (0.77, 1.01)	0.26	1.30 (0.72, 2.33)	-0.09	0.91 (0.78, 1.07)	0.06	1.06 (0.98, 1.15)
	K10 score	0.06	1.06 (0.99, 1.14)	-0.00	1.00 (0.88, 1.12)	-0.02	0.98 (0.91, 1.06)	0.01	1.01 (0.96, 1.07)

		Block X^2	Model X^2	R^2	Block X^2	Model X^2	R^2	Block X^2	Model X^2	R^2	Block X^2	Model X^2	R^2
	Model 1	1.53	1.53	0.11	6.42*	6.42*	0.11	1.27	1.27	0.02	6.73*	6.73*	0.06
	Model 2	1.30	2.83	0.04	0.05	6.48	0.11	0.27	1.53	0.02	3.41	10.14*	0.08
	Model 3	13.82	16.64	0.20	15.47	21.95*	0.35	6.25	7.78	0.11	5.16	15.30	0.13

[a] Odds ratio with 95% confidence interval. An OR of 1 indicates the event is equally probable in each group, >1 indicates that experiencing an injury was associated

with higher scores (e.g., higher PROMIS score), <1 indicates that experiencing an injury was associated with lower scores.

* $p<.050$; ** $p<.001$.

Discussion

This study examined factors associated with cognitive complaints in people with CNCP, differences in cognitive complaints based on opioid use duration, and the association between cognition and physical injuries. Participants reported a greater frequency of issues than reference populations, although these populations were from the U.S. and U.K. and may not have been representative. Additionally, recruitment strategies differed across these studies, meaning data may not be comparable. Nonetheless, this is consistent with several observational studies reporting subjective and objective cognitive deficits in CNCP groups [7-9, 33]. However, opioid dose and treatment duration were not associated with frequency of cognitive complaints on measures of prospective memory, retrospective memory, and general function. Other relevant factors such as pain and psychological distress may contribute to poor cognitive outcomes for CNCP cohorts.

Factors associated with cognitive complaints

The present results suggest that cognitive complaints are linked to pain and psychological distress among those with CNCP. Pain interference and psychological distress made significant, unique contributions to the frequency of cognitive complaints. Higher levels of pain interference were associated with more frequent complaints for prospective and retrospective memory, and higher levels of distress were additionally linked to more frequent general complaints (e.g., concentration lapses). This aligns with recent research reporting no differences in memory, attention, or executive function among those with CNCP depending on whether they took opioids, but poorer performance for both groups compared to healthy controls [9]. This suggests that pain may affect cognition to a greater degree than do opioids. Additionally, mood disorders may predict poor cognition. A recent meta-analysis found that depression severity was strongly correlated with memory, executive function, and attention in pain-free groups [12], with anxiety linked to deficits in working memory, processing speed and

inhibitory control deficits [13]. Both anxiety and depression have been linked to cognitive impairment in individuals with CNCP [33].

The role of pain interference and psychological distress in cognitive function is particularly important given their frequent co-morbidity with CNCP. In the present study, pain interference was high (7/10) and over half (59.6%) of respondents evidenced moderate-severe levels of distress. This finding mirrors that of a large-scale survey of Australians with CNCP (*N*=1,514), who evidenced high rates of moderate-severe depression (46.6%) and anxiety (22.8%) [3]. Further, a recent study on cognitive issues, chronic pain, and distress found high co-morbidity between pain interference and emotional distress [33]. This is likely due to the affective component of pain; emotional responses to pain may be a greater predictor of self-perceived cognitive function than pain itself [33]. This may also explain why pain severity scores were not uniquely associated with cognitive complaints in the current study.

Cognitive function and duration of opioid use

The lack of association between opioid dose and cognitive issues in the present study may relate to tolerance effects, which occurs when the body's pharmacologic response to psychotropic drugs decreases with repeated administration [34]. For opioids, this primarily applies to analgesic effects [34], though tolerance to cognitive effects may occur within days or weeks following initiation or dose change [35]. It is unclear whether tolerance develops at the same rate for the cognitive effects of opioids compared to analgesic effects. The present findings partially support this idea, with anecdotal support for poorer cognitive function in intermediate- (≤12 months) versus long-term consumers. However, most respondents (98.2%) were chronic consumers (i.e., >3 months) and had likely developed tolerance. Potentially, this may indicate an effect of opioid cessation related to side effects. Specifically, people who experience adverse effects (e.g., cognitive impairment) may cease taking opioids within less than a year of commencing use. This would explain why those who continue to use opioids in

the long-term evidence better cognitive function than those who have been taking opioids shorter-term.

Association between cognitive complaints and physical injuries

Notably, this study demonstrated an independent association between cognitive complaints and negative health outcomes (i.e., physical injuries) among people with CNCP, with cognitive issues closely related to experiencing minor and major injuries at home. This was less apparent for workplace injuries, likely due to a lack of statistical power; the rate of unemployment among the sample was high. Broadly, however, the present findings suggest that cognitive function is uniquely associated with experience of physical injuries. Given the potential for injuries to impact quality of life, identification of, and interventions for, cognitive issues may improve functional outcomes for people with CNCP.

Strengths and limitations

The use of an online mode of delivery enabled people who may not be able to attend laboratory settings (e.g., people with limited mobility) to participate. The PRMQ and PROMIS scales have demonstrated adequate correlations with objective and subjective measures of performance [24, 27]. However, subjective measures may not reflect objective functioning, with mixed findings regarding the association between subjective and objective cognitive task performance in people with CNCP [36]. This suggests that cognitive concerns may relate to co-morbid factors (e.g., mood, sleep) rather than objective performance [37]. Additionally, the survey used a self-selection, convenience design, which means people who felt strongly about opioids and cognition may have been more likely to participate than those with moderate views. The cross-sectional design also meant that the temporal order of events (e.g., changes in cognitive function with fluctuating opioid dose) could not be examined.

Finally, while the study included multiple covariates, it did not account for several. Sleep disorders were not examined, although disturbed sleep is a common complaint amongst those

with CNCP and can impair cognition [38, 39]. Additionally, the questionnaire used in this study did not explore the effects of different opioid types (e.g., non-typical opioids) on cognitive function nor did it specifically ask about use of gabapentinoids, which are commonly used for CNCP and may impair cognition. Future research may seek to examine these co-morbid factors to ensure all covariates are accounted for.

Conclusions

This study highlighted that opioid use is not always related to cognitive impairment, but that people with CNCP often experience cognitive dysfunction. Cognition appears to be related in part to emotional responses to pain: cognitive complaints are more common when individuals experience high levels of distress or pain interference. Importantly, cognitive complaints are in turn associated with a higher likelihood of experiencing physical injuries. Given this, promoting healthy cognitive function and injury awareness in people with CNCP should be a clinical priority.

Acknowledgements

Conflict of Interest

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CHAPTER 5: KNOWLEDGE OF IMPAIRMENT AND SIDE EFFECTS, DRIVING BEHAVIOURS, AND RISK PERCEPTIONS OF OPIOIDS AND DRIVING IN PEOPLE WITH CHRONIC NON-CANCER PAIN

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Preface

The previous studies described in this thesis—located in Chapters 1, 2, and 3—examined cognitive function among people who are prescribed opioids for CNCP. These studies highlighted that people with CNCP may experience some cognitive dysfunction, and that this can be related to real-world harms (e.g., physical injuries). A key area of harm not examined by these studies relates to the impacts of pain and opioids on driving, which is a real-world manifestation of cognitive function. Use of prescribed opioids has been associated with an increased risk of motor vehicle collisions (MVC) across several studies, but it is not well understood as to how people with CNCP perceive these risks and whether they engage in behaviours that might mitigate risks.

Given this, *Study 4* examined how opioid use impacts driving, how people with CNCP might overcome driving-related impairment (e.g., by engaging in safety precautions), and whether people with CNCP perceive driving after taking opioids to be risky. Risk perceptions are closely associated with actual driving behaviours, so we also wanted to examine what factors are associated with risk perceptions for driving after taking opioid medicines (e.g., current use of opioids). This study used an online delivery mode to increase accessibility, and included assessment of key co-variates (e.g., driving experience) in order provide a more nuanced understanding of real-world driving behaviours among people with CNCP.

Abstract

Introduction

Opioids—often prescribed for chronic non-cancer pain (CNCP)—can impair driving ability, but consumers may be unaware of risks and side effects. This study examined knowledge of opioid side effects and driving-related risks in opioid consumers versus non-consumers with CNCP.

Methods

In this cross-sectional study, people with CNCP (n=218) who had ever held a full driver's licence completed an online survey. Participants reported current use of opioids (including non-use), knowledge of side effects and past-year driving behaviour. They rated the likelihood of motor vehicle collision (MVC) involvement or legal consequences when driving under the influence (DUI) of alcohol or prescribed opioids. Key covariates (e.g. cognitive complaints) were included.

Results

Most participants (73% female) drove in the past year and 42% currently used opioids. While 65% of consumers had received information about driving impairment, over 80% drove within 3 hours of using opioids. Legal and MVC risk ratings were lower in current than non-consumers. Knowledge of side effects was similar between groups. Lower opioid risk ratings were related to lower alcohol risk ratings and past-year DUI of opioids. Lower MVC risk ratings were associated with current opioid use, cognitive dysfunction, and poorer knowledge of side effects.

Conclusions

While many people with CNCP receive information about opioid-related impairment, DUI of opioids is common. Perceived legal and MVC risks are also lower among current than non-consumers. Prescribers should engage consumers in high-quality discussions to help them understand the risks. Related factors, such as cognitive impairment, should be monitored.

Introduction

Prescription opioid use is widespread in Australia. In 2016–17, as many as 9 in 10 Australians who were prescribed opioids took these medicines for chronic non-cancer pain (CNCP) [1]. However, key bodies such as the Centers for Disease Control and Prevention advise against the use of opioids for CNCP [2]. Additionally, many people who take opioids for CNCP use strong opioids (i.e., Schedule 8 opioids such as oxycodone) [3]. Use of strong opioids is of concern as it can lead to unwanted side effects [4], including poisoning and death [5, 6]. Additionally, driving after taking strong opioid medicines may increase the risk of involvement in motor vehicle collisions (MVC) [7-9]. However, the extent to which people with CNCP are familiar with driving-related risks is not known.

Previous research has shown that the perceived risks of driving under the influence (DUI) predict real-world driving behaviours. Specifically, a higher perceived risk of adverse safety (i.e., motor vehicle collision involvement) or legal (e.g., apprehension by police for erratic driving) outcomes is associated with a lower likelihood of DUI of alcohol and illegal drugs [10, 11]. People who use drugs also often perceive DUI to be less risky than do non-consumers [12]. Additionally, consumers may perceive the risks of DUI of opioids to be less than for alcohol given that these medicines are prescribed by a doctor. This is problematic given that these medicines produce sedative and impairing effects similar to those of alcohol [4, 13].

Risk perceptions reflect a person's perceived susceptibility to threat, and involve cognitive appraisal of the likelihood of adverse outcomes versus benefits for a particular behaviour [14]. Risk perceptions are often predictive of health behaviours (such as driving under the influence) [14], and can be used as an indicator of real-world driving behaviours. In recent years, several studies have examined risk perceptions of driving after taking opioids and actual driving behaviours among people with CNCP [15, 16]. However, little is known about the association between risk perceptions, receipt of warnings about impairment, and associated factors. Given this, this cross-sectional study aimed to explore risk perceptions about DUI of opioids, driving-related safety behaviours, and previous DUI of prescription opioids among

people with CNCP, while also exploring related factors (e.g., pain, cognitive impairment, knowledge of other opioid side effects). The study examined this topic via four specific research questions:

1. To what extent are people with CNCP aware of driving-related risks and other side effects, and does this differ by opioid use status (never, lifetime but not current, current strong opioids, and current weak opioids)? Where do people source this information?

2. Do opioid consumers take precautions when driving with regards to opioid use?

3. Do people with CNCP perceive DUI of opioids to be less risky than for alcohol (over the limit), and does this differ by opioid use status (current, lifetime, never)?

4. What factors are associated with perceived increased risks of opioid DUI?

Methods

Study participants

From May–September 2019, participants aged 18–65 years who resided in Australia were recruited via advertisements on social media, pain organisation websites, and via Prolific Academic. Inclusion criteria included experience of chronic non-cancer pain (≥3 months) within the past year, lifetime history of having a full driver's licence, English as a first language, and access to a phone or computer to complete the survey. Exclusion criteria comprised current use of methadone or buprenorphine—in Australia, these medicines are indicated for the treatment of opioid use disorder—and current cancer diagnosis.

Participants were categorized as opioid non-consumers (i.e., never used opioids in their lifetime), lifetime consumers (i.e., used opioids in their lifetime but not currently) and current consumers (i.e., used opioids at the time of the survey). Current consumption was also classified as either 'weak' (i.e., Schedule 4 opioids—codeine and tramadol) or 'strong' (i.e., Schedule 8).

Procedure

In this cross-sectional study, participants completed a brief online questionnaire administered via REDCap. Survey responses were anonymous. Informed consent was obtained at the beginning of the survey. Upon completion, participants could enter the draw to win an AUD$50 voucher. Ethics approval was granted by the Tasmanian Social Sciences Human Research Ethics Committee (#H0018009).

Materials

Key measures are described below. The full survey is described in detail in Appendix C.

Demographic information. Participants were asked to report on age, gender identity, education level, and current employment status.

Pain severity, conditions, and duration. Participants reported the duration of their pain (months or years), the pain conditions they currently experienced, and whether they had

experienced pain on the day of survey completion. Pain severity was detailed via the Brief Pain Inventory (BPI) [17]. The severity scale consists of four items for which respondents rate pain severity (worst, least, currently, and on average over the last 24 hours) on an 11-point Likert scale (anchors: 0 'no pain'–10 'pain as bad as you can imagine'). Higher scores indicate greater pain severity.

Sleep disorders. Participants were asked whether a doctor had diagnosed them with a sleep disorder within the past 12 months. They also used the Epworth Sleepiness Scale to indicate the likelihood of falling asleep during everyday activities (e.g., watching television), via a 4-point Likert scale (anchors: 0 'highly unlikely'–3 'highly likely'). Ten items are summed to provide a total score, with higher scores indicating greater likelihood of a sleep disorder [18].

Mental health conditions. Participants were asked whether a doctor had diagnosed them with, or prescribed medicines for, a mental health condition within the past 12 months.

Patient Reported Outcomes Management Information System (PROMIS) Item Bank v2.0 Cognitive Function. The PROMIS Item Bank v2.0 Cognitive Function 4-item scale was used to assess past week cognitive failures [19]. This scale comprises 4 items assessing the frequency of various cognitive 'problems'. For example, "I have had difficulty multi-tasking." Responses were rated on a 5-point Likert scale (anchors: 1 'never'–5 'very often'). All items were summed to provide a total score, with higher scores indicating greater frequency of cognitive complaints. The PROMIS scale is an updated version of the PROMIS Applied Cognition-Abilities (AC-A) scale. This has demonstrated good concurrent validity, evidencing strong positive correlations with existing gold-standard measures of cognitive function including the Mini-Mental State Exam (MMSE) and the Saint Louis University Mental Status (SLUMS) test [20]. Further, the PROMIS AC-A has a high correlation with scores on the Instrumentals of Activities of Daily Living Scale (IADLS), indicating an association with real-world outcomes [20].

Opioid and concomitant medicines. Participants reported lifetime and current opioid use. Where they reported current use, participants were asked to report their typical daily dose, main opioid used, and patterns of use in the last 12 months (duration, frequency). Examples of

common brand names were provided for each opioid type and participants could select milligrams or micrograms as the dose. They also reported current prescribed use of benzodiazepines, antipsychotics, antidepressants, and gabapentinoids.

Opioid dose. For participants who reported current use of opioids, opioid medicines were converted to average daily opioid doses expressed as oral morphine equivalents (OME; mg) [21]. Where participants indicated use of multiple different opioids, only dose for the main opioid used was calculated. This was to reduce the potential for poor recall of use of breakthrough doses.

Perceptions of driving risk and knowledge of opioid side effects. Participants rated the likelihood of being involved in a motor vehicle collision (MVC) or intercepted by police for erratic driving if they drove soon after consuming opioids (as prescribed) or alcohol (over the legal limit). Responses were recorded on a 5 point-Likert scale (anchors: 1 'very unlikely'–5 'very likely'). They also reported whether anyone had ever explained the risks of driving soon after taking opioids, and identified common opioid side effects (e.g., constipation) from a list. The list comprised known side effects from opioids, with participants instructed to select any side effects that they believed were associated with use of opioids. An 'other' option was provided. For both outcomes, participants were asked where they obtained this information.

Driving behaviours. Driving behaviours over the past 12 months were assessed by asking participants to report frequency of driving, average hours and kilometres driven in a typical week, current licence/s and duration of longest-held licence, penalties incurred (i.e., demerit points lost), and reasons for not driving (if they reported not having driven within the past 12 months). Additionally, participants described safety behaviours relating to driving when in severe pain or soon after taking opioid medicines (e.g., choosing not to drive) and were asked whether they had driven within 3 hours of taking an opioid medicine in the past 12 months. Questions about opioid-related safety behaviours and driving under the influence of opioids were only asked of participants who reported using opioids within the past 12 months.

Statistical analysis

Power analysis was conducted using G*Power 3.1.9.2, with a proposed target sample size of 150. This calculation differed for different study research questions but yielded the same sample size. Research questions 1 and 2 involved descriptive analysis only, and did not require power analyses. For research question 3 ("Do people with CNCP perceive DUI of opioids to be less risky than for alcohol (over the limit), and does this differ by opioid use status (current, lifetime, never)?"), a sample size of 150 provided 80% power or greater to detect an odds ratio of 1.9 or higher for a predictor as statistically significant (alpha=0.05) with multiple predictors and the squared multiple correlation between the given predictor and the control variables was 0.1 or 0.2. For research question 4 ("What factors are associated with perceived increased risks of opioid DUI?"), assuming a meaningful effect (R^2=0.19, or 10% of variance), a sample size of 150 generated above 95% power to identify a statistically significant change in R^2 for a model including 4 covariates and a predictor.

Missing values. Individual missing values for the BPI were imputed via PRELIS 2.80, which uses response pattern scoring to determine missing values based on values taken from identical response patterns from other participants [22]. Less than 1% (0.9%) of data were generated in this way. The PROMIS Cognitive Function v2.0 was scored via the HealthMeasures service, which converts raw scores to standardised *t*-scores (*M*=50, *SD*=10) based on normative data derived from the U.S. general population [23, 24]. Missing values were accounted for via the HealthMeasures scoring service, which uses response pattern scoring [25]. Higher *t*-scores indicate fewer cognitive failures.

Statistical analyses. Analyses were conducted in jamovi version 1.1.5.0 [26], with separate analyses conducted for each specific research question (Table 5.1).

Research Question 1. Awareness of driving-related risks, knowledge of side effects, and sources of information were assessed descriptively. Differences in awareness of driving-related risks were assessed descriptively. Differences in mean number of correctly identified side effects by opioid use status (never, lifetime but not current, current strong opioids, and current

weak opioids) were assessed using a one-way ANOVA with independent samples *t*-tests planned as post hoc comparisons to examine differences between groups.

Research Question 2. Safety behaviours with regards to driving after taking opioids and when experiencing pain were assessed via descriptive analysis.

Research Question 3. Risk perceptions for opioids versus alcohol were assessed via Friedman non-parametric repeated measures ANOVA for i) MVC involvement, and ii) apprehension by police. To determine whether opioid use status impacted perceptions of opioid-related driving risk, we conducted Kruskal-Wallis non-parametric one-way ANOVA to compare risk ratings for opioids by opioid use status (never, lifetime but not current, current strong opioids, and current weak opioids). A separate Mann Whitney-U ANOVA was conducted for each outcome (risk rating for MVC, risk rating for police apprehension) with Dwass-Steel-Critchlow-Fligner pairwise comparisons to identify differences between the groups.

Research Question 4. Factors associated with perceived risks of driving after taking opioids was assessed via two linear regressions assessing associations between predictors and outcomes for i) MVC involvement, and ii) apprehension by police. Analyses were guided by theory, with opioid use status entered in Step 1 to determine if this uniquely accounted for variance in risk ratings. Demographic information (age, gender identity) were added in Step 2, and cognitive complaints (PROMIS t-score) was added in Step 3. In Step 4, we added hours driven in the past week, and in Step 5 we included the equivalent risk ratings for alcohol (i.e., where MVC risk ratings for opioids was the outcome, we included MVC risk ratings for alcohol as a predictor). Finally, number of opioid side effects correctly identified and awareness of opioid-related driving risks (i.e., yes, no) were added in Step 6.

Results

Survey responses were exported from REDCap to Microsoft Excel for cleaning. After removal of incomplete records (n=116), we screened records for eligibility and excluded participants who did not meet inclusion criteria (n=68). Reasons for exclusion included failure to provide consent (n<5), experience of pain for <3 months (n=20), current cancer diagnosis (n<5), current use of buprenorphine or methadone (n=14), no driver's licence in their lifetime (n=11), and age unspecified or outside 18–65 (n=20).

Participant demographic and clinical characteristics

Demographic and clinical characteristics. Included participants (n=218; 66 recruited via Prolific Academic) were predominantly female (72.9%) with a median age of 46 years (Table 5.2). Over two-thirds (68.3%) had completed Year 12, and 20.5% were currently unemployed.

Pain and opioid use. Participants reported experiencing pain for a median of 7 years. Common pain conditions included back pain, arthritis, and frequent or severe headaches. Over 9 in 10 people experienced pain on the day of survey completion, with a mean past 24 hour average pain severity of 4.6 out of 10. Most participants had taken opioids in their lifetime, with 42.2% reporting current use. Of these, most (81.3%) had been taking opioids daily or almost daily for >6 months. The two most commonly consumed opioids were codeine (28.6%) and oxycodone (22.0%). The median usual opioid dose among current consumers was 30mg OME, though this varied according to frequency and duration of opioid use.

Co-morbid factors. 1 in 2 (28.9%) participants had been diagnosed with a sleep disorder in the past year and 50.5% had been diagnosed with or prescribed medicine for a mental health condition. Use of concomitant medicines, particularly antidepressants, was common. Participants reported a mean cognitive scale t-score of 38.5 (SD=8.5). A one-sample t-test revealed that this was significantly lower than norms based on the U.S. general population (M=50, SD=10), p<.001. A one-way ANOVA revealed no significant differences in cognition by opioid use status (never, lifetime, current weak, current strong), F(3, 92.4)=2.01, p=.117.

Table 5.1. *Demographics, clinical characteristics and driving behaviour, all participants (n=218)*

Characteristic	Estimate
Demographic characteristics	
Median age (Interquartile range)	46.0 years (32.0–56.0)
% female	72.9
% completed Year 12 or above	68.3
% unemployed	20.6
% Pain condition, past year	
Low back pain	68.3
Arthritis/rheumatism	44.5
Frequent or severe headaches	44.5
Fibromyalgia	25.7
Visceral (organ) pain	5.5
Complex Regional Pain Syndrome (CRPS)	7.4
Other	41.3
Pain duration and severity	
Median pain duration, years (range)	7.0 (0.4–62.0)
% experienced pain today	90.4
Mean BPI severity score, current pain	4.6 (*SD*=2.5)
Mean BPI severity score, average pain in the past 24 hours	4.9 (*SD*=2.1)
% Lifetime and recent use of any opioid	
Never used any opioid	16.5 (*n*=36)
Used any opioid in lifetime (but not currently)	41.3 (*n*=90)
Used any opioid currently	41.7 (*n*=92)
Mainly used a strong opioid currently [a]	19.3 (*n*=43)
Mainly used a weak opioid currently [a]	19.7 (*n*=44)
Patterns of opioid use, all current consumers (%) (*n*=92)	
Used them daily or almost daily, for >6 months	81.3
Used them daily or almost daily, for <6 months	4.4
Used them intermittently, for >6 months	12.1
Used them intermittently, for <6 months	2.2
Main opioid type, current consumers (%) (*n*=92)	
Codeine	28.6
Oxycodone	22.0
Tapentadol	15.4
Tramadol	18.7
Other	15.4
Median usual opioid dose (OME [b]; mg), current consumers (*n*=85) [c]	
Total, current consumers	30.0 (0.2–338.0)
Current opioid consumers – strong opioids (n=42) [c]	40.0 (0.4–338.0)9.8 (7.5–300.0)
Current opioid consumers – weak opioids (n=43) [c]	20.0 (0.2–300.0)5.0 (25–7.5)
Sleep and mood disorders, past 12 months	
% diagnosed with a sleep disorder	28.9
Median Epworth sleepiness scale score from 0–24 (range)[d]	7.0 (0.0-22.0)
% diagnosed with/prescribed medicine for mental health condition	50.5
Mean cognitive scale *t*-score for cognitive complaints, past week	
All participants (n=218)	38.5 (*SD*=8.5)
Never used any opioid (n=36)	40.2 (*SD*=8.4)
Used any opioid in lifetime (but not currently) (n=90)	39.3 (*SD*=8.0)
Used a strong opioid currently (n=43)	36.5 (*SD*=7.0)
Used a weak opioid currently (n=44)	38.1 (*SD*=10.5)

Characteristic	Estimate
% Drove in the past year, participants who provided a response	
Total, all participants (n=218)	97.2
Never consumed opioids (n=36)	94.4
Lifetime opioid consumers (n=90)	95.6
Current opioid consumers (n=91)	100.0
% Drove within 3 hours of taking an opioid in the past year, current consumers	
% drove within 3 hours, strong opioid consumers (n=43)	81.4
% drove within 3 hours, weak opioid consumers (n=44)	81.8
% Received information on opioid-related driving impairment	
Total, all participants who provided a response (n=216)	62.0
Never consumed opioids (n=36)	28.6
Lifetime opioid consumers (n=90)	72.2
Current opioid consumers (n=91)	65.0
Current opioid consumers – strong opioids (n=43)	66.7
Current opioid consumers – weak opioids (n=44)	61.4

[a] 5.4% (*n*=5) of current opioid consumers (*n*=92) did not provide details of main opioid type.

[b] Oral morphine equivalents were calculated based on the conversion scale in Nielsen et al. [21].

[c] 'Weak opioids' comprised Schedule 4 opioids (i.e., codeine, tramadol) while 'strong opioids' comprised Schedule 8 opioids (e.g., morphine, oxycodone, tapentadol). 7.6% (*n*=7) of current opioid consumers (*n*=92) did not provide sufficient information to calculate usual dose.

[d] Epworth sleepiness scale scores are in the "normal" range (0–10) [18].

Note. Some participants did not respond to all questions. The base *n* has been provided in parentheses for break-downs by group.

Driving behaviour. Over 9 in 10 (97%, *n*=212) participants had driven a motor vehicle in the past 12 months. Three-quarters (76%) of these had held a full driver's licence for more than 10 years, 14.7% for 3-10 years, and 9.0% for ≤2 years. Participants drove for a median of 6 hours per week (*M*=9.3, *SD*=11.8). Almost one-third (32%) drove daily, 28% drove 4-6 days per week, 22% drove 2-3 days per week, and 18.3% drove once per week or less often. Most (89%) had not lost any demerit points in the previous 12 months, with smaller proportions reporting losing 1-3 (10.4%) or ≥4 (<1.0%) points. None had lost their licence in the previous 12 months.

Impacts of pain and opioids on driving. Over half of people who had driven in the past 12 months (*n*=212) reported that severe pain worsened their driving ability (Figure 5.1). Among people who had driven in the past 12 months and currently used opioids, 72% of strong

opioid consumers and 80% of weak opioid consumers said opioids did not impact their driving ability (Figure 5.1). Around 4 in 5 opioid consumers had driven within 3 hours of taking an opioid in the past 12 months, regardless of whether they used strong or weak opioids (Table 5.1). The median number of days driven within 3 hours of taking an opioid was 144 days (IQR: 10.5–358.0) for weak opioid consumers, and 180 (IQR: 7.5–365.0) for strong opioid consumers.

Figure 5.1. *Perceived effects of severe pain and prescribed opioid use on driving ability (per cent of participants who had driven in the past 12 months)*
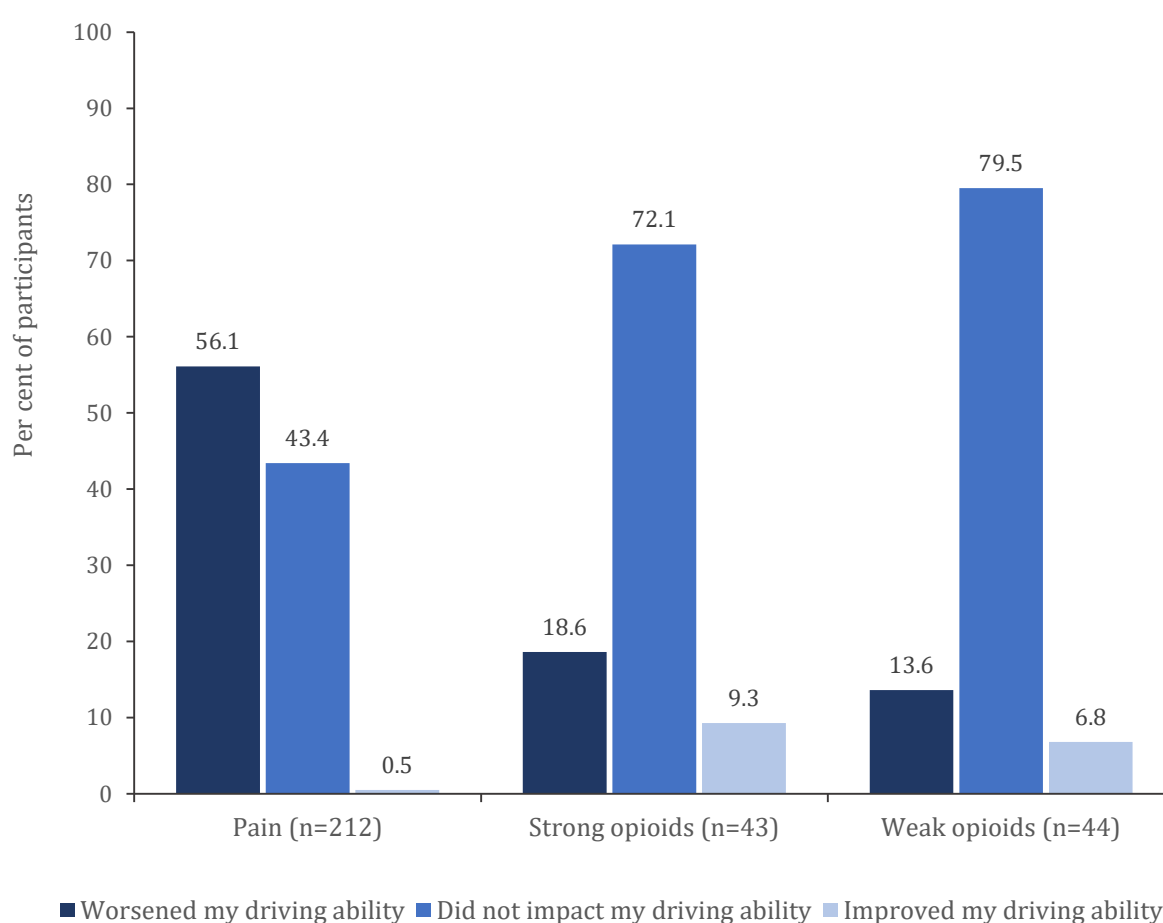
Note. Denominators: 'Pain' is participants who reported driving in the past 12 months (*n*=212) and did not use opioids; 'Strong opioids' is participants who reported having driven in the past 12 months and who currently used strong opioids (*n*=43); 'Weak opioids' is participants who reported having driven in the past 12 months and who currently used weak opioids (*n*=44).

Knowledge of driving-related risks and other side effects, and safety precautions taken

Over half (62%) of participants had received information about the effects of opioids on driving (Table 5.1). This figure was higher for people with current (65%) or lifetime (72%) opioid use, compared to those who had never used opioids (29%). Among current consumers, around two-thirds (67%) of people who used strong opioids had been informed about impairment effects. This was slightly higher than for people who used weak opioids (61%).

Overall, participants (*n*=218) correctly identified a mean number of 5.0 (*SD*=3.2) opioid side effects, out of 11 listed side effects. Mean number of correctly identified opioid side effects did not significantly differ between people who had never used opioids (*M*=5.3, *SD*=3.2), those with lifetime use (*M*=5.3, *SD*=3.0), and those who currently used strong (*M*=5.1, *SD*=3.5) or weak (*M*=5.0, *SD*=3.5) opioids, *F*(3,209)=0.11, *p*=.956 (Figure 5.2).

Figure 5.2. *Mean number of opioid side effects correctly identified, by opioid use status*
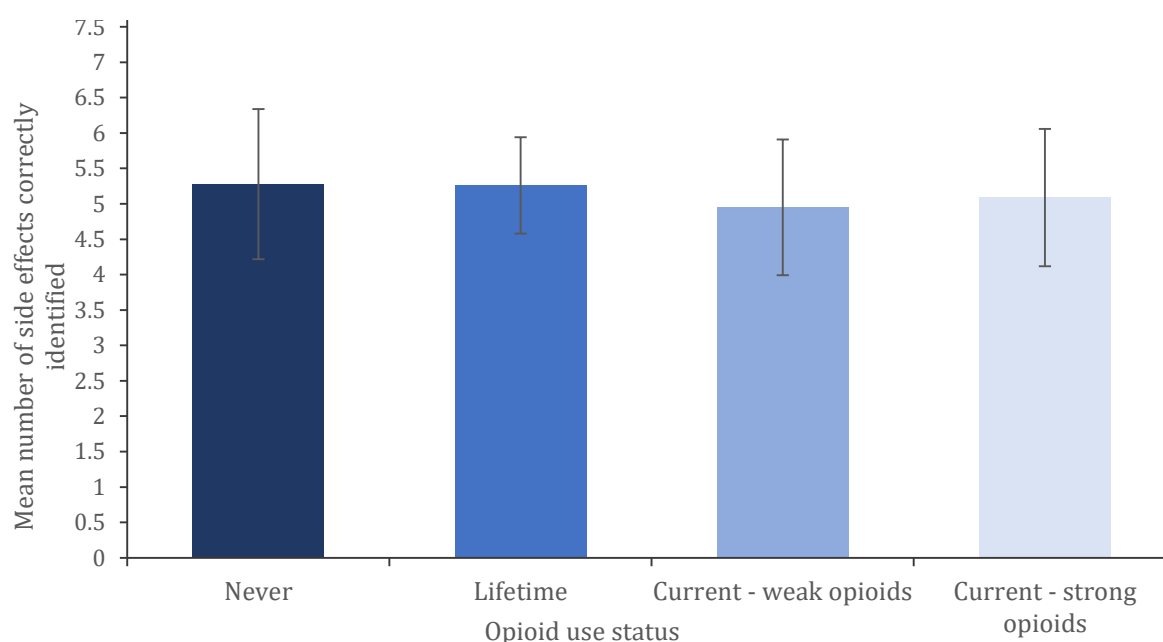
Note. Denominators: 'Never' is people who reported not having used any opioids in their lifetime (*n*=36); 'Lifetime' is people who reported having used opioids in their lifetime, but not currently (*n*=90); 'Current – weak opioids' is people who reported current use of codeine or tramadol (*n*=44); 'Current – weak opioids' is people who reported current use of fentanyl, morphine, oxycodone, or tapentadol (*n*=43).

Among people who currently used any opioid and provided a response (*n*=91), the most common sources of information for both opioid side effects and driving-related impacts were general practitioners (GPs), pharmacists, and medicine labels (Figure 5.3).

Figure 5.3. *Sources of information on opioid side effects and the effects of opioids on driving ability, people who currently consumed either strong (n=43) or weak (n=44) opioids (per cent of participants who were informed enough to respond)*
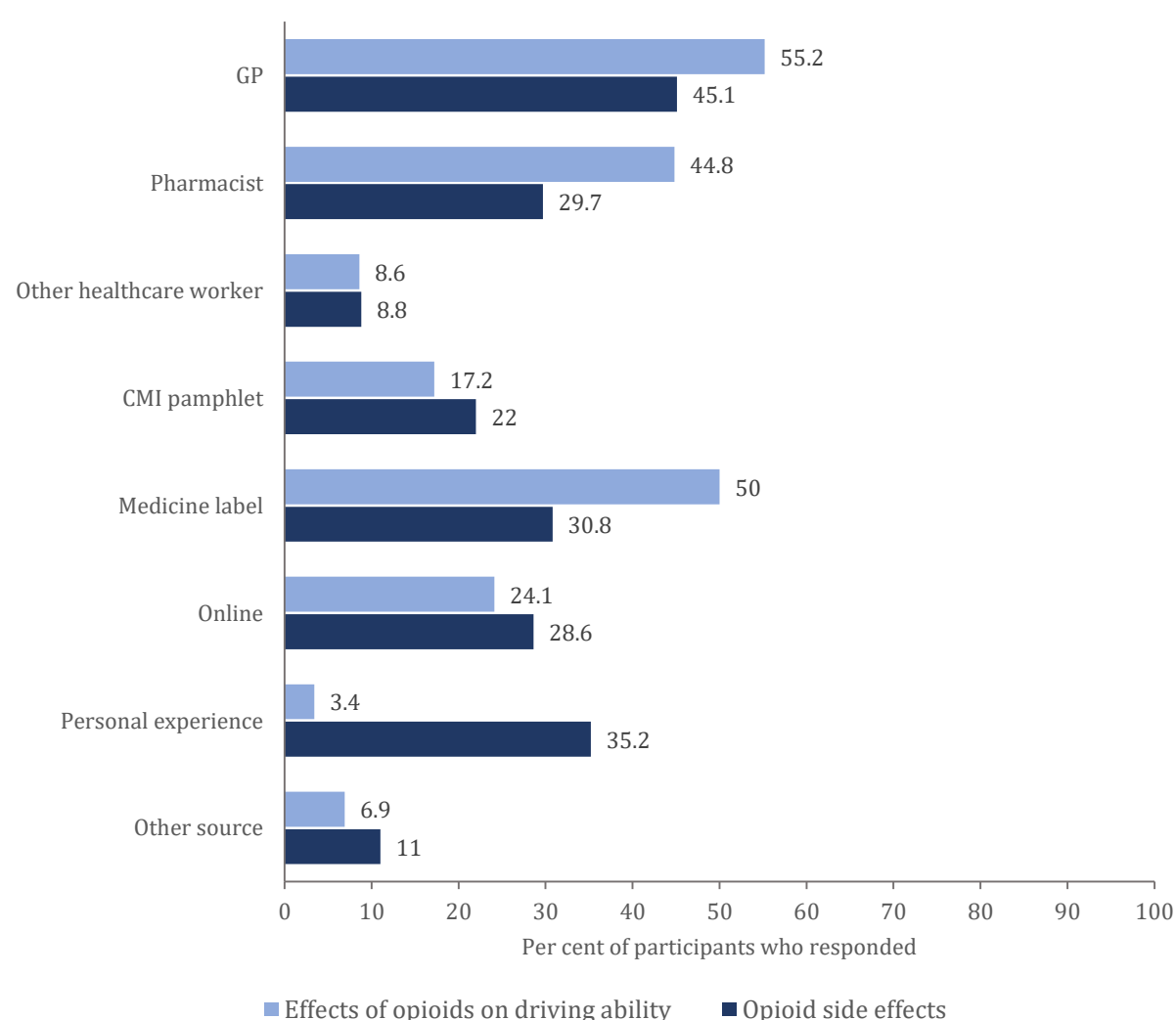
Note. Denominators: 'Effects of opioids on driving ability' is participants who indicated that they currently consumed any opioid, had received information about the effects of opioids on driving, and provided a response (*n*=58); 'Opioid side effects' is participants who currently used any opioid and provided a response (*n*=91). CMI=Consumer Information Pamphlet.

Safety precautions. Two-thirds (66%) of all recent drivers (*n*=212) said they took safety precautions in regards to driving when experiencing severe pain. Just under half (47%) of drivers who currently used opioids (*n*=91) said they had taken safety precautions with regards to driving while taking opioids in the past 12 months.

Driving when pain is severe. Among participants who took precautions with regards to severe pain and driving (*n*=139), 78% did not drive if pain was severe, 45% drove for only short distances, 22% drove only on familiar routes, 19.4% drove more slowly, 12.2% stopped driving entirely, and 5.8% took other precautions regarding driving when pain was severe.

Driving soon after taking prescription opioids. Among participants who currently used opioids and took precautions with regards to opioid use and driving (*n*=43), 63% did not drive soon after taking opioids, 21% drove for only short distances, 18.6% stopped driving entirely, 14.0% drove only on familiar routes, 7.0% took other medications to counter any side effects of opioids, 4.7% stopped taking opioids entirely, 4.7% drove more slowly, and 11.6% took other precautions when driving soon after taking opioids.

Perceptions of driving-related risks

Opioids compared to alcohol. Among participants who had driven in the past 12 months, there was a perception that driving soon after taking opioids was less risky than driving under the influence (DUI) of alcohol (Figure 5.4). A Friedman non-parametric repeated measures ANOVA revealed that mean risk ratings for being involved in a motor vehicle collision (*n*=197 respondents) were significantly higher for DUI of alcohol (*M*=4.0, *SD*=1.3) than for driving soon after taking prescription opioids (*M*=3.2, *SD*=1.4), Friedman X^2_1=39.2, *p*<.001. Similarly, mean risk ratings for being apprehended by police for erratic driving (*n*=198) were significantly higher for alcohol (*M*=4.2, *SD*=5.0) than opioids (*M*=3.3, *SD*=3.0), Friedman X^2_1=72.5, *p*<.001.

Figure 5.4. *Perceived risk of motor vehicle collision involvement or apprehension by police for erratic driving if driving soon after taking prescribed opioids or alcohol, people who had driven a motor vehicle in the past 12 months (n=212) (per cent)*
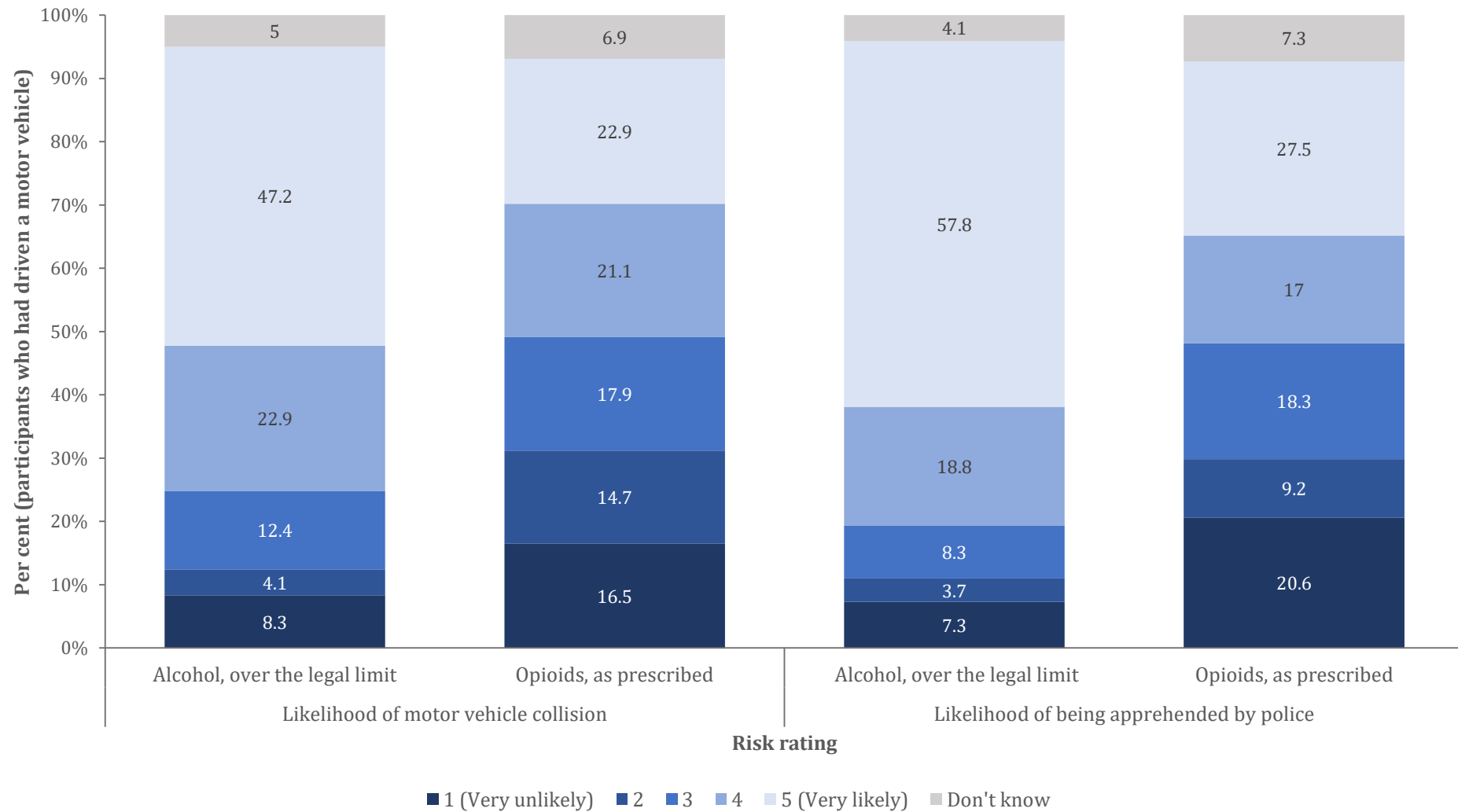
Perceptions of risk by opioid use status.

Risk of motor vehicle collision. Mean risk ratings for the likelihood of MVC involvement if driving after taking opioids significantly differed according to opioid use status, Kruskal-Wallis X^2_3=35.2, p<.001 (Figure 5.5). Dwass-Steel-Critchlow-Fligner pairwise post hoc comparisons showed that mean risk ratings for MVC were significantly lower among people who currently used strong opioids compared with lifetime (W=7.26, p<.001) and never consumers (W=6.03, p<.001). Risk ratings were also significantly lower for people who currently used weak opioids compared with lifetime (W=4.59, p=.006) and never consumers (W=4.03, p=.023). There were no significant differences between lifetime and never consumers (W=0.27, p=.997) or between current consumers who took strong or weak opioids (W=3.28, p=.093).

Risk of police apprehension. Mean risk ratings for the likelihood of being apprehended by police for erratic driving if driving after taking opioids differed according to opioid use status, Kruska-Wallis X^2_3=16.7, p<.001 (Figure 5.5). Dwass-Steel-Critchlow-Fligner pairwise comparisons showed that mean risk ratings for police apprehension were significantly lower among people who currently used strong opioids compared to lifetime (W=4.63, p=.006) and never consumers (W=4.75, p=.004). However, there were no significant differences for people who currently used weak opioids compared to lifetime (W=2.95, p=.157) and never consumers (W=3.32, p=.088). There were also no significant differences between lifetime and never consumers (W=1.41, p=.753), or current consumers who took strong or weak opioids (W=1.32, p=.787).

Figure 5.5. *Mean ratings (with 95%CIs) for the risk of motor vehicle collision involvement or police apprehension when driving after taking prescription opioids among participants who reported driving in the past 12 months, by opioid use status (currently used strong opioids, currently used weak opioids, lifetime use of any opioid, never used any opioid)*
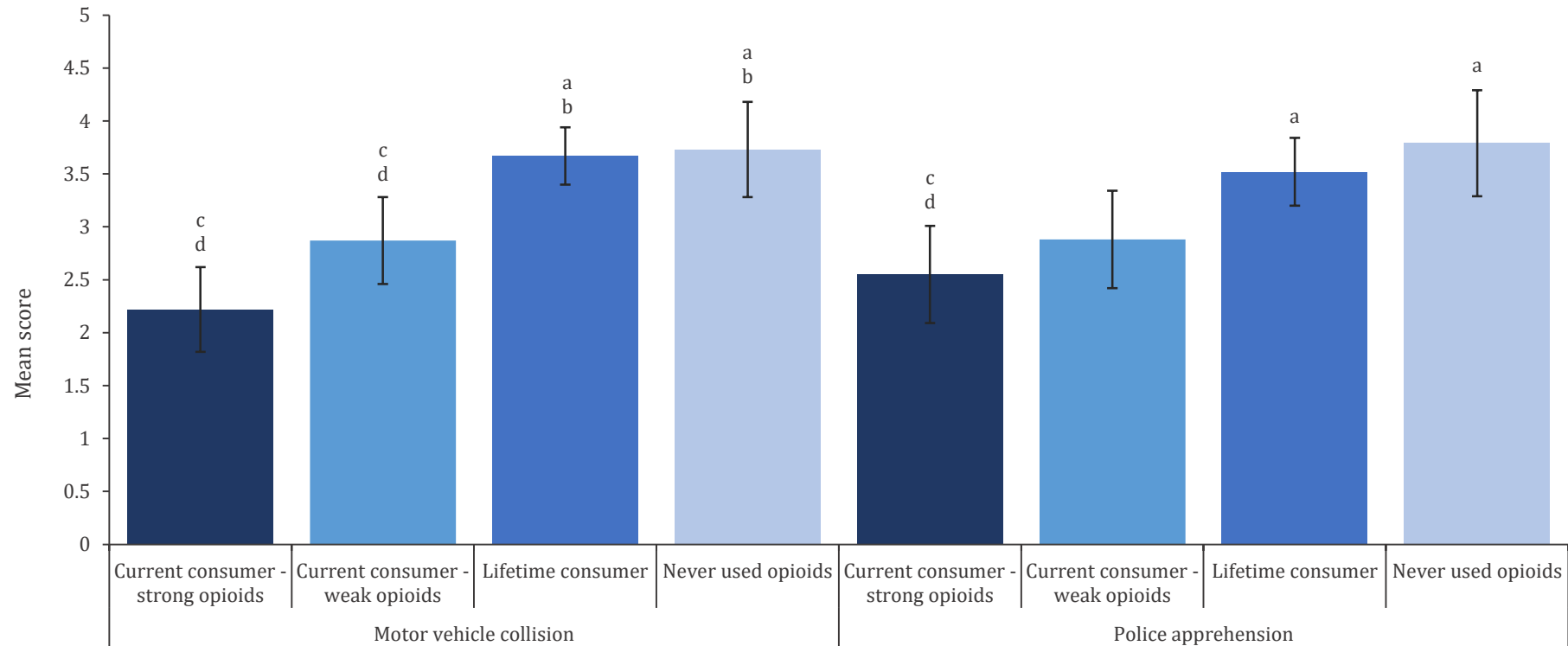
[a] Significantly different to risk ratings for people who currently used strong opioids, *p*<.050. [b] Significantly different to risk ratings for people who currently used weak opioids, *p*<.050. [c] Significantly different to risk ratings for lifetime opioid consumers, *p*<.050. [d] Significantly different to risk ratings for people who had never taken opioids, *p*<.050.

Note. Current opioid consumers *n*=41, Current weak opioids *n*=39, Lifetime opioid consumers *n*=86, Never consumed opioids *n*=33. Risk ratings range from 1 ('very unlikely') to 5 ('very likely'), excluding participants who responded "don't know".

Factors associated with risk perceptions for driving after taking opioids

Bivariate correlations (Spearman's rho) are reported in Table 5.3. Risk ratings for MVC and police apprehension when driving after taking opioids were significantly and positively correlated with each other, number of opioid side effects correctly identified, cognitive scale *t*-scores (i.e., better cognitive function was associated with higher risk ratings), and risk ratings for MVC and police apprehension for DUI of alcohol (*r*s≥0.14). Opioid risk ratings were also negatively correlated with the number of days the person had driven after taking opioids in the past year (i.e., fewer DUI occasions were associated with higher risk ratings). Notably, risk ratings were not associated with having received information about opioids and driving.

Table 5.2. *Bivariate correlations (Spearman's rho) for risk ratings for driving after taking opioids and factors associated with opioid use and knowledge of risks*

	Risk of MVC (opioids)	Risk of police apprehension (opioids)	N. side effects identified	Received information about opioids and driving	Age	Identifying as male	Cognitive scale t-score	Hrs driven, past week	Risk of MVC (alcohol)	Risk of police apprehension (alcohol)
Risk of MVC (opioids)	-	-	-	-	-	-	-	-	-	-
Risk of apprehension (opioids)	0.69**	-	-	-	-	-	-	-	-	-
N. side effects identified	0.22*	0.14*	-	-	-	-	-	-	-	-
Received info. about opioids and driving	0.11	0.06	0.07	-	-	-	-	-	-	-
Age	-0.05	-0.04	-0.21*	-0.01	-	-	-	-	-	-
Identifying as male	-0.02	-0.02	-0.11	0.05	0.01	-	-	-	-	-
Cognitive scale t-score	0.24**	0.14*	0.30**	-0.10	-0.24**	-0.10	-	-	-	-
Hrs driven, past week	-0.06	-0.06	-0.06	-0.03	0.11	0.03	-0.16*	-	-	-
Risk of MVC (alcohol)	0.36**	0.24**	-0.01	0.21*	0.09	-0.07	-0.03	0.05	-	-
Risk of apprehension (alcohol)	0.31**	0.49**	0.08	0.09	0.05	-0.04	0.02	0.03	0.62**	-
N. days DUI of opioids, past year	-0.44**	-0.39**	-0.02	0.01	0.23**	-0.00	-0.17*	0.22*	0.01	0.03

* $p<.050$. ** $p<.001$.

Factors associated with ratings for risk of motor vehicle collision. Current use of strong opioids was associated with lower risk ratings in all models, compared to never, lifetime, or weak opioid use. In Step 1, use of strong opioids explained a significant 17.2% (adjusted R^2=0.16) of the variance in MVC risk ratings for opioids (Table 5.3). The addition of cognitive scale t-score (Step 3), risk ratings for alcohol (Step 5), and knowledge of opioid side effects and driving-related impacts and previous days with opioid DUI (Step 6) significantly improved model fit. Other variables were not significantly associated with risk ratings for opioids.

The final model explained a significant 36.4% (adjusted R^2=0.32) of variance in risk ratings. In this model, current use of strong opioids was uniquely and negatively associated with risk ratings (i.e., people with never, lifetime, or current use of weak opioids gave higher risk ratings than those who used strong opioids). Cognitive scale t-scores, risk rating for alcohol-related MVC, number of correctly identified opioid side effects, and number of days with opioid DUI in the past 12 months were uniquely and positively associated with ratings for opioid-related MVC risk (i.e., higher scores were associated with higher risk ratings; Table 5.3).

Factors associated with risk ratings of apprehension by police. After controlling for related factors, current use of strong opioids was not associated with risk ratings for opioid-related police apprehension. In Step 1, current use of strong opioids explained a significant 7.5% (adjusted R^2=0.06) of the variance in risk ratings for police apprehension (Table 5.3). The addition of risk ratings for alcohol (Step 5) and knowledge of opioid side effects and driving-related impacts and previous days with opioid DUI (Step 6) significantly improved model fit. Other variables were not associated with opioid risk ratings.

The final model explained a significant 40.5% (adjusted R^2=0.38) of variance in risk ratings for police apprehension. In the final model, current use of strong opioids was not associated with risk ratings. However, risk rating for alcohol-related police apprehension and number of days with previous opioid DUI were uniquely and positively associated with risk ratings (i.e., higher scores were associated with higher ratings; Table 5.3).

Table 5.3. *Associations between opioid use, related factors, and risk ratings (MVC or police apprehension) when driving after taking opioids*

Step	$\beta_{Step\ 1}$ (95% CI)	$\beta_{Step\ 2}$ (95% CI)	$\beta_{Step\ 3}$ 95% CI)	$\beta_{Step\ 4}$ (95% CI)	$\beta_{Step\ 5}$ (95% CI)	$\beta_{Step\ 6}$ (95% CI)
			Risk of MVC when driving under the influence of opioids			
1 Opioid use status						
Never used – Current, strong	1.07 (0.62, 1.52)**	15.31 (8.90, 1.62)**	15.15 (8.86, 13.22)**	15.22 (8.91, 13.28)**	15.06 (9.32, 12.82)**	11.46 (4.67, 15.95)**
Lifetime – Current, strong	0.99 (0.62, 1.36)**	1.01 (0.64, 0.60)**	1.01 (0.64, 0.60)**	1.01 (0.65, 0.60)**	1.03 (0.70, 0.59)**	0.77 (0.38, 9.48)**
Current, weak – Current, strong	0.38 (-0.05, 0.80)	0.17 (-0.02, 11.04)	0.19 (<0.01, 0.85)*	0.19 (<0.01, 10.05)*	0.22 (0.05, 10.37)*	0.20 (0.03, 1.01)*
2 Age	–	<0.01 (-0.01, 0.01)	0.04 (-0.05, 0.20)	0.04 (-0.05, 0.02)	0.03 (-0.05, 0.02)	0.04 (-0.04, 0.01)
Gender identity						
Female – Male	–	1.81 (-2.39, 0.45)	0.09 (-0.22, 0.17)	1.07 (-2.57, 5.37)	0.63 (-2.68, 0.34)	-0.41 (-3.71, 0.12)
3 Cognitive scale *t*-score	–	–	0.31 (0.09, 0.32)*	0.02 (0.01, 0.02)*	0.03 (0.01, 0.54)**	0.03 (0.01, 0.12)*
4 Hours driven in the past week	–	–	–	-0.03 (-0.18, 0.08)	<0.01 (-0.01, <0.01)	<0.01 (-0.00, 1.53)
5 Alcohol risk rating (MVC)	–	–	–	–	4.04 (2.76, 3.29)**	0.90 (0.60, 0.38)**
6 Received information about driving risk						
No – Yes	–	–	–	–	–	-12.69 (-46.84, 2.34)
Number of side effects identified	–	–	–	–	–	0.05 (0.01, 0.04)*
Number of days with opioid DUI	–	–	–	–	–	-0.02 (-0.04, -0.00)*
ΔR^2	0.00	0.01	0.03	<0.01	0.14	0.05
ΔF	12.6**	0.44	7.98*	0.15	38.6**	4.56*
Adjusted model R^2	0.16	0.15	0.18	0.18	0.32	0.36
Model F	12.6**	6.5**	6.9**	6.0**	10.8**	9.7**
Model *n*						
			Risk of police apprehension for erratic driving when driving under the influence of opioids			
1 Opioid use status						
Never used – Current, strong	0.74 (0.26, 1.22)*	10.80 (3.99, 1.33)*	10.72 (3.95, 10.85)*	10.68 (3.88, 10.83)*	11.45 (5.69, 10.67)**	6.68 (<0.01, 8.28)
Lifetime– Current, strong	0.60 (0.20, 0.99)*	0.62 (0.22, 0.44)*	0.62 (0.22, 0.44)*	0.62 (0.22, 0.44)*	0.61 (0.27, 0.41)**	0.24 (-0.14, 0.27)
Current, weak – Current, strong	0.16 (-0.29, 0.61)	0.07 (-0.12, 8.28)	0.08 (-0.11, 0.65)	0.09 (-0.11, 7.66)	0.07 (-0.10, 6.40)	0.05 (-0.11, 5.68)
2 Age	–	<0.01 (-0.01, 0.01)	0.04 (-0.05, 0.21)	0.04 (-0.06, 0.02)	0.05 (-0.03, 0.02)	0.06 (-0.02, 0.02)
Gender identity						
Female - Male	–	1.62 (-2.81, 0.46)	0.09 (-0.24, 0.18)	1.09 (-2.84, 5.67)	0.67 (-2.66, 0.34)	-0.09 (-3.37, 0.13)
3 Cognitive scale *t*-score	–	–	0.20 (-0.03, 0.27)	0.02 (<0.01, 0.01)	0.02 (<0.01, 0.41)*	0.02 (<0.01, 0.09)
4 Hours driven in the past week	–	–	–	0.03 (-0.13, 0.12)	<0.01 (<0.01, 0.01)	<0.01 (<0.01, 1.97)
5 Alcohol risk rating (Apprehension)	–	–	–	–	5.53 (4.24, 4.23)**	1.28 (0.98, 0.50)**
6 Received information about driving risk						
No – Yes	–	–	–	–	–	-14.45 (-47.67, 2.04)
Number of side effects identified	–	–	–	–	–	0.02 (-0.02, 0.03)
Number of days with opioid DUI	–	–	–	–	–	-0.03 (-0.05, -0.01)**
ΔR^2	0.00	<0.01	0.01	<0.01	0.26	0.05
ΔF	4.92**	0.42	2.88	0.17	71.20**	5.10*
Adjusted model R^2	0.06	0.05	0.06	0.06	0.32	0.37
Model F	4.92*	3.10*	3.09*	2.66*	12.14**	10.83**
Model *n*						

* *p*<.050. ** *p*<.001.

Discussion

This study aimed to examine knowledge of perceptions of driving-related risks, knowledge of other opioid side effects, sources of information, real-world driving behaviours and safety precautions, and factors associated with risk ratings among people with CNCP. Around two-thirds of recent drivers who currently took opioids had been informed about the potential risks about driving soon after taking opioid medicines. People who took strong opioids were slightly more likely to have received information than those taking weak opioids. However, having received information about driving was not associated with how risky people believed it was to drive soon after taking opioids. Additionally, people who currently used strong opioids were less likely to perceive higher risk of motor vehicle collisions when DUI of opioids, compared to those with never, lifetime, or current weak opioid use. This appeared to be related to cognitive dysfunction to some degree. After controlling for other factors, cognitive scale *t*-scores were positively correlated with risk ratings for MVC, but not police apprehension (i.e., better cognitive function was associated with higher risk ratings).

Knowledge of driving-related risks and other side effects, and safety precautions taken

Notably, most participants reported driving regularly (4 or more days per week) and fewer than 1 in 10 did not drive at all. This was despite over half of drivers reporting that pain worsened their driving ability and 25% saying opioids did so. Across all participants, over 3 in 5 (62%) had received information about the risks of driving soon after taking opioids. On average, participants correctly identified 5 of 11 listed opioid side effects. The most common sources of information for both side effects and driving-related risks included GPs and pharmacists. The proportion of people who obtained information from medicine packaging could have been higher, given that impairment warnings are legally required on opioid packaging in Australia.

Notably, a substantial minority of opioid consumers (weak or strong opioids) reported that opioid medicines worsened their driving ability. Despite this, around 4 in 5 drivers who currently took opioids said they had driven within 3 hours of taking an opioid medicine at least

once in the past year, with similar proportions for both strong (81%) and weak (82%) opioid consumers. However, most people indicated that they did not do this every day. Additionally, many drivers reported taking safety precautions with regards to driving. These included electing not to drive when pain was severe or soon after taking opioids, or driving only short distances. This indicates that most people respond to their circumstances adaptively, using judgement to determine whether it is safe to drive or not.

This broadly aligns with previous research by the European Union's Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID) project. In the DRUID project, people with 'moderate' (as opposed to extensive) drug use were capable of judging their level of impairment reasonably accurately and implementing safety behaviours accordingly [27]. Conversely, this finding is at odds with literature on the effects of alcohol and benzodiazepines on meta-cognition, whereby higher levels of objective cognitive impairment are associated with less awareness of impairment [28]. Potentially, this may relate to the complex interaction between pain, opioid use, and cognitive function. Specifically, participants who use opioids may be more aware of their own baseline cognitive performance due to the impairing effects of pain.

Perceptions of driving-related risks

Opioids versus alcohol. Overall, the cohort rated the risk of both motor vehicle collision (MVC) involvement and apprehension by police for erratic driving to be lower for DUI of prescription opioids as opposed to alcohol. This may in part reflect the consistent and pervasive public health campaigns against drink-driving [29, 30], whereby people are well informed about the risks of driving over the legal limit for alcohol. Additionally, this may reflect the high proportion of current consumers (for both weak and strong opioids) who reported that opioids either did not change or improved their driving ability.

Opioid use status and risk perceptions. Notably, people who currently used opioids perceived driving under the influence to be less risky than did ex- or never-consumers. This aligns with previous research, where people who have consumed a given drug tend to report

lower risk ratings than those who have never taken said drug [12]. Potentially, and given that risk ratings were not related to knowledge of other side effects or information about driving in the regression analyses, this may relate to subjective experience. In this study, fewer than 1 in 5 people who currently used opioids believed that their opioid medicines worsened their driving ability. Conversely, people who no longer took opioids may have ceased due to unwanted side effects (including impairment), while those who reported never being prescribed opioids may have avoided these medicines due to concerns regarding side effects or impairment effects.

Factors associated with risk perceptions for driving after taking opioids

Risk ratings for the likelihood of MVC involvement and police apprehension if driving after taking opioids were both associated with person-level factors. In particular, both were associated with risk ratings for alcohol and past DUI of opioids. The former finding suggests that, even though people tend to perceive alcohol as less 'risky' than opioids, higher risk ratings for alcohol were associated with higher ratings for opioids. This may reflect higher levels of risk aversion among these participants. The latter finding aligns with previous research, in which past DUI is associated with a greater likelihood of future DUI of alcohol [31]. This is thought to relate to person-level factors, particularly the individual's level of risk aversion [14]. Notably, cognitive complaints were also associated with risk ratings, whereby people with higher impairment provided lower ratings of risk. This is concerning, as people with lower risk ratings were more likely to have previously driven soon after taking opioids but may be more impaired.

Notably, being explicitly told about driving-related risks was not associated with actual risk ratings. This may relate to the high proportion of people who reported receiving information from written sources such as medicine labels (50% of recent consumers who had received information) and online (24%), where information may be less salient. It could also reflect the relatively stronger influence of personal experience compared to conceptual knowledge (i.e., someone who is informed of the risks but does not think opioids impair their ability to drive may perceive risks to be low). Additionally, this may also indicate missed

opportunities among prescribers and healthcare workers to adequately engage with consumers about these risks. Potentially, the messages around opioid-related risks are not delivered in an explicit or clear manner, and clients may not engage with this information.

Strengths and limitations

A considerable strength of the present study was its online mode of delivery, which made it accessible to people of varying degrees of mobility and remoteness. The survey was also comprehensive in its examination of both opioid use and key co-morbid factors, including pain and the presence of mental health conditions. The survey was also one of few to examine perceived risks of driving-related harms for opioid medicines compared to alcohol. This examination enabled us to directly compare opioid risk perceptions with a 'benchmark' (i.e., alcohol, which has a legal limit for driving).

The study also had key limitations relating to the study design and participants. Firstly, the correlational and cross-sectional design meant we were not able to examine causative factors. Additionally, most participants in our study were women. While this reflects the higher proportion of women than men who experience CNCP [3], it may limit the generalisability of risk ratings to some extent. Specifically, data from previous research have indicated that women may perceive DUI of alcohol and other drugs to be more risky than do men [32]. This means that the risk ratings provided here may not reflect those of the driving population more broadly. Another minor limitation was that participants were asked whether they had been diagnosed with a mental health condition, but were not required to complete a screener for symptoms of anxiety or depression. Inclusion of a screening tool would have allowed us to account for the potential impacts of undiagnosed mental health disorders.

Additionally, there were several limitations relating to the sampling methods used here. Firstly, because the study was self-report, we were not able to corroborate what participants reported and their responses may be subject to recall bias or favourable responding. The use of a convenience sampling method and the fact that participants were self-selected were also

limitations, as people with stronger opinions about opioids and pain are more likely to have participated than those with mild opinions.

Clinical implications and future research directions

This study has key clinical implications. Firstly, there is scope for more detailed conversations between clients and clinicians regarding opioid-related risks and side effects, both at initial consults and via regular reviews. Importantly, changing people's perceptions about the risks associated with a particular behaviour (in this case, DUI of opioids) can help to change actual behaviours [14]. This is particularly relevant for people taking strong opioids, as this cohort perceived the risks to be lower than did people taking weak opioids. Additionally, this information is critical for the minority of people who will experience worsened driving ability when taking weak or strong opioids. For these individuals, the impact on quality of life (e.g., mobility) may be substantial.

Notably, many participants said they received information from a GP or a pharmacist about driving-related impairment, but this did not translate to higher risk ratings. Recent research has demonstrated that the way that clinicians speak to clients about medicine-related risks is important [16]. Messages that are direct and explicit better help clients to understand risks [16]. Given this, prescribers need to provide information to every client who receives opioid medicines, and also ensure that these messages are delivered in a clear way.

The present findings also highlight the need for clinicians to be aware of cognitive dysfunction among people with CNCP, regardless of opioid use. As a cohort, the sample demonstrated relatively poor cognitive function and this was associated with lower risk ratings for opioid DUI. Cognitive impairment has also been previously linked to adverse factors such as a higher frequency of physical injuries [33]. For this reason, screening for cognitive dysfunction should be a priority among pain clinicians. Future research should focus on developing cognitive interventions to help people with CNCP address dysfunction, as well as screening tools for clinicians.

Conclusions

Driving is an important activity for people with chronic non-cancer pain, but both pain and opioids may worsen the ability to drive. Understanding the risks associated with driving under the influence of prescription opioids is crucial as risk perceptions are associated with actual driving behaviours. While many people in this study had received information about opioid-related impairment, this was not associated with perceptions of driving-related risks. This indicates a need for improved quality of discussions between prescribers and consumers regarding the risks related to opioid use. Additionally, factors such as cognitive impairment that are also associated with risk perceptions should be screened for and monitored by clinicians.

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CHAPTER 6: TRENDS IN DETECTIONS OF OPIOIDS AMONG CRASH-INVOLVED MOTORISTS IN A JURISDICTION WITH ESCALATING OPIOID PRESCRIBING

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Preface

The previous chapters describe the effects of and attitudes towards opioid medicines among people with chronic non-cancer pain, as well as the experience of certain harms. While the studies described in these chapters offer insight into the impact that opioid use has on cohorts who experience CNCP, the effects of pharmaceutical opioids can extend beyond this. A range of research has highlighted that community utilisation of opioids positively corresponds with various population-level harms (e.g., higher rates of opioid-related deaths). However, this research has tended to focus on specific harms—primarily related to overdose—and not others. In particular, there is a lack of research examining opioid-related motor vehicle collisions (MVC), especially in geographic regions where use of opioids is relatively high.

Given this, the aim of the study described in this chapter (*Study 5*) was to examine the longitudinal relationship between increased prescription opioid dispensing and the incidence of opioid-related MVC in an Australian jurisdiction with high and escalating rates of opioid prescribing and very low levels of illegal opioid (i.e., heroin) use. The data described here encompass all positive opioid detections in biological samples taken from crash-involved drivers in the state of Tasmania across eight years, and compare these with population-level data on opioid dispensations. Importantly, these data do not specifically relate to individuals with CNCP, as medical records were not linked to crash databases. However, they do provide an indication of population-level harms that may be associated with increased dispensing of opioids for pain conditions, primarily CNCP.

Abstract

Introduction

Pharmaceutical opioid use and motor vehicle collision (MVC) are leading causes of morbidity and mortality in Australia. The association between increased opioid dispensations and opioid-related MVC is poorly understood, particularly in regions with high opioid utilisation. Tasmania, an Australian jurisdiction, is characterised by a high and increasing population rate of opioid dispensing. This study aimed to determine whether increased opioid dispensing in Tasmania is associated with rising detections of opioids in crash-involved motorists.

Methods

Aggregate data on the frequency of opioid and other drug detections among motorists involved in serious or fatal MVC from 2008 to 2016 were obtained from law enforcement records. These data were compared to opioid dispensation data to determine if trends in the number of opioids in MVC corresponded with dispensation rates.

Results

The number of opioid script dispensations increased by 36.9% from 2008 to 2016, but the percentage of MVC cases (driver or passenger) with a positive opioid detection was similar in 2008 (6.8%) and 2016 (6.9%). Aside from a rise and subsequent decline in detections from 2010 (13.1%) to 2011 (6.8%), this figure remained relatively stable. The rate of MVC opioid detections per 100,000 script dispensations also remained stable across time.

Conclusions

Despite increased dispensing, opioid-related MVC did not increase from 2008 to 2016. Opioids were present in a small but substantial percentage of MVC cases. This may indicate a need for improved consumer education, however the data could not distinguish drivers from passengers. Adverse incidents including MVC should be included in post-marketing surveillance of opioids.

Introduction

Opioid dispensations and detections among crash-involved motorists are increasing internationally [1]. More widespread community use is typically predictive of greater harms [2, 3]. This is evident in Australia, where increased harms related to pharmaceutical opioid use [4], including mortality [5], have been attributed primarily to a substantial rise in opioid dispensing. Aside from overdose, a key concern is that increased dispensing may be reflected in motor vehicle collisions (MVC). Opioids are known to impair psychomotor function (e.g., attention) [6] and, as with driving under the influence (DUI) of alcohol and other drugs, driving soon after consumption has been linked to increased risk of MVC [7-9]. As such, the increased use of pharmaceutical opioids over the past decade is potentially associated with increased road tolls.

The potential for opioids to impair driving ability is concerning. This is due to the significant burden of MVC on individuals and the community and the recent stall in the success of road safety strategies. In Australia, MVC is a leading cause of accidental death, with 1,143 road fatalities in 2018 [10]. Annual reductions in the rate of fatalities have slowed since 2013, remaining at around 5.0 deaths/100,000 people [10]. Conversely, the rate of hospitalised injuries increased from 148.8/100,000 population in 2010 to 155.7 in 2015 [10]. This has occurred despite improved safety of both roads and vehicles [11].

As evidenced by a growing body of literature, increased opioid dispensing may contribute to MVC injuries and fatalities [7-9]. Drug-related behaviours are known to vary geographically, with DUI crash data typically reflecting community use patterns [12]. For this reason, 'problem' drugs differ between regions and across time. For example, the number of detections of pharmaceuticals in crash-involved U.S. drivers has increased over the past decade, corresponding to a rising number of prescriptions dispensed [7, 13]. A recent U.S.-based study also demonstrated geographic variation in the incidence of opioid-related MVC, suggesting that regions with higher use rates may be affected more so than others [1]. In Australia, however, there is a lack of recent data about opioid-related MVC in the context of dispensation rates.

This study used police forensic data from the Australian jurisdiction of Tasmania to assess trends in the prevalence of opioid detections among people involved in fatal MVC and opioid dispensation rates. Tasmania is characterised by one of the highest rates of pharmaceutical opioid dispensing per capita [14], akin to the Southern, Appalachian, and Western regions of the U.S. [15]. Additionally, Tasmania has low heroin use [16, 17]. As such, Tasmanian crash data is reflective of pharmaceutical, not illicit, opioid use. The state also has the third highest rate of MVC-related fatalities per capita in Australia [18]. As such, Tasmanian data may offer unique insight into pharmaceutical opioid dispensing and opioid-related MVC.

Methods

Procedure

Aggregate data on opioid and other drug detections in blood samples from crash-involved motorists for 2008-16 were obtained from the database of Tasmania Police's forensic branch, Forensic Science Services Tasmania (FSST). All data were de-identified by FSST before being provided to the researchers. FSST conducts toxicological analyses on samples taken from drivers, and sometimes passengers, involved in any serious (involving an injury requiring hospitalisation for ≥24 hours) or fatal MVC. Per Tasmanian law, blood samples are collected within three hours of an MVC.

Additionally, MVC opioid detections were expressed as a rate per 100,000 each of drivers, population, and opioid dispensations. The number of people with a learner, provisional, or full licence were counted using Australian Bureau of Statistics (ABS) (2008) and DSG (2011-16) data [21, 22]. Tasmania's driving-age population (16-100+ years) for 2008-16 was then calculated using ABS data [23]; a learner's permit may be obtained from age 16. Lastly, the number of opioid packs dispensed under the Pharmaceutical Benefits Scheme (PBS) and Repatriation PBS (R-PBS) was counted [24]. Under the PBS, all government-subsidised medications are assigned a unique item code, including brand, strength, form, quantity, and indication [25], with the frequency of dispensations recorded in a central database. A search of this database included 112 opioid preparations (codeine, oxycodone, fentanyl, buprenorphine, tramadol) available in Tasmania from 2008-16. Oxycodone + naloxone was not listed until 2011; hydromorphone, methadone, morphine, and tapentadol were excluded.

Ethics approvals for this study were obtained from the Department of Police, Fire and Emergency Management (DPFEM Reference #A17/9586) and the Tasmanian Health and Medical Human Research Ethics Committee (#H0016430).

Assessment of blood samples

Using gas chromatography/mass spectrometry, FSST conducts comprehensive screening for 150 substances across 13 drug categories: amphetamines, anticonvulsants, antidepressants (sedating), antidepressants (non-sedating), benzodiazepines, cardiovascular drugs, cocaine, medical intervention drugs, methadone, opioids, tetrahydrocannabinol (THC), other impairing drugs (e.g., antipsychotics), and other non-impairing drugs (e.g., paracetamol). 'Opioids' included buprenorphine, codeine, dextromethorphan, dihydrocodeine, fentanyl, oxycodone, pethidine, norpethidine, dextropropoxyphene, norpropoxyphene, tramadol, o-desmethyltramadol, and heroin. The data obtained relate to the presence or absence of specific drugs, rather than quantitative data on drug levels. Manual database searching revealed zero positive heroin detections. Morphine was excluded as a 'medical intervention drug', as administration by paramedics can obscure time of use (pre- or post-crash). Tapentadol and hydromorphone were not screened by FSST; however, recent data indicate low utilisation in Tasmania [19]. As methadone comprised its own class, it was included in a separate analysis. As a method check, the total number of FSST samples were compared with the number of MVC-related injuries and fatalities listed by the Department of State Growth (DSG) [20].

Results

The DSG recorded 2,771 MVC-related serious injuries and fatalities between 2008 (n=316) and 2016 (n=303), with no substantial changes from year to year. On average, there were 37.3 (SD=10.0, range: 30–63) fatalities and 270.6 (SD=18.0, range: 241–290) injuries each year. Over this period, 2,302 samples (83.1%) were analysed by FSST. The percentage of total cases assessed annually increased over time, with samples from 91.2% of documented cases analysed by FSST in 2015 and 100% in 2016 (Supplementary Table 6.1). This suggests the FSST database captured the majority of available data for the time period.

Opioid detections across time

In 2016, opioids were detected in 6.9% of all FSST samples assayed (Figure 6.1). This was the fifth most common drug class behind THC (25.4%), other non-impairing drugs (21.5%), amphetamines (15.8%), and benzodiazepines (8.6%). Opioids were detected more frequently than non-sedating antidepressants (6.3%), cardiovascular medications (2.3%), sedating antidepressants (1.7%), anticonvulsants (1.7%), and other impairing drugs (5.0%). Methadone cases were infrequent across the period (≤2.2%) (Supplementary Table 6.1).

A proportion comparisons test revealed no significant difference between the percentage of cases with a positive opioid detection for 2008 (6.6%) and 2016 (6.9%), p=.955. This was relatively consistent each year, apart from a significant decrease in opioid detections from 2010 (13.1%) to 2011 (6.8%), p=.036. This represented a reversal of a non-significant increase in detections from 2008–10.

Figure 6.1. *Percentage of total FSST samples (positive or negative for any drug) that produced a positive detection for any opioid (excl. hydromorphone, methadone, morphine, tapentadol)*
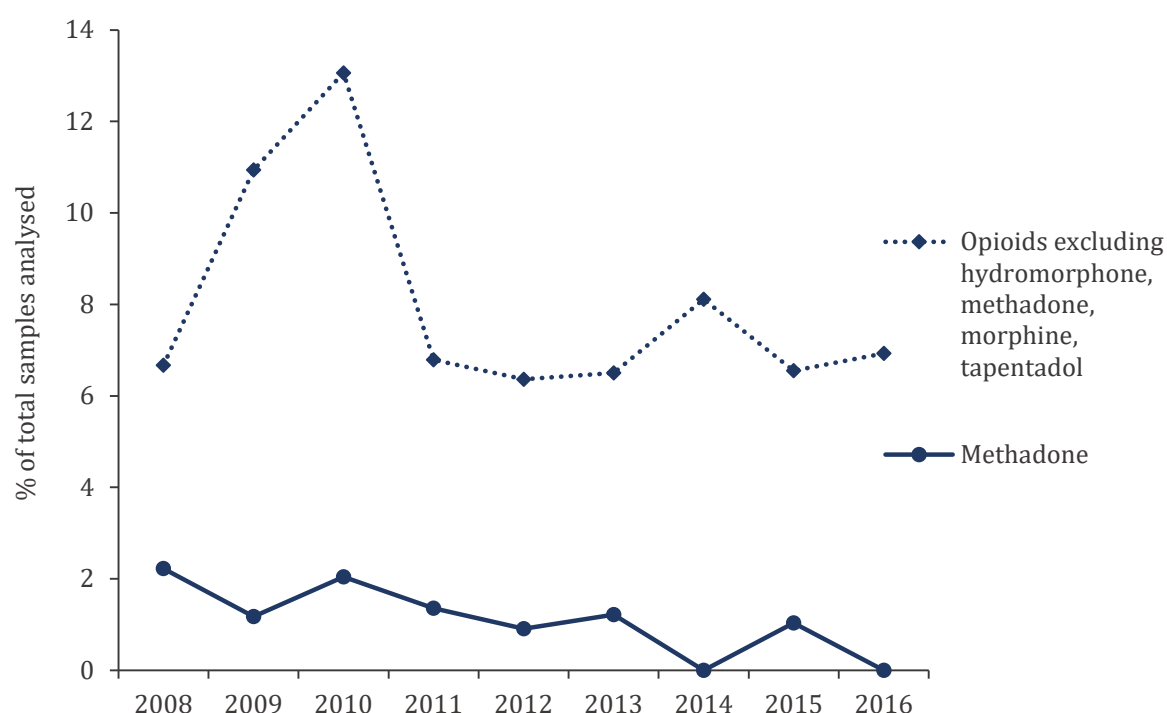
Sensitivity analyses

While the FSST database captured the majority of data across the period, the rate of samples assessed by the FSST increased over time; this could introduce bias (e.g., testing may have targeted at those suspected of drug use in earlier years). To counter this, sensitivity analyses were conducted, with cases with no toxicological analyses assumed to be i) all non-cases (i.e., all opioid-negative samples) and ii) all cases (i.e., all opioid-positive samples). When missing samples were coded as non-cases, the overall trend remained the same (Supplementary Table 6.2), with no significant differences between the percentage of cases with a positive opioid detection for 2008 (4.8%) and 2016 (6.9%), *p*=.323. This analysis retained the significant decline in detections from 2010 (11.1%) to 2011 (5.5%), *p*=.025. When missing data were assumed to be cases, there was a significant decline in the percentage of positive opioid detections from 2008 (33.5%) to 2016 (6.9%), *p*<.001. Additionally, there were significant

decreases in opioid detections from 2009 (35.4%) to 2010 (25.8%), and from 2015 (14.8%) to 2016 (6.9%), *ps*≤.011. These results indicate that, even if all cases not tested by FSST returned a positive opioid detection, there was a significant decline in positive identifications of opioids from 2008 to 2016; however, if no cases were positive, there were no changes across time.

In addition to the sensitivity analyses, data were assessed in 3-year blocks (Period 1: 2008–10, Period 2: 2011–13, Period 3: 2014–16) to increase the sample size for each data point. This analysis indicated a significant decrease in the percentage of cases positive for an opioid from 2008–10 (33.3%) to 2011–13 (17.6%), *p*<.001. This reversed from 2011–13 to 2014–16 (26.1%), *p*=.027. When comparing 2008–11 and 2014–16, there were no significant differences in the rate of positive opioid detections, *p*=.107. These results likely reflect the significant decline in detections from 2010–11, with relative stability across the remaining period.

Opioid detections in MVC across time in the context of number of scripts dispensed, number of licensed drivers, and population

From 2008–16, Tasmania saw a substantial rise in the number of opioid scripts dispensed (36.9%), as well as increases in population (6.6%) and number of licenced drivers (5.5%) (Supplementary Table 6.3). The rate of MVC opioid detections per opioid dispensations was relatively stable across the period, with 5.6 detections per 100,000 dispensations in 2008 and 5.8 in 2016 (Figure 6.2). In contrast, the rate of MVC opioid detections per driving-age population was higher in 2016 (5.0 per 100,000 persons) than 2008 (3.8 per 100,000). The rate of MVC opioid detections per licenced drivers was also higher in 2016 (5.5 per 100,000) than 2008 (4.2 per 100,000).

When assessing detections from year to year, there was an increase in the number of opioid detections per dispensations and population from 2008–10. This trend reversed in 2010–11, with a 54.9% decrease in the number of opioid detections per 100,000 opioid dispensations, from 11.3 to 5.1 (Figure 6.2). Similarly, the number of opioid detections per 100,000 population decreased by 53.5%, from 7.9 in 2010 to 3.7 in 2011.

Figure 6.2. *Number of opioid detections (excluding hydromorphone, methadone, morphine,*

tapentadol) per 100,000 PBS opioid dispensations, population aged 16 years or older, and licenced

drivers in Tasmania in each year, 2008–16
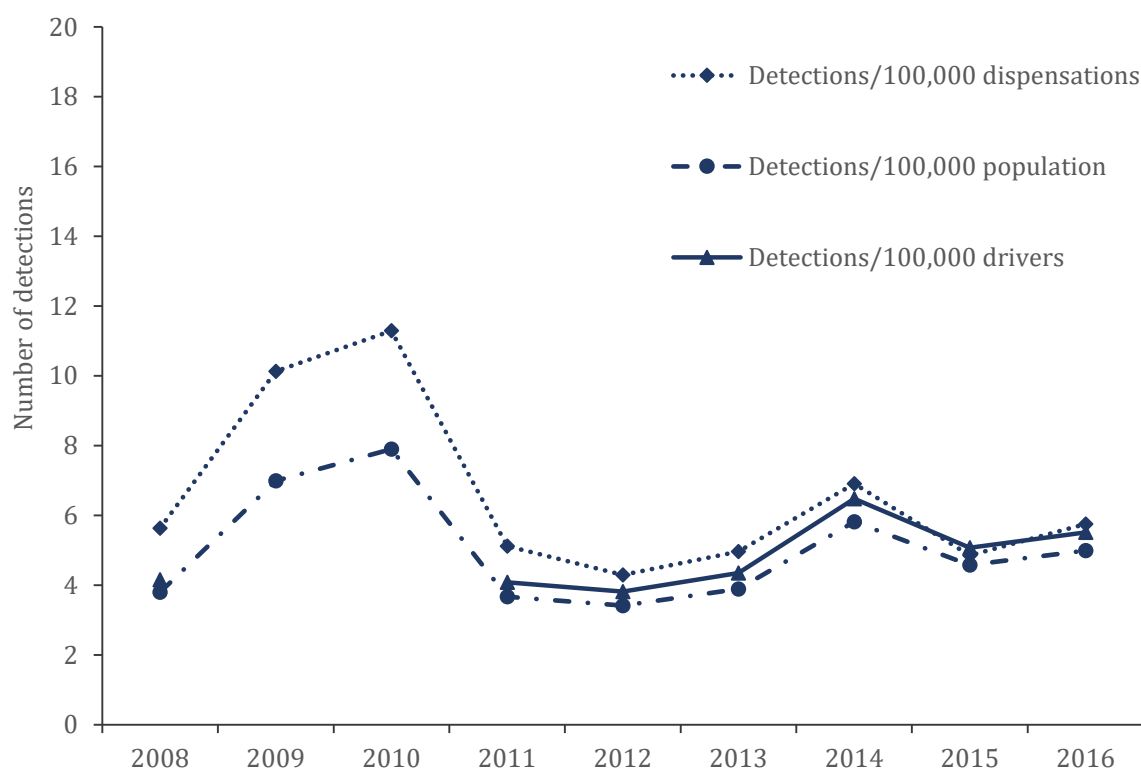
Discussion

From 2008–16, opioids were around the fifth most common drug group detected in blood samples from Tasmanian crash-involved motorists. In a typical year, 6–7% of cases were positive for an opioid. This was relatively stable across time, despite substantial increases in opioid dispensations [26]. These findings are consistent with two earlier studies. A review of data from 1990–2001 reported positive opioid detections in 3–5% of Australian MVC cases [12]. Another study found no change in the number of opioid detections in fatally-injured Australian drivers from 2000–13 [27]. Sensitivity analyses suggest that these findings may underestimate a decline in opioid detections from 2008–16. When missing cases were imputed as non-cases (i.e., negative detections), detections remained stable across the period. When imputed as cases (i.e., positive), however, our data showed a substantial decline in the percentage of positive opioid identifications, from one-third of cases in 2008 to 6.9% in 2016. This suggests either the same or fewer positive opioid detections since the mid-2000s, despite increased dispensing.

Tentatively, opioid detections in Tasmanian MVC may not directly relate to community opioid use. While these data contradict a broad finding that greater utilisation of opioids is predictive of increased harms [2, 3], region-specific factors may have mitigated potential harms. Increased regulatory scrutiny may have facilitated improved prescribing quality, particularly recent efforts by healthcare professionals to reduce opioid over-prescription, diversion (i.e., trading drugs), and extra-medical use [28, 29]. Australia's first real-time prescription monitoring program (Drugs and Poisons Information System Online Remote Access [DORA]), implemented in Tasmania in 2012, has enabled prescribers and pharmacists to access patient history to inform clinical decisions [30]. This is supported by relative stability in the number of opioid-related overdoses and fatalities in Tasmania from 2008–12 [31]. If these strategies are effective, the study highlights the utility in continued development of prescriber education.

While our findings may point to successful harm reduction strategies employed in Tasmania, it is difficult to draw clear conclusions from the present data given key limitations. The true number of opioid detections is likely higher than that reported here, due to the

exclusion of hydromorphone and tapentadol and underestimation of opioid use in PBS dispensation data [32, 33]. In 2014, PBS data did not capture 25.4% of total opioid dispensations [34]. In Australia, not all medicines are subsidised under the PBS scheme; for example, some over-the-counter codeine medicines are available via private prescription only.

Further, the structure of the FSST database prohibited extraction of complete cases. This means factors including speed, culpability, polydrug use, and opioid type and dose could not be examined [12]. The issue of culpability is particularly pertinent. Firstly, a significant limitation was that cases included drivers as well as passengers, and it was not possible to determine where a driver tested positive for opioids as opposed to their passenger. Additionally, opioids detected among non-culpable drivers could be explained by widespread community use, rather than impairment effects. Conversely, the exclusion of morphine may be a strength: a recent study on opioid detections in U.S. MVC noted that the increased prevalence of opioid-involved crash deaths over time was artificially inflated by administration of opioids to crash victims [1].

Another key limitation is that we were unable to identify cases where opioid detections may have reflected extra-medical use of medicines, including non-prescribed use [35]. Extra-medical opioid use of opioids is relatively uncommon, with 5.6% of Tasmanians reporting past 12 month non-medical use of any pharmaceutical drug in 2017 [36]. This delineation is important as cognition is differentially impaired by illicit, compared with prescribed, use [6]. Finally, the dataset did not provide details of opioid levels in blood samples; as impairment effects are dose-dependent [37], stability in opioid-related crashes may reflect low doses.

The limitations outlined above emphasise the need for collaboration between researchers, law enforcement agencies, and medical professionals to understand opioid-related harms. A recent review highlighted the need for effective post-marketing surveillance of pharmaceutical opioids to examine whether new products (e.g., abuse-deterrent formulations) reduce harms [38]. Specifically, while opioids undergo clinical trials to ensure their safety and efficacy, it is also critical to monitor their impact in 'real-world' settings [38]. However, as highlighted by the present study, pragmatic issues can hamper efforts to monitor opioid-related

harms: here, law enforcement data lacked important contextual information, particularly opioid use factors (e.g., extra-medical versus prescribed use, route of administration, type of opioid used, chronicity of use). Future efforts should focus on creating cohesion between researchers and stakeholders to facilitate detailed monitoring of opioid-related harms, including MVC.

Conclusions

Despite a substantial increase in pharmaceutical opioid dispensations, detections of opioids in serious and fatal MVC remained stable from 2008-16. However, opioids were nonetheless present in a small but substantial percentage of Tasmanian MVC, indicating a continued need for prescriber and consumer education programs and awareness of risks associated with pharmaceutical opioids. The present study highlights a need for better post-marketing surveillance of pharmaceutical opioids, to clarify whether MVC risk is associated with particular use factors.

Acknowledgements

Conflict of Interest

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CHAPTER 7: GENERAL DISCUSSION

Research overview

People who are prescribed opioids for chronic non-cancer pain (CNCP) may be concerned about how opioids affect their daily life. However, the effects of chronic opioid use on cognitive and behavioural function are poorly understood and difficult to disentangle from co-morbid factors. This thesis aimed to address five core questions relating to this topic:

1. Do people who take opioids for CNCP evidence objective performance deficits on cognitive tasks, compared with opioid-free controls (healthy or with CNCP) or opioid-free baseline?

2. What is the relationship between duration of opioid use and cognitive function among people with CNCP? Does cognition continue to change over time with chronic use?

3. Among people who take opioids for CNCP, is opioid dose positively correlated with harms such as cognitive dysfunction and physical injuries?

4. Are people with CNCP aware of opioid-related driving risks and what are their real-world driving behaviours? What factors are associated with risk perceptions?

    a. To what extent are people with CNCP aware of driving-related risks and other side effects, and does this differ by opioid use status? What sources of information do people use?

    b. Do people take precautions when driving with regards to opioid use?

    c. Do people with CNCP perceive DUI of opioids to be less risky than for alcohol (over the limit), and does this differ by opioid use status?

    d. What factors are associated with perceived risks of opioid DUI?

5. At the population level, is increased prescribing of opioids associated with a higher rate of opioid-related motor vehicle collisions?

Summary of studies contained in this thesis

Study 1 (Chapter 2) used a meta-analytical approach to determine whether people who take opioids for CNCP exhibit impaired cognitive performance (*Research Question 1;* Table 7.1).

The study included comparisons with healthy and opioid-free CNCP controls, and opioid-free baseline. The study was the first of its kind to consider the role of dose. It highlighted several gaps in the current literature, including a lack of data on residual effects (post-cessation).

Study 2 (Chapter 3) explored cognition among people with chronic opioid use for CNCP, compared with opioid-free controls and across time. This study was the first to examine objective cognitive function in people who had been taking opioids for >12 months, and only the second to examine the role of practice effects. The study also controlled for co-morbid factors including opioid dose and psychological distress. This allowed us to draw stronger conclusions than previous studies where these factors were poorly controlled for.

Laboratory settings, such as those in *Studies 1* and *2*, allow for control of confounds but are not necessarily an indicator of real-world function. For example, cognitive deficits may be compensated for by experience (e.g., for driving). *Studies 3* (Chapter 4) and *4* (Chapter 5) aimed to examine cognitive complaints, injuries, and driving behaviours in a community sample. *Study 3* explored the links between cognitive complaints, opioid use (including dose), and other harms (e.g., physical injuries). It was among the first of its kind to comprehensively examine cognitive complaints and associated factors in people prescribed opioids for CNCP. *Study 4* (Chapter 5) assessed knowledge of driving-related impairment, perception of risks relating to driving, and driving behaviours in people with CNCP. To the authors' knowledge, this is the first study to explore differences in knowledge of side effects and risk perceptions based on opioid use status. The online delivery mode was a particular strength of both *Studies 3* and *4*, as it allowed people who may otherwise have been unable to participate (e.g., due to limited mobility) to take part.

The final study (Chapter 6) aimed to examine population-level harms, exploring opioid-related motor vehicle collisions (MVC) across time with increased prescribing. This study had several key limitations, including that we were unable to examine prescribed use specifically. However, given that but most opioid use in the jurisdiction of Tasmania relates to pharmaceutical opioids, this study gives an important indicator of how increased opioid prescribing might translate to population-level harms in jurisdictions with high utilisation.

Table 7.1. *Key findings and conclusions for each research question addressed in the present thesis*

Research question	Chapter	Key findings	Conclusions
1: Do people who take opioids for CNCP evidence objective performance deficits on cognitive tasks, compared with opioid-free controls (healthy or with CNCP) and opioid-free baseline?	2, 3	In *Study 1* (Chapter 2), people who took opioids for CNCP evidenced small magnitude cognitive deficits in attention and memory compared with healthy controls, but not opioid-free controls with CNCP. They did not show worsened task performance in any cognitive domain post-opioid initiation, compared with opioid-free baseline. In *Study 2* (Chapter 3), there was evidence of moderate impairments for some tasks for consumers versus non-consumers (including differential practice effects), but these were inconsistent.	People who take opioids for CNCP show some impairments compared with healthy controls. There is no clear evidence that they are more impaired than opioid-free people with CNCP. Finally, there is no evidence that cognitive performance worsens from opioid-free baseline to for people who do commence opioid therapy.
2: Does cognitive function continue to change over time among people with CNCP after initiation of opioid therapy?	3, 4	In *Study 2*, there was no evidence of cognitive worsening from baseline to three months among people with chronic opioid use, and some evidence of improvements for some domains. In *Study 3* (Chapter 4) intermediate-term (<12 months) opioid consumers reported more frequent cognitive complaints and retrospective memory problems than did long-term consumers.	Cognition does not appear to worsen over time with chronic opioid use, and may improve for some people.
3: Among people who take opioids for CNCP, are higher opioid doses positively correlated with harms such as cognitive complaints and physical injuries?	2, 4	In *Study 1*, dose was associated with cognitive impairment when comparing people taking opioids for CNCP with healthy controls on attention measures. This association was not apparent for any other comparison. In *Study 3* (Chapter 4), dose was not associated with cognitive complaints or injuries.	There was some evidence of an effect of dose on performance for people with CNCP compared to healthy controls for attention, but not other measures. At the doses examined, opioid dose was not associated with cognitive complaints or injuries.
4a: To what extent are people with CNCP aware of driving-related risks and other side effects, and does this differ by opioid use status? What sources of information do people use? 4b: Do people take precautions when driving with regards to opioid use? 4c: Do people with CNCP perceive DUI of opioids to be less risky than for alcohol (over the limit), and does this differ by opioid use status? 4d: What factors are associated with perceived risks of opioid DUI?	5	4a: Most participants had received information about driving impairment and demonstrated adequate knowledge of side effects. Information sources included GPs and pharmacists. Current consumers were more likely to have received information about driving impairment, but had similar knowledge of side effects to non-consumers. 4b: Most drivers said they had taken precautions with regards to driving with severe pain or soon after taking opioids. 4c: Ratings of accident risk and risk of police apprehension were lower for opioids than alcohol. For opioids, current consumers provided significantly lower ratings of risk than lifetime or never consumers, even after controlling for factors like age and driving experience. 4d: Lower opioid MVC and legal risk ratings were associated with lower alcohol risk ratings and past-year DUI of opioids. Lower MVC risk ratings were also associated with current opioid use, cognitive dysfunction, and poorer knowledge of side effects.	People who take opioids for CNCP were not more aware of opioid side effects than people who did not take opioids, and were more likely to perceive the risks of driving after taking opioids to be low. Many people took precautions when driving, but DUI of opioids was relatively common. Previous DUI of opioids and risk ratings for alcohol were associated with risk ratings for opioids.
5: Is increased prescribing of opioids associated with a higher rate of opioid-related motor vehicle collisions at the population level?	6	In *Study 5*, the number of opioid-related motor vehicle collisions was stable from 2008–2016 despite increased prescribing. The rate of opioid-related MVC per 100,000 opioid scripts dispensed also remained stable.	Increased community use of pharmaceutical opioids does not appear to be associated with increased opioid-related MVC.

Chronic opioid use for CNCP and cognitive performance

Research Question 1: Objective cognitive performance in case-control and cohort studies

A key focus of this thesis was to examine objective cognitive task performance in people prescribed opioids for CNCP. Two studies (*Studies 1* and *2*) examined objective cognitive function between groups (i.e., cases versus controls) and pre- and post-opioid initiation. These are described below, according to the research question that they addressed.

Cognition in people prescribed opioids for CNCP compared to opioid-free controls.

Healthy controls. One study (*Study 1)* in this thesis examined cognitive performance for people with chronic use of opioids for CNCP compared to healthy controls. In this study, cases exhibited some cognitive deficits in comparison to controls, namely in attention and memory. These findings broadly fit with current understandings of the cognitive effects of opioids. Acute dosing studies have demonstrated that cognitive effects differ by cognitive domain and opioid dose and type [1-3]. Acute dosing studies have noted impairments in attention, with memory affected differentially by task [3-5]. This broadly aligns with our findings, where impairment was limited to these two domains.

Notably, the deficits noted in *Study 1* were unlikely to substantially impact everyday functioning in the real world. Attention and memory functions are fundamental for engaging in a range of everyday activities (e.g., driving, concentration). However, the deficits noted in *Study 1* were only of moderate magnitude, likely due to tolerance effects. Specifically, deficits may be lesser in people who use opioids chronically (in this case, up to 6.6 years) than opioid-naïve individuals. This is because tolerance to opioids can begin to develop within hours of commencing use [6]. Additionally, impairment was not apparent for tasks assessing motor performance, working memory, and executive functions in *Study 1*. Given this, it is unlikely that the deficits noted here substantially impacted everyday functioning, though they may mean people fatigue more easily than those without cognitive deficits. Additionally, these minimal deficits may become more apparent when people are fatigued (e.g., when driving for long periods).

Controls with CNCP. Two studies (*Studies 1* and *2*) examined cognitive performance for cases compared with opioid-free controls with CNCP. Both studies yielded limited evidence that people with chronic opioid use performed more poorly than their opioid-free counterparts. *Study 1* found non-significant, small magnitude differences in performance between groups for motor performance, attention, working memory executive functions, and memory. In *Study 2*, people with chronic opioid use evidenced some impairments compared with controls. However, there was no clear pattern to these deficits, and the opioid group also outperformed controls on several tasks. These findings add to a growing body of research suggesting cognitive dysfunction among people who take opioids for CNCP may relate primarily to pain or depression [7].

Cognitive function from opioid-free baseline to follow-up (cohort studies). While several studies in this thesis examined cognitive function in people with chronic opioid use for CNCP, only *Study 1* analysed cognition pre- and post-opioid initiation**.** Examination of studies with this design revealed no cognitive impairments from opioid-free baseline to opioid-present follow-up. Conversely, some improvements in performance were noted at follow-up, particularly for attention and working memory. These effects were apparent from 4 weeks and lasted up to 6 months post-initiation. These findings are particularly important for both consumers and prescribers who may be considering opioid therapy: at least in the intermediate-term and at the doses examined here (i.e., typical therapeutic levels), people who initiate opioid use are, on average, more likely to experience cognitive benefits than harms. However, one study found that cognitive outcomes differed between people: while many people experienced improved performance post-initiation of opioids, a substantial minority experienced cognitive worsening [8]. This likely reflects the substantial inter-individual variability in opioid metabolism and drug effects [8]. Given this, cognitive function in people on opioid therapy may need to be monitored in the early stages.

Research Question 2: Associations between duration of opioid use and cognitive function

While *Study 1* examined cognitive function from opioid-free baseline to intermediate-term follow-up, many people continue to use opioids for much longer than the durations examined (i.e., 12 months) [9]. Studies on shorter-term use have relatively consistently showed that the impairing effects of opioids dissipate as tolerance occurs [10]. However, very few studies have directly examined the association between duration of use and cognitive performance. Given this, two studies (*Studies 2* and *3*) examined the relationship between opioid use duration and cognitive function in people with chronic use for CNCP.

In *Study 2*, this examination involved comparing cognitive task performance in long-term opioid consumers (median 15.3 months duration) at an initial time point and again after three months. To our knowledge, this is the first study to examine cognitive trajectories in long-term consumers. Promisingly, this study detected no evidence of cognitive worsening over time, reporting stability or even improvement across cognitive domains. These improvements were not consistent across any domains, and were sometimes of smaller magnitude than for opioid-free controls with CNCP. This may indicate differential learning effects. However, these results are broadly positive, as they suggest cognition does not deteriorate following initial stability or improvements noted in many intermediate-term consumers (e.g., in *Study 1*).

Extending on *Study 2, Study 3* examined the effect of opioid use duration in two ways: i) by exploring the association between use duration and frequency of cognitive complaints, and ii) by comparing cognitive complaints for intermediate- (<12 months) versus long-term (≥12 months) opioid consumers. Interestingly, the comparison between intermediate- and long-term consumers revealed that intermediate-term consumers reported more frequent complaints for overall cognition and retrospective memory, though not prospective memory. This was somewhat unexpected, given that even intermediate-term consumers had been taking opioids for >3 months, a sufficient duration for tolerance to develop [11]. Possibly, tolerance to cognitive impairment effects may develop more slowly, or people who experience adverse

effects or poor analgesia may cease opioid use prior to 12 months [12, 13]. Experiencing side effects is a key driver of opioid discontinuation in people with CNCP [13].

Research Question 3: Associations between opioid dose, cognition, and behavioural harms

Two studies (*Studies 1* and *3*) examined the association between opioid dose and cognitive function. In *Study 1*, opioid dose was positively associated with impairment in cases compared with healthy controls for measures assessing attention, but not for other comparisons. This potentially reflects the variation in opioid effects across cognitive domains, and fits with the notion that attention-based tasks may be more sensitive to opioid impairment effects than other tasks [3]. In *Study 3*, opioid dose was not associated with frequency of cognitive complaints or physical injuries among people with chronic use of opioids for CNCP. These findings are inconsistent with the fairly robust evidence that higher opioid doses predict greater impairment than low doses when administered to healthy, opioid-naïve individuals [3]. However, the median duration of use reported by participants in this study was considerably longer than that in *Study 1*, and certainly long enough for tolerance to have occurred. Additionally, the outcome measure in this study was overall cognitive complaints. Given that opioids appear to affect cognitive domains differentially, potentially the deficits noted for objective cognitive function do not translate to noticeable global impairment.

Strengths, limitations, and future directions for studies examining opioid cognitive effects

The studies described in this thesis offered a comprehensive overview of the effects of opioids on cognitive and behavioural harms. Our use of different methodologies and broad research questions allowed for a nuanced and comprehensive examination of the real-world implications of opioid use among people with CNCP. In *Studies 1, 2,* and *3*, we were able to examine key co-morbid factors (e.g., pain severity, psychological distress, concomitant medicine use). Additionally, a key strength of *Study 3* was the use of an online delivery mode. Online surveys have not often been used to examine cognitive and behavioural outcomes in people with CNCP, but allow for greater accessibility. While this delivery mode does not allow for the

rigorous examination of cognitive function outlined in *Studies 1* and *2*, it also offers the benefit of capturing real-world opioid use and outcomes in a larger sample. The examination of opioid use in these studies was also comprehensive, and included factors such as opioid dose and duration of use. As highlighted by *Study 1*, there has previously been substantial heterogeneity in terms of controlling for even core co-morbidities such as pain, and often inadequate assessment of mental health conditions. Given that all these factors can impact cognitive function, this is a key strength of the present thesis programme.

This suite of studies also had key limitations. For example, we did not assess differences in cognition depending on whether people were taking full versus partial agonists, or immediate- versus sustained-release preparations. In *Study 1*, it was not possible to examine these factors due to limitations in available data. Across the remaining studies, the decision not to explore the effects of opioids in this level of detail was driven by a combination of factors including the burden on participants (e.g., checking whether medicine was sustained- versus immediate-release), potential problems with accuracy of recall or knowledge of medicines, and the pragmatics of classifying opioid use given that use of multiple opioids was common.

Both the strengths and limitations of these three studies highlight the potential for development of a standardised battery of measures for research purposes. This battery could include measures of pain and co-morbid factors such as mental health conditions (or psychological distress), pain interference, and cognitive failures. In the present thesis, *Study 1* highlighted the lack of consistency across studies in terms of controlling for co-morbid effects. For example, there was substantial variability in the assessment of pain severity across included studies, despite the known effects of pain on cognition. This meant we were not able to consistently account for even basic covariates (e.g., pain itself). However, *Studies 2* and *3* emphasised that comprehensively assessing co-morbid factors must be carefully weighed up against the risk of burdening a population who are already prone to both physical and cognitive fatigue. Development of a short, standardised assessment encompassing relevant co-morbidities would allow researchers to strike a better balance.

There are several existing examples that could be used as a basis for development of a standardised test battery for use in pain and opioid studies. Notably, the Pain and Opioids In Treatment study describes a set of measures, devised in consult with a panel of experts, that assess key co-morbid factors including pain, physical functioning, and mental health in people with CNCP [14]. These measures could be combined with existing measures of cognitive function devised for clinical populations. For example, the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) tool was developed to assess cognitive function in people with schizophrenia undergoing drug-based therapies [15]. Similarly, the Addictions Neuroclinical Assessment tool was developed to examine neurocognitive correlates in people with substance use disorders [16]. These existing measures could be combined to create a standard set of assessments for research on opioids and CNCP.

Additionally, the findings from *Study 2* highlighted some promising avenues for future research. In particular, cognitive function may improve for some people when they start taking opioids chronically. However, it is not well understood as to what may predict improved cognition, versus stability or decline. Given that opioids have numerous adverse effects, understanding who is likely to benefit from them in terms of improved cognition is a key avenue for future research. Further, few studies have examined the effect of opioid switching or discontinuation on cognition. In *Study 1*, only one study each examined the effects of switching from immediate- to sustained-release opioids [17] and tapering off opioids [18]. The latter detected moderate magnitude effects whereby people who tapered off opioids showed superior performance in some cognitive domains (motor performance, attention, working memory) compared to opioid consumers [18]. The mechanism of this effect is not well understood.

Opioid use and awareness of side effects and driving-related risks

The first three studies described in this thesis examined cognitive function in people with CNCP, as well as some associated harms (i.e., physical injuries). The latter two studies examined real-world manifestations of cognitive function, by examining driving behaviours and related harms among people who take opioids. These two studies are described below.

Research Question 4: Knowledge of side effects and perceptions of driving-related risks by opioid use status, and safety precautions taken while driving among people with CNCP

Study 4 highlighted the complexities relating to real-world driving behaviours and driving under the influence (DUI) of prescription opioids among people with CNCP. Over 9 in 10 people with CNCP had driven in the past 12 months and typically drove most days each week.

4a: Level of awareness of driving-related risks and other side effects, and sources of information. Broadly, participants in *Study 4* had some degree of awareness of driving-related risks and other side effects. People who currently consumed strong or weak opioids were more likely to have received information regarding the impairing effects of opioids on driving-related abilities. They often received this information via interaction with healthcare professionals (i.e., GPs, pharmacists), indicating that prescribers are engaging clients on this topic to some degree. However, current opioid consumers were not more aware of other opioid side effects than people who did not take opioids. Potentially, this may be due to several factors. For example, lifetime consumers having experienced adverse side effects that led to opioid discontinuation, while never-consumers may have researched opioid side effects and this may have impacted their decision not to take opioids. However, it indicates a need for improved quality of discussions about side effects with people who are prescribed opioids.

4b: Safety precautions taken when driving with regards to opioid use. Many recent opioid consumers indicated that they took some safety precautions when driving with regards to opioid use, including electing not to drive. This aligns with a previous study of community-dwelling people who took analgesics (*n*=2,257), in which 31.9% of respondents elected not to

drive after the last time they took opioids [19]. It also indicates a degree of meta-cognition among participants, whereby awareness of impairment allowed them to enact precautions with regards to driving. However, around two-thirds of recent opioid consumers had driven within 3 hours of taking opioids in the past 12 months. While most of them did not do so every day, this indicates that people may not be engaging in safety precautions in a consistent manner.

4c: Risk ratings for DUI of opioids compared to alcohol, by opioid use status. Notably, risk ratings for opioid-related MVC and police apprehension were lower for opioids than alcohol, and lower among opioid consumers than people who were either lifetime or never consumers of opioids. This is potentially due to the mitigating effects of opioids on pain, which was itself noted to worsen driving ability by over half of all participants. The lower risk ratings may also have been informed by the personal experiences of opioid consumers (i.e., they did not think opioids impaired their own driving ability). This is somewhat supported by previous research on illicit drugs, where consumers of a given drug were less likely than non-consumers to rate DUI of that drug to be very risky [19].

4d: Factors associated with risk perceptions of driving after taking opioids. *Study* 4 demonstrated that certain factors are associated with the perceived risks associated with driving after taking opioids. Notably, cognitive function was positively associated with risk ratings for MVC, whereby people with poorer cognitive function perceived the risks to be lower than those with higher functioning. Additionally, previous DUI of opioids was also positively associated with risk ratings. Conversely, having received information about driving-related risks was not associated with risk ratings. Together with the findings for *Research Question 4a*, these factors indicate that the quality of discussions around opioid-related driving impairment may be lacking. Prescribers and other healthcare workers appear to be missing opportunities to engage consumers about the risks associated with driving after taking opioids. Potentially, brief clinical interventions may help consumers to become more aware of these risks. Combined written and spoken interventions have been shown to improve knowledge of side effects and reduce opioid DUI in people prescribed opioids [20]**.** Pharmacist-led interventions have also

been shown to be successful for surveying and reducing adverse side effects related to opioid use disorders [21]. Pharmacists are well-positioned to administer such interventions as they are the last point of contact between consumers and the healthcare system [21]. Finally, these findings again emphasise the pervasive implications of cognitive impairment, which were associated with lower risk ratings here.

Research Question 5: Opioid-related motor vehicle collisions and opioid prescribing

The final study of the thesis programme (*Study 5*) was somewhat distinct from the other four, given both its sampling method and the fact that it did not specifically include people taking opioids for CNCP. However, this assessment seems important given that 9 in 10 people with chronic opioid use for CNCP reported driving in *Study 4*. In *Study 5*, we found that opioid-related MVC did not increase over time, with increased prescribing. This is somewhat different to research conducted in the U.S., where the rate of opioid-related fatal MVC have increased over time in some jurisdictions [22]. However, this may reflect regional and national transitions towards more informed prescribing (e.g., via real-time prescription monitoring) [23]. Additionally, these results may also reflect protective behaviours. For example, participants in *Study 4* reported avoiding driving, or taking other precautions, soon after taking opioids.

Strengths, limitations, and future directions for studies examining opioids and driving

The two studies in this thesis that examined opioids and driving—*Studies 4* and *5*—provided two very methodologically diverse approaches to examining the impacts of opioids on driving. *Study 4* enabled us to examine self-reported driving behaviours among people with CNCP, and to examine the factors that are associated with perceptions of risk in this cohort. We also examined numerous co-morbid factors, and asked people to describe whether and where they received information about opioids and driving-related impairment. This allowed us to provide a nuanced analysis of perceptions of and behaviours regarding driving after taking opioids. Another considerable strength of *Study 4* was the online delivery mode, which allowed

us to recruit a larger sample size and meant the survey was more accessible to people in regional or remote areas. A key strength of *Study 5* related to the long time-frame covered (2008–2016).

In addition to the strengths outlined, *Studies 4* and *5* had several key limitations. Firstly, *Study 4* used a convenience, self-selection sampling method. This means that people with stronger opinions regarding opioids and driving may have been more likely to participate than those with milder views. Additionally, the use of self-report scales potentiates recall bias and favourable responding. While a strength of *Study 4* was the assessment of key co-morbidities, this was conversely a key limitation of *Study 5*. In particular, we were not able to examine person-level factors such as driver demographics (age, sex), road conditions, and other factors that may contribute to MVC. Additionally, we were not able to differentiate prescribed use from extra-medical use or opioid administration by paramedics at the crash scene.

Study 4 indicates a need for improved quality of discussions around opioids and driving-related risks between prescribers and consumers. Risk perceptions are a key predictor of DUI, and changing how people perceive risk can result in actual changes to their driving behaviours [24]. Discussion around driving-related impairment should form part of a standardised clinical check-list or tool-kit for examining harms related to opioid. This is needed for every consumer, but particularly those initiating strong (i.e., Schedule 8) opioids. These topics could be incorporated into existing initial discussions and reviews, as well as retaining current medicine labels. Clinical discussions are particularly important given the relationship between cognitive dysfunction and risk perceptions regarding driving under the influence of opioids. In particular, there is a need for both prescribers and pharmacists to provide consistent information regarding opioid-related impairment. This should form part of a standardised review procedure, such as the existing reviews for people who are prescribed opioids. This would ensure that consumers are provided with the most current information, and are reminded of the risk of impairment routinely.

Additionally, both *Studies 4* and *5* highlight some promising avenues for future research. *Study 4* indicated that even people who have discussions with prescribers may not fully comprehend the risk of the medicines they are prescribed. Some research has been conducted examining communication techniques for clinicians, and has noted that clear and explicit language is beneficial [25]. Future research may seek to develop a clinical intervention to educate clients about opioid-related risks, and test the efficacy of this intervention. This is important to examine for opioids specifically (as opposed to other medicines), as pain itself can also be impairing and consumers may be less likely to notice impairment from opioids.

Finally, *Study 5* indicated a need for improved quality of data sources for drug-related MVC in Australia. Police forensic databases, such as that accessed in *Study 5,* are a comprehensive and reliable source of information on MVC data. However, they are not designed for research purposes, and extraction of crucial information that could help researchers to examine crash risk (e.g., driver demographics, road conditions) is not always possible. To overcome these issues, this type of indicator data should be routinely collected and analysed so that public health officials can identify trends early, and examine the impacts of policy (e.g., real-time prescription monitoring, up-scheduling of codeine) on opioid-related harms at the population level. Potentially, these data could be linked to PBS databases to enable a more comprehensive examination of MVC risk.

Representativeness and characteristics of participants described in this thesis

Three studies (*Studies 2, 3,* and *4*) recruited people with CNCP from the community. When examining the results from these studies, it is important to consider whether these participants are representative of people prescribed opioids for CNCP. Across all three studies, most participants were female and aged in their 40s (Table 7.2). This broadly aligns with existing data, where people who take opioids for CNCP are primarily females and older people [9]. However, our participants were younger and even more likely to be female than those in the Pain and Opioids In Treatment (POINT) study of Australians prescribed opioids for CNCP (*n*=1,514) [9]. In that study, 56% of respondents were female and the median age was 58 [9].

Table 7.2. *Demographic and clinical characteristics of participants recruited for Study 2, 3, and 4*

	Study 2 (n=14)	*Study 3 (n=226)*	*Study 4 (n=218)*
Opioid use in inclusion criteria	Current daily use	Current use	Use or non-use
Median age, years	42.6	46.0	46.0
% female	71.4%	87.6%	72.9%
Pain characteristics			
Median pain duration, years (range)	n.a.	8.0 (0.4–55.0)	7.0 (0.4–62.0)
% with multiple pain conditions	28.6%	85.4%	n.a.
Mean current pain severity (SD)	4.5 (0.8)	5.0 (1.2)	4.6 (2.5)
Opioid use			
% current use of opioids	100.0%	100.0%	41.7%
Median use duration, years (range)	1.3 (0.3-2.5)	4.0 (0.4-40.0)	n.a.
% daily/near daily use >6 months	n.a.	n.a.	81.3%
Opioid dose, OME mg (range) [c]	40.0 (8.6–180.0)	40.0 (1.8–418.0)	40.0 (3.0–338.0)
% used multiple opioids, past week	64.3%	51.8%	n.a.
Concomitant medicine use [d]			
% used antidepressants	71.4%	50.9%	43.1%
% used benzodiazepines	7.1%	28.3%	12.4%
% used gabapentinoids	50.0%	n.a.	16.1%
% used multiple medicines	71.4%	65.0%	n.a.
Mental health issues			
% moderate/severe psychological distress [a]	20.0%	59.6%	n.a.
% mental health conditions	n.a.	n.a	50.5%

[a] K10 score of 25-29 (moderate distress) or ≥30 (severe distress) in the past 30 days.

[b] Diagnosed with or prescribed medicine for a mental health condition in the past 12 months.

[c] *Study 2* and *Study* 3: average daily dose in the past week. *Study 4*: typical daily dose among consumers who reported taking opioids daily or near daily for >6 months (*n*=88).

[d] *Study 2* and *Study* 3: use in the past week. *Study 4*: current use.

While the reason for variation in sex distribution is unclear, the age difference likely reflects our recruitment strategy. Specifically, we excluded people aged 65 and over. The justification for this was dual: i) the primary focus was cognitive function, which is known to deteriorate naturally with age, and ii) the cognitive effects of opioids may be particularly burdensome for working-age people, who are typically community dwelling and are more likely to participate in the workforce than retirement aged people. However, for this reason the participants described in our studies may not be representative of all people who take opioids for CNCP, who tend to be older. For example, one-third (32%) of participants in the POINT study were aged 65 and over [9]. This may be viewed as a necessary limitation of these studies.

Pain. Participants experienced relatively high levels of pain and for long durations (Table 7.2). Pain conditions reported by participants broadly reflected common conditions reported in the Global Burden of Disease study (e.g., back pain, arthritis) [26]. The proportion of people with multiple pain conditions varied between *Studies 2* (28.6%) and *3* (85.4%). This may reflect the respective recruitment strategies of these studies. The online delivery mode may have enabled individuals with limited mobility to participate in *Study 3* but not *Study 2*, which involved attending a university campus. In sum, the participants described in these three studies reported pain severity and diagnoses consistent with CNCP.

Opioid use. The median opioid dose across all studies was below the recommended 50mg OME/day [27]. However, participants reported doses as high as 338 and 418mg/day in *Studies 4* and *3*, respectively. Use of strong opioids (primarily oxycodone) was also common, and many participants reported use of more than one opioid. Most participants in *Studies 2* (64.3%) and *3* (51.8%) had taken multiple opioids in the past week. Many people had been taking opioids for longer than the CDC's recommended three months [27]. In *Studies 2* and *3*, median use duration was >12 months. In *Study 4*, among people with recent opioid use, four in five (81.3%) reported daily or near-daily use for >6 months. This aligns with POINT data, where participants had been taking opioids for a median of 4 years at study entry [9]. These factors indicate that some people were prescribed opioids in a way that may increase risks of harm.

The role of co-morbid factors among people prescribed opioids for CNCP

Co-morbid factors were common across *Studies 1* to *4*. Firstly, most people were prescribed other psychoactive medicines. The use of benzodiazepines and gabapentinoids is particularly notable, as these drugs are sedating and can impair cognitive function [28, 29]. There was also a high proportion of people with a diagnosed mental health condition or moderate-severe levels of psychological distress. This aligns with the literature on pain and mental health [30], but is concerning as mental health issues like depression are independently associated with poorer cognitive outcomes [31, 32]. This is particularly important given that participants frequently evidenced subjective cognitive dysfunction across *Studies 3* and *4*.

Opioid use in the context of biopsychosocial models of pain

This thesis highlights the importance of viewing opioid use in the context of the person who is being prescribed opioids, per biopsychosocial models of pain. In *Studies 1* to *4*, opioid use was just one of many factors that might affect cognitive function. People with CNCP can and do experience cognitive dysfunction, regardless of whether they are prescribed opioids. Many are concerned about their cognitive abilities and experience problems concentrating and engaging in everyday tasks. Such problems can be distressing: they impact almost every area of life and, from a patient perspective, it is difficult to assess whether or how cognitive difficulties might be overcome. Indeed, almost every study detected an association between cognitive function and co-morbid mental health issues, with both of these related to physical injuries. In alignment with biopsychosocial models of pain, these findings emphasise that overall health outcomes are a product of many interactive factors in a person's life. In particular, the role of mental health (including psychological distress and pain interference) needs to be further examined.

Mental health and associated harms among people prescribed opioids for CNCP

Broadly, the experience of mental health conditions and high levels of psychological distress was common among participants recruited for studies in this thesis. Three different

studies (*Studies 2*, *3* and *4*) reported very high rates of mental health conditions and psychological distress among participants with CNCP (Table 7.2). In *Study* 3, one in four (43%) participants reported severe levels of psychological distress. Over half (51%) of people in *Study 4* reported that they had been diagnosed with or prescribed medicine for a mental health condition in the past 12 months. These estimates align with that of the POINT study, where around half (46.6%) of participants reported moderate/severe depressive symptoms in the previous 2 weeks, and 22.8% reported moderate/severe symptoms of anxiety [9]. Notably, these figures are substantially higher than for the general population. For example, National Health Survey data show that, in 2017–18, 13.0% of Australians experienced high/very high levels of psychological distress and 20.1% had a mental or behavioural condition [33].

The high proportion of people in our studies with mental health issues is particularly important given the associated risk of potential harm. As this was not the primary focus of the thesis, we did not comprehensively examine the association between mental health and related harms. However, in *Study 3*, people with higher levels of psychological distress were more likely to report both cognitive complaints and physical injuries. Additionally, cognitive impairment was associated with lower ratings of risk for the impacts of driving after taking opioids in *Study 5*. While these studies are correlational, they suggest there is a relationship between cognitive function and physical health, mental health, and driver safety. Finally, previous research has demonstrated that mental health conditions can exacerbate pain, and treatment is a priority.

Implications for policy and clinical practice

As with other adverse outcomes, empowering people with CNCP to understand and address issues with cognition and mental health is crucial for their overall wellbeing, and should be a clinical priority. Importantly, information about co-morbidities needs to be provided via an appropriate mode of delivery and to all clients, not just those who are prescribed opioids. This information should also be updated regularly. Many participants in *Study 4* reported that they obtained information from GPs, pharmacists, online, or via medicine

labels. These information sources may be useful for researching some side effects, but seem inadequate for addressing the problems of cognitive dysfunction and mental health conditions. Concerns about cognitive function may be missed in brief clinical discussions that focus on risks such as dependence and overdose, and written formats (i.e., online, medicine labels) may not adequately convey this information.

The findings of the present thesis are particularly timely given the recent release of the National Strategic Action Plan for Pain Management, released by the Australian federal government in 2019 [34]. The National Action Plan identifies chronic pain as a key public health focus, and outlines eight goals for improving treatment for pain. In particular, the National Action Plan re-iterates the importance of access to multi-disciplinary pain management teams [34]. Interdisciplinary treatment would ideally provide clients with better access to treatment for cognitive problems and mental health conditions. Psychologists have a particularly important role in terms of managing symptoms of mental health conditions (e.g., depression, and helping clients to develop coping strategies to reduce distress [35]. Importantly, this should be initiated early in the course of treatment. A pre-emptive approach could help clients avoid adverse outcomes associated with both cognitive dysfunction and mental health problems, such as physical injuries. Additionally, this may help clients to recognise symptoms of psychological distress or cognitive dysfunction early, improving treatment outcomes.

To aid clinicians, there is scope for future research to develop and implement a brief screening tool assessing cognitive function and mental health in people with CNCP conditions. Such a battery would greatly aid clinicians in terms of appropriately referring clients to mental health practitioners and facilitating discussions about cognitive and mental health. Related, there is scope for more research into possible interventions specifically to help people with CNCP address issues with cognitive function. While many interventions exist for managing the emotional elements of pain, very few if any specifically focus on cognitive wellbeing. Importantly, increasing and synthesising research activities in the field of pain management wis

listed as a goal in the National Action Plan [34]. This represents a timely opportunity for more research into the cognitive and mental health aspects of CNCP.

Notably, clients may experience difficulties accessing multi-modal treatment due to high costs and lack of service availability. Improving access to services for people experiencing CNCP is one of the goals of the National Action Plan [34]. In light of the present findings, provision of additional PBS-covered mental health sessions for people with CNCP would be particularly appropriate. The event of COVID-19 has also demonstrated the ability to deliver mental health consultations via remote options such as video link and telephone. This may be a useful option for clients with limited mobility or who live in regional/remote areas. In sum, there is much work to do to improve outcomes for people with CNCP, and mental and cognitive health should be a key focus. The release of the National Action Plan is timely, and offers opportunities for more research and clinical implementation of these findings.

Conclusions

The present thesis used a range of methodologies to examine the relationships between pharmaceutical opioids and cognitive and behavioural harms, including at the population level. There was some evidence of objective cognitive impairments for this cohort compared with healthy people, but these deficits were not global. Additionally, objective function was not significantly or consistently different for people with CNCP whether they were prescribed opioids or not. A complementary finding was that, broadly, opioid dose did not substantially impact objective cognitive performance, cognitive complaints or physical injuries. Further, cognitive performance actually improved following initiation of opioids for specific domains. Regarding driving, there was a perception that opioids are less 'risky' than driving under the influence of alcohol and current consumers of strong opioids perceived this risk to be lower than did people using weak opioids and non-consumers. Many participants received information about driving impairment and other side effects from health practitioners. However, many people took safety precautions when driving after taking opioids. At the population level, increased prescribing of opioids in Tasmania was not associated with a corresponding rise in pharmaceutical opioid-related motor vehicle collisions.

Broadly, the studies described in this thesis provide mounting evidence that chronic use of opioids does not predict poorer cognitive outcomes than the experience of pain itself. However, people with chronic opioid use for CNCP commonly experience a range of adverse outcomes that could reduce their quality of life, including cognitive dysfunction. In particular, mental health conditions and high levels of psychological distress are common among this cohort and may be related to other harms (e.g., physical injuries). Additionally, people who take opioids may not fully understand the risks associated with driving soon after taking opioid medicines. There is scope for improvement in terms of brief clinical interventions about the possible effects of opioids and more routine monitoring of risk factors aside from pain, particularly mental health.

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Appendix A: Chapter 2 supplementary materials

Supplementary Table 2.1. *PRISMA checklist for meta-analyses*

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Abstract page
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	pp. 1–3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	pp. 2–3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	p. 3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	pp. 3–4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	p. 4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	p. 3 (supplementary material)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	pp. 4–5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	pp. 4–5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	p. 5; pp. 3–4 (supplementary material)
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	p. 7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	pp. 7–8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	pp. 7–8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	p. 7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	p. 8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	p. 9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	pp. 8–15
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	p. 16; pp. 11–13 (supplementary material)
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	pp. 14–32 (supplementary material)
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency	16–19
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	20
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19–20
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	21–24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	24–25
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	21–24
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Title page

Notes. From Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA

Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.

Supplementary Table 2.2. *Full search term list for EMBASE*

Search term type	Concept 1: CNCP	Concept 2: Opioids	Concept 3: Cognition	Limits
Text words	"chronic pain".tw "persistent pain".tw "chronic non-cancer pain".tw migraine.tw fibromyalgia.tw arthritis.tw "back pain".tw sciatica.tw endometriosis.tw "chronic non-malignant pain".tw "neuropathic pain".tw	opioid$.tw opiate$.tw dextropropoxyphene.tw buprenorphine.tw tramadol.tw methadone.tw oxycodone.tw fentanyl.tw morphine.tw hydromorphone.tw codeine.tw tapentadol.tw hydrocodone.tw	cognit$.tw attention$.tw memory.tw neuropsych$.tw "executive function$".tw psychomotor.tw	2000–current No language limits
Emtree terms	chronic pain/ fibromyalgia/ arthritis/ low back pain/ sciatica/ endometriosis/ neuropathic pain/ migraine/	opiate/ exp narcotic analgesic agent/ morphine/ tramadol/ buprenorphine/ methadone/ oxycodone/ fentanyl/ hydromorphone/	cognition/ attention/ executive function/ learning/ memory/ mental performance/ perception/	

Supplementary Table 2.3. *Description of data extracted from included studies, including labels*

and definitions

Label	Description
Study design and setting	
First author surname	Surname of first author of paper
Year of publication	Year in which the study was published
Year of data collection	Specify year or range for data collection (e.g., June 2015–April 2016)
Country	Country in which study took place
Area covered by sample	Specify what area was covered in the study (e.g., province, city, country)
Name of area	Specify name of area, if provided
Study design (participants)	Specify design type (e.g., case-control, cohort)
Study design (duration)	Specify duration of study (e.g., cross-sectional, prospective)
Other relevant characteristics	List any other relevant characteristics (e.g., matched pairs)
Number of groups	Number of groups included in the study
Number of relevant groups	Number of groups relevant for inclusion in meta-analysis (e.g., excluding groups of people who use illicit opioids)
Group names	Names of groups, as described in the study
Group numbers	Sample size for each group
Total sample size	Total sample size
Specification of sub-groups	Describe any sub-groups
Number of sessions completed	Number of sessions completed, including familiarisation sessions
Sessions with cognitive tasks	Number of sessions where cognitive tasks were administered (e.g., some studies did not assess cognition at baseline)
Session time points	Times at which sessions were conducted (e.g., baseline and 4 weeks)
Definition of the sample	Describe the sample of interest (e.g., people with CNCP)
Definition of control group/s	Describe the control group or groups included (e.g., healthy controls, opioid-free controls with CNCP)
Sampling method	Describe sampling method (e.g., convenience)
Recruitment location	Describe where participants were recruited (e.g., hospital in-patients, outpatient clinics)
Age limitation for inclusion	Describe any age limitations (e.g., 18–65)
Sex limitation for inclusion	Describe any sex limitations (e.g., males only)
Inclusion criteria	List the inclusion criteria described in the study
Exclusion criteria	List the exclusion criteria described in the study
Demographic information of the sample	
Baseline differences	Describe any baseline differences between groups (e.g., age, sex)
Sex	Describe the number and percent of the sample who were male, female, and other
Race	Percent Caucasian, African-American, Latino, Native American, Asian, and other
Age	Mean or median current age of the sample, and age range
Education	Mean time spent in education or percent of sample with a high-school education
Employment	Number and percent unemployed, with definition of unemployment where provided
Homelessness	Number and percent homeless or in unstable housing, and timeframe (e.g., past year)
IQ	Mean IQ and name of measure used
Psychological distress	Mean psychological distress score and name of measure used
Anxiety	Mean anxiety score and name of measure used
Depression	Mean depression score and name of measure used
Socioeconomic area	Mean score, name of measure used, and timeframe (e.g., past year)
Disability	Number and percent who experience a disability
Smoking status	Number and percent smokers, and timeframe (e.g., current smokers)
Alcohol use	Mean days of alcohol use, and timeframe (e.g., past 30 days)
Other drug use	Describe use of or testing for illicit or other drugs (e.g., cannabis), and whether this was confirmed biologically
Clinical characteristics of the sample	
Opioid use duration	Mean or median opioid use duration (days, weeks, months, or years), and range
Frequency of opioid use	Describe how often participants took opioids (e.g., daily)
Opioid type	Drug type (e.g., morphine), with specification of other/mixed where type was not specified or the sample reported use of multiple opioid types
Duration of action	Specification of long- or short-acting opioid, where specified
Route of administration	Specification of oral, transdermal, or other ROA
Opioid dose	Mean opioid dose and measure used (e.g., m.g.), range of doses
Mean OME	Description of average OME/day, either based on the study description or calculated using doses for specific opioid types where provided
Assessment of opioid use	Describe how opioid use was assessed, including timeframe (e.g., 24 hours)
Biological confirmation	Indicate whether opioid use was confirmed biologically (e.g., via blood)
Pain conditions	Describe how pain was defined in the study (e.g., CNCP) with specification of included pain types if the study reported mixed pain conditions

Label	Description
	Mean number of pain sites or conditions
Number of pain sites	
Pain duration	Mean or median pain duration (months, years) and range, or percent of sample in categories of pain duration (e.g., 50% had pain duration >6 months)
	Mean or median pain level and range, name of measure used, and description of
Pain level	timeframe (e.g., current, past 24 hours)
	Total number of medicines used, or percent of sample who used benzodiazepines,
Concomitant medicine use	anticonvulsants, NSAIDs, stimulants, beta blockers, muscle relaxants, ACE inhibitors, CA++ antagonists, antidepressants, Z-drugs, or none
	Mean amount of sleep (minutes or hours) and range, or mean sleep score and name
Sleep/insomnia	of measure used
Cognitive outcomes	
Number of tasks	List the total number of tasks administered in each study
Name of task	List the name of the task, as described in the study
Task battery	Specify if each task was part of a test battery, and the name of the battery (e.g., CANTAB)
Method of administration	Specify how each task was administered (e.g., pen and paper, computer)
Task validity and reliability	Specify if each task is considered valid and reliable
Cognitive domain	Specify what cognitive domain each task assesses
Dependent variables	Specify all dependent variables for each task (e.g., reaction time, accuracy)
Sample description	Describe session time (e.g., baseline), group name (e.g., cases), and number of participants who completed each measure at each time
Test scores	List mean score and standard deviation for each group at each time point
Statistical analyses	
Statistical methods used	Name the statistical method or methods used in the study (e.g., ANOVA, *t*-tests)
Appropriateness of methods	Indicate whether the method used is appropriate for the study design
Identification of confounds	Indicate whether the authors identified confounds, and specify what the confounds were
Accounting for confounds	Indicate whether and how the authors accounted for confounds (e.g., inclusion as a covariate, use of matched pairs)
Potentially missing confounds	Identify any relevant confounds that were not assessed (e.g., psychological distress, sleep)
Original sample size	Describe the original sample size, at the beginning of the study
Final sample size	Describe the sample size at the end of the study
Number missing	List the number of participants missing, which groups or timepoints they are missing from, and why they are missing (e.g., two participants in the opioid group dropped out due to drug side effects)
Other relevant results	Describe any other relevant results reported in the study (e.g., MMSE)
Cognitive impairment noted	Indicate whether the authors concluded that cognitive impairment was noted among the relevant group (i.e., cases for case-control studies, and follow-up sessions for pre-post studies), and specify results for specific tasks if results were mixed

Supplementary Table 2.4. *Time points from longitudinal studies selected for data extraction and used in pre–post and case-control meta-analyses*

			Sessions selected for pre-post analyses								
Study	Baseline	3 weeks	4–6 weeks[a]			6–9 weeks[a]			3 months	6 months	12 months
		3 weeks	4 weeks	5–6 weeks	6–8 weeks	8 weeks	7–9 weeks				
Francis 2000	✓		✓								
Freo 2018	✓								✓	✓	
Jamison 2003	✓								✓	✓	
Kurita 2018	✓	✗		✓			✓				
Menefee 2004	✓					✓					
Panjabi 2008	✓		✓								
Raja 2002	✓				✓						
Tassain 2003[b]	✓								✓	✓	✓
			Sessions selected for case-control analyses								
Study	Baseline	3 weeks	4 weeks	5–6 weeks	6–8 weeks	8 weeks	7–9 weeks	3 months	6 months	12 months	
Francis 2000	✗		✓								
Kurita 2018	✗	✗		✗			✓				
Menefee 2004	✗					✓					
Panjabi 2008	✗		✓								
Raja 2002	✗				✓						
Tassain 2003[b]	✗							✗	✓	✗	

[a] Times were clustered in meta-analyses (e.g., "4–6 weeks" comprised sessions from 4 weeks (Francis 2000, Panjabi 2008), and 5–6 weeks (Kurita 2018). [b] 6 months was selected over 3 months for Tassain 2003 given issues with missing data at 3 months.

Note. Green cells indicate that a session was conducted at this time point **and** was included in these meta-analyses, and orange cells indicate that a session was conducted at this time point but **was not** included in these meta-analyses, and grey cells indicate that no session was conducted at this time point.

Supplementary Table 2.5. *Individual effect sizes for included case-control comparisons, by*

cognitive domain and control type

| Control type and study | Sample size | | | Effect size | 95%CI | |
	Cases	Controls	Total		Lower limit	Upper limit
Motor performance						
Healthy controls (*k*=5)						
Block 2014	30	30	60	0.70	0.19	1.22
Dagtekin 2007	26	90	116	0.25	-0.19	0.68
Gaertner 2006	24	90	114	0.35	-0.11	0.80
Sabatowski 2003	20	90	110	-0.06	-0.54	0.43
Sjogren 2005	19	64	83	-0.98	-1.51	-0.45
Pain controls (*k*=3)						
Block 2014	30	30	60	0.20	-0.30	0.70
Raja 2002	44	44	88	0.03	-0.38	0.45
Sjogren 2005	19	21	40	-0.29	-0.91	0.32
Taper-off controls (*k*=1)						
Kurita 2018	18	12	30	-0.42	-1.14	0.30
Attention						
Healthy controls (*k*=8)						
Block 2014	30	30	60	-0.35	-0.86	0.16
Byas-Smith 2005	21	50	71	-0.23	-0.74	0.28
Dagtekin 2007	26	90	116	-0.16	-0.60	0.28
Gaertner 2006	24	90	114	0.23	-0.22	0.68
Nilsen 2011	20	20	40	-0.94	-1.58	-0.30
Sabatowski 2003	21	90	111	-0.18	-0.65	0.30
Schiltenwolf 2014	37	25	62	-0.32	-0.82	0.19
Sjogren 2005	19	64	83	-0.65	-0.14	-2.48
Pain controls (*k*=7)						
Block 2014	30	30	60	-0.06	-0.56	0.44
Byas-Smith 2005	21	11	32	-0.17	-0.89	0.54
Nilsen 2011	20	20	40	-0.15	-0.75	0.46
Raja 2002	44	44	88	0.16	-0.26	0.57
Schiltenwolf 2014	37	33	70	-0.23	-0.70	0.23
Sjogren 2005	19	21	40	-0.32	-0.94	0.31
Tassain 2003	16	10	26	-0.14	-0.30	0.11
Taper-off controls (*k*=1)						
Kurita 2018	18	11	29	-0.55	-1.29	0.19
Working memory						
Healthy controls (*k*=1)						
Schiltenwolf 2014	37	25	62	-0.39	-0.89	0.12
Pain controls (*k*=2)						
Schiltenwolf 2014	37	33	70	-0.28	-0.75	0.19
Tassain 2003	16	10	26	0.36	-0.41	1.13
Taper-off controls (*k*=1)						
Kurita 2018	18	11	29	-0.43	-1.17	0.31
Executive functions						
Healthy controls (*k*=3)						
Baldacchino 2015	28	28	56	-0.31	-0.84	0.22
Block 2014	30	30	60	-0.08	-0.58	0.42
Schiltenwolf 2014	37	25	62	-0.79	-1.31	-0.27
Pain controls (*k*=3)						
Block 2014	30	30	60	0.0	-0.50	0.50
Schiltenwolf 2014	37	33	70	-0.55	-1.02	-0.08
Tassain 2003	16	10	26	-0.12	-0.89	0.65
Taper-off controls (*k*=1)						
Kurita 2018	18	12	30	0.47	-0.26	1.19
Memory						
Healthy controls (*k*=3)						
Baldacchino 2018	28	28	56	-0.46	-1.00	0.07
Block 2014	30	30	60	-0.45	-0.96	0.05
Schiltenwolf 2014	37	25	62	-0.19	-0.70	0.31
Pain controls (*k*=4)						
Block 2014	30	30	60	0.31	-0.20	0.81
Raja 2002	44	44	88	-0.03	-0.45	0.38
Schiltenwolf 2014	37	33	70	-0.40	-0.87	0.07
Tassain 2003	16	10	26	0.54	-0.24	1.33

Supplementary Table 2.6. *Individual effect sizes for longitudinal (cohort/pre-post) comparisons,*

by cognitive domain and follow-up time point

Follow-up time and study	Sample size	Effect size	95%CI	
			Lower limit	*Upper limit*
Motor performance				
4–6 weeks (*k*=2)				
Francis 2000	40	0.24	-0.07	0.55
Kurita 2018	19	0.15	-0.28	0.59
6–9 weeks (*k*=2)				
Kurita 2018	18	0.11	-0.34	0.55
Raja 2002	44	0.00	-0.29	0.29
3 months (*k*=1)				
Freo 2018	21	0.20	-0.22	0.62
6 months (*k*=1)				
Freo 2018	21	0.16	-0.26	0.57
Attention				
4–6 weeks (*k*=3)				
Francis 2000	40	0.12	-0.19	0.44
Kurita 2018	19	0.14	-0.30	0.57
Panjabi 2008	84	0.37	0.15	0.59
6–9 weeks (*k*=3)				
Kurita 2018	18	0.11	-0.34	0.56
Menefee 2004	23	0.20	-0.21	0.60
Panjabi 2008	44	0.16	-0.14	0.45
3 months (*k*=3)				
Freo 2018	21	0.44	-0.01	0.89
Jamison 2003	137	0.31	0.14	0.48
Tassain 2003	18	0.11	-0.33	0.56
6 months (*k*=3)				
Freo 2018	21	0.48	0.02	0.93
Jamison 2003	99	0.36	0.16	0.56
Tassain 2003	16	0.06	-0.41	0.52
12 months (*k*=1)				
Tassain 2003	11	0.12	-0.43	0.68
Working memory				
4–6 weeks (*k*=3)				
Francis 2000	40	0.11	-0.19	0.42
Kurita 2018	19	0.39	-0.06	0.83
Panjabi 2008	84	0.35	0.13	0.57
6–9 weeks (*k*=2)				
Kurita 2018	18	0.34	-0.11	0.80
Menefee 2004	23	0.08	-0.32	0.47
3 months (*k*=3)				
Freo 2018	21	0.38	-0.05	0.81
Tassain 2003	18	0.38	-0.08	0.84
6 months (*k*=2)				
Freo 2018	21	0.61	0.16	1.06
Tassain 2003	16	0.60	0.09	1.11
12 months (*k*=1)				
Tassain 2003	11	0.47	-0.11	1.04
Executive functions				
4–6 weeks (*k*=2)				
Francis 2000	40	0.32	0.00	0.63
Kurita 2018	19	0.20	-0.24	0.63
6–9 weeks (*k*=2)				
Kurita 2018	18	0.61	0.13	1.10
Menefee 2004	23	0.50	0.08	0.92
3 months (*k*=3)				
Freo 2018	21	0.31	-0.11	0.74
Jamison 2003	129	0.30	0.13	0.48
Tassain 2003	18	-0.12	-0.57	0.34
6 months (*k*=3)				
Freo 2018	21	0.36	-0.07	0.79
Jamison 2003	94	0.28	0.08	0.49
Tassain 2003	16	-0.16	-0.63	0.32

Follow-up time and study	Sample size	Effect size	95%CI	
			Lower limit	*Upper limit*
12 months (*k*=1)				
Tassain 2003	11	0.14	-0.42	0.69
Memory				
4–6 weeks (*k*=1)				
Francis 2000	40	0.31	-0.02	0.63
6–9 weeks (*k*=2)				
Menefee 2004	23	0.62	0.17	1.06
Raja 2002	44	0.22	-0.08	0.51
3 months (*k*=1)				
Freo 2018	21	0.22	-0.19	0.64
6 months (*k*=2)				
Freo 2018	21	0.10	-0.31	0.52
Tassain 2003	16	0.66	0.13	1.18
12 months (*k*=1)				
Tassain 2003	11	0.62	0.01	1.23

Supplementary Table 2.7. *Risk of bias assessment for included case-control studies*

	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definition of controls	Sample size	Non-response rate	Study controls for age and sex, or eliminates these as confounds	Study controls for any additional factors	Adequate ascertainment of exposure	Same method of ascertainment for cases and controls?	Assessment of the outcome	Statistical test	Score (0–12)
Baldacchino 2015	✓	✗	✓	✗	✗	✗	✓	✓	✗	✓	✓	✓	7
Baldacchino 2018	✓	✗	✓	✗	✗	✗	✓	✓	✗	✓	✓	✓	7
Block 2014	✓	✗	✗	✓	✓	✗	✓	✓	✓	✓	✓	✓	9
Byas-Smith 2005	✓	✗	✓	✗	✗	✗	✓	✓	✓	✓	✓	✓	8
Dagtekin 2007	✗	✗	✓	✗	✓	✗	✓	✓	✓	✗	✓	✓	7
Gaertner 2006	✓	✗	✓	✗	✓	✗	✓	✓	✗	✗	✓	✓	7
Kurita 2018	✓	✗	✗	✓	✓	✗	✓	✗	✗	✓	✓	✓	7
Nilsen 2011	✓	✗	✓	✓	✓	✗	✗	✓	✓	✓	✓	✓	9
Sabatowski 2003	✗	✗	✓	✗	✓	✗	✓	✓	✗	✗	✓	✓	6
Schiltenwolf 2014	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✓	✓	6
Sjogren 2005	✓	✗	✗	✗	✗	✗	✓	✓	✗	✗	✓	✓	5
Studies that met criterion (%)	18.2	0	63.6	27.3	54.5	0	90.9	90.9	36.4	63.6	100	100	

Note. Criteria are based on the Newcastle-Ottawa scale [29].

Supplementary Table 2.8. *Risk of bias assessment for included cohort studies*

	Definition of exposed cohort	Representativeness of exposed cohort	Demonstration that outcome of interest was not present at start of study	Sample size	Non-response rate	Study controls for age and sex, or eliminates these as confounds	Study controls for any additional factors	Ascertainment of exposure	Was follow-up long enough for outcome to occur (i.e., >2wks)?	Adequacy of follow-up of cohorts	Assessment of the outcome	Statistical test	Score (0–12)
Francis 2000	✓	✓	✗	✗	✗	✓	✓	✓	✓	✗	✓	✓	8
Freo 2018	✓	✓	✗	✗	✗	✗	✗	✗	✓	✓	✓	✓	6
Menefee 2004	✗	✗	✗	✗	✗	✗	✓	✗	✓	✓	✓	✓	5
Panjabi 2008	✓	✗	✗	✗	✗	✗	✗	✓	✓	✓	✓	✓	6
Tassain 2003	✓	✓	✗	✗	✗	✓	✓	✗	✓	✓	✓	✓	8
Studies that met criterion (%)	80	60	0	0	0	40	60	40	100	80	100	100	

Note. Criteria are based on the Newcastle-Ottawa scale [29].

Supplementary Table 2.9. *Risk of bias assessment for included case-crossover studies, with risk ratings*

	Jamison 2003	Raja 2002	Studies that met criterion (%)
Risk of bias due to the randomisation process			
Was the allocation sequence random?	✗	✓	50
Was the allocation sequence concealed until participants were recruited and assigned to interventions?	✗	✓	50
Were there baseline imbalances that suggest problems with randomisation?	✓	✓	100
Is a roughly equal proportion of participants allocated to each group?	✗	✓	50
If no/probably no, are period effects included in the analysis?	✗	–	0
Risk rating for randomisation process	High	Low	
Risk of bias due to deviations from intended interventions			
Were participants aware of their assigned intervention during each period of the trial?	✓	✓	100
Were carers/trial personnel aware of the participant's assigned intervention during each period of the trial?	✓	✓	100
If yes/probably yes/no information, were there deviations from the intended interventions beyond what would be expected in usual practice?	–	–	–
If yes to the above, were these deviations from intended interventions unbalanced between the two interventions and likely to have affected the outcome?	–	–	–
Was there sufficient time for any carry-over effects to have disappeared before outcome assessment in the second period?	✗	✓	50
Risk rating for deviations from intended interventions	High	Low	
Risk of bias due to missing data			
Were outcome data available for all, or nearly all, participants randomised?	✓	✓	100
If N/PN/NI, are the proportions of missing outcome data and reasons for missing outcome data similar across interventions?	–	–	–
If N/PN/NI, is there evidence that results were robust to the presence of missing outcome data?	–	–	–
Risk rating for missing data	Low	Low	
Risk of bias due to bias in measurement of the outcome			
Were outcome assessors aware of the intervention received by study participants?	✗	✓	50
If Y/PY/NI, was the assessment of the outcome likely to be influenced by knowledge of intervention received?	✓	–	100
Risk rating for bias in measurement of the outcome	Low	Low	
Risk of bias due to bias in selection of the reported result			
Are the reported outcome data likely to have been selected, on the basis of the results, from… Multiple outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	✓	✓	100
…. Multiple analyses of the data?	✓	✓	100
…. The outcome of a statistical test for carry-over?	✓	✓	100
Risk rating for bias in selection of the reported result	Low	Low	
Score (0–12)	8	12	

Note. Criteria are based on the Cochrane risk-of-bias tool for randomized trials (RoB 2) [30].

Supplementary Figure 2.1. *Random effects model forest plots with weighted effect sizes (Hedges' g) for cross-sectional comparisons of cases[a] and healthy controls on tasks assessing motor performance*
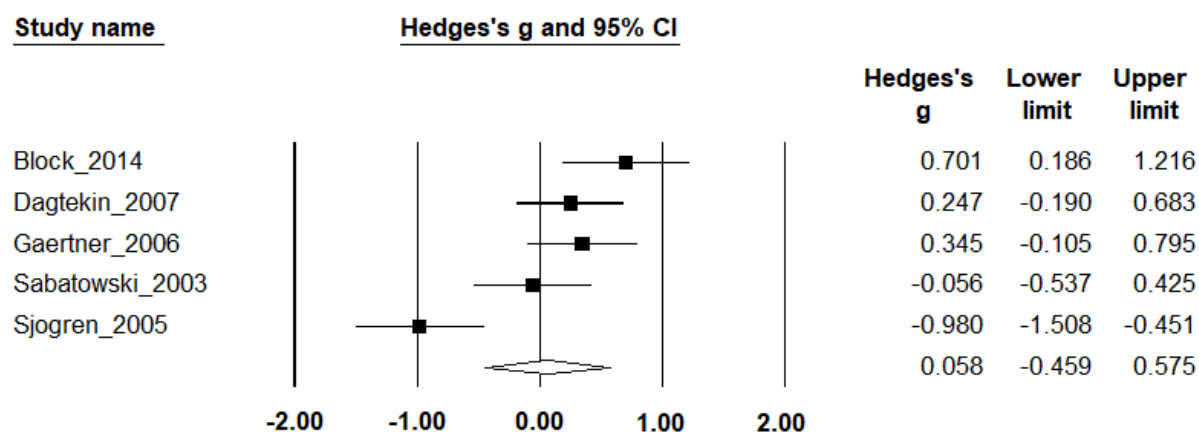
[a] Cases comprise people on long-term (>2 weeks) opioid therapy for chronic non-cancer pain.

Note. Negative values denote poorer performance among cases, compared with controls.

Supplementary Figure 2.2. *Random effects model forest plots with weighted effect sizes (Hedges' g) for cross-sectional comparisons of cases[a] and healthy controls on tasks assessing attention*

[a] Cases comprise people on long-term (>2 weeks) opioid therapy for chronic non-cancer pain.

Note. Negative values denote poorer performance among cases, compared with controls.

Supplementary Figure 2.3. *Random effects model forest plots with weighted effect sizes (Hedges' g) for cross-sectional comparisons of cases[a] and healthy controls on tasks assessing executive functions*

Study name	Hedges's g	Lower limit	Upper limit
Baldacchino_2015	-0.309	-0.835	0.217
Block_2014	-0.079	-0.581	0.422
Schiltenwolf_2014	-0.793	-1.314	-0.272
	-0.390	-0.804	0.024

[a] Cases comprise people on long-term (>2 weeks) opioid therapy for chronic non-cancer pain.

Note. Negative values denote poorer performance among cases, compared with controls.

Supplementary Figure 2.4. *Random effects model forest plots with weighted effect sizes (Hedges' g) for cross-sectional comparisons of cases[a] and healthy controls on tasks assessing memory*

Study name	Hedges's g	Lower limit	Upper limit
Baldacchino_2018	-0.464	-0.996	0.068
Block_2014	-0.452	-0.958	0.054
Schiltenwolf_2014	-0.194	-0.696	0.308
	-0.366	-0.662	-0.070

[a] Cases comprise people on long-term (>2 weeks) opioid therapy for chronic non-cancer pain.

Note. Negative values denote poorer performance among cases, compared with controls.

Supplementary Figure 2.5. *Random effects model forest plots with weighted effect sizes (Hedges'*

g) for cross-sectional comparisons of cases[a] and opioid-free pain controls on tasks assessing motor

performance

Study name	Hedges's g and 95% CI	Hedges's g	Lower limit	Upper limit
Block_2014		0.203	-0.297	0.704
Raja_2002		0.032	-0.382	0.446
Sjogren_2005		-0.294	-0.906	0.318
		0.017	-0.266	0.300

(Scale: -2.00 -1.00 0.00 1.00 2.00)

[a] Cases comprise people on long-term (>2 weeks) opioid therapy for chronic non-cancer pain.

Note. Negative values denote poorer performance among cases, compared with controls.

Supplementary Figure 2.6. *Random effects model forest plots with weighted effect sizes (Hedges'*

g) for cross-sectional comparisons of cases[a] and opioid-free pain controls on tasks assessing

attention

Study name	Hedges's g and 95% CI	Hedges's g	Lower limit	Upper limit
Block_2014		-0.061	-0.564	0.443
Byas-Smith_2005		-0.171	-0.886	0.544
Nilsen_2011		-0.145	-0.753	0.464
Raja_2002		0.157	-0.257	0.572
Schiltenwolf_2014		-0.234	-0.700	0.232
Sjogren_2005		-0.318	-0.942	0.307
Tassain_2003		-0.142	-0.911	0.626
		-0.094	-0.301	0.114

(Scale: -2.00 -1.00 0.00 1.00 2.00)

[a] Cases comprise people on long-term (>2 weeks) opioid therapy for chronic non-cancer pain.

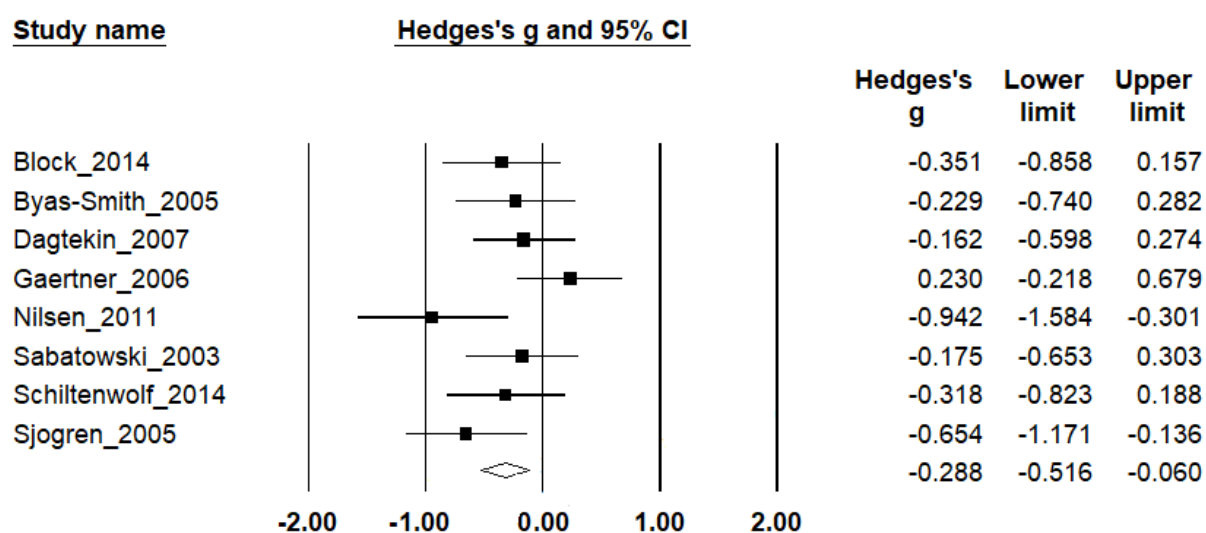*Note.* Negative values denote poorer performance among cases, compared with controls.

Supplementary Figure 2.7. *Random effects model forest plots with weighted effect sizes (Hedges'*

g) for cross-sectional comparisons of cases[a] and opioid-free pain controls on tasks assessing

working memory

[a] Cases comprise people on long-term (>2 weeks) opioid therapy for chronic non-cancer pain.

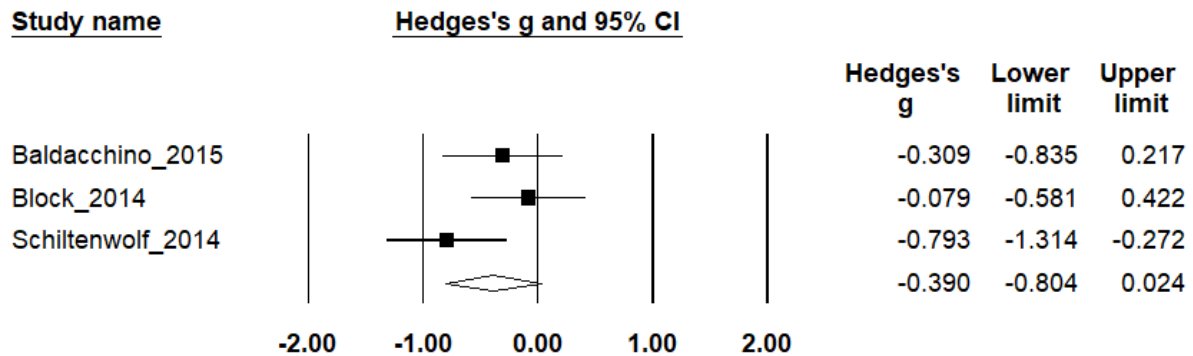*Note.* Negative values denote poorer performance among cases, compared with controls.

Supplementary Figure 2.8. *Random effects model forest plots with weighted effect sizes (Hedges'*

g) for cross-sectional comparisons of cases[a] and opioid-free pain controls on tasks assessing

executive functions

[a] Cases comprise people on long-term (>2 weeks) opioid therapy for chronic non-cancer pain.

Note. Negative values denote poorer performance among cases, compared with controls.
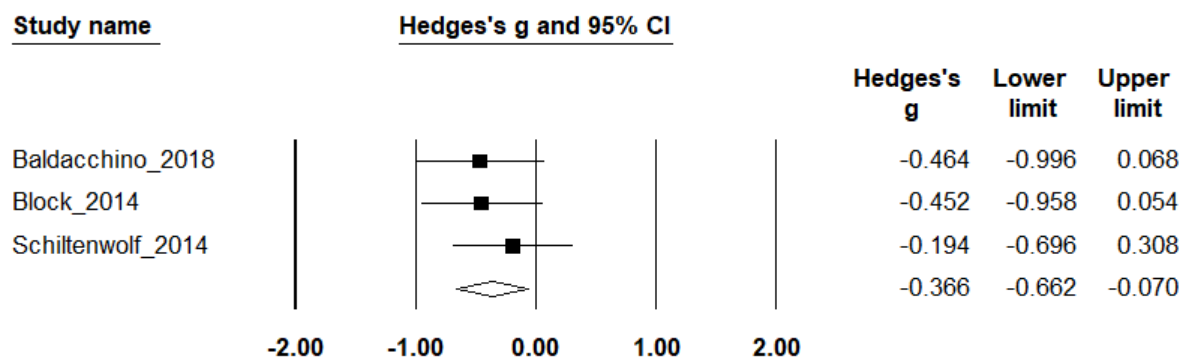
Supplementary Figure 2.9. *Random effects model forest plots with weighted effect sizes (Hedges'*

g) for cross-sectional comparisons of cases[a] and opioid-free pain controls on tasks assessing

memory

Study name	Hedges's g	Lower limit	Upper limit
Block_2014	0.306	-0.197	0.810
Raja_2002	-0.032	-0.446	0.382
Schiltenwolf_2014	-0.396	-0.865	0.073
Tassain_2003	0.544	-0.243	1.331
	0.043	-0.325	0.410

[a] Cases comprise people on long-term (>2 weeks) opioid therapy for chronic non-cancer pain.

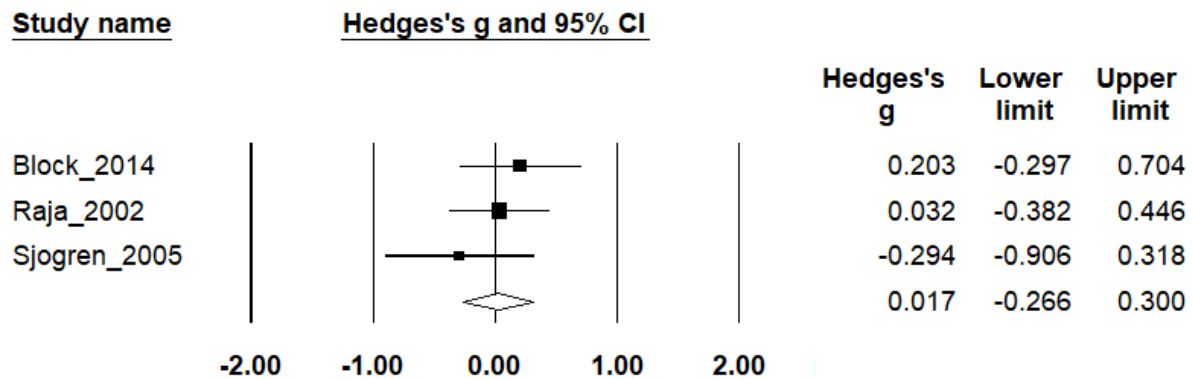*Note.* Negative values denote poorer performance among cases, compared with controls.
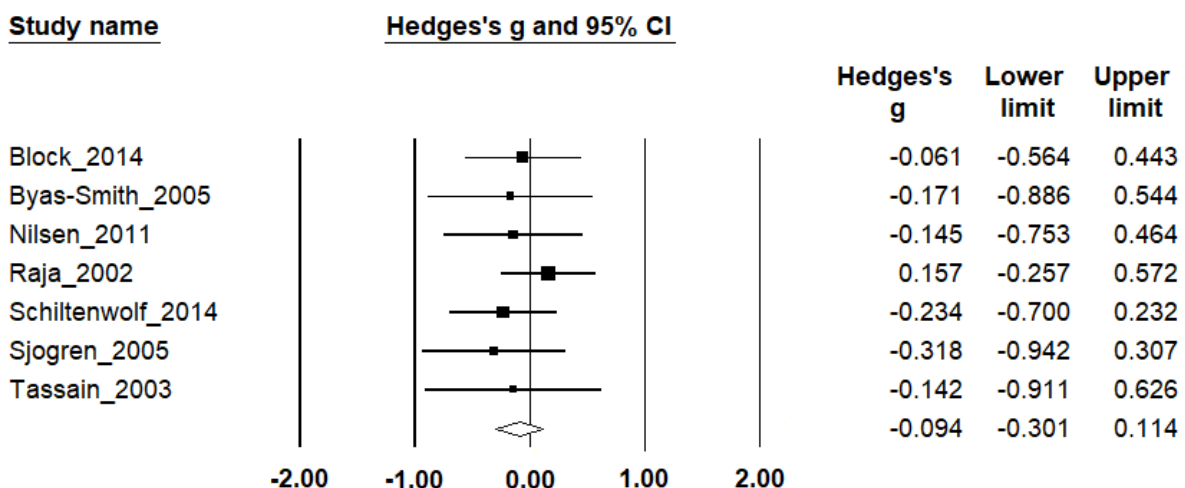
Supplementary Figure 2.10. *Random effects model forest plots with weighted effect sizes*

(Hedges' g) for longitudinal comparisons of people with CNCP at opioid-free baseline and opioid-

present follow-up on tasks assessing motor performance

Study name	Hedges's g	Lower limit	Upper limit
4-6 weeks			
Francis_2000	0.239	-0.073	0.551
Kurita_2018	0.152	-0.283	0.586
	0.209	-0.044	0.463
6-9 weeks			
Kurita_2018	0.109	-0.335	0.553
Raja_2002	0.000	-0.290	0.290
	0.033	-0.210	0.276
3 months			
Freo_2018	0.200	-0.215	0.616
	0.200	-0.215	0.616
6 months			
Freo_2018	0.157	-0.258	0.571
	0.157	-0.258	0.571
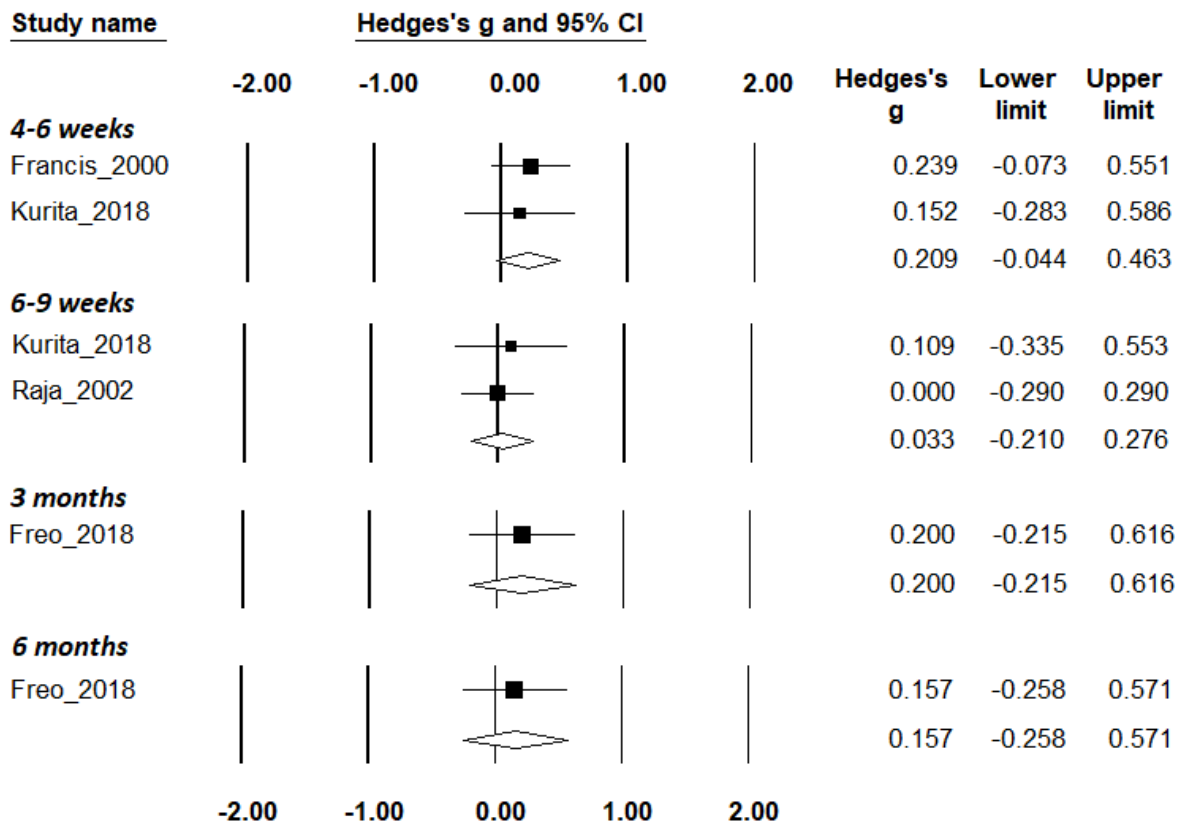
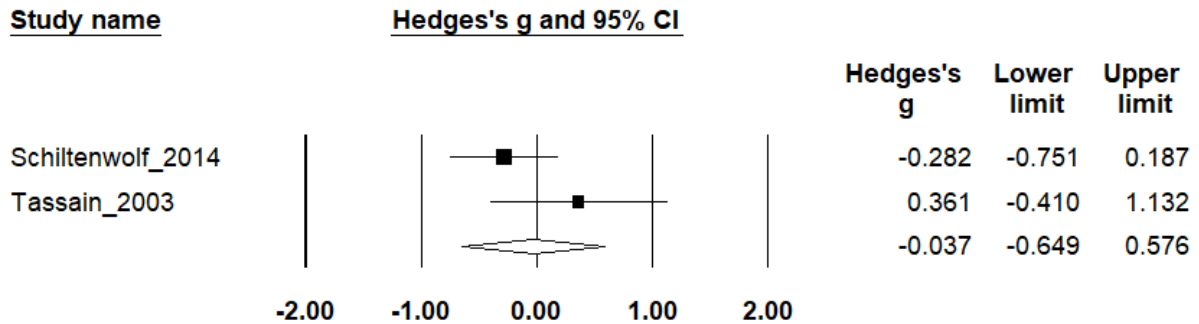*Note.* Negative values denote poorer performance at follow-up, compared with baseline.

Supplementary Figure 2.11. *Random effects model forest plots with weighted effect sizes*

(Hedges' g) for longitudinal comparisons of people with CNCP at opioid-free baseline and opioid-

present follow-up on tasks assessing attention

Study name	Hedges's g and 95% CI	Hedges's g	Lower limit	Upper limit
4-6 weeks				
Francis_2000		0.124	-0.186	0.435
Kurita_2018		0.138	-0.296	0.572
Panjabi_2008		0.371	0.151	0.591
		0.266	0.100	0.433
6-9 weeks				
Kurita_2018		0.110	-0.337	0.556
Menefee_2004		0.197	-0.210	0.604
Raja_2002		0.155	-0.137	0.447
		0.156	-0.053	0.366
3 months				
Freo_2018		0.442	-0.009	0.894
Jamison_2003		0.310	0.139	0.480
Tassain_2003		0.114	-0.332	0.560
		0.302	0.152	0.453
6 months				
Freo_2018		0.476	0.023	0.930
Jamison_2003		0.358	0.156	0.559
Tassain_2003		0.057	-0.410	0.524
		0.334	0.163	0.505
12 months				
Tassain_2003		0.122	-0.432	0.676
		0.122	-0.432	0.676

Note. Negative values denote poorer performance at follow-up, compared with baseline.

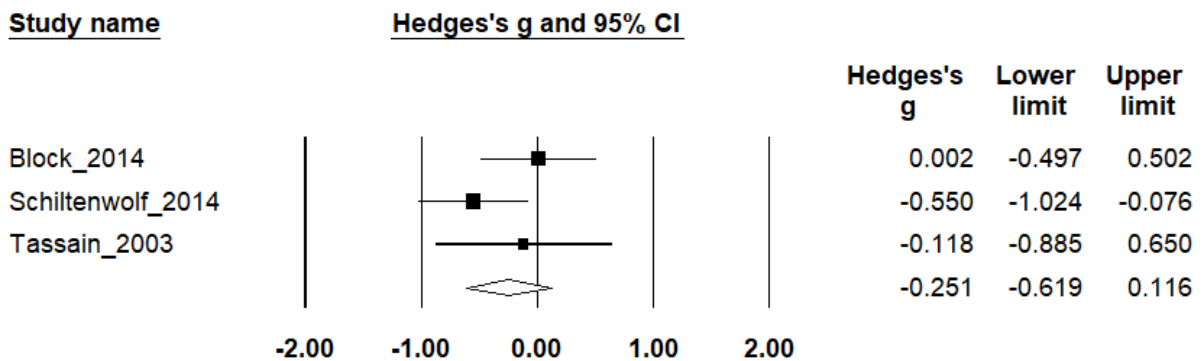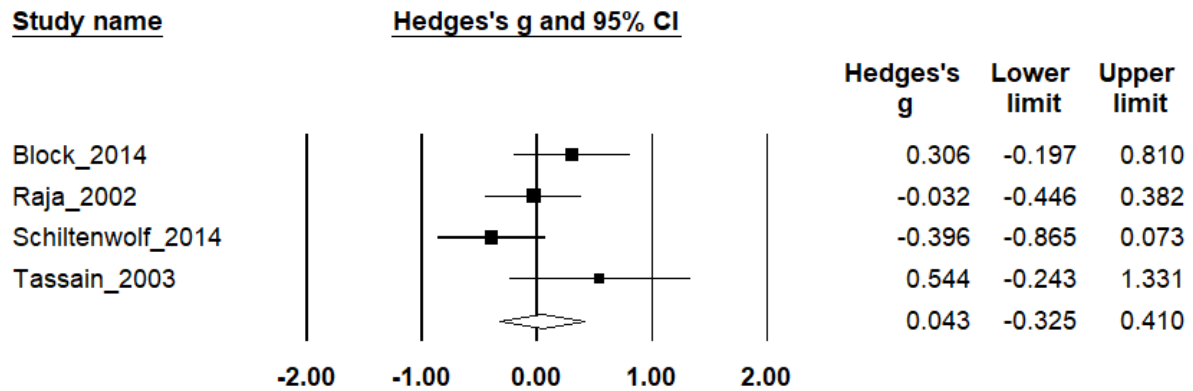**Supplementary Figure 2.12.** *Random effects model forest plots with weighted effect sizes*

(Hedges' g) for longitudinal comparisons of people with CNCP at opioid-free baseline and opioid-

present follow-up on tasks assessing working memory

Note. Negative values denote poorer performance at follow-up, compared with baseline.

Supplementary Figure 2.13. *Random effects model forest plots with weighted effect sizes (Hedges' g) for longitudinal comparisons of people with CNCP at opioid-free baseline and opioid-present follow-up on tasks assessing executive functions*

Note. Negative values denote poorer performance at follow-up, compared with baseline.

Supplementary Figure 2.14. *Random effects model forest plots with weighted effect sizes*

(Hedges' g) for longitudinal comparisons of people with CNCP at opioid-free baseline and opioid-

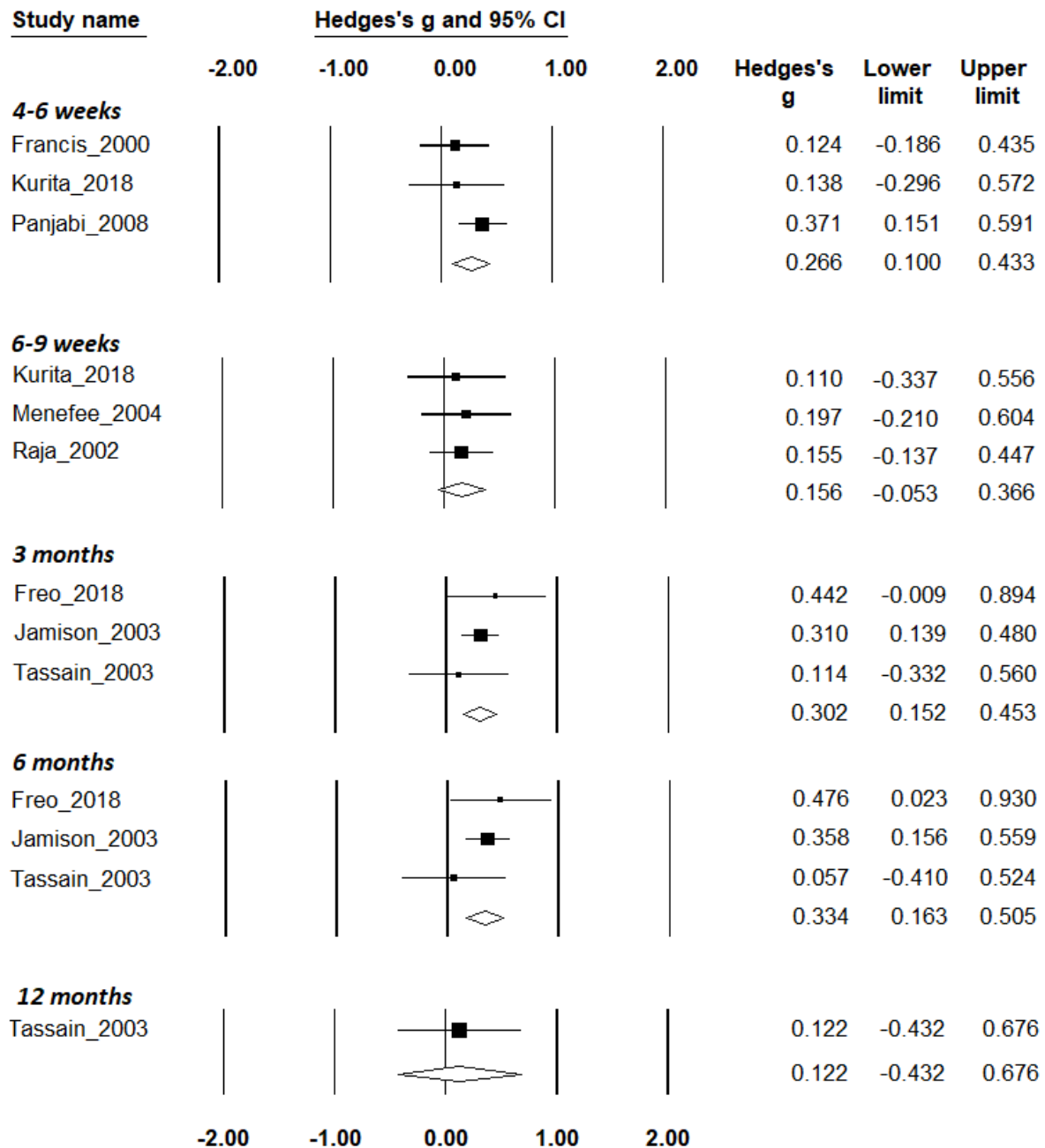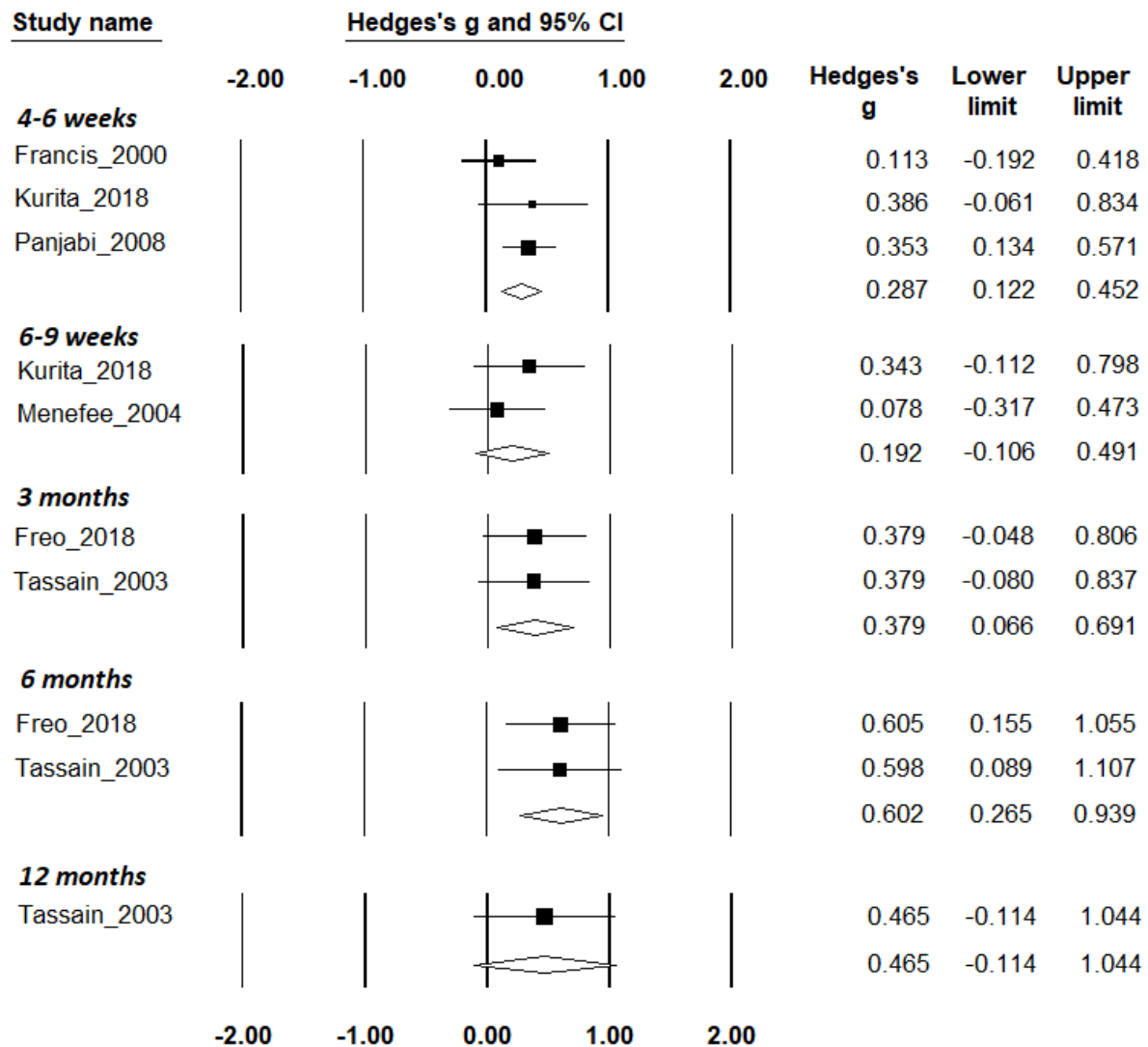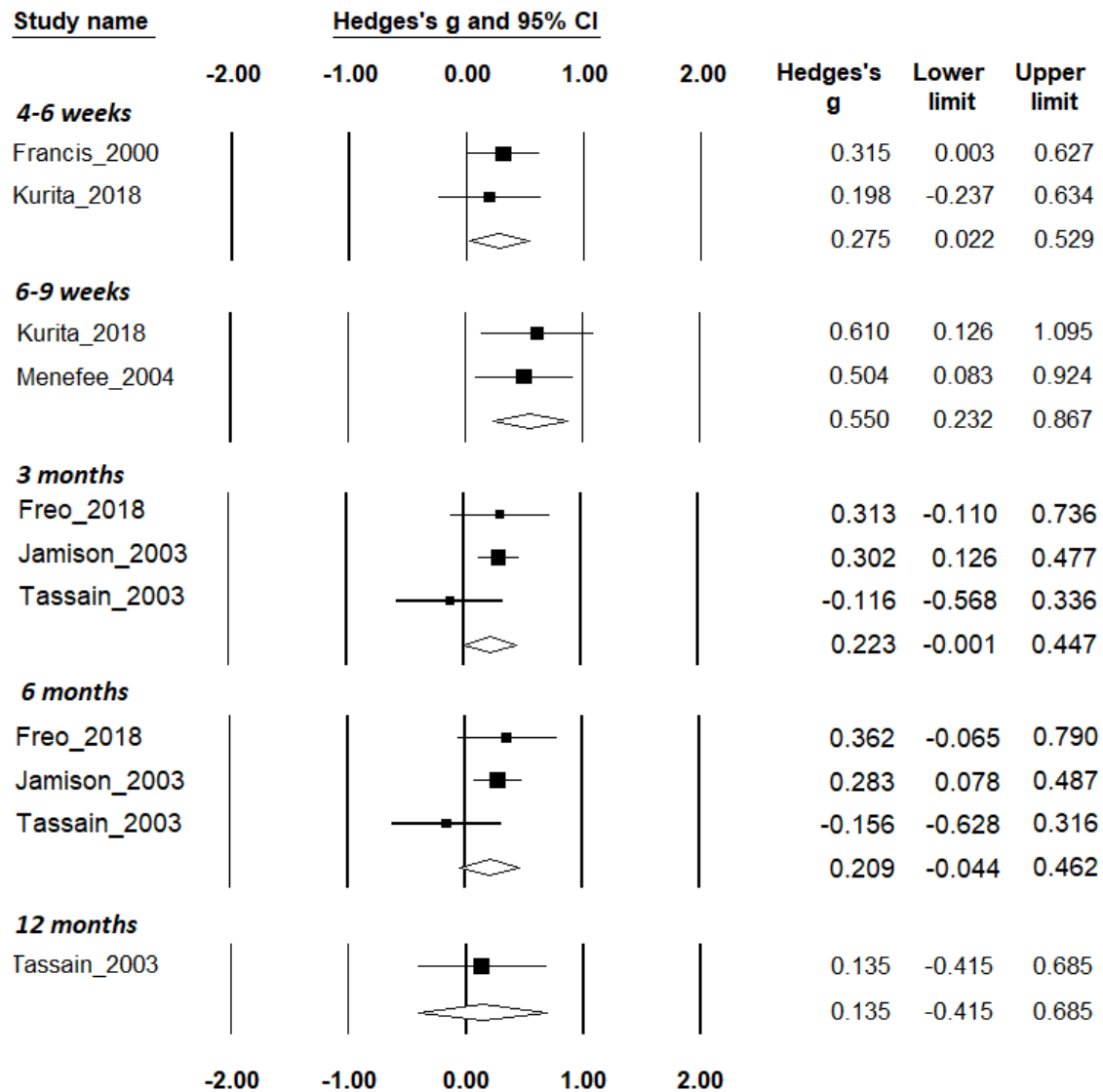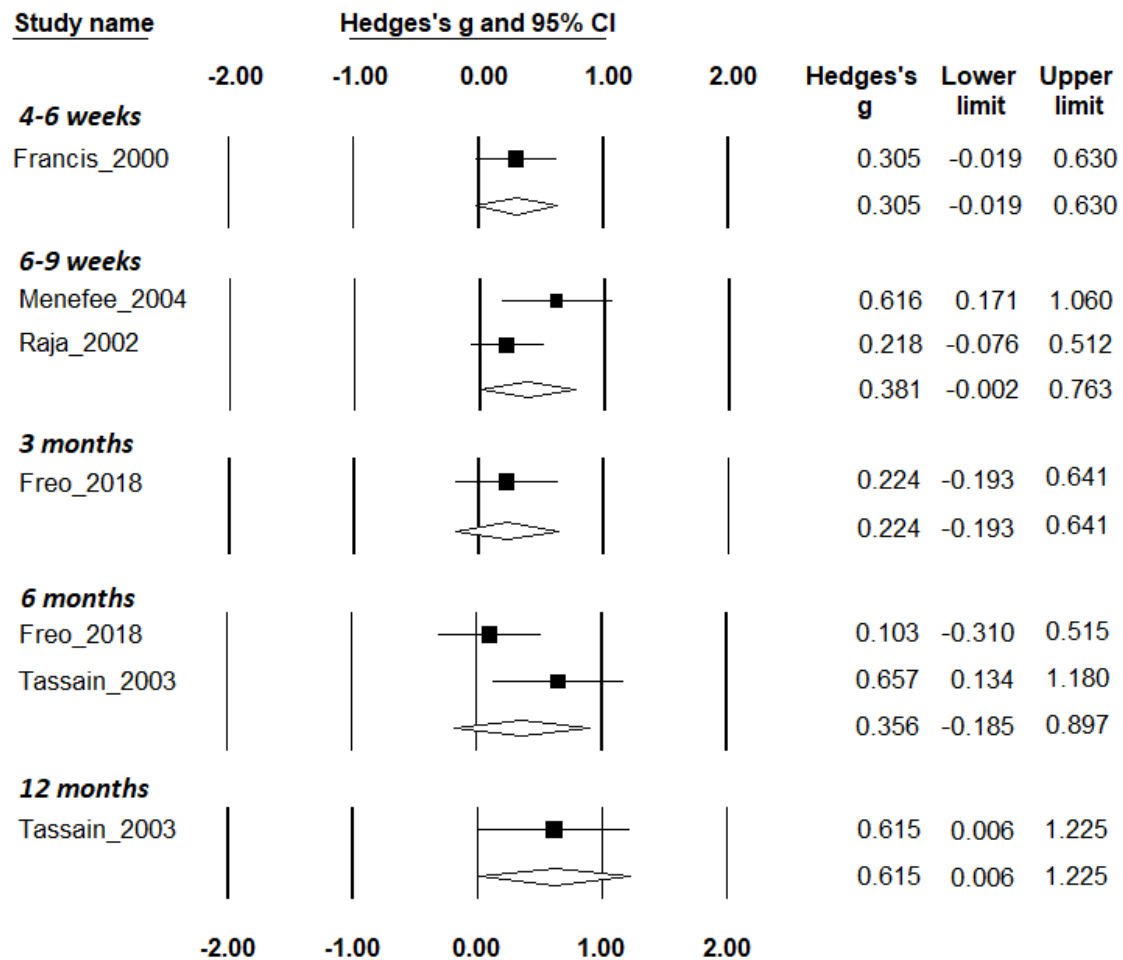*present follow-up on tasks assessing memory*

Note. Negative values denote poorer performance at follow-up, compared with baseline.

Supplementary Table 2.10. *Effect sizes for all included studies (case-control and cohort), by*

cognitive domain and study design

Domain & follow-up time	k [a]	Case n	Control n	Hedges' g	p	95%CI		Heterogeneity	
						Lower limit	*Upper limit*	I^2	Q
Motor performance									
Healthy controls	5	119	364	0.06	.826	-0.46	0.58	82.77%	23.21
Pain controls	2	93	95	0.02	.907	-0.27	0.30	0.00%	0.47
Taper-off controls	1	18	12	**-0.42**	.252	-1.14	0.30	–	–
Pre-post: 4-6wks	2	59	–	0.21	.106	-0.04	0.46	0.00%	0.10
Pre-post: 6-9wks	2	62	–	0.03	.792	-0.21	0.28	0.00%	0.16
Pre-post: 3 months	1	21	–	0.20	.345	-0.22	0.62	–	–
Pre-post: 6 months	1	21	–	0.16	.459	-0.26	0.57	–	–
Attention									
Healthy controls	8	198	459	-0.29	.013*	-0.52	-0.06	39.90%	11.65
Pain controls	7	187	169	-0.09	.375	-0.30	0.11	0.00%	2.35
Taper-off controls	1	18	11	**-0.55**	.147	-1.29	0.19	–	–
Pre-post: 4-6wks	3	143	–	0.27	.002*	0.10	0.43	0.50%	2.01
Pre-post: 6-9wks	3	85	–	0.16	.144	-0.05	0.37	0.00%	0.08
Pre-post: 3 months	3	176	–	0.30	<.001**	0.15	0.45	0.00%	1.06
Pre-post: 6 months	3	136	–	0.33	<.001**	0.16	0.51	0.00%	1.78
Pre-post: 12 months	1	11	–	0.12	.667	-0.43	0.68	–	–
Working memory									
Healthy controls	1	37	25	-0.39	.137	-0.89	0.12	–	–
Pain controls	2	53	43	-0.04	.907	-0.65	0.58	48.76%	1.95
Taper-off controls	1	18	11	**-0.43**	.254	-1.17	0.31	–	–
Pre-post: 4-6wks	3	143	–	0.29	.001*	0.12	0.45	0.00%	1.79
Pre-post: 6-9wks	2	41	–	0.19	.207	-0.11	0.49	0.00%	0.74
Pre-post: 3 months	2	39	–	0.38	.017*	0.07	0.69	0.00%	0.00
Pre-post: 6 months	2	37	–	**0.60**	<.001**	0.27	0.94	0.00%	0.00
Pre-post: 12 months	1	11	–	**0.47**	.115	-0.11	1.04	–	–
Executive functions									
Healthy controls	3	95	83	-0.39	.065	-0.80	0.02	48.14%	3.86
Pain controls	3	83	73	-0.25	.179	-0.62	0.12	23.80%	2.63
Taper-off controls	1	18	12	0.47	.206	-0.26	1.19	–	–
Pre-post: 4-6wks	2	59	–	0.28	.033*	0.02	0.53	0.00%	0.18
Pre-post: 6-9wks	2	41	–	0.55	.001*	0.23	0.87	0.00%	0.11
Pre-post: 3 months	3	168	–	0.22	.051	-0.00	0.45	31.71%	2.93
Pre-post: 6 months	3	131	–	0.21	.106	-0.04	0.46	37.35%	3.19
Pre-post: 12 months	1	11	–	0.14	.630	-0.42	0.69	–	–
Memory									
Healthy controls	3	95	83	-0.37	.015*	-0.66	-0.07	0.00%	0.69
Pain controls	4	127	117	0.04	.820	-0.33	0.41	50.20%	6.02
Taper-off controls	–	–	–	–	–	–	–	–	–
Pre-post: 4-6wks	1	40	–	0.31	.065	-0.02	0.63	–	–
Pre-post: 6-9wks	2	67	–	0.38	.051	-0.00	0.76	53.20%	2.14
Pre-post: 3 months	1	21	–	0.22	.293	-0.19	0.64	–	–
Pre-post: 6 months	2	37	–	0.36	.198	-0.19	0.90	62.43%	2.66
Pre-post: 12 months	1	11	–	**0.62**	.048*	0.01	1.23	–	–

* *p*<.050. ** *p*<.001.

[a] Comparisons that include only one study should be interpreted with caution.

Note. Hedges' *g* ≥0.40 indicated in **bold.**

Appendix B: Chapter 4 survey materials

Eligibility Screener

1. *Do you currently experience chronic pain, lasting 3 months or longer?*

    ☐ Yes

    ☐ No

2. *Are you currently using prescription-only opioids?*

NB: Prescription-only opioids are opioid medications that have been given to you by a doctor (e.g. a script for morphine). Over-the-counter medications are medications that you can buy at a pharmacy without a script from a doctor (e.g. Panadol or Nurofen). If you are using both prescription-only and over-the-counter medications, please answer "Yes".

    ☐ Yes - I currently use prescription-only opioid medications

    ☐ No - I do not currently use prescription-only opioid medications

3. *Do you have a past or current cancer diagnosis?*

    ☐ Yes

    ☐ No

4. *Are you currently being treated for opioid dependence (e.g. on the methadone program)?*

    ☐ Yes

    ☐ No

Section 1: Demographics

1. *What is your age? ………….*

2. *What is your sex?*

    ☐ Female

    ☐ Male

    ☐ Prefer not to answer

    ☐ Other

3. *Do you live in Australia?*

    ☐ Yes

☐   No

[Ask if country is not Australia]

4.   Which country do you live in? ....

Section 2: Medical history

1. Have you experienced any of the following chronic pain conditions in the past 3 months?

	Yes	No
Arthritis or rheumatism	☐	☐
Chronic back or neck problems	☐	☐
Frequent or severe headaches (e.g. migraines)	☐	☐
Visceral pain (organ pain inside the gut)	☐	☐
Fibromyalgia	☐	☐
Shingles pain	☐	☐
Complex Regional Pain Syndrome	☐	☐
Any other chronic pain condition (specify below)	☐	☐

Please specify 'other' chronic pain condition experienced: .....

2. How long have you been experiencing your current pain (e.g. 2 months)?

Days: ....

Weeks: ....

Months: ....

Years: ....

3. How long have you been using opioid medications?

Days: ....

Weeks: ....

Months: ....

Years: ....

Section 3: Prescription opioid medication use

1. Have you used any prescribed opioid medications (e.g. MS Contin, OxyContin) in the past week (7 days)?

- ☐ Yes

- ☐ No – go to [S3, Q4]

2. Which of the following opioid medications have you used in the past week (7 days)?

- ☐ Morphine, immediate release (e.g., Kapanol)

- ☐ Morphine, slow release (e.g. Ordine, Anamorph, Severedol)

- ☐ Oxycodone, immediate release (e.g. Endone, OxyNorm)

- ☐ Oxycodone, slow release (e.g. OxyContin, Targin)

- ☐ Codeine (e.g. Panadeine Forte)

- ☐ Methadone liquid (e.g. Biodone)

- ☐ Methadone tablets (e.g. Physeptone)

- ☐ Buprenorphine tablets (e.g. Subutex, Suboxone, Temgesic)

- ☐ Buprenorphine patches (e.g. Norspan)

- ☐ Fentanyl (e.g. Duragesic, Actiq)

- ☐ Tramadol, immediate release (e.g. Tramal, Zydol)

- ☐ Tramadol, slow release (e.g. Tramal SR, Zydol SR)

- ☐ Hydromorphone, immediate release (e.g. Dilaudid)

- ☐ Hydromorphone, slow release (e.g. Jurnista)

- ☐ Dextropropoxyphene (e.g. Di-Gesic)

- ☐ Other prescription opioid medications (please specify): …………

3. Please provide details of the brand and dose of [selected opioid] you have used in the past week (7 days), and on how many days you have used it. [Ask of all endorsed responses].

Brand: …………

Dose per day (e.g. 10mg): ………

Number of days used (e.g. 4): ………….

4. *Have you used any of the following prescription medications in the past week (7 days)?*

☐ Benzodiazepines (e.g. Kalma, Xanax, Valium)

☐ Antidepressants (e.g. Effexor, Lovan, Lexepro)

☐ Antipsychotics (e.g. Risperdal, Seroquel, Clozaril)

☐ Anticonvulsants (e.g. Depakote, Tegretol, Neurontin)

☐ Anti-inflammatory drugs (e.g. Celebrex, Mobic, Orudis)

☐ Antihistamines (e.g. Periactin, Unisom)

☐ Anti-hypertensives (e.g. Esidrex, Micardis, Olmetec)

☐ Anaesthetics (e.g. Lidnocaine, Capsaicin, Xylocaine)

☐ Other prescription medications (please specify): ………….

5. *Please provide details of the brand and dose of [selected medication] you have used in the past week (7 days), and on how many days you have used it. [Ask of all endorsed medications].*

Brand: ………..

Dose per day (e.g. 10mg): ………

Number of days used (e.g. 4): …………

6. *Have you use any of the following over-the-counter (non-prescription) medications in the past week (7 days)?*

☐ Aspirin (e.g. Disprin)

☐ Ibuprofen (e.g. Nurofen, Advil)

☐ Paracetamol (e.g. Panadol)

☐ Ibuprofen plus codeine (e.g. Nurofen Plus, Panafen Plus)

☐ Paracetamol plus codeine (e.g. Panadeine)

☐ Mersyndol

☐ Diclofenac (e.g. Voltaren)

☐ Naproxen (e.g. Naprogesic)

☐ Other over-the-counter medication (please specify): ………

7. *Please provide details of the brand and dose of [over-the-counter medication] you have used in the past week (7 days), and on how many days you have used it. [Ask for all endorsed over-the-counter medications].*

Brand: ………..

Dose per day (e.g. 10mg): ………

Number of days used (e.g. 4): …………

Section 4: Pain

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

    ☐ Yes

    ☐ No – go to [S5, Q1]

2. Please rate your pain by marking the box beside the number that best describes your pain...

    ….. At its worst in the last 24 hours: 0–10

    ….. At its least in the last 24 hours: 0–10

    ….. On average in the last 24 hours: 0–10

    ….. Right now: 0–10

3. In the last 24 hours, how much relief have pain treatments/medications provided? [0–100%, "N/A"].

4. Mark the box below the number that describes how, during the past 24 hours, pain has interfered with your:

    … General activity: 0–10

    … Mood: 0–10

    … Walking ability: 0–10

    … Normal work (includes both work outside the home and housework): 0–10

    … Relationships with other people: 0–10

    … Sleep: 0–10

    … Enjoyment of life: 0–10

Section 5: Cognitive functioning

The next questions relate to your memory functioning. Please answer each question by checking the box below the answer that best describes you:

1. Please choose the appropriate response for each item [Response options: Very often, quite often, sometimes, rarely, never].

☐ Do you decide to do something in a few minutes' time and then forget to do it?

☐ Do you fail to recognise a place you have visited before?

☐ Do you fail to do something you were supposed to do a few minutes later, even though it's there in front of you (like take a pill, or turn off the kettle)?

☐ Do you forget something that you were told a few minutes before?

☐ Do you forget appointments if you are not prompted by someone else or by a reminder (such as a calendar or diary)?

☐ Do you fail to recognise a character in a radio or television show from scene to scene?

☐ Do you forget to buy something you planned to buy, like a birthday card, even when you see the shop?

☐ Do you fail to recall things that have happened to you in the last few days?

☐ Do you repeat the same story to the same person on different occasions?

☐ Do you intend to take something with you, before leaving a room or going out, but minutes later leave it behind, even though it's there in front of you?

☐ Do you mislay something that you have just put down, like a magazine or glasses?

☐ Do you fail to mention or give something to a visitor that you were asked to pass on?

☐ Do you look at something without realising you have seen it moments before?

☐ If you tried to contact a friend or relative who was out, would you forget to try again later?

☐ Do you forget what you watched on television the previous day?

☐ Do you forget to tell someone something you had meant to mention a few minutes ago?

2. In the past 7 days… [Response options: Never, rarely (once), sometimes (2 or 3 times), Often (about once a day), very often (several times a day)]

☐ I have had trouble remembering new information, like phone numbers or simple instructions

☐ I have had trouble recalling the name of an object while talking to someone

☐ I have had trouble speaking fluently

☐ I have walked into a room and forgotten what I meant to get or do there

☐ I have needed medical instructions repeated because I could not keep them straight

☐ I have had to work really hard to pay attention or I would make a mistake

☐ I have forgotten names of people soon after being introduced

☐ My reactions in everyday situations have been slow

☐ Other people have told me I seemed to have trouble remembering information

☐ It has seemed like my brain was not working as well as usual

☐ I have had to work harder than usual to keep track of what I was doing

☐ My thinking has been slower than usual

☐ I have had to work harder than usual to express myself clearly

☐ I have had problems conversing with others

☐ I have had to use written lists more often than usual so I would not forget things

☐ I have had trouble keeping track of what I was doing when interrupted

☐ I have had trouble shifting back and forth between different activities that require thinking

☐ I have hidden problems with my memory, concentration, or making mental mistakes so that others would not notice

☐ I have been upset about my problems with memory, concentration, or making mental mistakes

☐ My problems with memory, concentration, or making mental mistakes have interfered with my ability to

☐ My problems with memory, concentration, or making mental mistakes have interfered with my ability to do things I enjoy

☐ My problems with memory, concentration, or making mental mistakes have interfered with the quality of my life

☐ I have had difficulty multi-tasking

Section 6: Experience of injuries

1. *How many accidents requiring medical attention have you had in the last 12 months, at work?*

☐ None

☐ 1-2

☐ 3-4

☐ 5-6

☐ More than 6

☐ NA - don't work

2. *How many accidents requiring medical attention have you had in the last 12 months, outside of work?*

☐ None

☐ 1-2

☐ 3-4

☐ 5-6

☐ More than 6

3. *In the last 12 months, how frequently have you had minor injuries (e.g. cuts and bruises) that did not require medical attention, at work?*

☐ Not at all

☐ Rarely

☐ Occasionally

☐ Quite frequently

☐ Very frequently

☐ NA - don't work

4. In the last 12 months, how frequently have you had minor injuries (e.g. cuts and bruises) that did not require medical attention, outside of work?

☐ Not at all

☐ Rarely

☐ Occasionally

☐ Quite frequently

☐ Very frequently

Section 7: Psychological distress

1. *During the last 30 days, how often did you feel ... [Response options: None of the time, a little of the time, some of the time, most of the time, all of the time].*

☐ ... tired out, for no good reason?

☐ ... nervous?

☐ ... so nervous that nothing could calm you down?

☐ ... hopeless?

☐ ... restless?

☐ ... so restless, you could not sit still?

☐ ... depressed?

☐ ... that everything was an effort?

☐ ... so sad that nothing could cheer you up?

☐ ... worthless?

Appendix C: Chapter 5 survey materials

Section 1: Demographics

1. *Which of the following best describes your current gender identity?*

   ☐ Female

   ☐ Male

   ☐ Non-binary/gender fluid

   ☐ Different identity: ....

2. *What is your age in years? ....*

3. *What is your current residential postcode? ....*

4. *What is the highest year of primary or secondary school you have completed?*

   ☐ Did not go to school

   ☐ Year 6 or below

   ☐ Year 7 or equivalent

   ☐ Year 8 or equivalent

   ☐ Year 9 or equivalent

   ☐ Year 10 or equivalent

   ☐ Year 11 or equivalent

   ☐ Year 12 or equivalent

5. *Have you completed any further qualifications?*

   ☐ Yes

   ☐ No – go to [S1, Q7]

6. *What is the highest qualification that you have completed?*

   ☐ Certificate I / II

   ☐ Certificate III / IV

   ☐ Associate Diploma

   ☐ Undergraduate Diploma

☐ Bachelor Degree

☐ Master's Degree, Postgraduate Degree, or Postgraduate Diploma

☐ Doctorate

☐ Other: …………………..

7. *What is your current employment status? Select all that apply.*

☐ Not employed

☐ Retired/pensioner

☐ Home duties

☐ Part time/casual work (less than 20 hrs/week)

☐ Full time work

☐ Other: ……………………

Section 2: Pain condition & medical history

1. *Do you currently experience chronic pain?*

☐ Yes

☐ No, I experienced pain at another time in the past 12 months

2. *For how long have you been experiencing, or did you experience, chronic pain?*

☐ Years: …………

☐ Months: …….

3. *In the past 12 months, what pain condition/s have you experienced? Select all that apply.*

☐ Low back pain

☐ Arthritis/rheumatism

☐ Frequent or severe headaches

☐ Fibromyalgia

☐ Visceral pain (organ pain)

☐ Complex Regional Pain Syndrome (CRPS)

☐   Shingles pain

☐   Other: ………………….

4.   *Throughout our lives, most of us have had pain from time to time (e.g., minor headaches). Have*

  you had pain other than these everyday kinds of pain today?

☐   Yes

☐   No

5.   *Please rate your pain by marking the box beside the number that best describes your pain….*

☐   At its worst, in the last 24 hrs: 0 'no pain'–10 'pain as bad as you can imagine'.

☐   At its least, in the last 24 hrs: 0–10

☐   On average, in the last 24 hrs: 0–10

☐   Right now: 0–10

6.   *How would you describe your pain level in the last 24hrs?*

☐   Typical; my pain is normally a similar level

☐   Worse than usual

☐   Better than usual

7.   *In the past 12 months, has a doctor told you that you have a sleep disorder (e.g., insomnia)?*

☐   Yes

☐   No

8.   *Please rate how likely it is that you would doze off during the activities listed below:*

☐   Sitting and reading: 0–3

☐   Watching TV: 0–3

☐   Sitting inactive in a public place: 0–3

☐   As a passenger in a car for an hour without a break: 0–3

☐   Lying down to rest in the afternoon when circumstances permit: 0–3

☐   Sitting and talking to someone: 0–3

☐   Sitting quietly after a lunch without alcohol: 0–3

☐ In a car, while stopped for a few minutes: 0–3

9. *In the past 12 months, have you received medication for a significant mood, anxiety, or other psychological illness, or has a doctor told you that you have such an illness?*

☐ Yes

☐ No

10. *In the past 12 months, have you been prescribed any of the following medications? Select all that apply.*

☐ Antidepressants (e.g., Pristiq, Endep)

☐ Antipsychotics (e.g., Seroquel)

☐ Benzodiazepines (e.g., Valium, alprazolam)

☐ Pregabalin (e.g., Lyrica)

☐ No – go to [S3, Q1]

11. *Which of the following best describes your use of [selected medications] over the past 12 months? [Ask for each endorsed in S3, Q10].*

☐ I was taking it daily or almost daily, for less than 6 months

☐ I was taking it daily or almost daily, for 6 months or more

☐ I was taking it every now and then, for less than 6 months

☐ I was taking it every now and then, for 6 months or more

Section 3: Opioid use and knowledge of side effects

1. *Have you ever been prescribed an opioid medication for a pain condition?*

☐ Yes

☐ No – go to [S3, Q8]

2. *Have you been prescribed an opioid medication in the past 12 months?*

☐ Yes

☐ No – go to [S3, Q8]

3. *In the past 12 months, which of the following opioids have you taken? Some examples are provided in brackets. Select all that apply.*

   ☐ Codeine (e.g., Panadeine Forte)

   ☐ Dextropropoxyphene (e.g., Digesic)

   ☐ Fentanyl (e.g., Duragesic)

   ☐ Hydromorphone (e.g., Dilaudid)

   ☐ Morphine (e.g., Kapanol, MS Contin)

   ☐ Oxycodone (e.g., Endone, OxyContin)

   ☐ Tapentadol (e.g., Palexia)

   ☐ Tramadol (e.g., Tramal)

   ☐ Other: ……………..

4. *In the past 12 months, which opioid did you use MOST OFTEN? Select one.*

   ☐ Codeine

   ☐ Dextropropoxyphene

   ☐ Fentanyl

   ☐ Hydromorphone

   ☐ Morphine

   ☐ Oxycodone

   ☐ Tapentadol

   ☐ Tramadol

   ☐ Other: …………..

[Ask of current opioid consumers]

5. *Which of the following best describes your use of opioids over the past 12 months?*

   ☐ I have been taking them daily or almost daily, for less than 6 months

   ☐ I have been taking them daily or almost daily, for 6 months or more

   ☐ I have been taking them every now and then, for less than 6 months

☐   I have been taking them every now and then, for 6 – 12 months

☐   I have been taking them daily or almost daily, for more than 12 months

[Ask of past 12-month opioid consumers]

6. *Which of the following best describes your use of opioids over the past 12 months?*

☐   I was taking it daily or almost daily, for less than 6 months

☐   I was taking it daily or almost daily, for 6 months or more

☐   I was taking it every now and then, for less than 6 months

☐   I was taking it every now and then, for 6 – 12 months

☐   I was taking it daily or almost daily, for more than 12 months

7. *When you have been taking [main opioid], what has been your usual dose per day (<u>not</u>*

<u>including</u> 'as needed' doses for breakthrough pain)?

☐   ….. mg/day

☐   ….. mcg/day

8. *Which of the following side effects do you think are associated with use of opioid medications?*

☐   Dizziness or faintness

☐   Sedation or drowsiness

☐   Headache

☐   Itching

☐   Constipation

☐   Mental cloudiness

☐   Nausea

☐   Vomiting

☐   Sweating

☐   Fatigue

☐   Dry mouth

☐   Other: ………..

9. *Where did you find out about [side effect] as a side effect of opioid use?* [Ask for each endorsed

    in S3, Q8].

   ☐ My GP

   ☐ A pharmacist

   ☐ Another healthcare worker

   ☐ From a Consumer Medicine Information pamphlet

   ☐ Medication packaging (e.g., a label on the packet)

   ☐ Online

   ☐ I did not hear about it from anyone (e.g., assumed, have experience)

   ☐ Other: …………..

10. *If you could choose, how would you like to find information about opioid side effects?*

   ☐ My GP

   ☐ A pharmacist

   ☐ Another healthcare worker

   ☐ From a Consumer Medicine Information pamphlet

   ☐ Medication packaging (e.g., a label on the packet)

   ☐ Online

   ☐ Other: …………..

11. *Have you ever received information about potential risks associated with driving soon*

    after taking an opioid medication?

   ☐ No

   ☐ Yes, from my GP

   ☐ Yes, from a pharmacist

   ☐ Yes, from another healthcare worker

   ☐ Yes, from a CMI pamphlet

   ☐ Yes, from medication packaging

☐ Yes, but I did not hear about it from anyone (e.g., assumed, have experience)

☐ Yes, from another source: …………...

Section 4: Driving behaviours

1. *Have you driven in the past 12 months?*

    ☐ Yes

    ☐ No – go to [S4, Q9]

2. *In the past 12 months, how do you think pain impacted on your driving ability on average?*

    ☐ Pain did not affect my driving

    ☐ Pain worsened my driving ability

    ☐ Pain improved my driving ability

3. *In the past 12 months, did you take any safety precautions in regards to driving when pain was severe? Select all that apply.*

    ☐ No, I did not take any precautions

    ☐ I stopped driving entirely

    ☐ I did not drive if pain was severe

    ☐ I drove more slowly if pain was severe

    ☐ I drove for only short distances if pain was severe

    ☐ I drove only on familiar routes if pain was severe

    ☐ Other: …………………………...

4. *How likely do you think it is that you would have an accident while driving if you were experiencing severe pain?* 1 'very unlikely' – 5 'very likely', DK

    [Skip to [S4, Q9] if [S3, Q2] or [S4, Q1] = 'No']

5. *In the past 12 months, how do you think your use of opioids impacted your driving ability?*

    ☐ Opioids did not affect my driving

    ☐ Opioids worsened my driving ability

    ☐ Opioids improved my driving ability

6. *In the past 12 months, when taking opioids, did you take any safety precautions in regards to driving? Select all that apply.*

  ☐ No, I did not take any precautions

  ☐ I stopped driving entirely

  ☐ I did not drive immediately after taking opioids

  ☐ I drove more slowly after taking opioids

  ☐ I drove for only short distances after taking opioids

  ☐ I drove only on familiar routes after taking opioids

  ☐ I stopped taking opioids entirely

  ☐ I took other medicines to counter any side effects of opioids

  ☐ Other: ………………..

7. *In the last 12 months, have you driven within three hours of taking opioid medications?*

  ☐ Yes

  ☐ No – go to [S4, Q9]

8. *In the last 12 months, on how many occasions have you driven within three hours of taking opioid medications? Please note that driving after taking opioid medications is legal.*

  ☐ ………………

9. *How likely do you think it is that you would have an accident while driving soon after taking the following:*

  ☐ Alcohol (over the legal limit): 1 'very unlikely'–5 'very likely', DK

  ☐ Pharmaceutical opioids: 1–5, DK

  ☐ Pregabalin (e.g., Lyrica): 1–5, DK

  ☐ Benzodiazepines: 1–5, DK

  ☐ Antidepressants: 1–5, DK

  ☐ Antipsychotics: 1–5, DK

10. *How likely do you think it is that you would be intercepted by police for driving*

erratically if you drove soon after taking the following:

 ☐ Alcohol (over the legal limit): 1 'very unlikely'–5 'very likely', DK

 ☐ Pharmaceutical opioids: 1–5, DK

 ☐ Pregabalin: 1–5, DK

 ☐ Benzodiazepines: 1–5, DK

 ☐ Antidepressants: 1–5, DK

 Antipsychotics: 1–5, DK

Section 5: Current licence & driving behaviours

[Skip to [S5, Q3] if [S4, Q1] = 'No']

1. *In the past 12 months, how often would you drive on the road in an average week?*

 ☐ Less than once per week

 ☐ At least one day per week

 ☐ 2 to 3 days per week

 ☐ 4 to 6 days per week

 ☐ 7 days per week (every day)

2. *In the past 12 months, for how many hours would you drive in an average week?*

 ☐ ……. [Numeric responses].

[Skip to [S5, Q4] if [S4, Q1] = 'Yes']

3. *What is the reason that you haven't driven on the road in the past 12 months? Select all that*

apply.

 ☐ Opioids negatively affect my driving

 ☐ Another medication affects driving

 ☐ I was concerned about the effects of pain on my driving

 ☐ I find it painful to drive

 ☐ A different medical reason (e.g., epilepsy)

    ☐ Location (e.g., can cycle/use public transport)

    ☐ Licence was suspended

    ☐ Other: ……………

4. *In the past 12 months, have you held a full driver's licence?*

    ☐ Yes

    ☐ No – go to [S6, Q1]

5. *Is this licence current? Note: excludes learner's permit & provisional licence.*

    ☐ Yes

    ☐ No – go to [S5, Q7]

6. *What licence/s do you currently hold?*

    ☐ Car, full licence

    ☐ Car, restricted licence

    ☐ Heavy vehicle licence

    ☐ Bus driver's licence

    ☐ Motorcycle, full licence

    ☐ Taxi/hire car licence

7. *For how long had you held your longest full driver's licence?*

    ☐ 6 months or less

    ☐ More than 6 months, but less than 12 months

    ☐ 1 – 2 years

    ☐ 2 – 3 years

    ☐ 3 – 5 years

    ☐ 6 – 10 years

    ☐ More than 10 years

8. *In the past 12 months, how many licence demerit points have you lost?*

    ☐ None

☐ 1

☐ 2 – 3

☐ 4 – 6

☐ 7 – 9

☐ 10 – 12

9. *In the past 12 months, how many times have you lost your licence due to traffic offences?*

☐ Never

☐ Once

☐ Twice

☐ 3 times

☐ 4 or more times

Section 6: Cognitive complaints

These questions relate to your mental function.

1. *In the past 7 days, my thinking has been slow:*

☐ Never

☐ Rarely (once)

☐ Sometimes (two or three times)

☐ Often (about once a day)

☐ Very often (several times a day)

2. *In the past 7 days, it has seemed like my brain was not working as well as usual:*

☐ Never

☐ Rarely (once)

☐ Sometimes (two or three times)

☐ Often (about once a day)

☐ Very often (several times a day)

3. *In the past 7 days, I have had to work harder than usual to keep track of what I was doing:*

☐ Never

☐ Rarely (once)

☐ Sometimes (two or three times)

☐ Often (about once a day)

☐ Very often (several times a day)

4. *In the past 7 days, I have had trouble shifting back and forth between different activities that*

require thinking:

☐ Never

☐ Rarely (once)

☐ Sometimes (two or three times)

☐ Often (about once a day)

☐ Very often (several times a day)

Section 7: Beliefs about medicines

[Ask of current opioid consumers]

1. *My health at present depends on my opioid medications*

☐ Strongly agree

☐ Agree

☐ Uncertain

☐ Disagree

☐ Strongly disagree

2. *Having to take opioid medications worries me*

☐ Strongly agree

☐ Agree

☐ Uncertain

☐ Disagree

☐ Strongly disagree

3. *My life would be impossible without my opioid medications*

    ☐ Strongly agree

    ☐ Agree

    ☐ Uncertain

    ☐ Disagree

    ☐ Strongly disagree

4. *Without my opioid medications, I would be very ill*

    ☐ Strongly agree

    ☐ Agree

    ☐ Uncertain

    ☐ Disagree

    ☐ Strongly disagree

5. *I sometimes worry about the long-term effects of my opioid medications*

    ☐ Strongly agree

    ☐ Agree

    ☐ Uncertain

    ☐ Disagree

    ☐ Strongly disagree

6. *My opioid medications are a mystery to me*

    ☐ Strongly agree

    ☐ Agree

    ☐ Uncertain

    ☐ Disagree

    ☐ Strongly disagree

7. *My health in the future will depend on my opioid medications*

    ☐ Strongly agree

☐ Agree

☐ Uncertain

☐ Disagree

☐ Strongly disagree

8. *My opioid medications disrupt my life*

☐ Strongly agree

☐ Agree

☐ Uncertain

☐ Disagree

☐ Strongly disagree

9. *I sometimes worry about becoming too dependent on my opioid medications*

☐ Strongly agree

☐ Agree

☐ Uncertain

☐ Disagree

☐ Strongly disagree

10. *My opioid medications protect me from becoming worse*

☐ Strongly agree

☐ Agree

☐ Uncertain

☐ Disagree

☐ Strongly disagree

Appendix D: Chapter 6 supplementary materials

Supplementary Table 6.1. *Total serious injuries/fatalities, cases tested by Forensic Science Services Tasmania (FSST), and FSST cases positive for*

specific drugs, 2008–2016

	2008	2009	2010	2011	2012	2013	2014	2015	2016
N serious injures/fatalities	316	353	287	272	291	300	331	318	303
FSST testing – *n* (%) *Cases not tested by FSST*	91 (28.8)	97 (27.5)	**42 (14.6)*#**	**51 (19.1)#**	71 (24.4)	**54 (18.0)#**	**35 (10.6)*#**	**28 (8.8)#**	**0 (0.0)*#**
Cases tested by FSST	225 (71.2)	256 (72.5)	**245 (85.4)*#**	**221 (81.3)#**	220 (75.6)	**246 (82.0)#**	**296 (89.4)*#**	**290 (91.2)#**	**303 (100.0)***
Positive FSST cases by drug type – *n* (%) *Opioids*	15 (6.7)	28 (10.9)	**32 (13.1)#**	**15 (6.8)***	14 (6.4)	16 (6.5)	24 (8.1)	19 (6.6)	21 (6.9)
Methadone	--	--	--	--	--	--	--	--	--
THC	51 (22.7)	68 (26.6)	67 (27.3)	46 (20.8)	38 (17.3)	60 (24.4)	74 (25.0)	69 (23.8)	77 (25.4)
THC-COOH	17 (7.6)	28 (10.9)	16 (6.50)	24 (10.9)	25 (11.4)	**11 (4.5)***	13 (4.4)	--	13 (4.3)
Amphetamines	11 (4.9)	15 (5.9)	24 (9.8)	--	17 (7.7)	22 (8.9)	27 (9.1)	**57 (19.7)*#**	**48 (15.8)#**
Cocaine	--	--	--	--	--	--	--	--	--
Benzodiazepines	35 (15.6)	52 (20.3)	**60 (24.5)#**	37 (16.7)	24 (10.9)	**19 (7.7)#**	**26 (8.8)#**	**19 (6.6)#**	**26 (8.6)#**
Antidepressants (sedating)	--	17 (6.6)	19 (7.8)	--	--	10 (4.1)	11 (3.7)	10 (3.4)	--
Antidepressants (non-sedating)	17 (7.6)	24 (9.4)	19 (7.8)	16 (7.2)	15 (6.8)	13 (5.3)	16 (5.4)	17 (5.9)	19 (6.3)
Anticonvulsants	--	--	--	--	--	--	--	--	--
Cardiovascular medications	--	12 (4.7)	13 (5.4)	--	12 (5.5)	--	--	--	--
Other impairing drugs	--	12 (4.7)	15 (6.1)	14 (6.3)	--	--	--	12 (4.1)	15 (5.0)
Other non-impairing drugs	40 (17.8)	59 (23.0)	**66 (26.9)#**	43 (19.5)	37 (16.8)	37 (15.0)	41 (13.9)	54 (18.6)	65 (21.5)

* Significantly different from the previous year, *p* < .050.

Significantly different from 2008, *p* < .050.

Note. Drug type percentages are expressed as a percentage of the total number of cases tested by FSST that year.

Supplementary Table 6.2. *Sensitivity analyses for positive opioid detections, 2008–2016, with non-tested samples assumed to be either positive or negative*

	2008	2009	2010	2011	2012	2013	2014	2015	2016
Opioid detections, as reported by FSST[a] – *n* (%)	15 (6.7)	28 (10.9)	32 (13.1)	**15 (6.8)****	14 (6.4)	16 (6.5)	24 (8.1)	19 (6.6)	**21 (6.9)**[#]
Opioid detections, with non-tested samples coded as cases[b] – *n* (%)	106 (33.5)	125 (35.4)	**74 (25.8)****	66 (24.3)	85 (29.2)	70 (23.3)	59 (17.8)	19 (14.8)	**21 (6.9)****, [#]
Opioid detections, with non-tested samples coded as non-cases[c] – *n* (%)	15 (4.7)	28 (7.9)	32 (11.1)	**15 (5.5)****	14 (4.8)	16 (5.3)	24 (7.3)	19 (6.0)	21 (6.9)

* Significantly different from the previous year.

[#] Significantly different from 2008.

[a] Actual number of positive opioid detections recorded by FSST, expressed as a percentage of the total number of tested cases.

[b] Number of positive opioid detections if all non-tested samples are assumed to be opioid positive (i.e., cases), expressed as a percentage of the total cases reported by the Department of State Growth (DSG) for that year.

[c] Number of positive opioid detections if all non-tested samples are assumed to be opioid negative (i.e., non-cases), expressed as a percentage of the total cases reported by the Department of State Growth (DSG) for that year.

Note. Significant differences highlighted in **bold.**

Supplementary Table 6.3. *Number of licenced drivers, opioid script dispensations, and persons in Tasmania, 2008–2016*

	2008	2009	2010	2011	2012	2013	2014	2015	2016
Licenced drivers [a] - *n*	361,253	365,241[c]	365,241[c]	367,489	366,980	367,888	370,575	374,753	381,122
Opioid script dispensations [b] - *n*	266,458	276,357	283,415	293,260	326,188	322,549	347,696	391,742	364,896
Driving-age population (16-100+) - *n*	394,972	400,385	405,149	408,764	140,115	411,381	413,055	415,408	421,161

[a] Includes all drivers with a learner, provisional (P1, P2), or full licence for a car, motorcycle, or heavy vehicle.

[b] Opioid script dispensations includes all available formulations of codeine, codeine with paracetamol, oxycodone, oxycodone with naloxone, fentanyl, buprenorphine, and tramadol dispensed under the PBS.

[c] Data for 2009-10 was not available; data have been imputed as the 5-year average for 2008-12.

Note. Data for licenced drivers was unavailable for 2009 and 2010.