Prevalence of Opioid Use and Misuse in Individuals with Spinal Cord Injury:

A Meta-Analysis

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Abstract

Background: Opioid analgesics remain a second-line treatment for chronic pain after Spinal Cord Injury (SCI), despite their addictive effects. However, varying estimates of opioid use have been reported in this patient group. *Aims*: To evaluate the rate of opioid use, in addition to sample (i.e., SCI type, lesion completeness, gender) and methodological characteristics (i.e., opioid measurement, method of data collection) associated with increased use in adults (aged >17 years) with a traumatic or non-traumatic SCI. *Methods*: A systematic search of CINAHL, Embase, Ovid MEDLINE, PsycINFO, PubMed, Scopus, and Web of Science was conducted. Study quality was assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist, and prevalence rates calculated in addition to 95% confidence intervals, *p* values, heterogeneity statistics, and fail-safe *N*s. These analyses followed a random-effects model. *Results*: Pooled data from 14 independent studies ($N_{participants}$ = 61311) indicated that one in four adults with a SCI had used opioids (.25 [CI: .16-.37], p <.01). Over 30% were prescribed opioids (.33 [CI: .24-.45], p <.01), although few met diagnostic criteria for substance use disorder (.02 [CI: .16 to.37], p <.01). Prevalence estimates remained high regardless of whether data were collected retrospectively or prospectively. Injury and demographic characteristics were also not significant moderators, although these subgroup analyses may have been underpowered. *Conclusions*: There remains a prescribing culture in spinal injury rehabilitation, with opioid use being highly prevalent. Further research to examine other viable treatments for chronic pain, given the potential for misuse in this population, is warranted.

Keywords: Spinal Cord Injuries, Opioids, Prevalence, Pain

Declaration

This thesis contains no material which has been accepted for the award for any other degree or diploma in any University, and, to the best of my knowledge, contains no materials previously published except where reference is made. I give permission for the digital version of this thesis to be made available on the web, via the University of Adelaide's digital thesis repository, the Library Search and through web search engines, unless permission has been granted by the School to restrict access for a period of time.

Evelyn Black

25th October 2020

Contribution Statement

In writing this thesis, my supervisor and I collaborated to generate research questions of interest and design the appropriate methodology. With the help of a Research Librarian, I conducted the literature search. My supervisor oversaw the initial screening of papers and all stages of the data extraction process. We determined the final list of studies for analyses collaboratively. My supervisor advised on the initial data analysis and guided me through the interpretation process. I wrote up all sections of the thesis, with review by my supervisor.

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Chapter 1

Introduction

1.1 Spinal Cord Injury

1.1.1 Aetiology and neurology. Spinal Cord Injury (SCI) involves neurological damage to the spinal cord with resultant loss of functional mobility or sensations. SCI can also include damage to other components of the spinal column, such as discs, ligaments, and vertebrae (Kirshblum et al., 2011). Global estimates of SCI range from 250,000 to 500,000 new injuries or 'cases' per year (World Health Organisation, 2013). Australian data are consistent with these international statistics, which indicate that SCI is a major cause of physical disability and a chronic lifelong condition that can negatively impact on quality of life (Krause, Dismuke-Greer, Reed, & Li, 2019; Noonan et al., 2014; Rivers et al., 2018).

SCI can be classified according to causation, whether *traumatic* (TSCI) or *non-traumatic* (NTSCI). The majority of cases involve traumatic injuries sustained in a motor vehicle accident or fall (Chen, Tang, Vogel, & DeVivo, 2013; Tovell, 2019). Conversely, NTSCI involves damage to the spinal cord and resultant symptoms arising from congenital disease (e.g., spina bifida) or degeneration of the spinal column (e.g., cervical myelopathy), rather than direct physical injury. Spinal tumours, infarction, haemorrhage, infections, and inflammation are also classified as NTSCIs (Badhiwala et al., 2020; New, Cripps, & Lee, 2014; New & Biering-Sørensen, 2017; New & Marshall, 2014). Some authors have argued that iatrogenic illness (i.e., spinal conditions resulting from treatment by a medical professional, e.g., laminectomy) could potentially be classified as either TSCI or NTSCI, although adherence to the International Classification of External Causes of Injury (ICECI) classifications would preclude these as NTSCIs (Alcanyis-Alberola, Giner-Pascual, Salinas-Huertas, & Gutiérrez-Delgado, 2011; Cramer, Maher, Pettigrew, & Kuntz, 2009; Lee et al.,

2010). Whilst NTSCIs are less common than TSCIs, their prevalence has been increasing – potentially reflecting the aging population and high prevalence of NTSCIs among older adults (Gupta, Taly, Srivastava, & Murali, 2009; New et al., 2014).

SCI results in varying degrees of functional impairment. Individuals with a *complete* injury have no voluntary movement and varying sensory function below the point of injury. In contrast, individuals with an *incomplete* injury retain some level of voluntary movement and sensory function below the point of injury (Angeli et al., 2018; Roberts, Leonard, & Cepela, 2017). Multiple syndromes can be diagnosed in individuals with an incomplete SCI, more commonly central cord syndrome, Brown-Séquard syndrome, anterior cord syndrome, cauda equina syndrome, and conus medullaris syndrome (Maynard et al., 1997). The distinction between a complete and incomplete injury is operationalised by the American Spinal Injury Association (ASIA) Impairment Scale, considered the 'gold standard' for evaluation of SCIs (Burns et al., 2012). According to this scale, a complete injury (ASIA-A) is when the individual has no sensory or motor functioning in the sacral (S4-5) segments. Incomplete injuries have one of four classifications: sensory incomplete (ASIA-B), where the individual has preserved sensory functioning below the injury level; motor incomplete (ASIA-C), where motor function is preserved at the lower sacral segments or the individual meets ASIA-B classification with some motor function below three levels, and motor incomplete (ASIA-D) with the ASIA-C criteria and key muscle functions below the level of injury. Normal functioning is classified as ASIA-E (Roberts et al., 2017).

SCIs are further defined by the level of neurological damage. For those with a *tetraplegic* (or quadriplegic) injury, the pelvic organs coupled with all four extremities (i.e., arms and legs) are impacted. In comparison, individuals with *paraplegia* have no impairment of arm functioning, though functioning of pelvic organs and legs may still be affected (Kirshblum et al., 2011).

Irrespective of the cause, full neurologic recovery is uncommon in individuals with a SCI (Marino, Ditunno Jr, Donovan, & Maynard Jr, 1999). Most patients have physical impairment, including restricted mobility in the limbs and pelvic muscles, as well as loss of control of normal bodily sensations. Chronic pain is also a frequent secondary complication of SCI that is difficult to treat. Indeed, up to 96% of adults with a SCI reporting lifetime pain prevalence while up to 63% report severe pain (Cardenas, Bryce, Shem, Richards, & Elhefni, 2004). Chronic pain can substantially decrease quality of life, including day to day functioning and ability to participate in enjoyable activities (Calmels, Mick, Perrouin-Verbe, & Ventura, 2009; Dijkers, Bryce, & Zanca, 2009; Henwood & Ellis, 2004; Ataoğlu et al., 2013; Siddall, 2009).

Pain following SCI may be musculoskeletal, visceral, or neuropathic in origin. Musculoskeletal pain occurs due to decreased physical activity, resulting in muscle atrophy (Chiodo, 2010). Visceral pain in the abdomen originates from the internal organs, often resulting from bowel issues such as faecal compression and impaction (Ebert, 2012; Sved, Siddall, McClelland, & Cousins, 1997). Neuropathic pain results from damage to the nervous system (e.g., trauma, cancer, metabolic), with miscommunication of nerve impulses to the brain producing feelings of pain, burning, cold, or electric shocks and tingling below the level of injury (Pain Australia, 2020). Neuropathic pain is further classified based on the point of origin of damage: *central* neuropathic pain arises from damage to the brain or spinal cord, whereas *peripheral* neuropathic pain results from damage to the peripheral nerve, plexus, dorsal root ganglion, or the nerve root (Haanpää & Treede, 2010). Levels of neuropathic pain following a SCI are highly variable – the pain can be constant and unrelenting, or can occur intermittently (Haanpää & Treede, 2010; Woolf & Mannion, 1993).

1.1.2 Epidemiology and economic impact. Demographic variability exists in the population of individuals with SCI, with differences in gender and age apparent between

injury types. In particular, males are more likely than females to sustain a TSCI, with most figures indicating approximately 80% of TSCIs occur in males - although geographical differences are evident (Australian Institute of Health and Welfare [AIHW], 2019; Chen et al., 2013). Whilst American figures suggest TSCIs most commonly occur between the ages of 16 and 30 due to motor vehicle accidents (National Spinal Cord Injury Statistical Centre, 2020), Australian data suggests that falls are the most common cause of TSCIs - accounting for 48% of all TSCIs in individuals aged 45 to 54 and 65 to 74 years (AIHW, 2019).

Not surprisingly, the permanent neurological damage and associated functional impairments that occur with a SCI place a significant burden and cost on society through loss of capacity and utilisation of healthcare services. The most recent comprehensive summary of the estimated economic costs of SCI in Australia reported approximate costs of $2 billion, with $1.3 billion associated with treatment for quadriplegia and $690 million relating to paraplegia (Access Economics, 2009; Collie et al., 2010). Further, individual lifetime economic costs were approximated as $9.5 million for individuals with tetraplegia and $5 million for individuals with paraplegia (Access Economics, 2009). These may even be conservative burden of disease estimates, given that medical advances continue to improve outcomes for individuals with SCI and extend life spans, with related increased costs (AIHW, 2019).

1.2 Treatments for SCI Pain

Persons with SCI living with chronic pain are at risk of experiencing increased levels of substance use disorders which, in turn, can heighten suicidal ideation and attempts. Concerningly, 5.8 to 11% of deaths in the SCI population are due to suicide (Banerjea, Findley, Smith, Findley, & Sambamoorthi, 2009; Calati, Laglaoui Bakhiyi, Artero, Ilgen, & Courtet, 2015; Heinemann, Doll, Armstrong, Schnoll, & Yarkony, 1991; Kennedy &

Garmon-Jones, 2017; McCullumsmith et al., 2015; Stubbs, 2016). Early and targeted treatment for SCI pain is therefore critical, not only to maximise functioning and participation but also quality of life.

Both physical therapies (e.g., activity modification, therapeutic massage, acupuncture, transcutaneous electrical nerve stimulation) and cognitive behavioural treatments (e.g., mindfulness, self-hypnosis, cognitive restructuring have demonstrated efficacy in SCI pain management (Bi, Lv, Chen, Fann et al., 2013; Li, & Wang, 2015; Norrbrink Budh & Lundeberg, 2011; Taylor-Schroeder et al., 2011). Less common are surgical treatments including insertion of a dorsal column stimulator or intrathecal pumps, or nerve blocks and ablation (Magrinelli, Zanette, & Tamburin, 2013).

Despite the availability of non-pharmacological treatments, the use of pharmaceutical-based pain management is frequently reported for patients with SCI. For example, neuropathic pain is often treated with tricyclic antidepressants, anticonvulsants, topical local anaesthetics and oral analgesics. Further, Non-Steroidal Anti-Inflammatory Drugs (NSAIDS) are suggested for inflammatory musculoskeletal pain, whilst opioids are prescribed for both types of pain. Concerningly, up to 17.6% of the SCI population self-report risk of misusing prescribed pain medications (Baastrup & Finnerup, 2008; Clark, Cao, & Krause, 2017; Hurlbert et al., 2015). There is also evidence to suggest that a polypharmacy approach is more prevalent in this population and is associated with a greater risk of drug related consequences, in comparison to matched controls without a SCI (Krause et al., 2019). It is therefore important to understand the prevalence of specific substance use and misuse to improve post-SCI physical and psychological outcomes.

1.2.1 Opioid treatment. Opioids are commonly suggested as a second order treatment for SCI pain when NSAIDS are proven to be ineffective, with the primary aim to improve the person's quality of life (Van Gorp, Kessels, Joosten, Van Kleef, & Patijn, 2015). However,

there is conflicting evidence as to the efficacy of opioid use, with individual studies reporting no significant reduction in SCI-related pain symptoms (Martell et al., 2007; Mehalick, McPherson, Schmaling, Blume, & Magnan, 2016). In their systematic review of 28 randomised controlled and non-controlled trials (i.e., prospective trials, cohort and case-studies) published over a 29-year period, Teasell et al. (2010) found limited evidentiary basis to support the use of opioids following SCI. Conversely, in their systematic review examining pharmacological treatments for SCI pain, Mehta et al., (2016) noted that opioids can be effective. However, this same review provided no information relating to disordered use or medication misuse. A more recent meta-analysis involving 16 randomized controlled trials comparing opioids to placebo for chronic non-cancer neuropathic pain, including SCI-pain, identified preliminary evidence for the short-term efficacy of opioids, with pain relief noted by patients over a period of 4 to 15 weeks (Sommer, Klose, Welsch, Petzke, & Häuser 2020).

Researchers have also argued against the use of opioids in SCI care based on the potential side effects (Bryce, 2018). There is evidence that those who have been prescribed opioids are likely to take increased dosages at higher rates over time, thereby increasing the likelihood of misuse and subsequent development of opioid use disorders (Hand, Krause, & Simpson, 2018). Additional adverse health implications of opioid use post-SCI mirror the detrimental consequences reported in the wider population. Adverse events include increased risks of falls, fatigue, lowering of bone mineral density and associated fractures, hypotension, urinary retention, constipation, autonomic dysreflexia, and even increased pain (Abrahamsen & Brixen, 2009; Carbone et al, 2013; Ensrud et al., 2003; Kirshblum & Lin, 2018; Lee, Miller, Townson, & Anton, 2010). Further, individuals with a SCI using pain medication daily (opioid or non-opioid) have a 51% increased risk of mortality (Krause, Cao, & Clark, 2017). Adverse effects from opioid use are compounded for people with SCI. For example,

transdermal fentanyl is absorbed at a faster rate in this population due to associated pathophysiology, such as higher body temperatures below the lesion. The rapid physiological response and potential for overuse of these medications can, therefore, result in an unintended euphoric state that further compounds effects and acts as a reinforcing agent for addiction (Kirshblum & Lin, 2018; Rechard & Anlona, 2001; Volkow & McLellan, 2016).

Opioid overdose is now described as an epidemic. The Centres for Disease Control and prevention (CDC) in the United States has reported quadrupling of prescriptions in the general population over the past two decades. Opioids are the leading cause of overdose fatalities, with the rate increasing by 200% since the year 2000 (CDC, 2019; Rudd, Seth, David, & Scholl, 2016). Pain medication misuse, including opioids, in persons with a SCI is also alarmingly high, with estimates ranging from 17.6% to 25.8% (Clark et al., 2017; Krause, Clark, & Saunders, 2015). An increased risk of misuse has been associated with more intense SCI pain sensation, restrictions on activity and mobility, use of pain relief, frequent nicotine or cannabis use, and comorbid depression and/or anxiety symptoms (Clark, Cao, & Krause, 2017; Krause et al., 2015). Further, individuals who are prescribed opioids may exhibit delays in locomotor recovery (e.g., walking speed and duration), increased development of pain, and increased risk of infection (Woller & Hook, 2013).

1.3 Methodological and Population Discrepancies in SCI Research

Prevalence estimates of opioid use following SCI are, however, highly variable: ranging from a low 1.8% to a staggering 98% (Chou, 2010; Dowell, Haegerich, & Chou, 2016; Graupensperger, Corey, Turrisi, & Evans, 2019; Raut, Nagar, Springer, Sawaki, & Salles, 2018). Similarly opioid medication misuse has ranged from 5 to 24%, with suggestion that opioid misuse in the SCI population is even higher than general pain medication misuse (e.g., 17.6%, Clark et al., 2017). This variability in estimates of opioid

use may be attributable to methodological and/or population differences both within and between SCI studies.

The use of different assessment tools, in particular, makes it difficult to quantify the scope of opioid use and misuse following SCI. For example, self-reported drug use may be influenced by social desirability bias - whereby individuals underreport undesirable traits (i.e., opioid use), producing deflated estimates (Latkin, Edwards, Davey-Rothwell, & Tobin, 2017). Self-reported data may also be characterised by well-established confounds, such as interviewer characteristics (i.e. experience in administering interviews) and treatment or research setting (i.e. whether bystanders were present) (Mabe & West, 1982). Indeed, estimates of self-reported opioid use among SCI studies are typically lower, ranging from 7% to 23% (Heinemann et al., 1991; Tate et al., 2016). In contrast, studies that have defined 'use' based on the number of prescriptions given and/or filled, as confirmed by medical records (e.g., Carbone et al., 2020; Tate et al., 2016) have produced estimates as high as 40% to 68% (e.g. Veterans Affairs databases; Carbone et al., 2013; Margolis et al., 2014). Relying on prescriptions filled can, however, lead to inaccurate results as one cannot rule out whether: a) the individual actually took the medication, and b) also did not take non-prescribed medication (e.g., Carbone et al., 2013; Rouleau & Gertin, 2011). Interestingly, this figure decreases to 3% for non-prescribed use among outpatient populations (Krause et al., 2019) - which may be a product of over-prescription in the SCI population, reducing the need for non-prescribed use. In contrast, screening tools for opioid misuse based on comprehensive and objective diagnostic criteria, such as the International Classification of Diseases (ICD-10, 2004), or validated tools developed for primary health care workers such as the 8-item Alcohol, Smoking and Substance Involvement Screening Test (World Health Organisation, 2002), have reported estimates in SCI groups considerably lower than the 5% rate identified among the general population (e.g., 1.8% Graupensperger et al., 2019; American Psychiatric

Association, 2013; World Health Organization, 2018). The suggestion is that a combination of both self—report and medical record review or diagnostic testing is required to accurately assess opioid use and misuse.

The method of data collection may also impede valid comparisons of opioid prevalence estimates across SCI studies. This includes whether data have been collected prospectively (e.g., following opioid use over time from hospital discharge), or retrospectively (e.g., examining medical charts for opioid prescriptions) (Ranganathan & Aggarwal, 2018, 2019). Each study design has their own strengths and limitations. Prospective studies are considered to provide more accurate data, as researchers can control for confounding variables and exposures. However, this comes at the cost of potential loss of data at follow-up, increased costs, and smaller sample sizes (Euser, Zoccali, Jager, & Dekker, 2009). In contrast, retrospective studies are time efficient as they rely on existing data, making sampling in a chronic but low prevalence condition, such as SCI, easier. However, such designs often rely on data collected for different purposes with researchers also being limited by the data previously collected (Euser et al., 2009). For example, Hand et al. (2018) compared the prevalence of opioid use in 1,454 individuals with and without a SCI using a matched control design. They utilised one of the largest research databases in the United States, MarketScan (IBM, n.d.). Notably, this database does not capture key sample parameters such as socioeconomic status (SES). Consequently, the higher rates of short and long-term acting opioid use noted among their SCI group may have been due to reasons beyond having a traumatic or non-traumatic injury. For example, lower SES has been reported to be related to higher levels of opioid prescriptions for individuals with back pain, indicating factors other than injury type could influence prevalence rates (Gebauer, Salas, & Scherrer, 2017). In addition, individuals in the SCI group may have had a higher use rate based on trait or behavioural differences, given that impulsivity and risk taking are noted to

be higher in individuals with SCI and, in turn, related to increased substance use (Moeller & Dougherty, 2002). This same study used convenience sampling based on medical admissions and insurance claims. It is argued that this method may provide an inflated prevalence estimate as individuals often present to hospitals when in more pain and are, therefore, more likely to be prescribed pain medications, with insurance typically utilised to pay for these (e.g., Hand et al., 2018; Raut et al., 2018).

Injury level differences in the sensation and perception of pain also need to be factored, with disparities noted based on the potential for localised nerve root compressions and sensory loss associated with a SCI (Hagen & Rekand, 2015; Siddall & Finnerup, 2006). Results in this area have, however, been conflicting (Nakipoglu-Yuzer, Atci, & Ozgirgin, 2013). For example, Siddall, McClelland, Rutkowski, & Cousins (2003) reported that overall pain was not associated with SCI type or completeness, although neuropathic pain was more prevalent in paraplegic than quadriplegic injuries. In contrast, Ullrich, Jensen, Loeser, and Cardenas (2008) noted that level of injury influenced the presence of pain: those with quadriplegic injuries were more likely to report pain than peers with paraplegia. Further, whilst Demirel, Yllmaz, Gençosmanoğlu, and Kesiktaş (1998), and Wollaars, Post, van Asbeck, & Brand (2007) noted a higher prevalence of pain among individuals with an incomplete injury, Summers, Rapoff, Varghese, Porter, and Palmer (1991) noted no difference in pain severity ratings based on injury completeness.

Gender differences in SCI pain experiences and, in turn, opioid prescriptions have also been identified, albeit in a limited number of studies. For example, Carbone et al. (2020) and Graupensperger et al. (2019) reported comparable, low rates of opioid use among their groups (0.4% males vs 0.2% females) in their retrospective review of health and medical records. Ataoğlu et al., (2013) also reported no differences in pain and subsequent opioid use based on gender, in their prospective study of 140 inpatients In contrast, Rouleau and Gertin

(2011) reported a discrepancy: 61.9% of males used opioids compared to 50% of females among a community sample of 175 persons with SCI. However, an inpatient study involving 456 SCI patients reported women had a higher level of opiate and NSAID use, which the authors attributed to a higher prevalence of nociceptive pain compared to males (53.8% vs 27.7%; Norrbrink Budh et al., 2003). Expanding beyond individuals with a SCI, multi-centre longitudinal studies of motor-vehicle accident admissions suggest that women may have higher use, due to reporting more psychological and somatic pain symptoms (e.g., Madsen et al., 2018). These mixed findings highlight a need to examine potential gender-specific differences in chronic pain and, in turn, the risk of developing negative long-term outcomes including opioid misuse.

1.4 The Current Study

Research examining the prevalence of opioid use in individuals with a SCI, in addition to potential methodological and sample moderators, is critical to the development of best practice treatment guidelines in SCI care. Meta-analytic evidence, in particular, would help determine whether over-prescription of opioids occurs in this population and assist health-professionals in determining potential indicators of prolonged opioid use to ensure that treatments are both targeted and beneficial. To date, there has not been a systematic and quantitative review of the growing body of studies in this area. The present study will therefore meta-analyse the literature on opioid use/misuse in individuals with a SCI to address the following aims:

1). Provide an accurate estimate of the prevalence of opioid use/misuse in individuals with a traumatic or non-traumatic SCI.

2). Evaluate the potential influence of methodological factors (i.e., assessment tool, data source), sample characteristics (i.e., gender), and SCI characteristics (i.e., SCI type, lesion type) on effect estimates.

3). Examine prevalence estimates in the context of reporting quality based on the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist.

Chapter 2

Methods

2.1 Literature Search

A comprehensive electronic search of CINAHL, Embase, Ovid MEDLINE, PsycINFO, PubMed, Scopus, and Web of Science was undertaken to source studies examining opioid use, including the prevalence of opioid-related disorders, in adults with SCI. Databases were searched from inception (CINAHL 1937; Embase 1947; Ovid MEDLINE 1946; PsycINFO 1967; PubMed 1996; Scopus 1960; Web of Science 1900) to March 30th 2020, with weekly email alerts established and monitored until June 1st 2020. In addition, four journals specific to SCI rehabilitation were searched: *Spinal Cord*, *Spinal Cord Series and Topics*, *The Journal of Spinal Cord Medicine*, and *Topics in Spinal Cord Injury Rehabilitation*. The search strategy, developed in conjunction with a specialist research librarian, included key terms associated with opioid-related disorders (e.g., '*opioid abuse*', '*opioid addiction*') and SCI (e.g., '*spinal injury*', '*spinal cord damage*', '*quadriplegia*') alongside truncation, wildcards, adjacency operators, MeSH and Emtree headings (see Appendix A for complete logic grids). Finally, the reference lists of all included studies and previous reviews investigating opioid or polysubstance use among chronic disability groups in general (see list in Appendix B) were examined to locate literature that may not have been captured by the electronic search strategy, although this process yielded no additional unique studies.

2.2 Eligibility Criteria and Study Selection

Study screening was undertaken by the student researcher (E.B) with records imported into Covidence systematic review software (Covidence systematic review software, Version 1.0, Veritas Health Innovation). To ensure reliability of the screening process, the

project supervisor (D.D) screened the titles and abstracts of 646 records, with 100% inter-rater agreement.

To be eligible for inclusion in this review, studies of any methodological design needed to examine opioid use - as determined by self-report or number of prescriptions filled, or opioid misuse - that is, problematic pattern of use based on clinician-administered assessment or interview, among an adult human sample (>17 years of age; the lowest common age specified for adult SCI services; Cripps et al., 2011) diagnosed with a non-traumatic or traumatic SCI. Studies that examined multiple trauma groups, where the data for individuals with SCI could not be separately extracted, were excluded. In addition, eligible studies were required to be published in a journal in the English language, or with English translation, to ensure results and methodological details could be extracted effectively and to maintain methodological rigour (Jüni, Holenstein, Sterne, Barlett, & Egger, 2002). Dissertations, conference proceedings and book chapters were excluded, as the focus was on original research that had been peer reviewed (Balshem et al., 2013).

2.3 Data Extraction

A purposely designed Microsoft Excel spreadsheet was generated to extract key information from all studies (see Appendix C), consistent with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher, Liberati, Tetzlaff, & Altman, 2009). Extracted data included: study characteristics (i.e., sample size, country, treatment facility, measurement of opioid use, data set source); sample characteristics (i.e., mean age – or estimated age based on grouped frequencies, gender, relationship status, ethnicity, type of SCI, completeness of injury, cause of injury, ethnicity), and effect size data (i.e., number of SCI participants prescribed opioids divided by total number of participants).

2.4 Study Reporting Quality

As per the PRISMA guidelines, each study was assessed in relation to risk of methodological bias and overall strength of evidence (Moher et al., 2009). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist was used for this purpose. This checklist consists of 22 criteria, 18 of which are common to cohort, case-control, and cross-sectional studies, whilst four are specific to each of these three study designs (Vandenbroucke et al., 2007). Each criterion was rated as "incomplete/unable to determine" (0), "partially complete, missing information" (1), or "complete" (2). A total score was obtained for each study by summing the 22 items (range 0-64). Studies we re-rated by the same student researcher after a period of 6 weeks. Intra-rater reliability was 89.4%, indicating a strong level of agreement (McHugh, 2012).

2.5 Effect Size Calculations

Effect size data were entered into Comprehensive Meta-Analysis software (CMA, Version 3.0, Biostat Inc). Proportions were used as the primary effect size estimate, with logit transformations applied to counteract the influence of outliers (Lipsey & Wilson, 2001). Inverse-variance weighting was used to weight the obtained proportions prior to averaging them (P_w) (Hedges & Olkin, 2014). Ninety-five percent confidence intervals (95% CIs) were additionally calculated for each effect in order to provide the upper and lower bound, or range that we can be 95% confident that the true prevalence rate of opioid use in the SCI population would fall (Cumming, 2012). Each proportion had an associated *p*-value calculated, which provided evidence as to whether the proportion reflects the true population value (Borenstein, Hedges, Higgins, & Rothstein, 2011) - values less than .05 indicated a significant difference form the population estimate. Both individual and pooled effect size estimates were represented graphically, through forest plots generated in Microsoft Excel (Ried, 2006).

The degree of between-study heterogeneity, or the variance in prevalence estimates, was assessed with three statistics. First, Cochran's *Q* value was used to test the viability of the null hypothesis that true effects are consistent across studies. A significant result (i.e., $p < .05$) provides evidence of between-study variation in true effects (Borenstein et al., 2011). The *Q* statistic may, however, be underpowered when studies have small sample sizes, or when few studies are included in a meta-analysis (Deeks, Higgins, & Altman, 2019). As such, Tau (τ) – which is analogous to the between-studies SD, and I^2 - which is expressed as a percentage and measures the extent of true dispersion, were also used (Borenstein et al., 2011; Borenstein, Higgins, Hedges, & Rothstein 2017). All analyses were conducted using a random-effects model, which assumes that the studies are estimating different, yet related, effects (Borenstein, Hedges, Higgins, & Rothstein, 2010). This was appropriate given the inherent variation in individuals with SCI as a population (Thompson, Mutch, Parent, & Mac-Thiong, 2015), in addition to varied definitions of opioid use adopted by the included studies.

The reliance on published data in this meta-analysis may have led to any pooled effect estimate being higher than the true effect size, given that published studies are typically characterised by strong and significant effects. This is particularly true for small *N* studies with large (but unreliable) effect sizes (Ioannadis, 2008). This issue of publication bias was acknowledged with two statistics. First, a funnel plot - which plots the observed effect size against the inverse of their standard errors, was generated to provide a graphical representation of publication bias across all included studies. The funnel plot was statistically checked with the Trim-and-Fill method (Duval & Tweedie, 2000) and Egger Regression Test (Egger, Smith, Schneider, & Minder, 1997). The Trim-and-Fill method removes studies that lead to asymmetry in the funnel plot to reduce the impact of publication bias on the effect estimate predicted by the remaining studies, then fills the funnel plot with imputed missing studies based on the bias-corrected overall estimate. Egger's regression intercept tests for

asymmetry in the funnel plot by regressing the standardised effect sizes (standardised estimate divided by its standard error) onto their precisions (reciprocal of the standard error of the estimate). Orwin's Fail-safe *N* statistic (N_{fs}) was then computed for each subsequent meta-analysis. N_{fs} estimates the number of non-significant studies that are required to reduce the observed effect size in a meta-analysis to some criterion value, typically reflecting small and non-significant finding (Orwin, 1983). For the purpose of this review, a criterion value of .05 was used based on established diagnostic criteria for past-year pharmaceutical opioid dependence (American Psychiatric Association, 2013; World Health Organization, 2018). Publication bias was considered unlikely if the N_{fs} value exceeded the total number of studies included in this meta-analysis.

2.6 Sensitivity and Subgroup Analyses

Between-study heterogeneity was explored with a one-study removed sensitivity analysis. Here, studies were removed one at a time and the meta-analysis re-run to determine impact on overall result (Borenstein et al., 2011). Potential outliers were identified if the removal of a single study resulted in a change in the overall prevalence estimate or significance associated with an estimate.

In addition, subgroup analyses were conducted to identify potential sources of heterogeneity, namely: assessment of opioid use (i.e., prescribed/non-prescribed, ICD diagnosis), method of data collection (i.e., retrospective or prospective), demographic characteristics (i.e., gender) and SCI severity (i.e., injury level and lesion completeness). There were sufficient studies to conduct these analyses (i.e.> 80 participants per subgroup; Deeks et al., 2019; Huedo-Medina, Sánchez-Meca, Marín-Martínez, & Botella, 2006). Cochrane's Q_B, akin to an ANOVA, was calculated to determine the significance of between-group differences (Borenstein et al., 2011).

CHAPTER 3

Results

3.1 Study Selection

The search process yielded 790 potentially relevant records, of which 144 were duplicates (see Figure 1). Individual journal searches were conducted, though this yielded no additional results. The titles and abstracts of the remaining 646 records were screened against the eligibility criteria, resulting in 617 potentially eligible articles. The full texts for these articles were then examined, resulting in 600 studies being excluded. During this process, five studies with overlapping data were identified: two co-authored by Carbone et al. (2013; 2014) utilised the Veteran's Affairs Spinal Cord Dysfunction Registry (2002-2007), and three studies co-authored by Cardenas (Cardenas & Jensen, 2006; Turner, Cardenas, Warms, & McClellan, 2001; Warms, Turner, Marshall, & Cardenas, 2002) included samples drawn from the Northwest Regional Spinal Cord Injury System. The two studies with the largest data pool were retained (i.e., Carbone et al., 2013; Cardenas & Jensen, 2006). The study by Warms et al., (2002) was also retained as it included a second survey with an independent sample. This process resulted in 15 independent samples, from 14 studies, for analysis.

3.2 Study Characteristics

Most studies were recent, with publication dates ranging from 1991 to 2020, and over half being published since 2016 ($N_{studies} = 8$). The majority were published in the United States ($N_{studies} = 14$), with a single study from Canada. Sample sizes varied, with most studies involving multi-centre trials ($N_{studies} = 9$). Data sources included prospective postal surveys ($N_{studies} = 2$), but also retrospective reviews of medical charts ($N_{studies} = 10$), and/or insurance claims records ($N_{studies} = 3$). The largest study, examining the Veteran Affairs' Spinal Cord

Injury and Disorders Outcomes (SCIDO) database (Hatch et al., 2018), comprised approximately 25% of the pooled sample.

Definitions of opioid use included number of prescriptions filled ($N_{studies}$ = 8), but also self-reported prescribed ($N_{studies}$ = 6) and non-prescribed use ($N_{studies}$ = 1). A single study (Graupensperger, 2019) examined opioid misuse, based on ICD-10 diagnostic criteria for opioid dependence (World Health Organisation, 2004). Complete data extraction results, per study, are presented in Appendix D.

3.3 Sample Characteristics

The pooled sample comprised of 61,311 individuals, with a mean age at recruitment of 47 years (*SD* = 5.94). Most participants resided in the community and over 80% were male, likely due to the reliance on large data sets focusing on war veterans (note: approximately 9% of US veterans are women; Vespa, 2020), but also consistent with the epidemiology of SCI (AIHW, 2019; Chen et al., 2013, Table 1). Based on the few studies that reported additional sociodemographic details ($N_{studies} \leq 6$), 58% of participants had obtained tertiary qualifications, 47% were married or in a relationship, and only 32% of participants were employed – a profile that is common in SCI research (Tovell, 2019). Ethnicity was unevenly distributed with just under 75% of participants identifying as Caucasian and 21% as African American. The remainder comprised of individuals from Hispanic, Native American, and Asian/Pacific Islander ethnicities.

SCI details were inconsistently reported. Where these data were available, both quadriplegic and paraplegic injuries featured (42% each), with 16% of cases described as ‘unknown’. Injury cause included TSCIs sustained from a motor vehicle accident or fall, although 18% of participants had a non-traumatic injury (e.g., ICD-9 criteria “SCI without

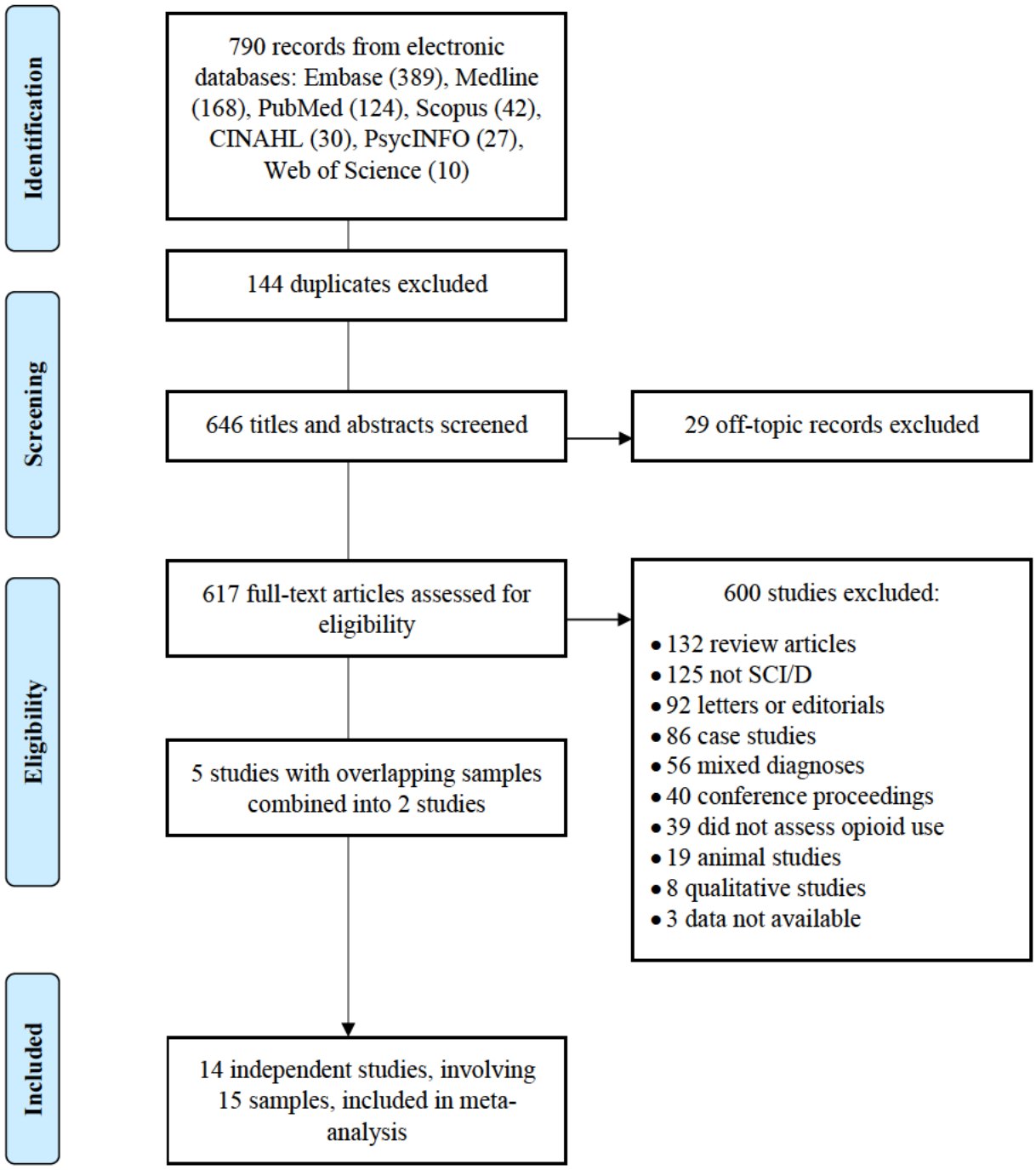


Figure 1. PRISMA flowchart for study selection process (Moher et al., 2009)

Table 1

Pooled Sample Characteristics

Variable	$N_{studies}$	$N_{participants}$ (%)	*M* (*SD*)	*Range*
Sample size	15	61311 (100)	4087.40 (4494.27)	28–13442
Age at study recruitment (years)	10	34890 (57)	47.58 (5.94)	39.50–57.96
Age at time of injury (years)	1	120 (0.2)	32.40 (11.50)	120
Time since injury (years)	4	660 (1)	11.80 (6.56)	4.30–20.00
Education				
Primary	4	88 (2)		
Secondary	6	1929 (40)		
Tertiary	6	2858 (58)		
Gender				
Male	14	40490 (81)		
Female	14	9557 (19)		
Marital Status				
Married/defacto	6	2557 (47)		
Divorced/separated/widowed	5	1278 (24)		
Single	6	1558 (29)		
Employment Status				
Employed	3	141 (32)		
Unemployed	3	241 (54)		
Student	2	22 (5)		
Retired	2	41 (9)		
Type/level of SCI				
Quadriplegia	13	17880 (42)		
Paraplegia	13	17854 (42)		
Unknown	5	6800 (16)		
Completeness of injury				
Complete (AIS A)	5	6544 (39)		
Incomplete (AIS B, C, D)	5	6913 (41)		
Unknown	3	3298 (20)		
Nature of injury				
Traumatic	9	25270 (68)		
Non-traumatic	4	6500 (18)		
Unknown	1	4964 (14)		
Injury cause				
Motor vehicle accident	2	131 (51)		
Fall	2	50 (18)		
Sports-related	2	28 (11)		
Violent	2	12 (5)		
Other	2	38 (15)		

Note: $N_{studies}$ = number of studies contributing to data; $N_{participants}$ = number of participants from studies contributing to data.

evidence of spinal bone injury"). Again, these figures align with previous SCI research (James et al., 2019).

3.4 Study Reporting Quality

The mean STROBE score across studies was 39.73 (*SD* = 8.54) out of a possible 64, with reporting quality ranging from a minimum of 19 (Rouleau & Guertin, 2011) to 49 (Hatch et al., 2018). The percentage of studies that met each criterion is depicted in Figure 2 with individual study ratings provided in Appendix E. Sufficient detail in relation to study design, rationale (including potential gaps in the literature), and objectives were provided (criteria 1a - 4). Participant recruitment and eligibility were also outlined, helping to enhance the generalisability of the results to the larger SCI population (criteria 5-7). Similarly, measurement of the key variable of interest – opioid use or misuse – was described in sufficient detail (criteria 7-8). However, the impact of confounding variables (e.g., history of opioid use) was not typically acknowledged (criterion 9), and a-priori or post-hoc sample size calculations not routinely provided (criterion 10). In addition, subgroup analyses (e.g. males versus females) were not always justified or consistent with the research questions (criteria 11-12b). The management of missing data, use of matched/sampling strategies, and sensitivity analyses were also not commonly reported (criterion 12d).

Studies also varied in the degree to which they reported the flow of participants during recruitment and assessment – detail which is crucial in order to assess the validity of a study's results (criteria 13a-17). Missing detail included reasons for non-participation (criterion 13b) and the inclusion of a flow diagram with final sample numbers (criterion 13c). However, participants and groups were adequately described (criterion 14a), despite limited information about the amount of missing data (criterion 14b). Effect size data (i.e. proportion of opioid users) were provided in addition to appropriate estimates of variance (i.e. CIs;

criteria 15 & 16a). There was less detail in relation to categorical variables (e.g., gender ratio) and any additional or unplanned statistical analyses (criteria 16b-17).

Finally, all studies reported key findings, with most including a thorough and balanced overview of potential limitations and sources of bias (criteria 18-20). However, few reported on the applicability of the results to the SCI population or explicitly stated their funding source - hence the potential for funding bias, whereby results more favourable for the funding sponsor are reported, could not be ruled out (criteria 21 & 22; Holman & Elliot, 2018). In summary, whilst the majority of STROBE criteria (72%) were met by over half the studies, there was a paucity of information in relation to efforts to address or adjust for methodological bias which likely decreased the precision of individual studies. In particular, validity and reliability may have been compromised and the generalisability of the pooled sample results to the broader SCI population reduced (Greenland et al., 2016; Vandenbroucke et al., 2007).

3.5 Prevalence of Opioid Use-Misuse

The pooled prevalence estimate across the 14 independent studies was 25% ([CI = .16, .37], p <.01) (Table 2): one in four adults with a SCI were using opioids. This finding was robust, as indicated by the high N_{fs} statistic: 60 studies with non-significant estimates would be needed to overturn this result. This was confirmed by funnel plot analysis (see Figure 3), Trim-and-Fill method (0 studies 'filled') and Egger's test (p = .07), all of which suggested no apparent bias in the overall effect.

There was, however, substantial variation in estimates across the studies, as indicated by the significant between-study heterogeneity (I^2 > 90%). The highest estimate was associated with Raut et al.'s (2018) audit of post-operative opioid use among inpatients in a rehabilitation hospital. Comparatively, Graupensperger et al. (2019) reported the lowest rate

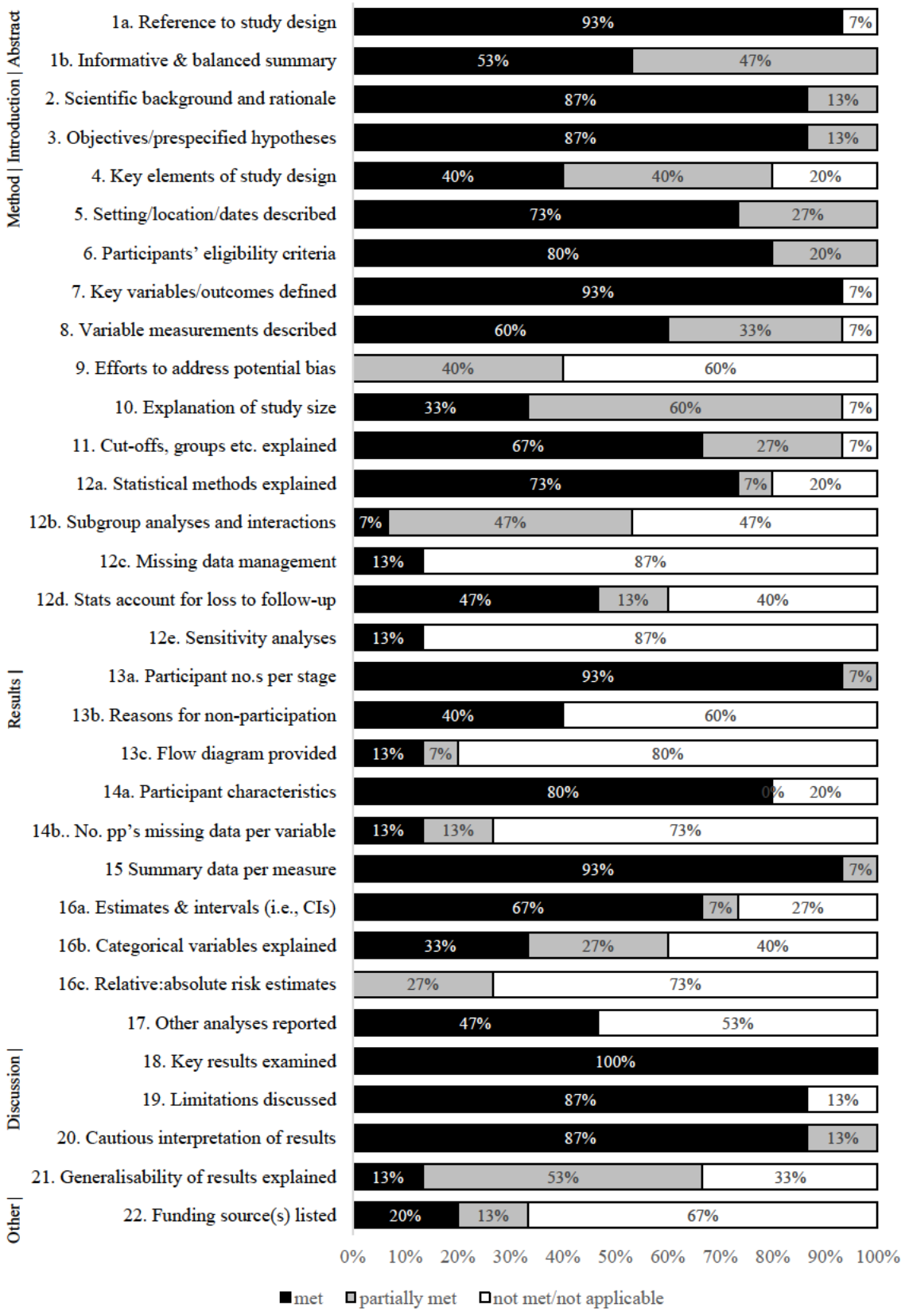


Figure 2. Percentage of studies meeting each criterion on the STROBE checklist

in their 20-year audit of inpatient and outpatient health records from a single medical centre. Notably, the estimate provided by Raut et al., (2018) was associated with a large CI - indicating some imprecision - although this may also be an artifact of their small *N*. In contrast, studies involving large datasets, such as that by Graupensperger et al. (2019), provided estimates of greater precision with relatively narrow CIs. Two studies reported prevalence estimates that were not significantly different from the population proportion: Rouleau and Gertin (2011) identified opioid use among 58% ([CI: .50-.65], $p = .06$) of 151 records from a medical centre in Canada, and Hand et al. (2018) reported a prevalence of 50% ([CI: .49-.51], $p = .30$) among 2,908 participants who made private insurance medical and pharmacy claims, as logged in the MarketScan database between 2012 and 2013. Notably, Rouleau and Gertin (2011) examined the use of multiple medications across both TSCI ($N = 82$) and NTSCI ($N = 69$), whereas Hand et al., (2018) used a case-control design to determine opioid use differences between individuals with and without a SCI.

3.6 Sensitivity Analysis

A one-study sensitivity analysis revealed that the removal of any one study did not significantly change the overall pooled prevalence estimate of .25 or the associated *p* value. The substantial estimate reported by Raut et al. (2018) ($p = .98$) was also assigned the smallest weighting due to its potentially underpowered sample size ($N = 28$). Several statistical outliers were, however, identified among the subgroup analyses. Specifically, the removal of low estimates by Krause et al. (2019) and Carbone et al. (2020) altered the *p* value associated with the prospective data - from a significant to non-significant value. The impact of these two studies on the pooled prevalence estimate was, however, minimal: the overall proportion of opioid users increased from 17.7% to 22.2% without Krause et al. (2019), and 21.7% without Carbone et al., 2020. In addition, five of the seven studies that used retrospective data could be classified as outliers – the removal of each changed the overall *p*

value from significant to non-significant (Brose et al., 2019; Graupensperger et al., 2019; Hand, 2018; Hatch et al., 2018; Margolis et al., 2014). The removal of Graupensperger et al.'s (2019) estimate also increased the pooled estimate for the retrospective data from 33.2% to 47.3%.

3.7 Subgroup Analyses

The aforementioned between-study variability highlighted a need for further exploration of potential study and sample moderators that may contribute to diversity in the underlying population. The results of each subgroup analysis are presented in Table 3 and discussed in more detail below.

3.7.1 Assessment tool. The prevalence of opioid use varied depending on the assessment tool used (Table 3). Studies that defined 'use' based on the number of individuals who received pharmaceutical prescriptions (e.g., number of outpatient scripts filled over past 6 to 18 months, or number receiving opiates on discharge) reported the highest estimate: one in three patients (33%) with SCI had been prescribed opioids. The significant between-groups Q_B value (153.71, p <.01) indicates that this estimate was considerably higher than the number reporting non-prescribed use (3%), as well as the number of individuals that met the criteria for an ICD-10 diagnosis of opioid disorder (2%). The latter two findings were, however, based on single studies - resulting in high publication bias (N_{fs} = 1).

3.7.2 Data source. The prevalence of opioid use varied depending on the data source (Table 3). The pooled estimate based on seven studies which collected retrospective data from medical or insurance audits indicated that approximately one in three people with SCI had used opioids (34%). In comparison, the eight studies that prospectively surveyed inpatients or outpatients provided a pooled estimate of 18%. Notably, both subgroups provided estimates associated with large CIs and substantial heterogeneity, suggesting that

the pooled figures may not be precise. Moreover, between-group differences in estimates for the two data sources were not statistically different (Q_B (1) = 1.83, p = .18). The large N_{fs} values do, however, indicate that these results are robust.

3.7.3 Gender. Pooled estimates indicated that males and females had comparable rates of opioid use (10% vs 8% respectively, Table 3). This was confirmed by the non-significant between-groups difference (Q_B (1) = 0.05, p = .88). However, even within each subgroup there remained substantial unexplained heterogeneity (I^2 > 90%). It is important to note that this heterogeneity may be an overestimate given that few studies contributed to each subgroup ($N_{studies}$ = 3). These results were additionally characterised by publication bias (N_{fs} $\leq$ 5).

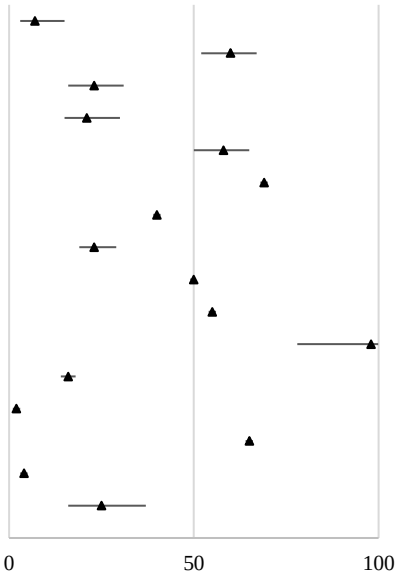
3.7.4 SCI type. Estimates of opioid use were high regardless of whether individuals had sustained a paraplegic or quadriplegic injury (Table 3). Notably, the point estimate for studies involving paraplegic injuries was significant: most of these individuals had used opioids (68%). Again, however, pooled estimates for each subgroup were characterised by large CIs and between-group differences were not statistically different (Q_B (1) = 1.23, p = .27). Specifically, Rouleau and Gertin (2011) reported a rate of 49.3% (quadriplegia) and 65.1% (paraplegia) opioid users among their community sample of traumatic and non-traumatic SCIs, whereas Carbone et al. (2020) reported slightly larger estimates of 50.9% (quadriplegia) and 69.9% (paraplegia) among veterans with TSCI. Despite, the large N_{fs} values, the findings were based on a limited amount of data ($N_{studies}$ = 2).

3.7.5 SCI lesion. Most individuals with an incomplete (66%) or complete (60%) lesion had used opioids (Table 3), with no significant differences noted between these group estimates (Q_B (1) = 0.45, p = .50). Although the point estimate for those with an incomplete level of lesion was significant, the two studies that contributed to this subgroup produced

Table 2

Proportion of opioid users by study and publication date

Lead author (date)	*N*	Proportion	95% CI		*p*	Forest plot of proportions ± 95% CI	Weight % (random)
			LL	UL			
Heinemann (1991)	86	.07	.03	.15	<.01		6.14
Warms (2002) *	163	.60	.52	.67	.01		6.96
Widerström-Noga (2003)	120	.23	.16	.31	<.01		6.83
Cardenas (2006)	117	.21	.15	.30	<.01		6.81
Rouleau (2011)	151	.58	.50	.65	.06		6.95
Carbone (2013)	7447	.69	.68	.70	<.01		7.12
Margolis (2014)	7048	.40	.39	.41	<.01		7.12
Tate (2016)	291	.23	.19	.29	<.01		7.00
Hand (2018)	10752	.50	.49	.51	.30		7.12
Hatch (2018)	13442	.55	.54	.56	<.01		7.12
Raut (2018)	28	.98	.78	1.00	<.01		2.52
Brose (2019)	1500	.16	.14	.18	<.01		7.10
Graupensperger (2019)	6192	.02	.01	.03	<.01		7.06
Krause (2019)	4670	.65	.64	.66	<.01		7.07
Carbone (2020)	8838	.04	.03	.05	<.01		7.10
Total	**61311**	**.25**	**.16**	**.37**	**<.01**		



Abbreviations: N = total sample size, CI = 95% confidence interval (with lower and upper limits), *p* = significance level. * includes data from independent sample to Cardenas et al. (2006)

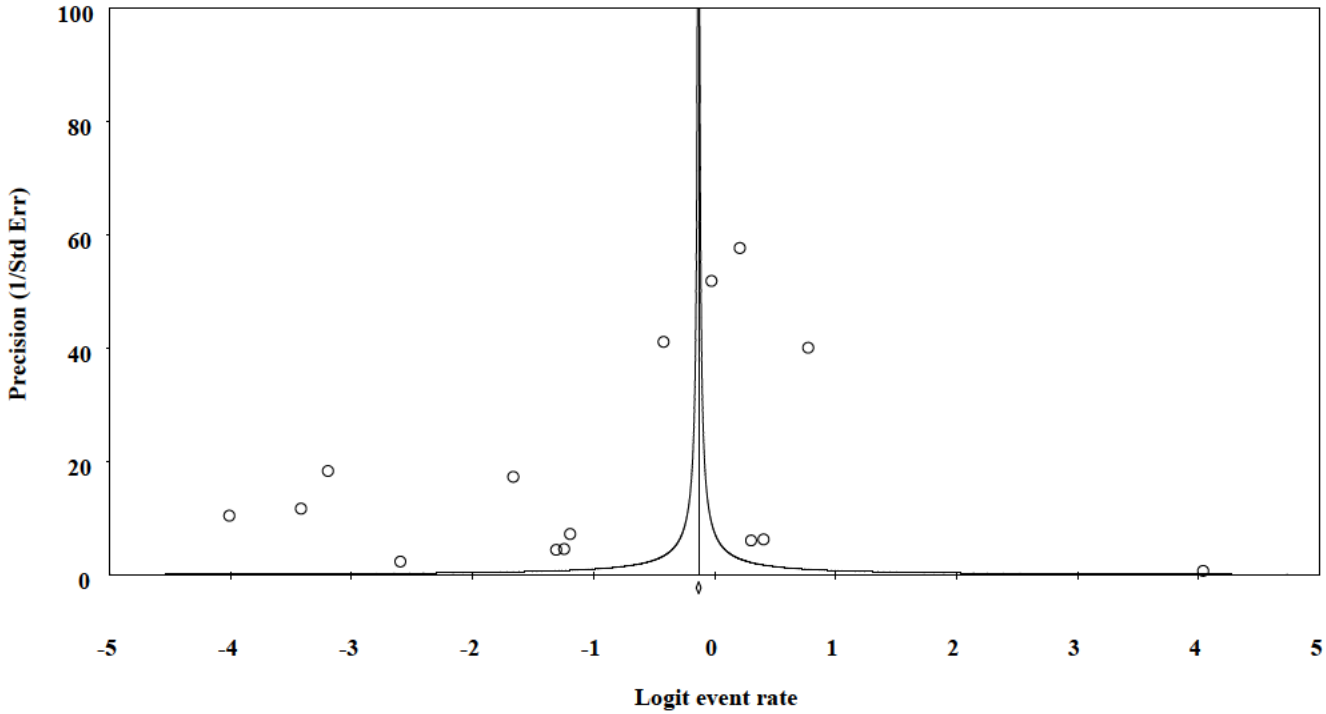


Figure 3. Funnel Plot of Precision (as Calculated by 1/Standard Error) Against Logit Event Rate

highly variable results. Rouleau and Gertin (2011) reported rates of 50.0% and 59.3%, among a small convenience sample of 28 complete and 118 incomplete injuries, whereas Carbone et al. (2020) estimated that up to 64.5% of complete injuries (N = 2724) and 71.1% of incomplete injuries (N = 3034) were using opioids. Although the N_{fs} values were large, few studies contributed to this analysis hence further research is needed to confirm these findings.

Table 3

Subgroup analyses grouped by methodological and sample characteristics

Subgroup	$N_{studies}$	$N_{participants}$	Proportion	95% CI LL	95% CI UL	p	N_{fs}	Forest plot of proportions ± 95% CI	Heterogeneity statistics Q	p	I^2	T
Assessment												
No. prescribed	13	50706	.33	.24	.45	<.01	73		5833.36	<.01	99.79	.87
No. non-prescribed	1	4413	.03	.02	.04	<.01	1					
No. ICD diagnosis	1	6192	.02	.01	.03	<.01	1					
Total	15	61311	.03	.02	.04	<.01	1		153.71	<.01		
Data								0 50 100				
Retrospective	7	47132	.34	.22	.48	.02	41		3989.43	<.01	99.85	.74
Prospective	8	14179	.18	.07	.39	<.01	21		1044.93	<.01	99.33	1.55
Total	15	61311	.30	.20	.41	<.01	75		1.83	.18		
Gender								0 50 100				
Male	3	11454	.10	.02	.38	.01	3		338.69	<.01	99.41	1.53
Female	3	3618	.08	.01	.41	.02	2		175.97	<.01	98.86	1.80
Total	6	15072	.09	.03	.27	<.01	5		.02	.88		
Injury type								0 50 100				
Paraplegia	2	4241	.68	.59	.76	<.01	25		3.21	.07	68.86	.25
Quadriplegia	2	3352	.58	.43	.73	.29	21		6.97	.01	85.66	.43
Total	4	7593	.65	.58	.70	<.01	48		1.23	.27		
Lesion								0 50 100				
Incomplete	2	3152	.66	.54	.77	.01	24		7.49	<.01	86.64	.35
Complete	2	2752	.60	.47	.72	.13	22		2.48	.11	59.71	.33
Total	4	5904	.63	.55	.72	<.01	46		.45	.50		
								0 Proportion (%) of users 100				

Abbreviations: $N_{studies}$ = number of studies contributing to these data, $N_{participants}$ = number of participants from studies contributing to these data, CI = 95% confidence interval (with lower and upper limits), p = significance level of effect estimate (proportion), N_{fs} = fail-safe N, Q = heterogeneity test; p = significance of Q; I^2 = proportional estimate of true effect variance over sampling error observed, T = standard deviation of underlying true effects across studies.

Chapter 4

Discussion

4.1 Key Findings

The current meta-analysis assessed the data from 14 independent studies to quantify the prevalence of opioid use and misuse in the SCI population. Contemporary research examining opioid use and misuse in individuals with a SCI has reported varying estimates of prevalence, with a lack of clarity around the underlying factors responsible for this variance. This places limitations on effective targeted evidence-based clinical care, producing an overreliance on opioid pharmacotherapy with inadequate regard for use and dependency-related concerns. This study aimed to remedy this by providing a more precise prevalence estimate, including examining potential moderators on prevalence use – namely *assessment tool, data source, gender, SCI type* and *SCI lesion*. The pooled results provided a high estimate for opioid use in this population, with no evidence of publication bias. There was, however, large heterogeneity. Further subgroup analyses indicated that significant differences in opioid use prevalence existed between different *assessment tools.* Less information was available to interpret the potential impact of *data source, gender, SCI type* and *SCI lesion*, thereby reducing the power of these subsequent analyses and limiting generalisability of the results.

4.1.1 Prevalence of opioid use and misuse. The finding that one in four people with a SSCI were using opioids is substantially lower than the general population of individuals with chronic back pain (43%, Martell et al., 2007), and higher than the incidence rate of general pain medication misuse in the SCI population (17.6%, Clark et al., 2017). However, there was also substantial variability across studies (16 to 37%), reducing the quantitative conclusions that can be made, though this is consistent with variability in SCI research

(Borenstein, et al., 2017; Gupta, Jaiswal, Norman, & DePaul, 2019). Whilst the overall prevalence estimate of opioid use in individuals with a SCI exceeded that of the general population estimates reported in the DSM-5 and ICD-11 of opioid misuse (5%)(American Psychiatric Association, 2013; World Health Organization, 2018). It should be noted that prevalence estimate of overall use in this study includes people prescribed opioids who do not meet diagnostic criteria, and the prevalence reported by studies that only used diagnostic criteria (1.8%) was substantially lower than both the overall pooled estimate and the estimates reported by DSM-5 and ICD-11. Notwithstanding this caveat, the figure is alarmingly high, particularly when considering the unique concerns associated with opioid use for individuals with a SCI coupled with the increased mortality rate of 51% (Krause et al., 2017; Volkow & McLellan, 2016). However, the results from this study help determine a more accuracy population estimate of opioid use in individuals with a SCI, indicating that many individuals in this population rely on opioids to manage SCI related pain.

4.1.2 Assessment tool. The variability in the overall prevalence estimate may be partially attributed to the different assessment tools utilised. Most of the studies ($N_{studies}$ = 13) relied on prescriptions filled or self-reported data, indicating approximately one third of patients had been prescribed opioids. The primary concern with reliance on prescriptions filled relates to the uncertainty as to whether the individual used the medication, resulting in prevalence overestimates (Carbone et al., 2013; Rouleau & Gertin, 2011). The use of self-report, subject to the influence of social desirability bias, may have resulted in reported prevalence figures may being lower than the actual level of opioid use in this population (Craig, Tran, & Middleton, 2008; Latkin et al., 2017). Individuals with a SCI may be using at higher levels than reported, meaning results need to be interpreted with caution and studies examining prescribed use may be more accurate. Prescribed use was significantly higher than both non-prescribed use (3%) and misuse (2%). The over-prescribing in this population

could lead to a decreased estimate of non-prescribed use. The study which used ICD-10 to identify misuse reported a lower prevalence rate (Graupensperger et al., 2019). As the ICD-10 is a stringent indicator of misuse, including additional criteria, such as withdrawal, tolerance, and functional impact, it is likely to produce lower prevalence estimates (Hasin, Hatzenbuehler, Keyes, & Ogburn, 2006). The reported figure was lower than that of the general population, indicating lower opioid misuse in the SCI population (American Psychiatric Association, 2013; World Health Organization, 2018). However, these results were based on one study which excluded "paraplegia or quadriplegia" from their medical record searches, as they could not confirm that the paraplegia/quadriplegia was a result of a SCI or another condition (e.g., cerebral palsy), which may have reduced estimates (Graupensperger et al., 2019).

4.1.3 Data source. The current findings indicate that opioid use prevalence estimates were high irrespective of whether data was collected retrospectively or prospectively. One advantage of prospective research is the accuracy of results (Euser et al., 2009). In the included studies, the retrospective designs often relied on medical and insurance databases, which are likely to contain more accurate data due to the stringent protocols employed in medical and insurance settings, potentially reducing any discrepancies between the two data sources. In this analysis, the prospective study designs with smaller sample sizes may have inhibited our capacity to discriminate between true effects and artifacts associated with small samples (Button et al., 2013). Whilst there was no significant difference between retrospective and prospective designs, there was a higher prevalence associated with retrospective designs, which may be related to potential overestimates due to reliance on hospital records where people are more likely to present due to pain and be medicated (Hand et al., 2018; Raut et al., 2018).

4.1.4 Gender. There was no evidence of opioid use differences between males and females, with both groups reporting low overall use. This contrasts with previous SCI research, which has suggested that either males (e.g., Rouleau & Gertin, 2011) or females (Norrbrink Budh et al., 2003) have higher use than the opposite gender. However, this does support findings from large, retrospective studies examining medical chart records, that suggested no significant gender differences (Carbone et al., 2020; Graupensperger et al., 2019). Whilst there was evidence of potential publication bias due to the small number of studies that examined gender as moderator, these were large scale studies which were assigned more weight, indicating that low overall use and lack of group differences may reflect the population prevalence, rather than being a product of publication bias.

4.1.5 SCI type. The prevalence estimates based on SCI type (paraplegic vs tetraplegic) indicated that both groups reported high incidence of opioid use. This contrasts with previous research, which has indicated that injury type moderates pain frequency in individuals with a SCI (Siddall et al., 2003; Ulrich et al., 2008). However, previous research has also been conflicting, with both injury types associated with increased pain prevalence. Whilst it is unlikely these findings were a product of publication bias, there was only a limited number of studies reporting on SCI type differences ($N_{studies} = 2$), indicating further research is required to investigate the impact of SCI type on pain and subsequent opioid use in individuals with a SCI.

4.1.6 SCI lesion. In contrast to previous research, which noted that individuals with an incomplete injury have higher levels of pain and therefore potential opioid use, the current findings indicate that there is no difference in opioid use between incomplete and complete injuries; both groups reported high levels of opioid use (Demirel et al., 1998; Wollaars et al., 2007). This contrasts the suggestion that the physiological location of the injury impacts on the pain perception, and therefore prevalence of opioid use (Hagen & Rekand, 2015; Siddall

& Finnerup, 2006). These results however, support Summers et al.'s (1991) findings that pain in individuals with a SCI injury is a complex product of psychosocial and not just physiological factors. Therefore, the higher level of opioid use reported for both complete and incomplete injury groups may relate to psychosocial factors (e.g., peer-group relations, family problems, employment, social support, history of substance use in family, media portrayal of substance use) that were not examined by the included studies (Gopiram & Kishore, 2014; Scherbaum & Specka, 2008). However, as with SCI type, there were limited studies involved in this analysis ($N_{studies} = 2$) and further research is required to determine the veracity of this claim.

4.2 Clinical Implications

Several important findings from this research have implications for interventions and treatment of pain related to SCI. Overall, there appears to be an over prescription of opioids in this population. Although there was limited evidence regarding the impact of SCI characteristics on opioid use, the figures reported indicate that opioid use is high irrespective of injury type or lesion level. Further, how opioid use is measured had a significant impact on opioid use prevalence.

The results of this meta-analysis indicate that assessment tool is an important factor in opioid prevalence estimates, with more stringent criteria producing lower estimates (Hasin et al., 2006). Reliance on self-report or medical databases of prescriptions filled may provide a larger data sample, however reduces the accuracy of the results based upon questionable reliability of recall and self-report, or uncertainty as to whether the individual used the prescribed opioids. The controversy surrounding the use of opioids for chronic pain often centres around discordant definitions of use and assessment measures of both pain and opioid use (Rosenblum, Marsch, Joseph, & Portenoy, 2008). Without consensus around definition of opioid use, it is difficult to ascertain the overall prevalence and potential for misuse in the

SCI population. Whilst desirable to use internationally agreed systems of nomenclature, such as the DSM-5 to operationalise substance use disorder (American Psychological Association, 2013), the specific criterion remain problematic when applied to the SCI population. Specifically, criterion A of DSM-5 which states the individual is "taking the substance in larger amounts or for longer than you're meant to", will not be met by people in the SCI population who are frequently prescribed large amounts over a long period of time in accordance with medical direction. Based on the current results, few individuals with a SCI injury take non-prescribed opioids, in part due to ease of access from their doctor, despite this being inconsistent with best practice (Bryce, 2018). A more accurate tool for measuring opioid use and potential misuse is required in this population (e.g., a modified ICD-10), taking into consideration the potential for over-prescription.

4.3 Limitations and Future Research

A number of methodological limitations were evident in the current review. In particular, several potential moderators were not reported on or examined by the included studies, and those subgroups that were able to be explored often were underpowered due to the limited number of studies (e.g., gender, SCI type, SCI lesion), reducing the ability to control potential confounding variables (e.g., demographic differences) and generalisability, and increasing the likelihood of publication bias impacting results. This is pertinent as research is often contrasting regarding the impact of potential moderators on opioid use in this population. Future research should explicitly divide samples based on other characteristics (e.g., age, time since injury) to determine the impact these have on opioid prevalence. Further, if psychological factors (e.g., anger, perceived caregiver support) are more important in the development and maintenance of pain, as suggested by Summers et al. (1991), examining these is important to determine their potential impact on opioid use.

Although assessment tool was a potential moderator, the number of studies examining non-prescribed use and diagnostic misuse were limited ($N_{studies}$ = 1), indicating that we cannot be confident there is any true difference in these groups. Additionally, it is difficult to determine what misuse levels are and how they compare to the general population. Further, studies often did not report whether misuse was screened for, and if so, how they screened for it, leading to a potential underestimation of misuse. Moreover, few studies were conducted in a manner allowing the determination of misuse based on diagnostic criteria (e.g., reliance on prescribed use does not determine if withdrawal or tolerance are present) resulting in potential decreased estimates of opioid misuse in individuals with a SCI (Furlan, Sandoval, Mailis-Gagnon, & Tunks, 2006). Future research should examine more appropriate assessment tools as it remains unclear whether opioid prescription equates to opioid use, and the subsequent impact on misuse prevalence.

Further, both non-prescribed use and misuse were reliant on one study each, reducing the generalisability of the results and increasing the potential for publication bias.

There was a paucity of available research examining the differences in this population based on data source, limiting our capacity for comparative analysis

Subgroup analyses examining the impact of ethnicity and culture could not be performed, as the majority of studies used samples derived from the United States. Moreover, those that did report on ethnicity characteristics did not examine these as potential subgroups. Research examining pain management indicates a relationship exists between culture and both pain prevalence and treatment, for example African Americans report a higher sensitivity to pain and more pain-related suffering (Campbell & Edwards, 2012). However, research examining this often is conducted in the US comparing African Americans to non-Hispanic whites, and is focused on pain management in general, rather than specifically

opioid use. Future studies examining the impact of culture and ethnicity on pain prevalence and subsequent opioid use in this population is warranted, given the paucity of research examining this and the cultural diversity evident in most countries.

Studies included in this analysis may not be representative of the overall population of individuals with a SCI. Reliance on medical, insurance, and veteran's affairs databases limits the generalisability of results through selection bias and the inability to adequately control for confounds (Hyman, 2015). For example, many studies examined veteran's samples (e.g., Carbone et al., 2013) which are likely biased towards males (Vespa, 2020). To reduce this, future studies should use data from multiple sources where possible, and report on potential confounds and how these were controlled for.

Finally, studies may have been missed due to never being published, being inappropriately indexed, or being rarely cited (Higgins et al., 2020). Whilst an extensive literature search was conducted including examination of the reference lists of relevant reviews, the inclusion criteria precluded non-published studies. This was to maintain methodological quality of the included studies, though may have led to publication bias. To counteract the potential impact of publication bias, N_{fs} statistics were calculated, although publication bias may still exist (Borenstein et al., 2010). Future research could include unpublished studies to capture missing data, though this may reduce the overall quality of the included studies, limiting the conclusions that could be drawn.

4.4 Conclusion

The current study combines an extensive body of research examining the use and potential misuse of opioids to treat SCI related pain. The present findings identified that 1 in 4 individuals with a SCI were using opioids; an alarmingly high estimate given the potential deleterious consequences on the individual and broader society. The data indicates that the method for assessing opioid use has a significant impact on the prevalence estimate, with

prescriptions filled being the most common measure, though this is also the least stringent. Whilst other factors did not appear to moderate the prevalence of opioid use, these were often characterised by a small number of studies and therefore low statistical power. Future research to develop tools aimed at providing a more accurate figure for use in this population and to identify misuse is warranted. This would improve treatment outcomes for individuals with a SCI by assisting in the development of appropriate treatment guidelines, reducing potential over-prescription of opioids.

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Appendix 1

Logic Grids

Journal	Opioid Use Disorder	Spinal Cord Injury
PubMed	"opioid-related disorders"[mh] OR Opiate Abus* [tiab] OR Opioid Abus* [tiab] OR Opium Abus* [tiab] OR Opioid Related Disorder* [tiab] OR Opioid-Related Disorder [tiab] OR Opioid Addict* [tiab] OR Opiate Addict* [tiab] OR Opium Addict* [tiab] OR Opioid Dependenc* [tiab] OR Opiate Dependenc* [tiab] OR Opium Dependenc* [tiab] OR Opioid Misuse [tiab] OR Opiate Misuse [tiab] OR Opium Misuse [tiab] OR Opioid Overdose [tiab] OR Opiate Overdose [tiab] OR Opium Overdose [tiab] OR Opioid Overuse [tiab] OR Opiate Overuse [tiab] OR Codeine Addict* [tiab] OR Morphine Addict* [tiab] OR Tramadol Addict* [tiab] OR Fentanyl Addict* [tiab] OR Codeine Dependenc* [tiab] OR Tramadol Dependenc* [tiab] OR Morphine Dependenc* [tiab] OR Fentanyl Dependenc* [tiab] OR Tramadol Abus* [tiab] OR Morphine Abus* [tiab] OR Fentanyl Abus* [tiab]	"spinal cord injuries"[mh] OR "spinal injuries"[mh] OR "back injuries" [mh] OR "back pain" [mh] OR Spinal Cord Injur* [tiab] OR Spinal Injur* [tiab] OR Spine Injur* [tiab] OR Spinal Cord Trauma* [tiab] OR Spine Trauma* [tiab] OR Spinal Trauma* [tiab] OR Spinal Cord Damage [tiab] OR Spinal Damage [tiab] OR Spine Damage [tiab] OR Spinal Cord Fracture [tiab] OR Spinal Fracture* [tiab] OR Spine Fracture* [tiab] OR "paraplegia" [mh] OR Parapleg* [tiab] OR "quadriplegia" [mh] OR Quadripleg* [tiab] OR Tetrapleg* [tiab] OR Traumatic Myelopath* [tiab] OR Spinal Cord Transection* [tiab] OR Spinal Cord Transsection* [tiab] OR Spinal Cord Contusion* [tiab] OR Spinal Cord Compression* [tiab] OR Spinal Cord Transverse Lesion* [tiab] OR Central Cord Syndrome [tiab] OR Autonomic Dysreflexia [tiab] OR Brown-Sequard Syndrome [tiab] OR Vertebra Compression* [tiab] OR Vertebral Compression* [tiab] OR Vertebra Dislocation* [tiab] OR Vertebral Dislocation* [tiab] OR Vertebra Fracture* [tiab] OR Vertebral Fracture* [tiab] OR Back Injur* [tiab]

Ovid Medline	Exp Opioid-related disorders OR ((opiate OR opioid OR opium OR codeine OR morphine OR tramadol OR fentanyl).ti,ab adj5 (disorder* OR abus* OR addict* OR dependen* OR misus* OR overdose* OR overus*).ti,ab)	Exp spinal cord injuries OR Exp spinal injuries OR Exp back injuries OR Exp back pain OR Spinal Cord Injur*.ti,ab OR Spinal Injur*.ti,ab OR Spine Injur*.ti,ab OR Spinal Cord Trauma*.ti,ab OR Spine Trauma*.ti,ab OR Spinal Trauma*.ti,ab OR Spinal Cord Damage.ti,ab OR Spinal Damage.ti,ab OR Spine Damage.ti,ab OR Spinal Cord Fracture.ti,ab OR Spinal Fracture*.ti,ab OR Spine Fracture*.ti,ab OR Exp paraplegia OR Parapleg*.ti,ab OR Exp quadriplegia OR Quadripleg*.ti,ab OR Tetrapleg*.ti,ab OR Traumatic Myelopath*.ti,ab OR Spinal Cord Transection*.ti,ab OR Spinal Cord Transsection*.ti,ab OR Spinal Cord Contusion*.ti,ab OR Spinal Cord Compression*.ti,ab OR Spinal Cord Transverse Lesion*.ti,ab OR Central Cord Syndrome.ti,ab OR Autonomic Dysreflexia.ti,ab OR Brown-Sequard Syndrome.ti,ab OR Vertebra Compression*.ti,ab OR Vertebral Compression*.ti,ab OR Vertebra Dislocation*.ti,ab OR Vertebral Dislocation*.ti,ab OR Vertebra Fracture*.ti,ab OR Vertebral Fracture*.ti,ab OR Back Injur*.ti,ab
PsycINFO	Opioid-related disorders.sh OR ((opiate OR opioid OR opium OR codeine OR morphine OR tramadol OR fentanyl).ti,ab adj5 (disorder$ OR abus$ OR addict$ OR dependen$ OR misus$ OR overdose$ OR overus$).ti,ab)	spinal cord injuries.sh OR spinal injuries.sh OR back injuries.sh OR back pain.sh OR Spinal Cord Injur*.ti,ab OR Spinal Injur*.ti,ab OR Spine Injur*.ti,ab OR Spinal Cord Trauma*.ti,ab OR Spine Trauma*.ti,ab OR Spinal Trauma*.ti,ab OR Spinal Cord Damage.ti,ab OR Spinal Damage.ti,ab OR Spine Damage.ti,ab OR Spinal Cord Fracture.ti,ab OR Spinal Fracture*.ti,ab OR Spine Fracture*.ti,ab OR paraplegia.sh OR Parapleg*.ti,ab OR

		quadriplegia.sh OR Quadripleg*.ti,ab OR Tetrapleg*.ti,ab OR Traumatic Myelopath*.ti,ab OR Spinal Cord Transection*.ti,ab OR Spinal Cord Transsection*.ti,ab OR Spinal Cord Contusion*.ti,ab OR Spinal Cord Compression*.ti,ab OR Spinal Cord Transverse Lesion*.ti,ab OR Central Cord Syndrome.ti,ab OR Autonomic Dysreflexia.ti,ab OR Brown-Sequard Syndrome.ti,ab OR Vertebra Compression*.ti,ab OR Vertebral Compression*.ti,ab OR Vertebra Dislocation*.ti,ab OR Vertebral Dislocation*.ti,ab OR Vertebra Fracture*.ti,ab OR Vertebral Fracture*.ti,ab OR Back Injur*.ti,ab
Embase	'Opiate addiction'/exp OR ((opiate OR opioid OR opium OR codeine OR morphine OR tramadol OR fentanyl):ti,ab NEAR5 (disorder$ OR abus$ OR addict$ OR dependen$ OR misus$ OR overdose$ OR overus$):ti,ab)	'spinal cord injury'/exp OR 'spine injury'/exp OR 'backache'/exp OR 'paraplegia'/exp OR 'quadriplegia'/exp OR 'spinal cord injur':ti,ab OR 'spine injur*':ti,ab OR 'spinal injur*':ti,ab OR 'spinal cord trauma*':ti,ab OR 'spine trauma*':ti,ab OR 'spinal trauma*':ti,ab OR 'spinal fracture*':ti,ab OR 'spine fracture*':ti,ab OR 'parapleg*':ti,ab OR 'quadripleg*':ti,ab OR 'tetrapleg*':ti,ab OR 'traumatic myelopath*':ti,ab OR 'spinal cord transection*':ti,ab OR 'spinal cord transsection*':ti,ab OR 'spinal cord laceration*':ti,ab OR 'spinal cord contusion*':ti,ab OR 'spinal cord compression':ti,ab OR 'spinal cord transverse lesion*':ti,ab OR 'central cord syndrome':ti,ab OR 'autonomic dysreflexia':ti,ab OR 'Brown-Sequard Syndrome':ti,ab OR 'vertebra compression*':ti,ab OR 'vertebral compression*':ti,ab OR 'vertebra dislocation*':ti,ab OR 'vertebral dislocation*':ti,ab OR

		‘vertebra fracture*’:ti,ab OR ‘vertebral fracture*’:ti,ab OR ‘back injur*’:ti,ab
Scopus	“opioid-related disorders” OR “Opiate Abus*” OR “Opioid Abus*” OR “Opium Abus*” OR “Opioid Related Disorder*” OR “Opioid Addict*” OR “Opiate Addict*” OR “Opium Addict*” OR “Opioid Dependenc*” OR “Opiate Dependenc*” OR “Opium Dependenc*” OR “Opioid Misuse”	“spinal cord injuries” OR “spinal cord injur” OR “spine injur*” OR “spinal injur*” OR “spinal cord trauma*” OR “spine trauma*” OR “spinal trauma*” OR “spinal fracture*” OR “paraplegia” OR “parapleg*” OR “quadriplegia” OR “quadripleg*”
Web of Science	“opioid-related disorders” OR “Opiate Abus*” OR “Opioid Abus*” OR “Opium Abus*” OR “Opioid Related Disorder*” OR “Opioid Addict*” OR “Opiate Addict*” OR “Opium Addict*” OR “Opioid Dependenc*” OR “Opiate Dependenc*” OR “Opium Dependenc*” OR “Opioid Misuse”	“spinal cord injuries” OR “spinal cord injur*” OR “spine injur*” OR “spinal injur*” OR “spinal cord trauma*” OR “spine trauma*” OR “spinal trauma*” OR “spinal fracture*” OR “paraplegia” OR “parapleg*” OR “quadriplegia” OR “quadripleg*”
CINAHL	(QL "opioid-related disorders”) OR Opiate Abus* OR Opioid Abus* OR Opium Abus* OR Opioid Related Disorder* OR Opioid Addict* OR Opiate Addict* OR Opium Addict* OR Opioid Dependenc* OR Opiate Dependenc* OR Opium Dependenc* OR Opioid Misuse	(QL "spinal cord injuries”) OR spinal cord injur* OR spine injur* OR spinal injur* OR spinal cord trauma* OR spine trauma* OR spinal trauma* OR spinal fracture* OR paraplegia OR parapleg* OR quadriplegia OR quadripleg*

Appendix 2

List of Reviews Scanned

Ballantyne, J. C., & Mao, J. (2003). Opioid therapy for chronic pain. *New England Journal of Medicine*, *349*(20), 1943-1953.

Ballantyne, J. C., & Shin, N. S. (2008). Efficacy of opioids for chronic pain: A review of the evidence. *The Clinical Journal of Pain*, *24*(6), 469-478.

Beal, B. R., & Wallace, M. S. (2016). An overview of pharmacologic management of chronic pain. *Medical Clinics*, *100*(1), 65-79.

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Chaparro, L. E., Furlan, A. D., Deshpande, A., Mailis-Gagnon, A., Atlas, S., & Turk, D. C. (2013). Opioids compared to placebo or other treatments for chronic low-back pain. *Cochrane Database of Systematic Reviews*, (8).

Craig, A., Tran, Y., & Middleton, J. (2009). Psychological morbidity and spinal cord injury: A systematic review. *Spinal Cord*, *47*(2), 108-114.

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Furlan, A. D., Sandoval, J. A., Mailis-Gagnon, A., & Tunks, E. (2006). Opioids for chronic noncancer pain: A meta-analysis of effectiveness and side effects. *CMAJ*, *174*(11), 1589-1594.

Jensen, M. P., Moore, M. R., Bockow, T. B., Ehde, D. M., & Engel, J. M. (2011). Psychosocial factors and adjustment to chronic pain in persons with physical

disabilities: A systematic review. *Archives of Physical Medicine and Rehabilitation, 92*(1), 146-160.

Kalso, E., Edwards, J. E., Moore, R. A., & McQuay, H. J. (2004). Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. *Pain, 112*(3), 372-380.

King, S. A. (2012). Chronic pain management in the elderly: An update on safe, effective options. *Consultant, 52*(5), 326-31.

Martell, B. A., O'Connor, P. G., Kerns, R. D., Becker, W. C., Morales, K. H., Kosten, T. R., & Fiellin, D. A. (2007). Systematic review: Opioid treatment for chronic back pain: prevalence, efficacy, and association with addiction. *Annals of Internal Medicine, 146*(2), 116-127.

Mehta, S., McIntyre, A., Janzen, S., Loh, E., Teasell, R., & Spinal Cord Injury Rehabilitation Evidence Research Team. (2016). Systematic review of pharmacologic treatments of pain after spinal cord injury: An update. *Archives of Physical Medicine and Rehabilitation*, *97*(8), 1381-1391.

Mouravska, N., Zielinski, L., Bhatt, M., Sanger, N., Bawor, M., Dennis, B., ... & Laplante, P. (2017). Adverse outcomes associated with opioid prescription for acute low back pain: A systematic review protocol. *Systematic Reviews*, *6*(1), 163.

New, P. W. (2018). Severe chronic pain following spinal cord damage: A pragmatic perspective for prescribing opioids. *Spinal Cord Series and Cases, 4*(1), 65.

Noble, M., Treadwell, J. R., Tregear, S. J., Coates, V. H., Wiffen, P. J., Akafomo, C., ... & Chou, R. (2010). Long-term opioid management for chronic noncancer pain. *Cochrane Database of Systematic Reviews*, (1).

Porter, R. W., & Ralston, S. H. (1994). Pharmacological management of back pain syndromes. *Drugs*, *48*(2), 189-198.

Sng, B. L., & Schug, S. A. (2009). The role of opioids in managing chronic non-cancer pain. *ANNALS Academy of Medicine Singapore*, *38*(11), 960-966.

Stein, C., Reinecke, H., & Sorgatz, H. (2010). Opioid use in chronic noncancer pain: Guidelines revisited. *Current Opinion in Anesthesiology*, *23*(5), 598-601.

Teasell, R. W., Mehta, S., Aubut, J. A. L., Foulon, B., Wolfe, D. L., Hsieh, J. T., ... & Spinal Cord Injury Rehabilitation Evidence Research Team. (2010). A systematic review of pharmacologic treatments of pain after spinal cord injury. *Archives of Physical Medicine and Rehabilitation*, *91*(5), 816-831.

Van Gorp, S., Kessels, A. G., Joosten, E. A., Van Kleef, M., & Patijn, J. (2015). Pain prevalence and its determinants after spinal cord injury: A systematic review. *European Journal of Pain*, *19*(1), 5-14.

Vowles, K. E., McEntee, M. L., Julnes, P. S., Frohe, T., Ney, J. P., & van der Goes, D. N. (2015). Rates of opioid misuse, abuse, and addiction in chronic pain: A systematic review and data synthesis. *Pain*, *156*(4), 569-576.

Widerström-Noga, E. G., & Turk, D. C. (2003). Types and effectiveness of treatments used by people with chronic pain associated with spinal cord injuries: Influence of pain and psychosocial characteristics. *Spinal Cord*, *41*(11), 600-609.

Appendix 3

Data Extraction Sheet

Citation (Lead author & year)	
Age (years)	
Country	
Gender	1. Male 2. Female
Relationship Status	3. Married/defacto 4. Divorced/separated/widowed 5. Single
Education Level	6. Primary 7. Secondary 8. Tertiary
Employment Status	9. Employed 10. Unemployed 11. Student 12. Retired 13. Full-Time 14. Part-Time 15. Volunteer
Time Since Injury (Years)	
Type of SCI	16. Tetraplegic 17. Paraplegic 18. Unknown
Completeness of Injury	19. Complete 20. Incomplete 21. Unknown
Nature of Injury	22. Traumatic 23. Non-traumatic 24. Unknown
Cause of Injury	25. MVA 26. Falls 27. Sport-related 28. Violent 29. Other
Treatment Facility (e.g., Outpatient)	
Opioid Use Measure	30. Average Daily Dose 31. Self-report Usage 32. ICD10 Diagnosis 33. No. Prescriptions Filled
Data Set Source	
Ethnicity	34. White 35. Black 36. Native American 37. Hispanic 38. Asian/Pacific Islander 39. Other/Unknown
Proportions (Effect Size)	40. Number of Participants Prescribed Opioids versus Total Number of Participants

Appendix 4

Data extraction summary table

Table 4

Study characteristics, participant demographic and SCI characteristics per study

Lead author (date)	Country	*N* (M:F)	Mean age (SD)	Mean time (years) since injury (SD)	SCI type	Opioid measure
Brose (2019)	US	-	-	-	-	avg daily dose based on prescriptions
Carbone (2013)	US	7447:0	57.96 (12.84)	-	TSCI	avg daily dose based on prescriptions
Carbone (2020)	US	7989:849	54.39 (12.98)	-	TSCI/NTSCI	avg daily dose based on prescriptions
Cardenas (2006)	US	85:32	48.80 (11.70)	-	TSCI	self-report prescribed use
Graupensperger (2019)	US	3368:2824	-	-	-	ICD10 diagnosis
Hand (2018)	US	720:734	46.05 (12.65)	-	-	prescriptions filled
Hatch (2018)	US	12948:494	-	-	TSCI/NTSCI	prescriptions filled
Heinemann (1991)	US	59:27	39.50 (-)	13.10 (10.20)	TSCI	self-report prescribed use
Krause (2019)	US	3466:1204	-	-	-	self-report non-prescribed use
Margolis (2014)	US	3866:3182	48.25 (12.85)	-	TSCI/NTSCI	prescriptions filled
Raut (2018)	US	22:6	47.95 (-)	-	NTSCI	self-report prescribed use
Rouleau (2011)	Canada	97:54	-	-	TSCI/NTSCI	prescriptions filled
Tate (2016)	US	215:76	50.70 (12.50)	20.00 (10.50)	TSCI	self-report prescribed use
Warms (2001)	US	-	42.30 (13.31)	7.50 (-)	TSCI	self-report prescribed use
Widerström-Noga (2003)	US	94:26	40.60 (12.10)	9.80 (5.20)	-	self-report prescribed use

Note: (-) data not reported or available, US = United States, TSCI = traumatic spinal cord injury, NTSCI = non-traumatic spinal cord injury, mixed = sample included inpatients and outpatients

Appendix 5

STROBE evaluation for each study

Table 5

Evaluation of included studies using the STROBE checklist

	Title & Abstract	Intro	Methods																Results													Discussion					
Lead author (year)	1a. Reference to study design	1b. Informative & balanced summary	2. Scientific background and rationale	3. Objectives/prespecified hypotheses	4. Key elements of study design	5. Setting/location/dates described	6. Participants' eligibility criteria	7. Key variables/outcomes defined	8. Variable measurements described	9. Efforts to address potential bias	10. Explanation of study size	11. Cut-offs, groups etc. explained	12a. Statistical methods explained	12b. Subgroup analyses and interactions	12c. Missing data management	12d. Stats account for loss to follow-up	12e. Sensitivity analyses	13a. Participant no.s per stage	13b. Reasons for non-participation	13c. Flow diagram provided	14a. Participant characteristics	14b. No. pp's missing data per variable	15 Summary data per measure	16a. Estimates & intervals (i.e., CIs)	16b. Categorical variables explained	16c. Relative: absolute risk estimates	17. Other analyses reported	18. Key results examined	19. Limitations discussed	20. Cautious interpretation of results	21. Generalisability of results explained	22. Funding source(s) listed	Total (0-64)
Brose (2019)	●	◖	●	◖	◖	●	◖	●	●	○	◖	◖	●	○	○	●	○	●	○	○	○	○	◖	○	○	○	○	●	●	◖	○	◖	29
Carbone (2013)	●	●	◖	●	○	●	◖	●	●	◖	◖	●	●	○	●	○	●	●	○	○	●	●	●	●	◖	○	○	●	●	●	○	◖	42
Carbone (2020)	●	●	◖	●	●	●	●	●	●	◖	◖	●	●	◖	●	●	●	◖	○	○	●	◖	●	●	◖	○	●	●	●	●	◖	○	48
Cardenas (2006)	●	●	●	◖	◖	◖	●	●	●	○	◖	○	○	○	○	○	○	●	●	○	●	○	●	●	◖	○	○	●	●	●	◖	○	34
Graupensperger (2019)	●	●	●	●	●	●	●	●	●	◖	●	●	●	○	○	●	○	●	○	○	●	○	●	●	●	○	○	●	●	●	●	●	47
Hand (2018)	●	●	●	●	●	●	●	●	●	◖	◖	●	◖	○	○	◖	○	●	●	◖	●	○	●	●	●	◖	○	●	●	●	◖	○	45
Hatch (2018)	●	●	●	●	●	●	●	●	●	○	●	●	●	◖	○	◖	○	●	●	●	●	○	●	●	●	◖	◖	●	●	●	◖	○	49
Heinemann (1991)	○	◖	●	●	○	◖	●	●	●	◖	◖	●	○	○	○	○	○	●	●	○	○	○	●	○	○	○	○	●	○	●	●	○	28
Kraus (2019)	●	◖	●	●	◖	●	●	●	●	○	●	●	●	◖	○	●	○	●	○	○	●	◖	●	●	●	◖	◖	●	●	●	◖	●	47

(Continued on next page)

Table 5 (cont)

Evaluation of included studies using the STROBE checklist

	Title & Abstract	Intro	Methods												Results														Discussion					
Lead author (year)	1a. Reference to study design	1b. Informative & balanced summary	2. Scientific background and rationale	3. Objectives/prespecified hypotheses	4. Key elements of study design	5. Setting/location/dates described	6. Participants' eligibility criteria	7. Key variables/outcomes defined	8. Variable measurements described	9. Efforts to address potential bias	10. Explanation of study size	11. Cut-offs, groups etc. explained	12a. Statistical methods explained	12b. Subgroup analyses and interactions	12c. Missing data management	12d. Stats account for sample strategy	12e. Sensitivity analyses	13a. Participant no.s per stage	13b. Reasons for non-participation	13c. Flow diagram provided	14a. Participant characteristics	14b. No. pp's missing data per variable	15 Summary data per measure	16a. Estimates & intervals (i.e., CIs)	16b. Categorical variables explained	16c. Relative: absolute risk estimates	17. Other analyses reported	18. Key results examined	19. Limitations discussed	20. Cautious interpretation of results	21. Generalisability of results explained	22. Funding source(s) listed	Total (0-64)
Margolis (2014)	●	●	●	●	●	●	●	●	◖	◖	◖	●	●	◖	○	●	○	●	○	○	●	○	●	●	●	○	●	●	●	◖	◖	○	44
Raut (2018)	●	●	●	●	●	●	●	●	◖	○	●	◖	●	◖	○	○	○	●	○	○	●	○	●	◖	◖	○	●	●	●	●	◖	○	40
Rouleau (2011)	●	◖	●	●	○	●	◖	○	○	○	○	◖	○	○	○	○	○	●	○	○	○	○	●	○	○	○	○	●	○	●	○	○	19
Tate (2016)	●	◖	●	●	◖	◖	●	●	◖	○	◖	●	●	◖	○	●	○	●	●	●	●	●	●	●	○	◖	●	●	●	●	○	○	45
Warms (2001)	●	◖	●	●	◖	●	●	●	◖	○	◖	◖	●	◖	○	○	○	●	○	○	●	○	●	○	○	○	●	●	●	●	◖	○	35
Widerström-Noga (2003)	●	◖	●	●	◖	◖	●	●	◖	○	●	●	●	●	○	●	○	●	●	○	●	○	●	●	○	○	●	●	●	●	○	●	44
Total *(% met)*	93	76	93	93	60	86	90	90	76	20	63	80	76	33	13	13	13	96	40	16	80	20	96	70	46	13	46	100	86	93	40	26	

Scoring criteria: ● = Present (score of 2); ◖ = present with limitations (score of 1); ○ = absent or unable to determine (score of 0).
Abbreviations: CI = Confidence interval; Intro = Introduction; No. = number; Pp's = participants