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Characterizing the Interrelationships of Prescription Opioid and Benzodiazepine Drugs With Worker Health and Workplace Hazards

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Abstract

Objective—Prescription opioid and benzodiazepine drug use, which has risen significantly, can affect worker health. Exploration of the scientific literature assessed (1) interrelationships of such drug use, occupational risk factors, and illness and injury, and (2) occupational and personal risk factor combinations that can affect their use.

Methods—The scientific literature from 2000 to 2015 was searched to determine any interrelationships.

Results—Evidence for eight conceptual models emerged based on the search yield of 133 articles. These models summarize interrelationships among prescription opioid and benzodiazepine use with occupational injury and illness. Factors associated with the use of these drugs included fatigue, impaired cognition, falls, motor vehicle crashes, and the use of multiple providers.

Conclusion—Prescription opioid and benzodiazepine drugs may be both a personal risk factor for work-related injury and a consequence of workplace exposures.

The sale of prescription opioid drugs increased almost four-fold between 1999 and 2014,[1] while the percentage of adults filling a benzodiazepine prescription each year saw an increase of about 30% between 1996 and 2013.[2] Although data from recent years show a small reduction in prescriptions issued for opioids,[3] the United States continues to be in the midst of a prescription opioid overuse epidemic.[4,5] Indeed, prescription opioids and benzodiazepines are commonly coabused[6–8] and overlapping opioid and benzodiazepine prescriptions have been found to be associated with the potential to use or prescribe these medications inappropriately.[9–12]

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Prescription drug (PD) use involving opioids and/or benzodiazepines is increasingly becoming recognized as a factor that merits investigation.[1,3–5,8,13,14] An improved understanding of the medically sanctioned or "appropriate" use of prescription opioid and/or benzodiazepine medications is important to better understand issues of overuse and abuse, as using these PDs, particularly in combination, is associated with an increased risk of addiction and death from overdose.[6,14,15] Providers may prescribe these drugs to workers in a medically appropriate manner in order to manage occupational and nonoccupational illnesses and injuries.[16,17]

Schulte et al[18] have described the use of conceptual, heuristic models to describe the combined effect of occupational risk factors (ORFs) and personal risk factors (PRFs) on health outcomes.[19] Although such models may require further research and testing in order to optimally elucidate the mechanisms upon which to base prevention and informed interventions, these models function to illustrate known or theorized relationships. As regards to PD use, the question arises as to the interrelationships of this use with ORFs, and illness and injury, and occupational and PRF combinations that can affect this use. In order to consider such relationships in this context, evaluating the evidence regarding occupational and nonoccupational factors that can affect PD use is fitting. Such models may inform the development of a more comprehensive, preventive, approach toward workers achieving a longer, healthier, work life.[18] To this end, conceptual, heuristic models are presented, within the context of the theoretical framework proposed by Schulte et al,[18] Pandalai et al,[19] and colleagues, which describe the combined effect of ORFs and PRFs on PD use.

Recent occupational health and safety literature reveals that the use of these drugs may negatively affect the performance of safety-sensitive tasks at work such as driving or operating machinery[20–22] and that using these drugs, in combination, increases workers' compensation costs.[8] In addition, the use of one or both classes of these drugs may be initiated or escalated in the treatment of occupational injuries or illnesses.[8]

Guidance, by various organizations regarding appropriate PD use and workplace safety, continues to evolve. The American Pain Society advises that patients should be counseled regarding transient or lasting cognitive impairment that may affect driving and work safety when opioids are used.[20] The American College of Occupational and Environmental Medicine (ACOEM) Evidence-based Practice Opioids Panel advises comprehensive monitoring for adverse effects that may be seen with opioid use.[21] The ACOEM Practice Guidelines recommend preclusion of opioid use in safety-sensitive jobs and that caution should be used when prescribing other depressant medications such as benzodiazepines.[22]

An enhanced understanding the interrelationships of PD use with ORFs, and illness and injury, and occupational and PRF combinations that can affect this use, may help to target the development of relevant preventive measures and determine their effectiveness. A primary approach to prevention may be taken by recognizing and modifying situations that may lead to an increased chance of a PD being prescribed, such as occupational injury or illness due to a musculoskeletal disorder or increased stress at work. Secondary efforts at prevention may involve mitigating occupational situations associated with an increased risk for injury or disability when PDs are used by workers, such as while performing safety-

sensitive tasks. Tertiary efforts at prevention may involve identifying occupational situations, which potentially foster increased and/or inappropriate PD use. This paper has two objectives: (1) to assess the interrelationships of how PD use, combined with ORFs, affects illness and injury, and (2) to assess occupational and PRF combinations that can affect PD use.

METHODS

The scientific literature was searched using PubMed. English language primary literature (original research articles) and secondary literature (review articles) from 2000 to 2015 were reviewed. The objective was to find scientific evidence that would potentially support models involving the interrelationships of PD use, ORFs, and illness and injury, as well as ORF and PRF combinations that can affect PD use. The search strategy did not a priori rely on evidence from scientific studies conducted solely in the occupational setting, as nonoccupational literature may inform on potential outcomes in the occupational setting, and as such be of relevance. Indeed, risk factors in the workplace can contribute to health problems unrelated to work and vice versa. PD use can arise out of work as well as through nonwork-related factors and can affect work just the same. This search strategy served two purposes: 1) to allow an evaluation of how the nonoccupational literature may inform problems in the occupational setting; and 2), to gauge the current state of how researchers and clinicians publishing their research are evaluating ORFs and PRFs in the literature. For example, on the one hand, ORFs and PRFs could be the focus of studies and other activities that evaluate both types of factors. However, information on these factors could be found in separate published studies, not examined in a combined fashion. Hence, this approach allows for evaluation of relevant occupational and non-occupational literature in the search for risk factors that may affect the health of working populations.

The concept of evaluating multiple risk factors to develop heuristic models through the use of studies from both the occupational and nonoccupational published literature is based on prior work.[18,19] The models are not meant to be definitive causal pathways but rather heuristics for relationships that may warrant further investigation. They do not delineate specific molecular, cellular, organ, or system-level causal pathways, etiologic steps, epidemiological mechanisms, or statistical relationships with respect to illnesses or injuries.

A two-phase approach literature search, based on previous work by Schulte et al,[18,19] was employed. During the first phase, both occupational and nonoccupational literature was drawn upon to compile a pool of potentially relevant information. Pair-wise search of terms representing both the occupational and nonoccupational issues related to a risk factor using the “AND” Boolean operator were employed. The terms used were identified by examining Medical Subject Heading (MeSH) lists related to the factor of interest, keyword lists of pertinent reviews, and author team and subject matter expert consultation. These search results were then combined using the “OR” Boolean operator. This allowed the collection of a first pool of literature, which contained publications from occupational and nonoccupational domains related to PD use and health outcomes.

During the second phase, a more tailored subset of the first phase of literature results was developed. The first phase search results were examined for terms, which suggested occupational or PRFs. The search was further expanded in a focused manner if publications suggested that other literature was seminal or foundational and should be evaluated.

Finally, the resultant pool of literature was reviewed to ensure that the publications used in the construction of heuristic models had some measure of effect to be considered for constructing the models, as such studies suggest a degree of rigor. The exact measure of effect size was not calculated in the development of these heuristic models, as the overall search strategy to assess multiple risk factors used to inform the heuristic models is qualitative at this stage. One of the key issues in evaluating evidence for or against associations of risk factors and outcomes is bias in publication; however, formal, statistical assessment of publication bias is not within the scope of this work. The most conservative approach was to include all publications. The result is a qualitative, evidence-based, consideration of the literature allowing the identification of multiple risk factors found in the studies. Using such evidence resulted in the creation of conceptual, heuristic, models, which may allow a better understanding of the interrelationships of PD use, ORFs, and illness and injury, as well as ORFs and PRF combinations that can affect their use.

Parameters Used for the Literature Search

The first search used the terms of opioid, benzodiazepine, and occupational and nonoccupational health outcomes[4,5] (Fig. 1). A literature search on PD use by workers in specific occupations and on workers' return-to-work status after work injury was also conducted during this phase. A list of terms related to opioid/benzodiazepine use, occupational health, and health outcomes, as well as risk factors for opioid/benzodiazepine use and outcomes as a result of opioid/benzodiazepine use was identified. This was done by examining MeSH, keyword lists from review articles on prescription opioid/benzodiazepine use, and by consulting with subject area experts. The literature was then searched for potential examples of primary, secondary, and tertiary prevention of outcomes related to PD use and keyword lists from related publications. During this phase, each term for PD use was paired with occupational health terms, and health outcomes, both occupational and nonoccupational, using the "AND" Boolean operator. The results for each of these paired searches were combined with the "OR" Boolean operator. The terms included in the search from keyword lists and MeSH terms for the results of searches on primary, secondary, and tertiary prevention of adverse health effects due to PD use were also searched in pairs with the "AND" Boolean operator and then combined with the "OR" Boolean operator. Search results from the pairing of PD use terms and workers in specific occupations, and from PD use and workers' status after work injury terms, both using the "AND" Boolean operator, were also included in the pool of literature at this phase using the "OR" operator.

This first phase, which yielded 1825 publications, formed the foundation of literature on which this research is based. The risk factors and/or outcomes for PD use identified during this first search were fatigue, injury, age, disability, substance abuse, low income, and multiple providers.

The second literature search was conducted pairing PD use, in either the occupational or nonoccupational setting, with the risk factors and/or outcomes that were identified during the first search. Some search terms yielded no results, namely PD use before occupational injury and PD use associated with incident occupational injury. These iterative methods resulted in the identification of 713 publications. This pool served as the base for a targeted literature search to find articles where a measure of effect was found to support a relationship that could be modeled through the heuristic framework proposed. The final pool used in construction of the models included 133 sources (Fig. 1).

Rationale Behind Development of the Models

Selection of sources for this research was based upon the consideration of four basic conceptual models that were originally proposed by Schulte et al[18] as a theoretical framework for considering the health of working people in a comprehensive manner. Templates used to develop the models are found in Fig. 1. The models consider PD use as a PRF affecting health and safety outcomes in the workplace when it acts with an existing ORF resulting from workplace exposures. Models also consider the combination of various PRFs and ORFs in the workplace that affect PD use.

These heuristic models are intended to suggest considerations for prevention or intervention, and potentially for future research and policy development. Evidence found that supports models other than the four heuristic types, is discussed as appropriate. With an eye to future research and knowledge gaps, search terms that did not yield any published literature are also discussed. Indeed, as the research evolves, alternate models for sets of factors and outcomes may be developed.[23]

The body of evidence supporting the importance of a nonwork-related factor for PD use needs to be considered when examining any potential impact of PD use on the occupational setting or the importance of their use to the occupational setting even if the results of such studies are not necessarily extrapolated to the occupational setting. This approach continues the methodology developed in previous work that evaluated the inter-relationships of multiple factors with health outcomes in the occupational setting.[18,19]

Method Used to Evaluate and Grade the Literature Used to Support Models

Articles supporting models developed in this research were identified. Each article was classified according to study design. Categories used were experimental, cohort, case crossover, case control, cross-sectional, case report/series, and meta-analysis, as well as literature review and discussion articles (Fig. 2). Each study was then given a score of I, II, or III based upon the criteria used in the *Methodology to Update the Recommendations in the American College of Occupational and Environmental Medicine's Practice Guidelines*[24] and *ACOEM Practice Guidelines for Opioids and Safety Sensitive Work*.[22] Score "I" was used for experimental studies. Score "II" was used for cohort studies, prospective comparative studies, case-crossover, and large population-based studies. Score "III" was for retrospective, case–control, or cross-sectional studies. Review and discussion articles were also given a score of "III." Scores for specific groups of studies are available upon request from the authors.

RESULTS

The health outcomes associated with overall PD use were identified and paired with activities, which may occur both at work and outside of work. These findings were then modeled according to the framework proposed by Schulte et al,[18] which considers the interplay of occupational and PRFs to address overall worker health. Although many health outcomes associated with PD use were identified, only those, which could be theorized to function in the previously proposed models, were further explored in this project. Figure 2 depicts the number of studies in each study design category on which the heuristic, conceptual models presented are based.

The following models show that the use of opioids and benzodiazepines has the potential of being a PRF for adverse outcomes in the occupational setting. The use of opioids and benzodiazepines was also found to be potentially precipitated by occupational situations. The term PD is used when referring to opioid and/or benzodiazepines. This distinction is being made, as some studies focus on both classes of medications while others focus on only one or the other medication. Evidence may be relevant for health outcomes having an association with each of the classes of drugs, or with the combined use of the drugs.

Workplace Situations in Which Opioid or Benzodiazepine Use, as a Personal Risk Factor (PRF), May Combine With Occupational Risk Factors (ORF) to Affect Injury or Illness

Model 1.1: PD Use Acting Independently Along With Shiftwork to Produce Decreased Psychomotor Performance—The use of both opioids and benzodiazepines has been found to be associated with psychomotor slowing.[25–28] Drowsiness has been reported by patients taking opioids for nonmalignant pain in cross-sectional studies,[26,27] and fatigue and somnolence reported by 15% to 30% of patients on benzodiazepine therapy.[29] In a randomized controlled trial (RCT) examining driving tests among healthy male subjects ages 25 to 35 years, the administration of a single 2mg dose of lorazepam showed an increase in lane-keeping variables, such as inappropriate line crossings and weaving of the vehicle where there was deviation from a steady lateral position in the slow lane of the road, when compared with those administered placebo ($P < 0.001$).[30] Psychomotor performance in the Digit Symbol Substitution Test (DSST), which measures total number of symbols drawn and drawn correctly and eye-hand coordination, was impaired when 0.5 mg of alprazolam and 10 mg of oxycodone, (usual therapeutic doses) were given together.[31] Furthermore, short-term and long-term memory were impaired by alprazolam in this study.

An experimental study among methadone maintained individuals revealed that participants exhibited poor performance on tasks of psychomotor speed, especially during the initial phases of therapy.[32] The tests used in this study were the Continuous Performance Task (CPT) designed to assess selective attention and impulsivity and the DSST described earlier. Methadone maintained participants exhibited slower reaction times (RTs) on correct responses on the CPT ($F_{[1,33]} = 7.68$; $P = 0.009$), and completed fewer accurate substitutions on DSST ($F_{[1,33]} = 6.07$; $P = 0.019$), than healthy controls.

In another experimental study, long-term opioid therapy (use >3 months) for chronic back pain was associated with a reduction in reduced spatial memory capacity, cognitive

flexibility for concept change, and performance in working memory assessment, in patients treated for chronic back pain, when compared with healthy controls and with patients with similar chronic low back pain (LBP) who did not take opioids.[33] In this study, a longer time in information processing was noted among the opioid users than both comparison groups. Although this study was limited by small numbers in each group and may have limited external validity given the specific nature of testing, reviews of the most prevalent cognitive effects of long-term therapy include memory deficits.[34,35]

Sleep loss associated with shiftwork may also produce notable effects on fatigue including difficulty concentrating[36] and with other aspects of performance such as reaction speed and accuracy, vigilance, and hand-eye coordination.[37] Visual psychomotor vigilance testing in an experimental study revealed increased RTs among both regular shift workers and nonshift workers throughout a sleep deprivation night.[38] Significant increases were observed for median RT ($F_{[7,134]} = 2.6$, $P < 0.05$), mean slowest RT ($F_{[7,134]} = 3.2$, $P < 0.01$), and the number of lapses ($F_{[7,134]} = 3.4$, $P < 0.01$). When individuals working regular night shifts and working rotating shifts were selected from a community-based sample and compared with day workers, an association was demonstrated between accidents and presence of sleepiness symptoms related to shiftwork ($F_{[1,2438]} = 15.55$, $P < 0.001$).[39] A large community study involving telephonic interviews of 3345 New York residents revealed that working outside the regular daytime hours in either fixed night or rotating shifts was strongly associated with sleepiness [odds ratio (OR) = 3.3, 95% confidence interval (95% CI): 1.9 to 6.0) and OR = 1.5 (95% CI: 1.0 to 2.2)], and driving accident risk [OR = 3.9 (95% CI: 1.5 to 10.6) and OR = 2.1 (95% CI:1.0 to 4.8)].[40] Experimental studies show that working before 6 AM or after 10 PM on the previous day is associated with poorer performances in immediate free recall ($P = 0.029$), delayed free recall ($P = 0.021$), and selective attention ($P = 0.032$),[41] and that RT is affected by the time spent awake during night shifts ($P < 0.01$) and by accumulated sleep debt during morning shifts ($P < 0.05$).[42]

Whether shift workers are more likely to use opioids and benzodiazepines than nonshift workers was not found to be a significant focus of studies in the literature reviewed, with the exception of one study conducted among a group of Italian police officers, which failed to show any association between shiftwork and the use of benzodiazepines and other hypnotics. A self-report questionnaire was utilized in this study.[43] There was a lack of corroborating studies to address this relationship.

Approximately one half of the studies supporting a model where both shiftwork and PD use affect psychomotor performance were rated as having high-quality evidence. The remaining half of the studies with supporting evidence were cross-sectional or case– control studies. They supported an association between either shiftwork or PD use and decreased psychomotor performance. On the basis of the nature and magnitude of this evidence, these two factors together, namely shiftwork and PD use, suggest a model with combined effects on decreased psychomotor performance (Table 1).

Model 1.2 PD Use Acting to Modify Risk for Motor Vehicle Crashes (Mvc) With Occupational Transportation and Material Moving—The ACOEM practice guidelines on opioid and safety-sensitive work, updated in 2014, reveals risk estimates

ranging from 29% to greater than 800% for an increased risk of motor vehicle crashes (MVCs) when drivers use both strong and weak opioids.[22] The guidelines do not recommend acute or chronic use of opioids for persons who perform safety-sensitive jobs. This includes motor vehicle operation. This recommendation is based on the association found between PD use of opioids and increased risk of MVC in many epidemiological studies.[44–55] A meta-analysis of epidemiological and experimental studies has also shown that benzodiazepine use is associated with increased MVC [OR = 1.61 (95% CI:1.21 to 2.13), $P < 0.001$ for case–control studies; OR = 1.60 (95% CI:1.29 to 1.97, $P < .0001$) for cohort studies], as well as increased deviation of a steady lateral position on the slow lane of the road in driving tests [standardized mean difference 0.80 (95% CI: 0.35 to 1.25), $P = 0.004$].[56]

Highway transportation incidents are the leading cause of occupational fatalities in the United States.[57,58] Fatality data show that across all industries, motor vehicle related incidents are consistently the leading cause of work-related fatalities in the United States, and they are the first or second leading cause of these fatalities in every National Occupational Research Agenda (NORA) sector.[59] Workers employed in transportation and material moving occupations are at the highest risk of fatality.[57]

Few studies have specifically examined occupational MVC with respect to PD use. However, in one case–control study of drivers operating a single or combination-unit heavy truck, with a gross vehicle weight rating of greater than 26,000 pounds or with a truck-tractor (cab only, or with any number of trailing units; any weight), the use of opioid analgesics was associated with a greater odds of committing an unsafe driving act (OR = 2.80, 95% CI:1.64 to 4.81).[60] Other studies have identified that a variety of organizational processes combined with PD use of opioid and/or benzodiazepine medications may produce error or violation conditions in the workplace that, when combined with other factors, may subsequently precipitate driver accidents.[61] Three studies scored II according to methodology based on *ACOEM Practice Guidelines*.[22]

This evidence informs the conceptual model that outlines the relationship of PD use and MVC in the transportation and material moving workplace setting (Table 1).

Model 1.3: Occupational Use of Ladders Affecting the Risk of Falls With PD use—Trips and falls have been shown to account for approximately one quarter of all nonfatal occupational injuries resulting in days away from work, and over 14% of fatal occupational injuries.[62,63] Approximately 20% of occupational falls among workers involve ladders: 80% among construction workers. The construction industry had the highest fatal ladder fall injury rate compared with all other industries, as revealed by data from the US Bureau of Labor Statistics in 2011. An analysis of workers' compensation records among health care workers in British Columbia revealed that frequent use of ladders was thought to be the factor that explained the increased relative risk of falls among facility support workers compared with registered nurses [risk ratio (RR) = 6.29, 95% CI: 4.56 to 8.69].[64] Areas for intervention may lie in the occupational realm and may be extrinsic, for example, ladder safety training at work, or may be intrinsic, for example, related to individual factors such as PD use.[62,63]

Although there were no studies identified documenting PD use specifically in the context of a work-related fall, there is evidence to indicate that both opioid and benzodiazepine medications have been associated with increased risks of falls.[65–78] Altered balance and postural control was thought to be a factor in a study among 20,551 veterans compared with an age and sex-matched comparison group, which found that more patients with a fall coded encounter used opioid analgesics (11.21% vs 9.09%), and benzodiazepines (7.60% vs 5.96%), $P < 0.002$.[65] Increased risk of fall-related injury was found to be pronounced among young subjects (18 to 25 years old), when dispensed an opioid within 28 days before injury using a case crossover study design where groups of opioid-naive patients functioned as their own controls (OR = 7.17, 95% CI: 5.04 to 10.2).[73] Increased fracture risks ranging from 1.4- to 5-fold in users of opioid analgesics have been reported in epidemiologic studies,[72–76] with just one prescription use (multivariable adjusted OR = 2.70, 95% CI: 2.34 to 3.13), suggesting that central nervous system (CNS) effects such as sedation and dizziness leading to falls contribute to fractures more so than long-term effects on bone metabolism, which may also occur with opioid use.[70]

Many of the studies identified to support a conceptual model in which PD use of opioids and/or benzodiazepines impacts the risk of falls were prospective cohort or case crossover studies and therefore scored II according to the *ACOEM Practice Guidelines*.[22] Retrospective cohort, cross-sectional, case–control, and review studies (scored III) also support this relationship. The incidence of falls within the workplace is documented by one prospective cohort (scored II), one cross-sectional, and one review article (scored III) in this search. However, no research was identified that examined the association between the number and severity of falls in workplace situations and PD use by calculating or examining measures of effect. A model that suggests PD use of opioid and benzodiazepine medications, whether alone or in combination, may be associated with a workplace activity such as falls from ladders is supported (Table 1).

Model 1.4: PD use is Associated with Increased Claim Costs: PD Use is also Associated With Use Of Multiple Providers; Multiple Providers and Occupational Low Back Pain are also Associated With Health Care Cost—PD use has been associated with higher occupational injury claim costs, both medical only and indemnity. Concomitant use of benzodiazepines was found to be associated with a higher likelihood of high-dose opioid prescriptions (OR = 1.75, 95% CI:1.42 to 2.16) in a cross-sectional study involving the Kaiser Permanente Northwest (KPNW) region[79] as well as an increased cost of claims (≥$100,000) in a cohort study involving 11,394 lost time claims filed with the Louisiana Workers' Compensation Corporation (LWCC), (OR = 2.74 benzodiazepine use alone, 4.69 benzodiazepine and short-acting opioids, 14.24 benzodiazepine and long-acting opioids).[8] Another analysis using the LWCC data showed that compared with claimants who were never prescribed opioids, the odds of having claim costs at least $100K were higher in those using short-acting opioid (OR = 4.3, 95% CI: 3.49 to 5.33), long-acting opioids (OR = 8.6, 95% CI: 6.32 to 11.61), and with any use of anti-anxiety agents (OR= 1.6, 95% CI:1.29 to 1.92).[80]

An association has also been found between the use of opioid medications alone or with benzodiazepines, and obtaining prescriptions from multiple providers.[81–84] Individuals who

used more than five different prescribers for prescriptions obtained in a calendar year also obtained three- to six-fold more cumulative morphine-equivalent amounts of Schedule II opioid per individual per year than the general population.[82] Avoiding the prescribing of high doses of opioids in the state workers' compensation system of Washington State has been associated with a decline in opioid overdose deaths,[85] although a substantial risk for serious opioid-related toxicity and overdose still exists at even relatively low maximum prescribed daily morphine equivalent doses.[86] Obtaining prescriptions from multiple providers has been shown to be a significant additional factor associated with opioid overdose deaths.[16,17,87,88] PD use, whether prescribed or associated with misuse, may also be associated with higher rates of seeing multiple providers through emergency room (ER) utilization.[89–92] The CDC has identified the use of multiple providers as a risk for opioid misuse and abuse,[93] and recommends that this parameter should be monitored in guidelines for safe prescribing of opioids.[16,88,94]

Opioids are commonly prescribed for LBP,[80,95–104] and their use by such patients adds substantial cost to health plans.[8,96–103] Occupational LBP has been found to be associated with substantial indirect health care costs due to lost work productivity in both reviews[95,105] and case–control[96] studies. LBP occurs in 42.6% of all U.S. workers 40 to 65 years of age, and workers with LBP exacerbations account for 71.6% of lost work time costs.[105] More than half of regular opioid users report back pain, and rates of per capita use of potent opioids are higher in North America than in other developed countries.[105] The analgesic efficacy of opioids for acute back pain is inferred from evidence in other acute pain conditions.[95] Opioids are not demonstrated to expedite "return to work" in injured workers or improve functional outcomes of acute back pain in primary care.[100–104] The use of opioids for more than 7 days ($P = 0.013$) was found to be significantly associated with lost time and increased costs among randomly selected claims of occupational LBP from workers' compensation data, which represented approximately 8% of the private US workers' compensation market in 44 state jurisdictions and the District of Columbia.[97]

The use of multiple providers was also found to be significantly associated with increased costs through increased utilization of specialty referrals ($P = 0.013$) and provider visits ($P < 0.001$) in this study. In addition, when opioids were dispensed directly by physicians, rather than pharmacies, 78% higher medical costs, 57% higher indemnity costs, and 85% higher frequency of lost-time days were incurred.[106] The use of a small, integrated network of providers had a positive effect on the duration of lost-time and workers' compensation costs in a case–control study, compared with patients treated within an integrated provider network to those treated by several providers without integrated management of the cases,[107] consistent with other data.[108] The study compared cases treated out of system to those treated in system for average and median costs of the 25 ICD-9 codes with the highest mean costs. The average and median costs for cases treated outside the system was $12,542 and $5793, whereas the average and median costs for cases in system was almost half as expensive—$6749 and $3015. The authors estimated that only a small part of this difference could be attributed to discounted medical payments to in network providers ($120), even when assuming all medical expenses out of network were not subject to discount. The mean differences were also statistically significant ($P < 0.01$) for lost-time days. The average and

median number of lost-time days for cases out of system were almost twice as high (95.0 and 58.0 out of system and 53.4 and 34.0 with a small in network of providers).

These data form the basis on which a model considering the impact of PD use on increased claim costs may be further exacerbated by (1) the association of PD use with use of multiple providers, (2) the association of multiple providers with increased claim costs; and (3) the association of occupational LBP with increased claim costs, is constructed. This model is supported by three prospective cohort studies, which scored level II, and 29 studies that scored level III.

Workplace Situations in Which Occupational Risk Factors (ORF) may Combine With Other Personal Risk Factors (PRF) to Contribute to Use of Opioid and Benzodiazepine Medications

Model 2.1 Psychosocial Stress at Work and Advancing Age Combine to Impact PD Use—

Psychosocial stress is often encountered in the workplace.[109] Elements of psychosocial stress such as job insecurity[110] and high demand/low control jobs[111] are associated with generalized anxiety disorder[110,111] and depression[110] in both cohort[111] and cross-sectional[110] studies. Reviews have reported that behavioral intervention are variably successful, and benzodiazepines are often prescribed to manage inadequately alleviated anxiety due to high job demand.[112–114] In the Tyrolean Workplace study, increased consumption of drugs labeled as “analgetics” and “tranquilizers” was associated with an atmosphere at work perceived as bad (12.6%) versus good (3.7%; $P = 0.019$). Similarly, low job satisfaction was associated with increased usage of these drugs (42.9% vs 3.3% with high job satisfaction, $P = 0.001$).[115] Workplace bullying was found to be strongly positively correlated with use of psychotropic medication, including benzodiazepines, in a large cross-sectional study of working individuals in France ($P < 0.001$).[116] This study also showed that the prevalence of drug use increased with age.

Increased use of benzodiazepines with age was also documented in a retrospective descriptive analysis using pharmacy data, which included 60% of the US population. In 2008, approximately 5.2% of US adults aged 18 to 80 years used benzodiazepines with highest utilization seen in age groups 51 to 64 years (7.4%) and 65 to 80 years (8.7%).[117] The U.S. Bureau of Labor Statistics projects an increase in the percentage of the workforce aged 55 years and older from around 20% in 2012 to more than 25% in the subsequent 10 years.[118] Older Americans are working for longer time periods, sometimes moving to another job after retirement. Among older individuals, benzodiazepines use poses the risk of serious adverse effects, including impaired cognitive functioning (multivariable adjusted hazard ratio = 1.60; 95% CI: 1.08 to 2.38),[119] and increased risks of hip fracture from falls especially during the first 2 weeks after starting benzodiazepines (incidence rate ratio = 2.05; 95% CI: 1.28 to 3.28).[120] A review article identified 66 studies, published between 1960 and June 2009, which reported a relationship between benzodiazepines and traffic injury or accident risk ($n = 36$; 54%), responsibility or culpability in accidents ($n = 13$; 20%), injury or accident severity ($n = 16$; 24%), or other outcomes (ie, impairment or mortality, $n = 8$; 12%).[121] A model in which psychosocial stress encountered at work combines with the PRF of increasing age to produce an increased likelihood of being

prescribed benzodiazepines (Table 2) is supported by 13 studies, two of which are prospective cohort and score II. However, the majority of evidence to support this model is based upon cross-sectional review, or retrospective cohort studies, which are given a score of III. The degree to which each of the factors contributes to the likelihood of PD use of benzodiazepines is another model suggested by the literature.

Model 2.2: The Occupational Risk Factor of Workplace Ergonomic Demands is Modified by the Personal Risk Factor of Musculoskeletal Disorders to Impact PD Use—Occupational factors such as workplace ergonomic hazards may impact opioid use. In a double-blinded RCT, acute administration of the opioid analgesics fentanyl (1 μg/kg) resulted in improved lifting performance, especially affecting the ability to resist fatigue.[122] Ergonomic workplace factors may also contribute to fatigue and disability. Both sitting and raising arms frequently are associated with greater work disability (OR = 2.8; 95% CI:1.3 to 6.2; and OR = 3.1; 95% CI:1.4 to 7.0).[123] A history of heavy manual labor or a repetitive use of the hand has also been linked to osteoarthritis.[124,125] By addressing workplace ergonomic factors in inflammatory arthritis, studies have demonstrated a positive effect on the ability to continue working[126] and to avoid work disability.[127] Studies support the effectiveness of ergonomic intervention as a viable method to reduce work limitation among employed persons with arthritis, though the generalizability of various types of interventions continues to be investigated.[126] Data are lacking regarding the determination as to whether a worker who perceives work limitations from musculoskeletal conditions, such as arthritis, attempts to achieve relief through use of opioid prescription.

Opioids are often prescribed for chronic noncancer pain, including musculoskeletal disorders such as arthritis.[128,129] A trend study examining office visits and analgesic prescriptions for chronic musculoskeletal pain in US for 1980 versus 2000 found that the use of more potent opioids (hydrocodone, oxycodone, morphine) increased from 2% to 9% of visits (relative risk = 4.5; 95% CI: 2.18 to 6.87). This corresponds to 5.9 million visits in 2000 where potent opioids were prescribed.[128] A review of clinical trials in osteoarthritis shows that beneficial effects on pain control, sleep quality, and functional capacity are reported,[129] although the duration of these effects is not well quantified.

Thus, a model in which workplace ergonomic factors and symptoms of musculoskeletal conditions, such as arthritis, combine to affect PD use of opioids (as summarized in Table 2) is supported by two studies that scored I (RCT and experimental), one prospective cohort study (scored II), and five cross-sectional, discussion, and review studies (scored III). Workplace ergonomic challenges and musculoskeletal conditions have been shown to impact opioid PD use, but the extent to which these two factors combine together is unclear.

Model 2.3 Drug Free Workplace Initiatives Modify Substance Abuse Risk Factors to Impact PD Use—Increasing rates of substance abuse have important implications for the workplace. According to the 2012 National Survey on Drug Use and Health, up to two-thirds of current nonmedical drug users aged 18 years or older in the United States (n~13.1 million individuals) were employed full-time or part-time.[130,131] In an effort to address the negative effects of substance abuse such as absenteeism, diminished productivity, poor morale, injuries, and an increase in health insurance claims that may occur

in the workplace, surveys suggest that workplace substance abuse prevention activities, especially drug testing, are used by more than one-half to two-thirds of major U.S. businesses.[132,133] Drug-free workplace programs have been associated with a reduction in drug use in some industries.[134] Workplace drug testing programs have an important role in mitigating adverse impacts of substances such as marijuana or heroin.[134] However, PD use may not be detected in most programs, as the results of the drug test are reported to the employer as negative, if a legitimate prescription is supplied.[134,135] Legitimate does not mean lack of adverse effects, however, as approximately 60% of all opioid analgesic overdoses occur among patients who have a legitimate prescription.[134,136] Indications that marijuana use may vary inversely with opioids use was suggested by an ecological study showing that states with medical cannabis laws saw 24.8% lower mean annual opioid overdose mortality rate (−37.5% to −9.5%; $P = 0.003$) than states without these laws.[137]

The association between opioid misuse and other substance abuse has been described in multiple studies.[95,136–141] The literature supports the premise that previous substance abuse may be associated with prescription opioid use[139] and that the use of prescription opioids may in turn be associated with substance abuse.[138,140,141] The use of heroin was associated with previous use of prescription opioids among 75% of 18 to 25-year-old respondents in a retrospective cohort of subjects admitted for substance abuse treatment.[138] In a cross-sectional study among adolescents, both medical users (6%) and nonmedical users (65.9%) of opioids reported more substance abuse than those who had never used opioids ($P < 0.01$).[141]

Data support a link between illicit drug use and PD use. However, the evidence to support a model in which PD use may occur among working individuals in lieu of other substances that may produce a positive drug test result is supported by mainly cross-sectional and review studies (Score = III). A model in which this occurs may be considered and is presented in Table 2.

Model 2.4: Occupational Injury Impacts PD Use; Low Income Impacts Disability; PD Use and Disability can be Associated—Data indicate that one-third of individuals with LBP who are off work due to injury receive opioids during the first 6 weeks following injury.[85] Similar numbers are reflected in the nonoccupational setting[16,17,142] Occupational medicine guidelines do not support extensive use of opioids, and according to a review by the American Pain Society and the American College of Physicians, opioids have not been shown to be superior to placebo for conditions such as acute LBP in any RCTs.[16,17] A cross-sectional study in Canada revealed that higher doses of morphine (>120 MED) are associated with workers' compensation patients than the general population (OR = 2.06; 95% CI: 1.58 to 2.69).[143]

The use of opioids has been associated with disability. Despite the increasing use of prescription opioid analgesics among adult Americans in recent years, no association with improvements in disability and health status among users was found.[101,144–147] Among recipients of the Workers Compensation Fund of Utah, the odds of chronic work loss was found to be 11 to 14 times greater for claimants who had opioid prescriptions of any type versus those who did not during a period of at least 90 days.[146] A study evaluating outcomes

following occupational injury revealed that being given more than one opioid prescription or being given a course of opioids lasting more than 7 days is significantly associated with work disability at 1 year.[147] Although opioid use may be a marker of more severe injury, even after 1 year of interdisciplinary functional restoration, dependence on opioids is associated with an increased odds for failure to return to work (OR = 1.43; 95% CI:1.02 to 2.00)[102] and those reporting the highest opioid use are 11.6 times as likely to be receiving Social Security Disability Income/Supplemental Security Income compared with groups reporting no opioid use when they started the program.[148]

Work injuries vary between socioeconomic positions and are a potentially avoidable source of socioeconomic inequalities. Those with household incomes below 150% of the federal poverty line are approximately three times more likely to experience a work disability across a 36-year period, and 4.5 times more likely to experience a severe work disability compared with those above the poverty level.[149] Lower socioeconomic level as determined by income, educational attainment, and type of occupation is associated with an increased likelihood of filing an occupational injury claim.[150] Low income has also been found to be associated with PD use.[142,151–154] For example, after filing a claim, progression to long-term use of opioids was more likely to occur among Australian workers in the lower two deciles of socioeconomic index for area (SEIFA) (OR adjusted for injury type and type of opioid = 1.78; 95% CI: 1.51 to 2.10).[142] Among a Norwegian group, persistent opioid use was associated with a number of factors, including receiving a disability pension, not working, being in the lower quartile of income, and having only compulsory education (no more than 10 years).[151] In the US, fatal overdoses involving opioid analgesics among the Medicaid population are associated with claims for routine medical care for pain management.[152] Rates of overdose are three to six times higher than those for non-Medicaid patients.[152,153]

The factors in this model are further interrelated in that occupational injury itself affects income levels negatively. Some studies show up to 75% lost productivity immediately following injury.[154] This model is supported by four prospective cohort studies (score = II) and 14 other studies (score = III) (Table 2).

In summary, as seen in Table 1, four models describe PD use as a possible PRF in an occupational setting, and in Table 2, four models illustrate PD use as an adverse health outcome (Table 2). In each model, one or more literature sources were identified to support a relationship (represented by a solid arrow) between a PRF and an ORF with a particular outcome. Dotted arrows represent relationships between factors, which were not the primary focus of the models but may further characterize PD use.

DISCUSSION AND CONCLUSION

This study identifies eight models that demonstrate the interrelationships among ORFs/PRFs and PD use in the occupational setting. Preventing adverse exposures in the workplace may decrease PD use, and workplace safety may be improved by minimizing PD use. Although literature was not identified with the goal of conducting mathematical calculations of actual personal and occupational risk associated with PD use in the settings described, these models may serve to guide further research. The models proposed herein are based on the

current state of scientific knowledge. As science evolves, our understanding of interrelationships among ORFs, PRFs, and outcomes will evolve.

Methodologic limitations include the use of a qualitative approach to the evaluation of the published literature. Refinement of this approach, as well as possible use of more statistical rigor, are areas of future exploration of questions regarding hazard identification for multiple factors.

This study is also limited in that much of the research identified to support the relationships presented here is observational in nature. In addition, the literature does not target the workplace alone. In some cases, literature specific to the occupational setting was identified (ie, Model 1.3). In other cases, findings from nonoccupational settings were used to model similar situations, which may occur in the workplace. For example, literature was not identified to describe PD use specifically in the context of working on ladders in an occupational setting (Model 1.2). However, the literature supported the association between PD use and falls,[44,65–78] including support for fall injuries from ladders[63,64] and regardless of where PD use originates, their use can moderate occupational outcomes. Research gaps are highlighted, such as the need for experimental studies, which better elucidate hazard definition, exposure assessment, risk assessment, and risk management of various exposures in the workplace in combination with PD use. Safety and performance in the context of PD use as medication-assisted therapy for opioid use disorder also warrants further investigation. However, investigating PD use in the workplace raises various ethical and legal questions surrounding a worker's right to privacy in drug testing, potential disciplinary actions, and employers' responsibilities in workplace risk management. Although these issues are not the focus of this paper, it should be noted that the models presented here raise issues, such as these, that should be acknowledged before developing workplace programs to address the types of interrelationships described. For example, commercial motor vehicle safety may not only impact public health but may also be affected by PD use.[22] Privacy concerns may need to be weighed given the current opioid epidemic.[59]

Challenges also exist in being able to distinguish appropriate PD use from PD overuse, misuse, and abuse.[88,155,156] Although not the focus of this paper, guidelines are evolving from various professional societies, which address the appropriate use of opioids for pain control. In 2009, the expert panel of the American Pain Society and American Academy of Pain Medicine concluded that long-term opioid therapy can be an effective therapy for carefully selected and monitored patients with chronic noncancer pain,[16,17] some of whom may belong to the working population. Most recently, in 2016, the CDC put forth guidelines for prescribing opioids for chronic pain, which include combining opioids with nonpharmacological and nonopioid therapies to provide greater benefit. The guidelines recommend prescribing the lowest effective dosage and quantity needed for expected duration of pain, starting with immediate release opioids, regularly monitoring patients to ensure benefits of opioids for pain and function outweigh harms, and avoiding coprescription of opioids and benzodiazepines whenever possible.[157] These guidelines were based on emerging evidence that may be further developed by consideration of the workplace setting in investigating, evaluating, and addressing occupational risks associated with PD use or that lead to PDs being prescribed. Guidelines for the appropriate use of

benzodiazepines have been controversial.[158] Evidence may be developed through research on how the use of these prescriptions may affect or result from workplace activities. Future studies may add to the evidence base for the linkages shown in this paper and/or identify other linkages. Efforts directed at identifying the misuse or abuse of opioid and/or benzodiazepine medications may be strengthened by the recognition of workplace factors that lead to increased PD utilization or that impact baseline PD use. These heuristic models, based on available evidence, suggest interrelationships of PD use, ORFs, and illness and injury, as well as occupational and PRF combinations that can affect their use.

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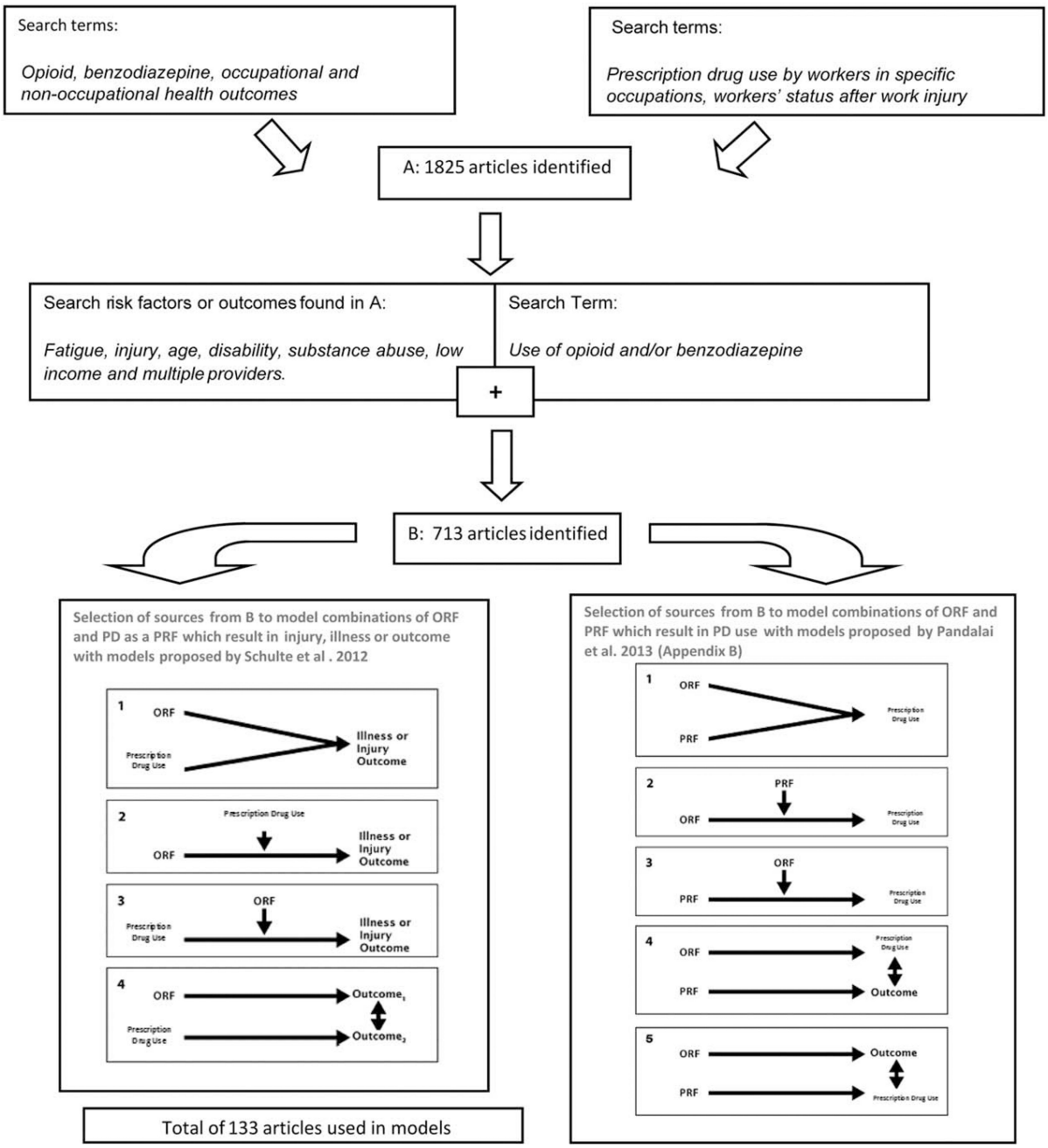


FIGURE 1.

Search terms and iterative search process used to identify the 133 articles used in the models.

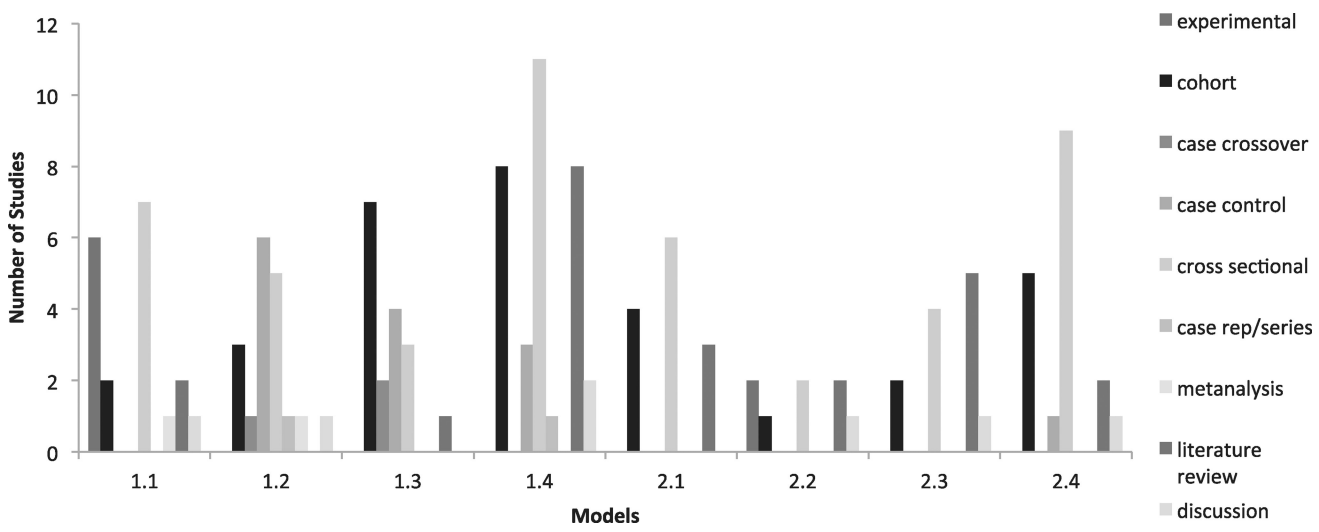
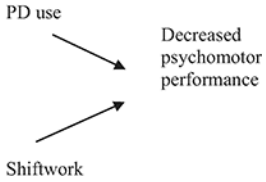
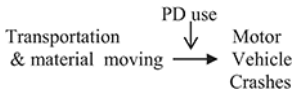
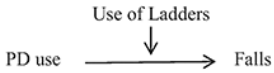
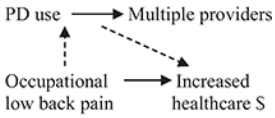


FIGURE 2.
The number of studies used in each model classified by study design.

TABLE 1

Examples of the Impact of the Combination of Prescription Drug Use as a Personal Risk Factor and Various Occupational Risk Factors (ORFs)

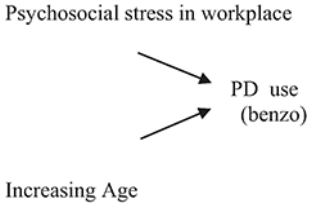
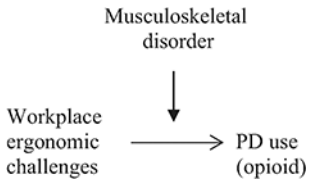
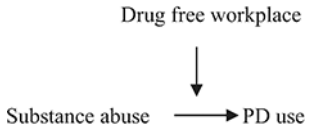
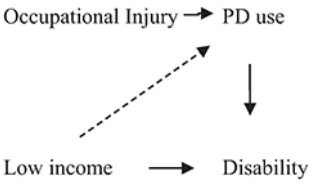
Conceptual Model			Selected References	Score*
1.1	PD use and an ORF independently impact occupational performance		25–43	I(6), II (3), III (10)
1.2	PD use impacts an ORF–occupational injury association		44–61	I(0), II (3), III (15)
1.3	An ORF impacts PD use in an occupational injury association		62–78	I(0), II (6), III (11)
1.4	PD use impacts one outcome, an ORF impacts another, and the two outcomes can be associated with each other		8,16,17,79–108	I(0), II (3), III (29)

Adapted from a figure originally published in studies by Schulte et al[18] and Pandalai et al.[19]

*Score based on methodology used in ACOEM Practice Guidelines: Opioids and Safety Sensitive Work.[22]

TABLE 2

Examples of the Impact of the Combination of Occupational Risk Factors (ORFs) and Personal Risk Factors (PRFs) on Prescription Drug (PD) Use

Conceptual Model			Selected References	Score*
2.1	An ORF and a PRF independently impact PD use		109–121	I(0), II(2), III(11)
2.2	A PRF impacts an ORF–PD use association		122–129	I(2), II(1), III(5)
2.3	An ORF impacts a PRF-PD use association		130–141	I(0), II(0), III(12)
2.4	An ORF impacts PD use; a PRF impacts another outcome; PD use and that health outcome can be associated		16,17,85,101,102,142–154	I(0), II(4), III(14)

Adapted from a figure originally published in studies by Schulte et al[18] and Pandalai et al.[19]

*Score based on methodology used in ACOEM Practice Guidelines: Opioids and Safety Sensitive Work.[22]