Evidence-Based Practice Group Answers to Clinical Questions

"Causal Association between Attention Deficit Hyperactivity Disorder and Chronic Pain"

A Rapid Systematic Review

By

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Clinical Services – Worker and Employer Services

About this report

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About the Evidence-Based Practice Group

The Evidence-Based Practice Group was established to address the many medical and policy issues that WorkSafeBC officers deal with on a regular basis. Members apply established techniques of critical appraisal and evidence-based review of topics solicited from both WorkSafeBC staff and other interested parties such as surgeons, medical specialists, and rehabilitation providers.

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Background and Objective

Chronic pain patients often complain of cognitive changes, particularly in the ability to concentrate and recall. It is unclear whether such comorbidities are actually caused by the pain or are related to factors that may predispose someone to develop chronic pain[92]. Studies have also found chronic pain to be associated with more "formal" psychiatric disorders such as depression. These associations may have significant clinical implications such as in cases where psychiatric disorders affecting chronic pain go undetected by the attending physicians and may lead to poorer treatment outcomes and greater levels of disability[180].

Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder with symptoms of inattention, hyperactivity, and impulsivity that lead to dysfunction in daily life[181]. Initially, ADHD was viewed as a disease of childhood that declined or disappeared in adulthood. However, research over the past 30 years found that ADHD persisted into adolescence and adulthood for 50% to 60% of childhood ADHD cases; extreme ranges from between 4% to 80% have also been reported[178]. Studies also show an age-dependent decline of hyperactivity and impulsivity, however, problems with inattention in particular seem to persist into adulthood[183]. Further, a recent, cross sectional study (level of evidence 5. Appendix 1) from Germany[155] suggested that affective, anxiety and behaviour disorders, including ADHD, may be early risk factors for chronic pain among adolescents (13-18 years old), thereby highlighting the relevance of studying childhood mental disorders for pain medicine.

With regard to this potential association between mental health disorders, particularly ADHD, and chronic pain, the Evidence-Based Practice Group was recently asked to investigate whether there is such (causal) an association between ADHD and chronic pain in adults.

Methods

- A systematic literature search was conducted on September 19, 2017.
- This literature search was conducted on commercial medical literature databases, including BIOSIS Previews® (1969 to 2008), Embase® (1974 to 2017 September 18), Health and Psychosocial Instruments® (1985 to July 2017), Medline Epub Ahead of Print®, Medline In-Process & Other Non-Indexed Citations®, Medline Daily Update® and Medline® (1946 to Present), that are available through Ovid®platform.
- The search was done by employing keyword combinations, as follows:

((Attention **ADJ** deficit **ADJ** hyperactivity **ADJ** disorder) **OR** (attention **ADJ** deficit **ADJ** disorder)) **AND** (chronic **ADJ** pain)

- No limitations, such as on the language or date of publication, were implemented in any this search.
    - One hundred and seventy-six[1-176] published studies were identified through this search.
    - Upon examination of the titles and abstracts of these 176[1-176] published studies, nine[2,51,92,104,145,151,155,156,159] studies were thought to be relevant and were retrieved in full for further appraisals.
- Manual searches were also done on the references of the studies that were retrieved in full.
    - Nine[177-185] further studies were thought to be relevant and were retrieved in full for further appraisals.

Results

- Of the eighteen[2,51,92,104,145,151,155,156,159,177-185] published studies that were retrieved in full, eleven[2,92,104,145,155,177,178,180,181,183,185] were not relevant or did not provide any data relevant to the objective of this systematic review and will not be discussed further.
- Of the remaining seven studies, four[151,156,179,182] were in the form of case series (level of evidence 5. Appendix 1), one[184] is an expert review (level of evidence 5. Appendix 1), one[51] is a small case-control study (level of evidence 3. Appendix 1) and one[159] is a systematic review (level of evidence 1. Appendix 1).
- A medium size (n=740) cross sectional study (level of evidence 5. Appendix 1) investigating the association between ADHD symptoms and pain in a general adult population was reported by Stickley et al.[151]. In a multiple logistic regression model adjusted for some variables (incl. age, sex, education level, race, income, physical health condition and common mental disorders), the authors found that persons screened as having ADHD showed an odds ratio (OR) of 1.6 (95% confidence interval (CI) 1.0-2.6) of having extreme pain. However, in this model, being diagnosed with having one of the common mental disorders (such as generalized anxiety disorders, phobia or obsessive compulsive disorders) or having a physical health condition (such as asthma, allergy, stroke, heart disease etc.) or being in a low income level demonstrated an odds ratio of 4.4 (95% CI 3.2-6.0), 6.1 (95% CI 3.2-11.7), 2.5 (95CI 1.5-4.4) of having extreme pain, respectively. *It should be noted that ADHD was not a clinical diagnosis but was categorized using a screening tool for which reporting bias cannot be discounted; as well, pain was categorized*

based on the SF-12 questionnaire of pain concerning to what degree pain interfered with normal activities as opposed to pain being measured with a valid pain scale and as such, measurement bias cannot be excluded. This cross sectional study had a relatively low response rate (57%) and there was no information assessing potential differences between respondents and non-respondents, and as such potential selection bias cannot be excluded. Multiple statistical tests were presented in this paper without any adjustments to the level of type 1 error, and as such chance cannot be excluded in the observed association. The examination of potential factors that may affect the reported association between pain and ADHD was limited, especially to those collected and as such the role of confounders cannot be excluded from the observed association between ADHD and extreme pain. Further, the data collected in this study represent prevalence data from which temporal association between ADHD and pain cannot be established.

- In a small case series (n=45 chronic pain patients) (level of evidence 5. Appendix 1) reported in the form of an abstract only, Tennant et al.[156] reported the prevalence of ADHD in chronic pain patients. ADHD was categorized based at least 5 positive answers on a 16-item questionnaire. The authors found that 17 (37.8%) respondents answered positively on 5 or more questions and hence were thought to have ADHD. *It should be strongly noted that the validity of the questionnaire employed in diagnosing ADHD is not clear; also ill-defined were: the type of chronic pain, the patient selection process, the role of other potential risk factors, as well as the temporal association between ADHD and chronic pain in this patient population*.
- Kessler et al.[179] reported on a large cross sectional study (n > 4000) (level of evidence 5. Appendix 1) investigating the prevalence and correlates of ADHD in adults among employees of a large manufacturing firm. The authors found the prevalence of ADHD (*which was identified for the purpose of this study by questionnaire results, as opposed to clinical diagnosis)* in this adult population was 1.9%. Further, the authors found that the OR of having arthritis, chronic back-neck pain, migraine or other chronic pain in the ADHD "diagnosed" respondents were 1.5 (95% CI 0.7-31.), 1.5 (95% CI 0.9-26), 1.5 (95%CI 0.7-3.3) and 1.8 (95% C(1.0-3.5), for each respective condition. *It should be noted that ADHD was not identified by a clinical diagnosis but was categorized using a screening tool for which reporting bias cannot be discounted, and pain was categorized based on a self-reported questionnaire of disease conditions affecting participants in the last 12 months, and as such, measurement bias cannot be excluded. This cross sectional study had a relatively low response rate (35% to 38%) and there was no information assessing*

potential differences between respondents and non-respondents, and as such potential selection bias cannot be excluded. Multiple statistical tests were presented in this paper without any adjustments to the level of type 1 error, so chance cannot be excluded in the observed association. An examination of potential factors that may affect the association between pain and ADHD was not provided within the study report; as such the role of confounders cannot be excluded from the observed association between ADHD and extreme pain. Further, the data collected in this study represent prevalence data from which a temporal association between ADHD and pain cannot be established.

- Another large (n=4014) cross sectional study (level of evidence 5. Appendix 1) investigating the prevalence and correlates of ADHD with comorbidities among adults in Ontario was reported by Vingilis et al.[182] The authors found that the overall prevalence of ADHD in this population was 3.3% with 3.6% among females and 3.0% among males. The authors found that the crude OR of using pain medication (with and without prescription) was 1.96 ($p<0.001$) among participants positively screened for ADHD. Adjusted for age, marital status, education and employment status, the authors found that the OR of being prescribed pain medication among males and females "diagnosed" with ADHD was 1.3 (95% CI 0.7-2.4) and 2.0 (95% CI 1.2-3.3), respectively. *It should be noted that ADHD was not clinically diagnosed for the purpose of this study but was categorized using a screening tool (thereby introducing the risk of reporting bias). Pain was categorized based on whether respondents had ever consumed any prescribed or non-prescribed pain medication during the 12-month survey periods, and as such measurement bias cannot be excluded. This cross sectional study had a relatively low response rate (52.9%) and there was no information assessing potential differences between respondents and non-respondents, and as such potential selection bias cannot be excluded. Multiple statistical tests were presented in this paper without any adjustments to the level of type 1 error, so chance cannot be excluded in the observed association. The examination of potential factors that may affect the association between pain and ADHD was limited; as such the role of confounders cannot be excluded from the observed association between ADHD and extreme pain. Further, the data collected in this study represent prevalence data from which a temporal association between ADHD and pain cannot be established.*
- An expert review paper (level of evidence 5. Appendix 1) reporting on clinical and pre-clinical studies investigating pain related alterations in cognition was reported by Moriarty et al.[184] With regard to the association between attention and pain, at best, the authors found conflicting evidence for this association. *It should also be noted that it*

is not clear how studies were selected for inclusion in this expert review paper.

- Fuller-Thomson et al.[51] investigated the association between self-reported ADHD (*i.e. the respondent was asked whether they had ADHD*) and health profiles among females in a large case-control studies (107 "ADHD" cases and 3801 non-"ADHD" controls) (level of evidence 3. Appendix 1). Within this female-only participants, the prevalence of self-reported ADHD was 2.6%. The authors further found that the OR of having pain that prevented activities was 3.9 (95% CI 2.4-6.1) among self-diagnosed ADHD participants adjusted for age, race, education and income. *It should be noted that ADHD cases within this study were not determined by clinical diagnosis and it was not clear how valid the answers provided by respondents with regard to their ADHD diagnosis was. Pain was categorized based on whether respondents were usually free from pain or discomfort, and if not, then whether this pain/discomfort prevented none/some/a few or most of their activities; the validity of these questions was not discussed and as such measurement bias cannot be excluded. This case-control study had a relatively good response rate (69%); however, there was no information on assessment of potential differences between respondents and non-respondents, and as such potential selection bias cannot be excluded. Multiple statistical tests were presented in this paper without any adjustments to the level of type 1 error, and as such chance cannot be excluded in the observed association. The examination of potential factors that may affect the association between pain and ADHD was limited to those collected; as such the role of confounders cannot be excluded from the observed association between ADHD and pain. Further, the data collected in this study represents prevalence data from which a temporal association between ADHD and pain cannot be established.*

- Troy et al.[159] hypothesized that attention had been shown to modulate pain perception and as such impaired attention would be associated with increased pain intensity. Accordingly, the prevalence of pain would be higher in populations of patients with attention deficit. To test this hypothesis, the authors conducted a systematic review to identify studies supporting the use of attention modulation for improved pain-related outcomes in patients with chronic pain. However, at the time of presentation in 2014, no studies directly testing this hypothesis were found. This study was published in an abstract format only, and as such the quality of this systematic review cannot be appraised due to lack of methodological information in the abstract.

Summary

- There is some evidence, from low level, low quality studies, to suggest an association (as measured by odds ratio (OR)) between having pain/chronic pain and having a "diagnosis" of ADHD. However, to date, there is no evidence to show a causal association between having chronic pain and ADHD. Although there are no 'hard and fast' or universally accepted rules of evidence that could be used to unambiguously decide on any cause/effect relationship, in general, experts agree that in order to show an association to be causative in nature, there are several criteria that need to be fulfilled, such as[186]:
    - the consistency of the association
    - the strength of the association
    - the specificity of the association
    - the temporal relationship of the association
    - the coherence of the association

  To date, studies on the association between ADHD and (chronic) pain have not shown such evidence or data which fulfills the above critieria to suggest causality.

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Appendix 1

WorkSafeBC - Evidence-Based Practice Group Levels of Evidence

(adapted from 1,2,3,4)

1	Evidence from at least 1 properly randomized controlled trial (RCT) or systematic review of RCTs.
2	Evidence from well-designed controlled trials without randomization or systematic reviews of observational studies.
3	Evidence from well-designed cohort or case-control analytic studies, preferably from more than 1 centre or research group.
4	Evidence from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled
5	Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

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