The nosological classification of whiplash-associated disorder: a narrative review

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Whiplash-associated disorder (WAD) is the most common complaint and purported cause of chronic disability associated with motor vehicle collisions in North America. However, its construct validity remains controversial. This narrative review of the literature summarises the evidence underlying the most commonly theorised biological and psychosocial mechanisms of WAD pathogenesis. While the face validity of WAD is good, empirical evidence supporting the various constructs suggesting a causal link between a trauma mechanism and the development of symptoms is poor. Because individual expectations of recovery are outcome-predictive, future research is necessary to develop a better understanding of how to enhance expectancies in order to help affected motorists gain a greater sense of control over their health and wellbeing.

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KEY WORDS: whiplash; injury; pathology; nosology; expectancies; chiropractic

Classification nosocomiale du traumatisme cervical en coup de fouet : revue narrative
Le traumatisme cervical en coup de fouet (whiplash cervical) constitue le symptôme le plus fréquent lié aux accidents de la route en Amérique du Nord. C'est aussi la cause prétendue de l'invalidité chronique résultant de ce type d'accidents. La validité conceptuelle de ce traumatisme soulève toutefois des controverses. La présente revue narrative de la littérature résume les preuves qui sous-tendent les mécanismes biologiques et psychologiques les plus théorisés de la pathogenèse du traumatisme cervical en coup de fouet. Alors que l'interprétation de ce traumatisme est juste en apparence, des preuves empiriques appuient diverses interprétations semblant indiquer que le lien de causalité entre le mécanisme de traumatisme et le développement de symptômes est faible. Comme les attentes individuelles d'un rétablissement constituent un élément prédictif de l'évolution, il faudrait mener d'autres recherches pour mieux comprendre la façon d'accroître les attentes pour aider les automobilistes à développer un sens plus aigu de la maîtrise sur leur santé et de leur bien-être.

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MOTS CLÉS : traumatisme cervical en coup de fouet; atteinte; pathologie; nosologie; attentes; chiropratique

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Introduction

Whiplash-associated disorder (WAD) is the most commonly reported clinical presentation by individuals involved in motor vehicle collisions (MVCs) with an annual incidence that has been estimated to be 300 per 100,000 people in North America.[1] The term "*whiplash*" was first introduced by Crowe in 1928 when he described the motion of sudden acceleration-deceleration of the cervical spine as the result of a collision.[2] Crowe did not intend for the expression to reflect the name of a new disease.[3] In spite of this goal, clinicians, patients and lawyers have accepted whiplash as a clinical entity with a wide variety of sequalae, purportedly caused by trauma to the spine and its surrounding structures.

The *Quebec Task Force on Whiplash Associated Disorders* classifies WAD based upon the severity of a person's symptoms and signs:[4]

- Grade 0: No complaints about neck pain. No physical signs.
- Grade I: Neck complaint of pain, stiffness or tenderness only. No physical signs.
- Grade II: Neck complaint and musculoskeletal signs including decreased range of motion and point tenderness.
- Grade III: Neck complaint, musculoskeletal signs and neurological signs including decreased or absent deep tendon reflexes, muscle weakness and sensory deficits.
- Grade IV: Neck complaint and fracture or dislocation.

The clinical presentation of WAD is highly variable. In one study of 6481 Saskatchewan residents who filed auto insurance claims, only 0.4% of respondent complaints were restricted to neck pain alone, with pain often extending into the head, shoulder girdle, upper, mid and lower back, and the upper and lower extremities.[5] A variety of psychological symptoms may also be associated with WAD, including depression, anger, fear, anxiety, and hypochondriasis.[6]

Several kinematic studies have attempted to glean more information with respect to the forces applied to the body during a collision that may be helpful in understanding the etiology of WAD and inform its management. Suggested sites of tissue injury include the facet joint, capsule and its ligaments[7,8], intervertebral disc[9], spinal ligaments[10], and skeletal muscle[11]. Evidence also exists to suggest that central nervous system involvement[12], as well as psychosocial factors[13,14] play a role in the development and persistence of WAD.

Given the pertinence of periodic review to revise our understanding of the scientific literature on the etiology of WAD, the aim of this narrative review is to summarise the evidence underlying the most commonly suggested mechanisms of WAD pathogenesis and to provide an updated appreciation of the subject matter in the 25 years since the last such review was performed by Stovner[15] as part of a treatise on the etiopathology of WAD.

This review also considers whether a causal link between a trauma mechanism and the development of symptoms is reasonable. This is accomplished through the widely accepted guidelines for causation, established by Sir Austin Bradford Hill[16], though not without controversy[17-19], to discern the fundamental prerequisites and assessment criteria of the cause-effect relationship as it relates to WAD pathogenesis.

Methods

Search strategy

A MEDLINE/PubMed search was performed using the following search string "whiplash [Title/Abstract] AND injury [Title/Abstract] AND pathogenesis [Title/Abstract]" from January 1, 1994 to December 31, 2019, yielding 1237 entries, which were exported to EndNote X9 for reference management and tracking of the screening process.

Selection of studies

Studies were included if they met the following criteria: 1) published in English and in a peer-reviewed journal; 2) study designs included experimental (Randomised Clinical Trials) and observational (Cohort and Case-Control) studies; 3) study populations include adults (19+ years old); 4) study populations confined to traffic collisions; 5) studies that suggest damage or injury to, or aberration of, commonly suspected anatomical structures of the body including: the facet joint and/or capsule, skeletal muscle, and the central nervous system; 6) studies that suggest psychological factors associated with WAD such as psychological distress, catastrophisation, and patient expectancies, and 7) studies that consider compensation and its role in health outcomes. Because limited evidence exists to substantiate the notion that intervertebral disc[20-22]

Table 1.
Level of Evidence

A1	Systematic review of ≥2 A2-level studies
A2	Randomised, double-blinded clinical trial of good quality and adequate size
B	Comparative/controlled studies failing to satisfy criteria for A2
C	Non-comparative studies
D	Expert opinion

Table 2.
Strength of conclusion

Level	Conclusion based on
1	A1 study or ≥2 A2-level studies
2	One A2-level study or ≥2 independent B-level studies
3	One B-level or C-level study
4	Inconclusive or inconsistent results between various studies

and spinal ligament[23,24] involvement materially contribute to the development of WAD, summary regarding the validity of these particular structures as potential causes of WAD was not included in this review.

Studies concerning grade IV WAD, the pediatric population, esophageal, ocular, oropharyngeal, otologic, temporomandibular joint or vascular manifestations that may be associated with the condition, as well as cadaveric studies, kinematic studies, case reports, opinions, comments, letters to the editor, and articles without scientific data or a report of their methodology were excluded.

Level of evidence
A level of evidence rating was given to every study, based on the study design (Table 1), according to the 2005 classification system of the Dutch Institute for Healthcare Improvement CBO. Randomised double-blinded comparative clinical research of good quality and efficient size obtained a level of evidence A2, while cohort studies not meeting these criteria or case-control studies obtained a level of evidence B. Non-controlled trials obtained a level of evidence C. The level of evidence for each study is listed in the corresponding table of studies suggesting a cause of WAD, and the overall level of evidence for the cluster of studies represented in each table is listed under the respective table.

Strength of conclusion
Subsequently, the strength of conclusion (ranging from 1 to 4) was calculated for each cluster of studies reflecting one outcome parameter (Table 2) and is placed under the respective table representing a cluster of studies suggesting a cause of WAD. Strength of conclusion 1 was assigned for a study of level A1 or at least 2 independently conducted studies of level A2. Strength of conclusion 2

was given when at least 2 independently conducted studies of evidence level B or one trial of evidence level A2 was included in the cluster, and strength of conclusion 3 was assigned if one study of evidence level B or C was present. Strength of conclusion 4 was given in case of inconclusive or inconsistent results between various studies.

The author reviewed all entries, of which, 43 duplicates were removed, and 1194 citations were screened by title and abstract. Two hundred and five full-text articles were screened. Of those, 39 articles met the inclusion criteria and were eligible for critical appraisal. Reasons for exclusion during the full-text screening phase were study design (n=30), research question (n=34), outcome of interest (n=94), and population of subjects (n=7) (Figure 1).
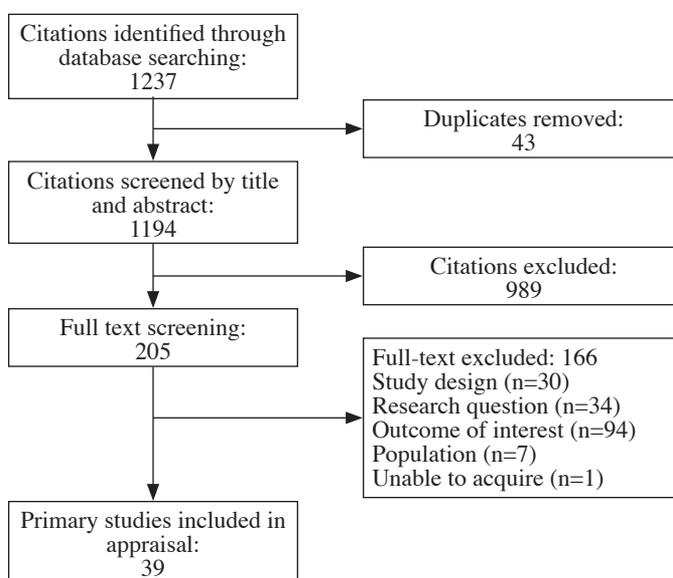

Figure 1.
Study selection process

Table 3.
Studies suggesting facet injury is a cause of WAD

First Author	Year Published	Treatment Administered	Study Design	Summary of Findings	Level of Evidence
Lord	1994	Anesthetic block	Double-blinded RCT	Complete HA relief in 13/55 patients Neck pain relief in 14/55 patients	A2
Barnsley	1995	Anesthetic block	Double-blinded RCT	Neck pain relief in 27/50 patients	A2
Lord	1996	Radiofrequency neurotomy	Double-blinded RCT	50% pain relief for mean of 263 in treatment group vs 8 days in control group	A2
Lord	1996	Anesthetic block	Placebo-controlled RCT	Neck pain relief in 31/52 patients	A2
McDonald	1999	Radiofrequency neurotomy	Cohort	Pain relief in 20/28 patients	C
Govind	2003	Radiofrequency neurotomy	Cohort	Complete pain relief at 90 days F/U in 43/48 patients	C
Barnsley	2005	Radiofrequency neurotomy	Cohort	Adequate pain relief in 36/45 patients for mean of 36 weeks	C
Smith	2014	Radiofrequency neurotomy	Cohort	Pain, disability, psychological distress & pain catastrophising ↓ at 1, 3 mo.	C

Level of evidence: A1; Strength of conclusion: 4; HA: Headache, F/U: Follow-Up

Table 4.
Studies suggesting change in muscle morphology is a cause of WAD

First Author	Year Published	Study Design	Summary of Findings	Level of Evidence
Elliott	2015	Prospective longitudinal cohort study	MFI values were significantly higher in the severe group when compared to the recovered/mild group at 2-weeks and 3-months	C
Karlsson	2016	X-sectional case-control	Participants with severe disability after a whiplash injury had higher MFI in the multifidus compared to controls and to those with mild/moderate disability secondary to WAD	B
Pedler	2018	X-sectional case-control	Global differences in MFI are not a feature of chronic WAD, with differences in MFI limited to the cervical spine musculature	B
Abbott	2018	X-sectional case-control	Increased MFI within cervical multifidus of WAD patients compared to controls	B

Level of evidence: B; Strength of conclusion: 4; MFI: Muscle fatty infiltrates, WAD: Whiplash-associated disorder

Table 5.
Studies suggesting central sensitisation is a cause of WAD

First Author	Year Published	Study Design	Summary of Findings	Level of Study
Borchgrevink	1997	X-sectional case-control	No significant alterations in CNS morphology identified	B
Radanov	1999	X-sectional cohort	No alterations in CNS perfusion by PET or SPECT scan	C
Freitag	2001	X-sectional case-control	Significant decrease in BOLD signal in symptomatic patients vs. asymptomatic patients and controls	B
Lorberboym	2002	X-sectional cohort	Regional CNS perfusion abnormalities by SPECT in 13/20 WAD patients	C
Sundstrom	2006	X-sectional case-control	No significant changes in WAD group, while non-traumatic neck pain group showed significant altered rCBF pattern compared to controls	B
Sturzenegger	2008	X-sectional case-control	No difference in ventricle-brain ratio between WAD patients and healthy controls	B
Obermann	2009	X-sectional case-control	Significant decreases in ACC and dorsolateral DLPFC at 3 mo.; resolved by 1 y	B
Linnman	2009	X-sectional case-control	Regional CNS perfusion increases & decreases by PET scan	B
Linnman	2010	X-sectional case-control	Availability of a pain processing (NK1) receptor was decreased in WAD patients	B
Bakhtadze	2012	X-sectional cohort	Parietal and frontal perfusion decreased with increased levels of pain	C

Level of evidence: B; Strength of conclusion: 4; CNS: Central Nervous System, PET: Positron Emission Tomography, SPECT: Single-Photon Emission Computed Tomography, BOLD: Blood-Oxygen-Level-Dependent imaging, rCBF: regional Cerebral Blood Flow, ACC: Anterior Cingulate Cortex, DLPFC: Dorsolateral Prefrontal Cortex, NK1: Neurokinin receptor 1, WAD: Whiplash-associated disorder

The studies selected for further analysis were clustered according to the following theorised mechanisms of WAD pathogenesis: 1) evidence of facet joint and/or capsule injury (Table 3); 2) evidence of change in skeletal muscle morphology (Table 4); 3) evidence of central nervous system involvement (Table 5); 4) evidence of a role of psychological distress and patient expectancies (Table 6); and 5) evidence of the role of compensation resulting in poor health outcomes (Table 7).

Table 6.
Studies suggesting that pain catastrophising and expectancies impact WAD prognosis

First Author	Year Published	Treatment Administered	Study Design	Summary of Findings	Level of Study
Carroll	2009	Rehabilitation	Cohort	Patients who expected to recover soon recovered in 1/3 of the time	C
Ozegovic	2009	None	Cohort	Those who expected to recover experienced global recovery 42% faster	C
Ozegovic	2010	None	Population-based cohort	Depression, ↓ income, ↓ education & male gender associated with delayed RTW	C
Ferrari	2011	None	X-sectional cohort	High correlation between expectations and injury severity perception scores	C
Bostick	2013	Physiotherapy & Chiropractic	Longitudinal cohort	Expectations inversely correlated, catastrophising directly correlated with pain severity at 6 mo	C
Carriere	2015	Rehabilitation	Longitudinal cohort	Expectancies mediate the relationship between pain catastrophizing fear of movement & RTW	C
Chiarotto	2015	Manual therapy; motor & sensorimotor control training	Longitudinal Cohort	Baseline pain intensity & pain catastrophising predict response	C
Falla	2016	None	Longitudinal cohort	Female gender, unsettled insurance claims & financial status predict pain	C
Smith	2016	Radiofrequency neurotomy	Longitudinal cohort	Baseline pain catastrophising & disability predict response	C
Carriere	2017	Rehabilitation	Longitudinal cohort	Expectancies mediate the relationship between perceived injustice & RTW	C
Soderlund	2018	Multimodal therapy	Longitudinal cohort	Expectation of recovery, distracting & supportive feedback from significant others predict recovery outcome	C
De Pauw	2018	None	X-sectional case-control	Fear avoidance symptoms of central sensitisation, & pain predict motor impairment	B
Elphinston	2018	Rehabilitation	Longitudinal cohort	Expectations inversely correlated, catastrophising directly correlated with pain severity	C

Level of evidence: B; Strength of conclusion: 3; RTW: Return to Work

Table 7.
Studies suggesting that compensation impacts WAD prognosis

First Author	Year Published	Study Design	Summary of Findings	Level of Evidence
Schrader	1996	Retrospective cohort questionnaire	Expectation of disability, a family history, and attribution of pre-existing symptoms to the trauma may be more important determinants for the evolution of the late whiplash syndrome	C
Obelieniene	1999	Prospective controlled inception cohort study	Symptoms of acute whiplash injury are self-limiting	C
Cassidy	2000	Population-based cohort	The elimination of compensation for pain and suffering is associated with a decreased incidence and improved prognosis of whiplash injury	C
Rydman	2018	Cohort	Non-recovery rate was 51% in non-compensated group and 73% in compensated group	C

Level of evidence: C; Strength of conclusion: 3

Results

Facet joint and capsule injury

Of the various tissues in the cervical spine that may be injured during whiplash, the facet (zygapophysial) joint and facet capsule/ligament are the most extensively documented structures. A proposed mechanism of facet joint injury is undo strain upon the facet capsule, which has been documented in several *in vitro* biomechanical, and *in vivo* animal, studies.[25-32] Given that such studies are not possible in live humans, attempts to infer injury to the facet joint have been made by way of eight clinical trials documenting pain relief when the facet joint and capsule are specifically targeted via medial branch blocks or percutaneous radiofrequency neurotomy with some meaningful pain relief achieved. Of these studies, four were randomised clinical trials[33-36]; three involved anesthetic block[33-35] and five radiofrequency neurotomy[36,38-41].

Two of the three RCTs involved WAD patients with headaches ± neck pain who underwent facet blocks. In two of these studies, patients were randomly assigned to receive an initial radiographically-guided block with either short-acting 2% lignocaine or longer-acting 0.5% bupivacaine.[33,34] A positive diagnosis of cervical zygapophysial joint pain was made only if both blocks relieved a patient's pain and bupivacaine provided longer relief, which occurred in 13 of 55 patients with headache complaints and 14 of 55 patients with neck pain.[33] The second study saw 27 of 50 patients obtain neck pain relief based on a similar protocol.[34] In the third study, patients who presented with dominant headache and obtained relief following third occipital nerves blocks satisfied the authors' criteria for C2-C3 zygapophysial joint pain, and non-responders along with patients who presented with dominant neck pain underwent blocks of cervical zygapophysial joints at several levels below C2-C3.[35] Responders were then diagnosed with cervical zygapophysial joint pain at the respective level that offered them relief. The major limitation of the aforementioned studies, pertaining to the current discussion, was the outcome of interest (headache relief vs neck pain relief) coupled with the heterogeneous sample of patients, suggesting a significant risk of selection bias.

The only parallel-group RCT[36] involved 24 patients presenting with what the authors deemed to be cervical zygapophyseal joint pain at levels C3-C7; confirmed with the use of local anesthetic blocks. Patients with C2–C3 zygapophyseal joint pain were excluded because a previous study[37] had shown that treatment at this level by radiofrequency neurotomy was technically difficult. Each subject received either active or mock radiofrequency neurotomy (n = 12 per group) and was followed by telephone interviews and clinic visits until they reported that their pain had returned to 50% of its preoperative level. The treatment protocol in the two arms was identical, except that the temperature of the electrode tip was raised to 80°C for 90 seconds in the active group and maintained at 37°C in the control group. Six patients in the control group and three in the active-treatment group had a return of their accustomed pain immediately following the procedure. At 27 weeks, one patient in the control group and seven in active-treatment group remained pain free with a median time of eight days and 263 days, respectively, before the return of at least 50% of their preoperative pain.[36] Notably, a higher proportion of patients involved in ongoing litigation were assigned to the control group. How this may have affected the study results remains unclear given the lack of information provided regarding these patients' circumstances.

The remaining four clinical trials employing radiofrequency neurotomy were uncontrolled.[38-41] The aforementioned studies operate on the following assumption: if we accept that a patient reported no pain prior to an MVC but reports pain thereafter, which is successfully treated with facet blocks or radiofrequency neurotomy, the inference is that the facet joint is the source of the patient's pain and, therefore, was injured or implicated in some way during the MVC. This is a common logical fallacy known as *post hoc ergo propter hoc* (from the Latin meaning: "with this, therefore because of this") – where credit is awarded to the treatment administered rather than considering a condition's natural history, regression to the mean, or the impact of narratives proffered to a patient, coupled with the power of the placebo effect and the contextual factors surrounding a patient's particular circumstances that work in concert to bring about recovery.

High-quality evidence demonstrates significant variability in the diagnostic utility of cervical facet joint nerve blocks in individuals with chronic spinal pain; with prevalence rates ranging between 36% to 67% and false-positive rates of 27% to 63%.[42] Moreover, because studies of healthy and clinical populations find little difference in

the prevalence of anatomical impairment to warrant procedural intervention[43-46], in turn, challenging the practice of assigning a structural cause for the perception of pain in the absence of detectable tissue pathology, an appreciation for the neurobiology of persistent pain is recommended[47].

In the context of WAD, it is noteworthy that the reporting of symptoms is not synonymous with the presence of injury, which refers to damage to the body produced by energy exchanges that have relatively sudden discernible effects.[48] Additionally, the perception of pain may arise from an emotional experience[49], as the correlation between pain and bodily damage is equivocal.

Although treatment interventions targeted at the facet joint have been shown to provide symptomatic relief for a small cohort of patients, the conclusion that injury to the facet joint is therefore the cause of WAD cannot be drawn *ipso facto*.

Muscle involvement

Muscle pain is a prevailing symptom reported by motorists involved in traffic crashes. Though, evidence of direct muscle injury as a cause of WAD remains inconclusive.[50] Several studies have documented findings in neck muscles by ultrasonography, including muscle deformation during real-time movement[51,52], muscle twitching[53], and the temporal development of fatty infiltration of the multifidus following MVC exposure[54-57]. In a single-center longitudinal cohort study by Elliot and colleagues[54], 36 people with acute WAD (≤1 week) were followed and assessed for temporal development of muscle fatty infiltrates (MFI) in the cervical multifidii and the findings were measured against self-reported pain and disability via the Neck Disability Index (NDI). Study subjects were dichotomised into two groups via NDI (0–28%, recovered/mild disability and 30–100%, moderate to severe disability). Mean percent MFI by group and time revealed little variation in the within group changes in the recovered group, the modest mean changes between one week and three months were statistically significant (p=0.023). In the moderate/severe disability group, mean percent MFI significantly increased across all time points (p<0.002). Comparing the recovered/mild to moderate/severe groups indicated no significant difference at 1 week (p=0.31) with significant differences at two weeks (p=0.0009) and at three months (p<0.0001). Although underpowered, this study provides some evidential support for the differential development of MFI in participants with varying levels of functional recovery following whiplash. Similar findings are noted by Karlsson *et al*.[55] and Abbott *et al*.[56], when comparing 31 individuals with severe disability (chronic WAD lasting >6 months and <3 years) to healthy controls.

In a cross-sectional study by Pedler *et al*.[57] comparing 43 individuals with chronic WAD (>3 months and <10 years) and 16 healthy controls, the authors found no significant differences in MFI in the soleus muscle between people with chronic WAD and a demographically similar asymptomatic control group, despite between-group differences in MFI at the cervical multifidus – suggesting the potential of local mechanisms at the cervical spine contributing to the differences noted.

The mechanism behind how these aforementioned findings might contribute to the clinical presentation of WAD remains to be elucidated. Nevertheless, it is conceivable that disuse; as a consequence of fear-avoidance behaviour[58] and passive coping strategies[59], which has been shown to produce reductions in muscle volume as well as intramuscular fatty infiltration[60,61], may play a role in the development of the notable changes in muscle morphology.

Central sensitisation

Where peripheral sensitisation is often associated with acute WAD, increasing evidence exists to suggest that prolonged noxious input manifests as central sensitisation; the amplification of neural signaling within the central nervous system that results in pain hypersensitivity, and that these changes can remain long after nociceptive input has disappeared.[62-63] The two hallmark characteristics of central sensitisation are the presence of allodynia (pain due to a stimulus that does not usually provoke pain) and hyperalgesia (increased pain from a stimulus that usually provokes pain). While the mechanism of central sensitisation is still not well understood, the processes involved in this phenomenon result in increased responsiveness to a variety of stimuli including mechanical pressure[64], chemical substances[65], cold temperature[66], heat temperature[67], and electrical stimuli[64,68]. When the central nervous system is sensitised, tissue damage is not required to induce pain. This may explain the discrepancy between the absence of tissue damage and persistent pain complaints in chronic WAD patients.[69]

It is unclear when the central nervous system starts sensitising and when general widespread hypersensitivity appears. Four studies suggest that central sensitisation occurs three to six months after the initial onset of WAD.[66,70-72] At the same time, it is important to recognize that the chronic WAD population is heterogeneous and that central sensitisation is not present in all WAD patients.[73]

As it relates to alterations in structural brain morphology, one study examining structural abnormalities shortly after MVC exposure (within two days), found no signs of edema or lesion in the acute WAD group when compared with healthy controls, nor could a prediction of symptom development be made.[74] Obermann *et al.*[75] conducted a cross-sectional case-control study that performed voxel-based morphometry in WAD patients with post-traumatic headache and neck pain within 14 days of MVC exposure. The authors found no structural brain alterations in the acute phase (initial 14 days). However, in those patients that developed chronic headache lasting longer than three months, decreased grey matter volume in the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) was observed, and resolved after one year – coinciding with the cessation of headache symptoms. Another study analyzing the ventricle-brain ratio (VBR), found no difference in VBR between patients with chronic WAD and healthy controls.[76]

As it relates to alterations in brain function, a cross-sectional case-control study conducted by Freitag *et al.*[77] examining 17 subjects; five symptomatic chronic WAD patients (duration 14 to 34 months), five asymptomatic WAD patients, and seven healthy volunteers, all with no evidence of structural brain damage, confirmed by T_2-weighted magnetic resonance imaging (MRI), found that chronic WAD patients showed a significantly decreased performance in psychophysical tasks of coherent motion detection and corresponding functional MRI (fMRI) activation in the middle temporal (MT) and middle superior temporal (MST) regions of the brain, which are known to be important cortical sites of visual motion processing, compared to asymptomatic patients and healthy volunteers. Linnman *et al.*[78] aimed to explore whether Neurokinin 1-receptor (NK1R) availability is altered in chronic pain patients as compared to healthy controls, and whether changes in NK1R expression are related to behavioural aspects of chronic pain.

The NK1R is a member of the tachykinin receptor family that preferentially binds to Substance P (SP); the neuropeptide that regulates affective behaviour, emesis, and nociception[79], and both NK1 and SP have been implicated in locomotive activity[80] and in pain processing[81].

The authors found a decrease of NK1R availability in chronic WAD patients, and observed a negative correlation between kinesiophobia and NK1R availability per patient scores on the self-reported Tampa Scale for Kinesiophobia (TSK) Questionnaire. That is to say, patients found to have decreased NK1R density also had higher TSK scores; reflecting increased pain-related fear and avoidance behaviour.

Five studies examined alterations in brain perfusion/metabolism through single-photon emission tomography (SPECT) and positron emission tomography (PET) imaging[82-86], of which, only Radanov *et al.*[82] found no indication for changes of brain perfusion. Sundström *et al.*[83] demonstrated that patients with chronic idiopathic neck pain showed decreased regional cerebral blood flow (rCBF) compared to healthy controls, which was most obvious in the parahippocampal and temporal regions, and the cerebellum. However, no such alterations could be observed in patients suffering from chronic WAD compared with healthy controls. Linnman *et al.*[84] found alterations in the left and right parahippocampal gyrus, left lingual gyrus, left and right posterior cingulate gyrus, right caudate nucleus and right pulvinar nucleus of the thalamus in chronic WAD patients. Bakhtadze *et al.*[85] found decreased perfusion of the parietal and frontal regions in patients with moderate to severe chronic idiopathic neck pain symptoms when compared to patients with only mild symptoms. Lastly, Lorberboym *et al.*[86] found regional CNS perfusion abnormalities by SPECT in 13/20 chronic WAD patients (range six months to five years).

However, these abnormalities were not equal for all patients. In 8 patients, perfusion abnormalities were observed in the temporal lobes, in three patients in the occipital lobes, in two patients in the frontal lobes, and another two patients in the basal ganglia.

Therefore, while some evidence exists demonstrating alterations in brain structure, function, perfusion and metabolism in individuals with chronic neck pain, the nature and location of these alterations is not entirely clear. Contradictory findings also exist, suggesting that multiple mechanisms may be responsible for the brain's neuroplasticity associated with the perception of pain.

The patient's psychological state

WAD patients may experience considerable psychological strain. In a meta-analysis of 24 studies, involving 4502 patients, elevated psychological distress was associated with WAD with a large effect size (Cohen's d = 0.90); appreciably larger than that observed amongst patients with spinal cord injuries (d = 0.69) or mild to moderate traumatic brain injury (d = 0.23).[87] Moreover, evidence exists suggesting that patients with persistent WAD are more likely to have had a pre-MVC history of psychiatric morbidity.[88]

Pain catastrophising; a person's "tendency to magnify the threat value of pain stimulus and to feel helpless in the context of pain, and by a relative inability to inhibit pain-related thoughts in anticipation of, during or following a painful encounter,"[89] has been linked with poorer clinical outcomes in WAD patients[90-95].

Extensive research has also been published on the impact of patient expectations with respect to recovery from WAD.[96-106] Throughout these studies, the expectations most commonly studied were expectation of pain resolution and expectation of return to work; and in each study, patients' initial expectations of recovery were outcome-predictive.[96-100,103,106] In one cohort study involving 6015 adults with WAD, those who expected to recover, recovered at more than three times the pace of those who did not anticipate recovery.[99] In another study, expectation of recovery was found to predict resumption of not just work, but also routine engagement in activities.[104] Expectation of recovery has also been shown to serve as a mediator of pain catastrophising and fear of movement.[97]

Consequently, possessing higher levels of self-efficacy has been shown to be associated with enhanced physical functioning and health status, and lower pain intensity, perceived disability, depressive symptoms and fatigue in individuals with chronic musculoskeletal pain.[107]

The impact of compensation

The legal concept of pain and suffering emerged from the origins of civil tort law in early England, and Western society has long recognized that compensation for a loss caused by another is an acceptable effort to make one whole.[108] Yet, it is hypothesised that observing WAD as a compensable phenomenon may result in worse health outcomes.[109] This understanding stems from the belief that fault-based compensation systems are harmful to health because such systems require individuals to prove poor health and functional decline in an adversarial environment, which, in turn, is thought to negatively affect recovery.[110] Moreover, the prospect of financial gain is presumed to motivate some individuals to exaggerate the severity of their symptoms or health status.[111]

These views were corroborated by a population-based study of 7462 road traffic accident claimants, conducted by Cassidy *et al*.[112], that saw a 28% reduction in the incidence of whiplash claims along with a reduction in the median time to close claims by more than 200 days, despite increases in the number of vehicle-damage claims and the number of kilometers driven after the province of Saskatchewan switched to a no-fault insurance system from its previous fault-based system. Similar findings were reported in the state of Victoria, Australia, following the introduction of legislation limiting court actions and compensation for whiplash.[113] In keeping with this theme, Cameron *et al*.[114] conducted an interrupted time series to assess whether a change in legislation improved health status and quality of life for people with whiplash in New South Wales, Australia. The authors compared three independent groups at baseline (after injury and lodgement of the insurance claim) and two years later. The first group included whiplash claimants who were involved in a motor vehicle crash in the period July to September 1999, before the legislative change. The second group included whiplash claimants who were exposed to MVC during the period July to December 2001, approximately two years after the legislative change. The third group included whiplash claimants who were exposed to MVC between July 2003 and March 2004. Adjusted analysis for the three groups to control for additional factors such as age or gender, and other possible confounders revealed recovery rates of 37%, 52% and 49% in groups 1, 2, and 3, respectively. Reductions in pain intensity were also significantly improved (p = 0.03) in groups 2 and 3 compared to group 1, as were improvements in physical component scores (p = 0.001) and health status (p = 0.01), measured by SF-36 – demonstrating that health outcomes for people with whiplash were substantially improved after legislative change that restricted access to compensation for noneconomic loss, introduced clinical guidelines for the management of whiplash and provided earlier acceptance of compensation claims and greater provision of early treatment.

The notion that regional sociocultural factors may in-

fluence patterns of behaviour led Schrader and colleagues to study the natural evolution of WAD in Lithuania; a country where, at the time, most drivers did not have personal injury insurance, and with little public awareness, even among Lithuanian doctors, about whiplash and its potential to cause disability.[115] The authors conducted a retrospective questionnaire-based cohort study of 202 individuals and found that the incidence of chronic neck pain was no higher among individuals involved in MVCs than those in the general population. While recall bias may account for the study findings, the data noted comports with the evidence that individual expectancies; which are not only influenced by one's hardiness, but also through social learning,[116] duly predict outcomes. In a subsequent cohort study of 210 Lithuanian motorists involved in MVCs conducted by Obelieniene and colleagues, the authors found no significant differences between motorists involved in rear end collisions and the control group concerning frequency and intensity of neck pain, and headache symptoms after one year.[117]

Rydman *et al*.[118] offer further support for the compensation hypothesis based on a longitudinal cohort study of 144 individuals reporting neck pain after being involved in a motor vehicle collision. The authors noted a higher non-recovery rate among individuals who filed insurance claims (73%) compared to those who did not (51%) over a period of two to four years. The authors further noted an overrepresentation of patients with elevated levels of mental distress at the time of the collision that may have influenced their compensation-seeking behaviour.

Other factors

In addition to the aforementioned negative risk factors associated with poor WAD prognosis, namely; catastrophisation, and compensation and legal factors, some evidence exists to suggest that post-MVC pain and disability[119-125], and early use of healthcare[121] negatively affect WAD prognosis.

Interestingly, factors identified as not being associated with WAD prognosis include post-MVC MRI or radiologic findings[121,126], motor dysfunctions[127], and collision factors; such as the direction of impact, use of seatbelts or headrests, and the speed of the vehicle at the time of impact[119,121,122,124]. The clinical presentation and prognosis of WAD are also not affected by pre-existing disc degeneration.[21] This notion is further supported by a prospective

ten-year follow-up study that compared WAD patients and asymptomatic subjects using MRI. The study revealed that progressive decreases in the signal intensity of the intervertebral discs was observed more frequently among WAD patients than the healthy controls, while structural changes in the cervical spine, including posterior disc protrusion, disc space narrowing, and foraminal stenosis, progressed almost equally in both groups. Furthermore, the clinical symptoms observed in both the WAD patients and the healthy controls were not associated with any of the MRI findings. These findings suggest that, although some WAD patients may suffer from long-lasting clinical symptoms, whiplash exposure may not necessarily accelerate the symptomatic structural deterioration of the cervical spine. Instead, the progression of disc degeneration observed in the majority of WAD patients might be attributed to the normal ageing process, similar to the changes seen in the healthy controls.[128] Another prospective 11-year follow-up study that compared the incidence and prevalence of Modic changes in the cervical spines of WAD patients compared with healthy controls, found that Modic changes were not related to clinical symptoms. Instead, the development of new Modic changes was significantly associated with age, heavy labour, and preexisting disc degeneration, but not with the details of the MVCs.[129]

Discussion

Establishing a causal inference between a trauma mechanism and WAD

Where a disease denotes a condition characterised by functional impairment, structural change, and the presence of specific signs and symptoms, a disorder is defined by functional impairment without structural change.[130] Consequently, a diagnosis is the informed opinion of a clinician who provides a label to the patient advising them of their condition. A widely accepted definition of causation is that a specific occurrence serves as an antecedent event or condition that was necessary for the development of a specific condition or injury at the moment that it occurred, given that other circumstances are fixed.[131] In order to ascertain the nosological classification of WAD, a causal relationship linking MVC exposure to symptom development that comports with detectable evidence of one or more of the aforementioned suggested mechan-

isms of WAD development must be constituted. This is achieved through consideration of the nine principles, proposed by Bradford Hill, in determining whether a causal inference is reasonable.[16] The practical application of Hill's criteria is especially useful in determining the credibility of a cause-and-effect relationship in a forensic setting (in individuals evaluated for a legal matter) in order to answer two major forensic questions: "could the exposure have caused the injury or condition outcome in this case?" and "did the exposure cause the injury or condition outcome in this case?"

Herein, the application and interpretation of each of Hill's criteria, as they pertain to the etiology and pathology of WAD, is considered.

Strength of association refers to a strong statistical association for causality. Nolet *et al*. conducted a systematic review and meta-analysis to examine the association between MVC-related neck injury and future neck pain compared to the prevalence of neck pain in the general population, and calculated an unadjusted relative risk of future neck pain in the MVC-exposed population with neck injury of 2.3; reflecting a 57% attributable risk.[132] At face value, this finding demonstrates a positive association between MVC-related neck injury and future neck pain. However, the broad operational definition of injury applied by the authors: "self-reported injury, primary care or emergency room physician diagnosed injury or an injury that had been filed with an automobile insurance company"[132] raises the risk of overestimating injury incidence. If we were to apply the injury definition provided in this paper, a strong statistical association between MVC exposure and WAD would be less likely.

Consistency means that several studies involving various groups of patients produce the same conclusion. WAD has been described among distinct populations with significant differences in its incidence and prevalence.[112-116,133,134] There is also considerable variation in the clinical presentation of WAD; owing to a lack of consistency.

Specificity refers to the degree to which an exposure derives a particular effect. For example; the most common mechanism of lateral ankle sprain is excessive inversion and internal rotation of the hindfoot while the leg is in external rotation, placing maximal strain on the lateral ankle ligaments.[135] Conversely, the descriptive validity of WAD; the degree to which it can be distinguished from

other similar conditions as a result of a specific cause, is inadequate.[136,137]

Temporality, described as the obvious principle that cause must precede effect, is perhaps the sole universally agreed upon principle deemed essential for causal inference – where symptom development weeks after a collision would refute causation. At the same time, temporal subsequence does not necessarily imply consequence; as illustrated in an elaborately-designed study by Castro *et al*., where 51 healthy adults underwent a mock collision that resulted in almost 20% of the subjects indicating "whiplash-like" symptoms within three days of exposure.[138] None of the test subjects raised any doubts about having been in a real collision after being exposed to 0.03 *g*-force; equivalent to four to five times less than the force applied when a person takes their first step to initiate walking. Yet, symptoms were reported and attributed to this exposure, which lacked the biomechanical potential to induce injury. In this example, where the timing of symptom development may adhere to the principle of temporality, the development of symptoms in the absence of trauma violates the principles of strength of association, consistency, specificity, biological gradient, biological plausibility, coherence, experiment and analogy.

Biological gradient (*dose-response relationship*) – Hill wrote that "if a dose response is seen, it is more likely that the association is causal."[16] Meaning that greater exposure should generally lead to an increased incidence of the effect. Some authors suggest that a "limit of harmlessness" in low-velocity collisions (<15km/h) lies between 10-15km/h,[139] whereas Davis argues that although vehicle damage may not occur up until impacts reach speeds of 15km/h, 4km/h impacts can induce physical injury.[140] Giannoudis *et al*. conducted a retrospective study of 101 consecutive polytrauma patients at a Level I Trauma Centre, and found that the incidence of whiplash is relatively low (13%) following high-energy trauma; concluding that "there is no dose-response relationship between the magnitude of trauma severity and incidence of whiplash injury."[141] In this study, whiplash injury was defined according to the Quebec Task Force guidelines as neck pain, stiffness, or headache following the original inciting event, and trauma severity was defined in the following ways: high-energy trauma; reflecting a fall from a height of more than two metres, high-velocity road traffic accidents; reflecting collisions occurring at speeds great-

er than 30km/h, and an Injury Severity Score (ISS) >16; reflecting major trauma.[142,143]

Biological plausibility means that the association between cause and effect must appear reasonable based on our current biological knowledge. The primary concern regarding WAD pathogenesis is the lack of detectable tissue pathology to substantiate the notion that a traumatic mechanism accounts for the development of post-MVC symptoms. This understanding by no means discounts the patient's pain experience, but rather highlights the impact that psychosocial factors and expectancies associated with WAD can have on symptom chronicity and the patient's perception of disability and recovery.

Coherence is viewed as being similar to biological plausibility where "the cause-and-effect interpretation of our data should not seriously conflict with the generally known facts of the natural history and biology of the disease."[16] The principle of coherence is not satisfied in the absence of gross, biochemical or histopathological evidence to substantiate a mechanistic construct for the development of WAD.

Experiment – Hill explained that evidence drawn from experimental manipulation may lead to the strongest support for causal inference. Implementation of this strategy has been attempted by way of several *in vitro* biomechanical, and *in vivo* animal studies demonstrating collagen fibre disorganisation and/or disruption and hyper-laxity[25-28], in addition to axonal swelling changes, hyper-excitability, and permanent alterations in neuronal signaling within the spinal cord[29-32]. However, the effects noted are generally imperceptible in live humans, negating this principle's utility in drawing a cause-and-effect relationship.

Analogy has been interpreted to mean that when one causal agent is known, the standards of evidence are lowered for a second causal agent that is similar in some way.[144] The cause-and-effect relationship between a trauma mechanism and the development of WAD is generally rejected, as this phenomenon violates the common traumatological and wound healing principles that inform our current understanding of hard and soft tissue injuries.[145-147] In application; if we once again consider lateral ankle sprain – the primary tissue injury (anterior talofibular ligament and/or sometimes the calcaneofibular ligament) is easily detectable, the mechanism of injury is well-defined, there is a clear pathomechanical im-

pairment associated with the condition, and a significant improvement in mechanical stability is realised for the majority of individuals within a timeline that comports with the normative processes of wound healing.[148] If we attempt to infer a trauma mechanism for the development of WAD, and predict its prognosis using this principle of analogy, we fall short given our inability to 1) detect structural tissue damage and 2) correlate the persistence of symptoms with a narrative that supports the notion that physical injury accounts for the patient's condition. This line of reasoning is further corroborated by the findings noted in a retrospective survey investigating the occurrence of acute and chronic neck pain in demolition derby drivers. Of the 40 derby drivers surveyed, reporting exposure to a median of 1632 lifetime collisions, with mean and maximum collision speeds of 41.6 km/h and 72 km/h, respectively, only two reported their worst post-participation neck pain lasting more than three months, and for one it lasted more than a year. For the majority, the worst neck pain event lasted less than 21 days.[149] These findings suggest that motivational differences between derby drivers and people sustaining whiplash injuries in the general population may account for outcome differences. While this study is at risk of both recall and selection bias, as a group, the derbyists demonstrated that they were less likely to succumb to perceptions of victimhood or illness behaviour and symptom amplification – characteristics known to prolong recovery. Habituation; a form of nonassociative learning that refers to any decrease in innate responsiveness to a repeated stimulus, may also play a role in the derbyists responses to collision exposures.[150,151]

To this end, establishing a distinct cause-and-effect relationship between a trauma mechanism and the development of WAD via the aforementioned framework is untenable. As WAD is a disorder that is diagnosed clinically following a patient's report of symptoms that are commonly attributed to the temporality of MVC exposure in the absence of detectable tissue pathology, it may then be viewed, primarily, as a social construct that is significantly impacted by psychosocial factors, which may amplify otherwise benign bodily symptoms, or transform the possibility of a minor injury into one that is viewed as serious – in turn generating anxiety that sets in motion the phenomenon of symptom expectation and self-imposed functional disability. Those who may reject this inference might employ the *ad ignorantiam* argument by retorting

with the popular aphorism: "absence of evidence is not evidence of absence". While there is some truth to this statement, absence of evidence may constitute evidence of absence when negative evidence has probative value to support a particular hypothesis over another, to the extent that negative evidence is more likely to draw a scientifically sound conclusion under the favoured hypothesis than under the alternative hypothesis.[152]

Limitations

Although a comprehensive summary regarding the evidence underlying the most commonly theorised biological and psychosocial mechanisms of WAD pathogenesis was attempted, a primary limitation of this review includes finite access to data, hence the use of a single search database. The author is also cognisant that employing a narrow string of search terms may have unintentionally missed other published research studies pertaining to some aspect of WAD pathology.

Conclusion

A definitive etiopathological pathway displaying a causal relationship between MVC exposure and WAD development remains to be elucidated. While the face validity of WAD is good; as both clinicians and patients recognise the condition, the evidence supporting the various purported constructs suggesting a causal link between a trauma mechanism and the development of symptoms is inadequate. In the absence of a defined injury mechanism, a sophisticated understanding of the interconnected nature of biological, psychological, and social states and processes involved in the perception of pain is recommended. Therefore, future research is required to develop a better understanding of how to enhance individuals' expectations and abilities to adapt and self-manage in the face of physical, emotional, and social challenges, as this appears to significantly impact recovery.

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