In search of evidence-based treatment for concussion: characteristics of current clinical trials

Matthew J. Burke¹, Michael Fralick², Nasrin Nejatbakhsh³, Maria C. Tartaglia¹,⁴, & Charles H. Tator⁴,⁵

¹Division of Neurology, ²General Internal Medicine, ³Undergraduate Medicine, University of Toronto, Toronto, ON, Canada, ⁴Toronto Western Hospital, Toronto, ON, Canada, and ⁵Division of Neurosurgery, University of Toronto, Toronto, ON, Canada

Abstract

Objective: To assess the characteristics of current clinical trials investigating the treatment of concussion.

Background: Recent systematic literature reviews have concluded that there is minimal evidence to support any specific treatment for concussion, including the principles of return-to-activity protocols such as type or duration of rest.

Design/methods: Clinical trial data was extracted from Clinicaltrials.gov and seven additional World Health Organization primary registries. The trial databases were accessed up until 3 October 2013. This study used search terms of ‘concussion’ or ‘mild traumatic brain injury’ (mTBI) and filtered for interventional trials. Trials that were terminated, already published or not interventional trials of concussion/mTBI were excluded.

Results: Of the 142 concussion/mTBI interventional clinical trials identified, 71 met inclusion criteria. Trials had a median estimated enrolment of 60 participants. There was a wide-range of treatments studied, including cognitive/behavioural therapies (28.2%), medications (28.2%), devices (11.3%), dietary supplements (8.5%), return-to-activity/rest (1.4%) and others (22.4%). Heterogeneity among trials for concussion identification/diagnosis and primary outcomes utilized was evident. Symptom-based questionnaires (39.4%) and neuropsychological tests (28.2%) were the most common outcome measures.

Conclusions: Diverse, potentially promising therapeutics are currently being studied for the treatment of concussion. However, several deficiencies were identified including a paucity of trials addressing return-to-activity principles. Also, small sample size and trial heterogeneity may threaten scientific evaluation and subsequent clinical application.

Keywords

Brain concussion, brain injuries, clinical trials, post-concussion syndrome, therapeutics

Introduction

The current mainstay of concussion treatment is to follow graduated protocols for return to play, school and/or work. These protocols have largely been developed through sports-related concussion research and consist of an algorithmic approach to physical and cognitive rest/activity [1]. However, there is minimal evidence for their fundamental principles, such as type or duration of rest and, consequently, they rely heavily on expert opinion. This was identified as a concern with the initial protocols [2] and recent systematic literature reviews corroborate this [3–5]. Furthermore, these recent reviews also evaluated the potential role for therapies that have been proposed to speed recovery and/or reduce symptoms for patients with prolonged post-concussive symptoms. They all concluded that there is no evidence to support the use of any specific treatment.

Numerous clinical trials are underway to try to strengthen the evidence-base for concussion treatment. With the advent of regulated clinical trial registries, most notably Clinicaltrials.gov, detailed information on such trials can be publicly accessed. Trial registration in these databases has increased considerably over recent years, enhancing their representation of the clinical research enterprise [6]. This growth is attributed to strengthened government-led legislations [7] as well as mandates by the International Committee of Medical Journal Editors (ICMJE) that clinical trials must be registered as a pre-requisite to publication in ICMJE member journals [8].

The purpose of the present study is to assess the characteristics of current clinical trials investigating the treatment of concussion, focusing on study demographics, methodologies, target populations, outcome measures and types of interventions.

Methods

Several clinical trial registries were utilized to develop a representative sample of clinical trials investigating the
treatment of concussion. The registries included: Clinicaltrials.gov, EU Clinical Trials Register (EU-CTR), International Standard Randomized Controlled Trial Number Register (ISRCTN), Australian New Zealand Clinical Trials Registry (ANZCTR), Chinese Clinical Trial Registry (ChiCTR), Brazilian Clinical Trials Registry (ReBec), Clinical Trials Registry India (CTRI) and the Pan African Clinical Trial Registry (PACTR). ClinicalTrials.gov is the largest and most comprehensive of these clinical trial databases. Their trial registration process, data entry requirements and data quality have been well described elsewhere [6, 9]. The other seven databases have been less studied; however, all are primary registries in the World Health Organization (WHO) Registry Network [10] and all meet the requirements of the ICMJE.

The trial databases were accessed between 3 June and 3 October 2013. All searches occurred through each database’s independent online interface as opposed to a group search through organizations, such as WHO, that combine multiple databases. The search terms ‘concussion’ or ‘mild traumatic brain injury’ (mTBI) were used and interventional trials filtered for. It should be noted that registry search engines followed keywords as opposed to MeSH subject headings.

All search results were individually evaluated by MB and NN. Trials that were not interventional trials of concussion/ mTBI (on further manual review) were excluded. Terminated or already published trials, as of 3 June 2013, were also excluded. Data from trial entries were captured and analysed using descriptive statistics.

Results

Of the 142 concussion/mTBI interventional clinical trials identified, 71 met the study inclusion criteria (Figure 1). The most common reason for exclusion was diagnosis/condition other than concussion/mTBI. Thirty-six trials matched the search term ‘concussion’, with 26 of these trials also matching ‘mTBI’. Thirty-five trials were listed under ‘mTBI’ only. The distribution of trials by registry database is shown in Figure 2. No trials were listed in more than one registry.

The demographic and design characteristics of the 71 included trials are presented in Table I. The majority of trials were based in the US (69%) and a minority were industry funded (7%). Almost half (47.9%) were listed as currently recruiting participants, while the other half were predominantly trials not yet open for recruitment (23.9%) or recently completed (21.1%). The median number of participants per trial was 60 (IQR = 35–95) and 80.3% had an estimated enrolment of less than 100 participants. Just over half the trials reported a trial phase and, of these, only 4.2% were phase III clinical trials. Trials were split between those focusing only on concussion/mTBI (45.1%) and those that had a concussion/mTBI arm as part of a larger traumatic brain injury study (54.9%). 90.1% of trials were randomized and 47.9% were double-blind.

Clinical trial study populations, primary outcomes and treatment types are presented in Table II. The majority of trials enrolled patients with unspecified causes of injury (56.3%). The specifically targeted populations included the military (35.2%) and athletes (8.5%). In 83.1% of trials, participants were studied during the sub-acute to chronic phases after injury (>48 hours). Elderly subjects over 65 years of age and children/adolescents less than 18 years of age were excluded from participation in most trials; 60.6% and 85.9%, respectively.

Trials were heterogeneous with respect to the criteria used for the identification or diagnosis of concussion. There was also heterogeneity in the evaluation measures after intervention. Almost half did not state any criteria used to define/diagnose concussion; for those that did, inconsistencies in the detail and format of the provided information precluded an accurate qualitative comparison. Primary outcomes varied considerably between trials. Symptom-based questionnaires (39.4%) and neuropsychological tests (28.2%) were the most commonly used primary outcome measures.

There was a wide-range of treatments studied, including medications (28.2%), cognitive/behavioural therapies (28.2%), devices (11.3%), dietary supplements (8.5%), return-to-activity/rest (1.4%) and others (22.4%). The treatment types are presented in Tables III–V.
Discussion

This study examined 71 ongoing or recently completed trials of the treatment of concussion or mTBI. The findings provide an overview of the direction of current potential therapies, but, most importantly, identify critical deficiencies in treatments and sub-populations studied as well as concerns pertaining to small sample size and trial heterogeneity.

There are a number of diverse, potentially promising therapeutic strategies currently being investigated for the treatment of concussion or mTBI. Many trials are assessing therapies commonly used for other conditions, which are being applied to treat specific somatic and neuropsychiatric post-concussive symptoms [11]. Such treatments are used intuitively, despite limited or no evidence specific to concussion. Treatments that have previously shown encouraging preliminary results, such as nutritional supplementation [12] and cognitive therapy/restructuring [3], are also being studied.

There were relatively few novel pharmacotherapies tailored specifically towards mechanisms presumed operative in the pathogenesis of concussion symptoms. Despite proposed neurometabolic models [13], the pathogenesis of concussion is still largely unknown [14] and, thus, there are considerable challenges in identifying drug targets of interest. Also, industry has shown minimal interest in the field of

### Table I. Clinical trial demographic and design characteristics \( (n = 71) \)

| Country/region          | n (%) |
|-------------------------|-------|
| US                      | 49 (69.0%) |
| Australia/New Zealand  | 8 (11.3%) |
| Canada                  | 6 (8.5%)  |
| Europe                  | 6 (8.5%)  |
| Asia                    | 2 (2.8%)  |
| Lead sponsor            |        |
| University/Hospital      | 55 (77.5%) |
| Government              | 11 (15.5%) |
| Industry                | 5 (7.0%)  |
| Recruitment status      |        |
| Recruiting              | 34 (47.9%) |
| Not yet open for recruitment | 17 (23.9%) |
| Completed               | 15 (21.1%) |
| Ongoing (but not recruiting) | 3 (4.2%)  |
| Enrolling by invitation | 1 (1.4%)  |
| Not available           | 1 (1.4%)  |
| Clinical trial phase    |        |
| 1                       | 12 (16.9%) |
| 2                       | 18 (25.3%) |
| 3                       | 3 (4.2%)  |
| 4                       | 5 (7.0%)  |
| Not available           | 33 (46.5%) |
| Estimated trial enrolment |          |
| Median (IQR)            | 60 (35–95) |
| <101                    | 57 (80.3%) |
| 101–1000                | 14 (19.7%) |
| >1000                   | 0        |
| Allocation              |        |
| Randomized              | 64 (90.1%) |
| Non-randomized          | 4 (5.6%)  |
| Not available           | 3 (4.2%)  |
| Blinding                |        |
| Open                    | 17 (23.9%) |
| Single                  | 19 (26.8%) |
| Double                  | 34 (47.9%) |
| Not available           | 1 (1.4%)  |
| Comparator group        |        |
| Placebo                 | 36 (50.7%) |
| Cognitive/behaviourial | 10 (14.1%) |
| ‘Standard of care’       | 8 (11.3%) |
| Drug (head to head)     | 0        |
| Not-applicable          | 17 (23.9%) |
| Inclusion of other brain injury conditions |        |
| Yes; moderate TBI       | 26 (36.6%) |
| Yes; moderate and severe TBI | 13 (18.3%) |
| No                      | 32 (45.1%) |

IQR, interquartile range; TBI, traumatic brain injury.

### Table II. Clinical trial study populations, primary outcomes and treatment types \( (n = 71) \)

| Study population | n (%) |
|------------------|-------|
| Patients (unspecified)* | 40 (56.3%) |
| Military          | 25 (35.2%) |
| Athletes          | 6 (8.5%)  |
| Gender            |        |
| Male and female   | 71 (100%) |
| Exclusion of elderly (>65 years) | 43 (60.6%) |
| No                | 28 (39.4%) |
| Exclusion of children (<18 years) | 61 (85.9%) |
| No                | 10 (14.1%) |
| Clinical criteria for concussion/mTBI stated | |
| Yes               | 40 (56.3%) |
| No                | 31 (43.7%) |
| Timeframe of intervention |        |
| Acute (<48 hours post-injury) | 10 (14.1%) |
| Sub-acute/chronic | 59 (83.1%) |
| Both              | 2 (2.8%)  |
| Primary outcome   |        |
| Symptom-based questionnaire | 28 (39.4%) |
| Neuropsychological testing | 20 (28.2%) |
| Time to return to work/sport | 5 (7.0%)  |
| Neuroimaging      | 4 (5.6%)  |
| Feasibility assessment | 4 (5.6%)  |
| Other             | 10 (14.1%) |
| Intervention      |        |
| Drug              | 20 (28.2%) |
| Cognitive/behavioural | 20 (28.2%) |
| Device therapy    | 8 (11.3%) |
| Dietary supplement | 6 (8.5%)  |
| Hyperbaric oxygen | 5 (7.0%)  |
| Physical therapy  | 5 (7.0%)  |
| Rest              | 1 (1.4%)  |
| Other             | 6 (8.5%)  |

*Patients with unspecified sources of injury (37.5% of these patients were enrolled through the emergency department).

### Table III. Symptom-based pharmacological treatments.

| Drug name       | Symptom               | Class                   |
|-----------------|-----------------------|-------------------------|
| Amitriptyline   | Headache              | Antidepressant          |
| Metoclopramide  | Headache              | Anti-emetic             |
| Gabapentin      | Insomnia              | Anti-epileptic          |
| Melatonin       | Insomnia              | Supplement              |
| Armodafinil     | Fatigue               | Neurostimulant          |
| OSU6162         | Fatigue               | Unknown                 |
| Valproate       | Mood                  | Anti-epileptic          |
| Donepezil       | Memory/Cognitive      | AChEI                   |
| Risperidone     | Memory/Cognitive      | Supplement              |
| Ondansetron     | Not specified         | Anti-emetic             |

AChEI, acetylcholinesterase inhibitor.
concussion management. The 7% industry sponsorship for concussion trials was far less than the estimated 32.4% sponsorship for all trials in the Clinicaltrials.gov database [15].

Of much greater surprise and concern was the marked deficiency of studies investigating rest/return-to-activity recommendations, which are fundamental to current concussion management guidelines. Animal models have provided a theoretical basis for the value of rest in the first few days following injury; however, a recent review of rest and other treatments for concussion showed that human studies have been very limited and have yielded inconclusive results [5]. Indeed, there has only been one randomized clinical trial of rest [16]. Clinicians are desperate for evidence to complement the expert-opinion that currently drives decision-making for return-to-activity protocols.

The majority of trials enrolled patients with unspecified causes of injury and, of the trials that targeted a specific sub-population, most focused on military personnel. This may be a reflection of recent concerns surrounding the high incidence and poor outcome of repetitive mTBI and blast injury in the military [17]. A limited number of trials specifically targeted athletes, although many sports-related concussions were likely included with other causes such as motor vehicle accidents and work-place injuries to comprise the unspecified patient groups in many trials. In the authors’ view, separate treatment trials should be targeted towards an homogeneous population of concussion patients with a common mechanism of injury. For example, sports-related concussions pose unique assessment and management considerations [18] and merit specific treatment trials.

Paediatric populations were excluded from a great majority of trials. This is consistent with previous tendencies to neglect this demographic in concussion research [19]. However, there is a need for the evaluation of treatment strategies specific to the paediatric sub-group. First, research suggests that the developing brain of a child/adolescent may follow a more complicated and protracted clinical trajectory after concussion [20]. Second, emergency room visits for concussion amongst children/adolescents have doubled over recent years [21]. There is also a need to study treatment of concussion in those over age 65, who represent a considerable number of cases, but have been excluded from most trials.

Table V. Non-pharmacological treatments.

| Drug name                        | Mechanism of action                  | Class                        |
|----------------------------------|--------------------------------------|------------------------------|
| Sildenafil                       | Cerebral blood flow                  | PDE-5 inhibitor             |
| Hyperosmolar sodium lactate      | Cerebral energy metabolism           | n/a                          |
| DHA                              | Anti-inflammatory and anti-oxidant   | Supplement                   |
| N-acetyl-cysteine                | Antioxidant                          | Supplement                   |
| 3% hypotonic saline              | Intracranial pressure                | n/a                          |
| Progesterone                     | Neuroprotective                      | Steroid                      |
| Pregnenolone                     | Neuroprotective                      | Steroid                      |
| Atorvastatin                     | Neuroprotective                      | Statin                       |
| Somatropin (rHGH)                | Not specified                        | Neurohormonal                |
| Branched chain amino acids       | Not specified                        | Supplement                   |
| Citicoline                       | Not specified                        | Neurostimulant               |
| MLC901                           | Not specified                        | Supplement                   |

**Table IV. Pharmacological treatments without an indicated target symptom.**

| Drug name                        | Mechanism of action                  | Class                        |
|----------------------------------|--------------------------------------|------------------------------|
| Sildenafil                       | Cerebral blood flow                  | PDE-5 inhibitor             |
| Hyperosmolar sodium lactate      | Cerebral energy metabolism           | n/a                          |
| DHA                              | Anti-inflammatory and anti-oxidant   | Supplement                   |
| N-acetyl-cysteine                | Antioxidant                          | Supplement                   |
| 3% hypotonic saline              | Intracranial pressure                | n/a                          |
| Progesterone                     | Neuroprotective                      | Steroid                      |
| Pregnenolone                     | Neuroprotective                      | Steroid                      |
| Atorvastatin                     | Neuroprotective                      | Statin                       |
| Somatropin (rHGH)                | Not specified                        | Neurohormonal                |
| Branched chain amino acids       | Not specified                        | Supplement                   |
| Citicoline                       | Not specified                        | Neurostimulant               |
| MLC901                           | Not specified                        | Supplement                   |

PDE, phosphodiesterase; DHA, docosahexaenoic acid; rHGH, recombinant human growth hormone.

*Exercises used to elicit somatic sensations in an attempt to extinguish or lessen the fear reaction to these sensations.

*Behavioural feedback/operant conditioning exercises.

*12-month supported employment programme aimed to improve quality-of-life and community integration for military veterans.

*PoNS™ device for neuromodulation (through stimulation of the tongue) as an adjuvant to improve the effectiveness of vestibular rehabilitation.

*The use of a frequency modulation assistive device and/or a computerized auditory training programme.

*Targeted implementation of guidelines for healthcare encounters.

*Using text messaging between patient and care provider for symptom assessment/follow-up.

Concussion management. The 7% industry sponsorship for concussion trials was far less than the estimated 32.4% sponsorship for all trials in the Clinicaltrials.gov database [15].
Overall, the study sample sizes were small, with only 19.7% of trials having an estimated enrolment over 100 participants. This can be compared to 38% for all trials registered in the Clinicaltrials.gov database [15]. Even the 38% from this report was suggested by the authors to be too small. The main concern is that small trials may be underpowered and unable to reliably establish the effectiveness of the intervention studied [22]. The heterogeneity of the trials is equally concerning because inconsistencies between studies in the diagnostic criteria for concussion/mTBI, as well as lack of standardized primary outcomes, may hinder interpretation of results and scientific comparisons. Also, combining such trials for meta-analysis for later evaluation may not be possible [23]. The risk of heterogeneity hampering the advancement of concussion treatment research has been considered previously [24]. Unfortunately, disagreement and variation in practice regarding the definition/diagnosis of concussion continues to plague the field, despite recent definition revisions and advances in diagnostic tools. Even fundamental considerations such as whether or not concussion and mTBI are interchangeable or distinct conditions have not been resolved [25]. Different approaches to monitoring concussion resolution are also pervasive and manifest in research as variability of outcome measures. This is exemplified by the numerous National Institute of Neurologic Disorders and Stroke (NINDS) Common Data Elements (CDEs) listed for mTBI outcome measures [26]. Independent of heterogeneity, the current standard of symptom-based measures and/or neuropsychological testing are far from the ideal of objective and validated outcome measures deemed necessary for the development of high quality evidence [27, 28].

The findings from this study yield many important implications. Going forward it is evident that more trials investigating optimal progression to return-to-play/school/work are needed. Other important areas of focus should include further study surrounding management of persistent post-concussion symptoms, such as headache and mood disorder, that continue to pose considerable challenges for clinicians. The predominant current practice of applying symptom-based therapies, whose evidence-base is derived from studies of other disease cohorts (e.g. chronic migraine or major depressive disorder) is inadequate. Studying symptom-based treatments with a multi-modal and multi-disciplinary approach, specific to concussion populations, needs to be a priority. Also, as knowledge of concussion pathophysiology continues to grow, it will be increasingly important for proposed treatment trials to recognize and target implicated mechanisms. Finally, more targeted study of athlete, paediatric and elderly populations would limit potential inappropriate generalizations to these sub-groups.

Understanding and addressing the methodological concerns raised in this study may pose a greater challenge. Given the high incidence of concussion, there should be the potential for large studies. There are many possible explanations for the relatively small sample sizes and there are probably overlapping factors. First, obstacles may exist that impede recruitment such as low rates of concussed patients who seek medical attention and the highly variable settings of initial presentation. More collaboration between disciplines (such as sports medicine, emergency medicine, family medicine, paediatrics, physiatry, neurology, psychiatry and neurosurgery) as well as between research centres could improve study recruitment. Second, a relative lack of industry sponsorship may make it difficult for investigators to find funding to support large sample studies. Third, the majority of current treatments for concussion are in their infancy of development. Thus, studies are taking the form of small pilot trials aimed at providing proof of principle rather than phase 3 trials sufficiently powered to show efficacy. Until such latter studies are completed, the level of evidence for these interventions will not be deemed adequate to impact guidelines and influence clinical practice.

With regards to the heterogeneity, many of the concerns surrounding inconsistencies in diagnosis and outcome monitoring could be solved by an objective concussion biomarker. This is by no means a novel assertion, but a strong testimony to its utility. Attempts to identify putative biochemical and neuroimaging biomarkers are well underway, but so far none have been able to transition from research to mainstream clinical practice [29–31].

**Limitations of the study**

Using Clinicaltrials.gov and other clinical trial registries as a research tool has many limitations. First, the quality of the data extracted is dependent on the accuracy and completeness of information provided by the registrants. Quality assurance procedures to review individual records exist but have inherent limitations themselves [6]. The validity of outcome measure data has been a particular concern [7]. Second, trial registries do not capture all interventional research studies and it is likely that many smaller studies of concussion treatment may have been missed in the assessment. Third, although it was attempted to achieve a global representation by including international registries, it is clear that this study includes mainly US-based trials. This may have influenced certain findings, such as the high representation of military studies. It is not known why there are so few concussion trials registered in other countries as this study cannot delineate to what extent this may be a result of overall lower rates of clinical trial registration vs. a relative lack of interest or resources for concussion treatment trials. Using clinical trial registry data for the purpose of analysing general trends or characterizing the state of research in a specific field is growing but still relatively novel. Many other areas of medicine have been investigated in this manner [15, 32].

Other limitations are related to the composition of the included trial set. Approximately half the trials incorporated concussion/mTBI as an arm of a larger TBI trial rather than being the sole focus of study. In the authors’ opinion, treatment trials of concussion/mTBI should not include more severe brain injuries. This study also did not exclude any sub-types of mTBI, such as blast injury, which may or may not represent a unique clinical entity compared to non-blast concussive injuries [33, 34]. These studies were included in an attempt to cover all treatments that may have the potential to be applied to concussion/mTBI.
Conclusions
Concussion research has recently expanded greatly. Within the past 2 years, there have been numerous reviews, commentaries and guideline revisions of concussion definitions and management and they have brought attention to the lack of evidence-based treatment. The current clinical trials represent a move forward; however, several deficiencies may threaten the ability of these studies to influence clinical practice and accordingly temper the optimism that evidence-based treatments are imminent. It is suggested that more appropriately targeted research efforts with enhanced methodological rigour are required in order to adequately address the ongoing need for evidence-based treatment of concussion.

Declaration of interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References
1. McCrory P, Meeuwisse WH, Aubry M, Cantu B, Dvorák J, Echemendia RJ, Engebretsen L, Johnston K, Kutcher JS, Raferty M, et al. Consensus statement on concussion in sport: The 4th International Conference on Concussion in Sport held in Zurich, November 2012. British Journal of Sports Medicine 2013;47:250–258.
2. Collins MW, Lovell MR, Mccag DB. Current issues in managing sports-related concussion. The Journal of the American Medical Association 1999;282:2283–2285.
3. Giza CC, Kutcher JS, Barth J, Getchius TS, Gioia GA, Gronseth GS, Guskevich K, Mandel S, Manley G, et al. Summary of evidence-based guideline update: Evaluation and management of concussion in sports: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013;80:2250–2257.
4. Harmon KG, Drezner JA, Gammons M, Guskevich K, Halstead M, Herring S, Kutcher J, Pana A, Putukian M, Roberts W. American Medical Society for Sports Medicine position statement: Concussion in sport. British Journal of Sports Medicine 2013;47:15–26.
5. Schneider KJ, Iverson GL, Emery CA, McCrory P, Herring SA, Meeuwisse WH. The effects of rest and treatment following sport-related concussion: A systematic review of the literature. British Journal of Sports Medicine 2013;47:304–307.
6. Zarin DA, Tse T, Williams RJ, Califf RM, Ide NC. The ClinicalTrials.gov results database: Update and key issues. New England Journal of Medicine 2011;364:852–860.
7. Dickersin K, Rennie D. The evolution of trial registries and their implications and management and they have brought attention to the lack of evidence-based treatment. The current clinical trials represent a move forward; however, several deficiencies may threaten the ability of these studies to influence clinical practice and accordingly temper the optimism that evidence-based treatments are imminent. It is suggested that more appropriately targeted research efforts with enhanced methodological rigour are required in order to adequately address the ongoing need for evidence-based treatment of concussion.
8. Tator CH. Concussions and their consequences: Current diagnosis, management and prevention. Canadian Medical Association Journal 2013;185:975–979.
9. Califf R, Zarin D, Kramer JM, Sherman R, Aberle L, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. The Journal of the American Medical Association 2012;307:1838–1847.
10. Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. soldiers returning from Iraq. New England Journal of Medicine 2008;358:453–463.
11. Meehan III WP. Medical therapies for concussion. Clinics in Sports Medicine 2011;30:115–124.
12. Kirkwood MW, Yeates KO, Wilson PE. Pediatric-sport related concussion: A review of clinical management of an oft-neglected population. Pediatrics 2007;120:1359–1374.
13. Comper P, Bisschop SM, Carmide N, Tricco A. A systematic review of treatments for mild traumatic brain injury. Brain Injury 2005;19:863–880.
14. Tator CH. Let’s standardize the definition of concussion and get reliable incidence data. The Canadian Journal of Neurological Sciences 2009;36:405–406.
15. National Institute of Neurological Disorders and Stroke Common Data Elements [Internet]. Bethesda, MD: National Institute of Health; Available online at: http://www.commondataelements.ninds.nih.gov, accessed 5 March 2014.
16. Moher D, Schulz KF, Alard J, Altman D. CONSORT Statement: Revised recommendations for improving the quality of reports of parallel-group randomized trials. The Journal of the American Medical Association 2001;285:1987–1991.
17. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ, GRADE Working Group. GRADE: An emerging consensus on rating quality of evidence and strength of recommendations. British Medical Journal 2008;336:924–926.
18. Jeter CB, Hergenroeder GW, Hylin MJ, Redell JB, Moore AN, Dash PK. Biomarkers for the diagnosis and prognosis of mild traumatic brain injury/concussion. Journal of Neurotrauma 2013;30:657–670.
19. Zetterberg H, Smith DH, Blennow K. Biomarkers of mild traumatic brain injury in cerebrospinal fluid and blood. Nature Reviews. Neurology 2013;9:201–210.
20. Bigler ED. Neuroimaging biomarkers in mild traumatic brain injury. Neuropsychology Review 2013;23:169–209.
21. Todd JL, White KR, Chiswell K, Tasneem A, Palmer SM. Using ClinicalTrials.gov to understand the state of clinical research in pulmonary, critical care, and sleep medicine. Annals of the American Thoracic Society 2013;10:411–417.
22. Belanger HG, Proctor-Weber Z, Kretzmer T, Kim M, French LM, Vanderploeg RD. Symptom complaints following reports of blast versus non-blast mild TBI: Does mechanism of injury matter? The Clinical Neuropsychologist 2011;25:702–715.
23. Erickson JC. Treatment outcomes of chronic post-traumatic headaches after mild head trauma in US soldiers: An observational study. Headache 2011;51:932–944.