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Pain in Patients with Polytrauma: A Systematic Review

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PREFACE

VA's Health Services Research and Development Service (HSR&D) works to improve the cost, quality, and outcomes of health care for our nation's veterans. Collaborating with VA leaders, managers, and policy makers, HSR&D focuses on important health care topics that are likely to have significant impact on quality improvement efforts. One significant collaborative effort is HSR&D's Evidence-based Synthesis Program (ESP). Through this program, HSR&D provides timely and accurate evidence syntheses on targeted health care topics. These products will be disseminated broadly throughout VA and will: inform VA clinical policy, develop clinical practice guidelines, set directions for future research to address gaps in knowledge, identify the evidence to support VA performance measures, and rationalize drug formulary decisions.

HSR&D provided funding for the two Evidence Based Practice Centers (EPCs) supported by the Agency for Healthcare Research and Quality (AHRQ) that also had an active and publicly acknowledged VA affiliation—Southern California EPC and Portland, OR EPC—so they could develop evidence syntheses on requested topics for dissemination to VA policymakers. A planning committee with representation from HSR&D, Patient Care Services, Office of Quality and Performance, and the VISN Clinical Management Officers, has been established to identify priority topics and to ensure the quality of final reports. Comments on this evidence report are welcome and can be sent to Susan Schiffner, ESP Program Manager, at Susan.Schiffner@va.gov.

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Pain in Patients with Polytrauma

INTRODUCTION

Polytrauma is defined in the VHA Polytrauma Rehabilitation Centers Directive dated June 8, 2005 as: "injury to the brain in addition to other body parts or systems resulting in physical, cognitive, psychological, or psychosocial impairments and functional disability." The definition of polytrauma has since expanded to include concurrent injury to two or more body parts or systems that results in cognitive, physical, psychological or other psychosocial impairments. Traumatic Brain Injury (TBI) often occurs in polytrauma and in combination with other disabling conditions including amputation, auditory or visual impairments, spinal cord injury (SCI), post-traumatic stress disorder (PTSD), and other mental health conditions.

Pain resulting from polytraumatic injuries poses numerous challenges during rehabilitation treatment and afterwards. Treatments typically used to reduce pain in these individuals (for example, oral opioids) have the potential to interfere with the active rehabilitation needed to restore function.

The objectives of this report are to systematically review the literature to address the assessment and management of pain in patients with polytraumatic injuries, to identify patient, clinician and systems factors associated with pain-related outcomes in these patients, and to describe current or planned research addressing the key questions.

Background

Major advances in body armor technology and battlefield medicine have improved survival from combat injuries that would have been fatal in previous wars.(1) Data from the Department of Defense indicate that the lethality of war wounds has decreased from 24% in the Vietnam and Persian Gulf Wars to 10% in the current Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) conflicts.(2) Survivors of polytraumatic injuries among soldiers returning from the current conflicts tend to have more complex injuries and emotional trauma than typically seen in the past wars.(3, 4)

Among 119 casualties admitted to Walter Reed Army Medical Center from OIF during March 1 to July 1, 2003, 39% had sustained gunshot wounds, 31% sustained blast and shrapnel injuries, and 34% had blunt/motor vehicle collision mechanisms.(5) Among these 119 patients there were 184 injured areas, and the location of injury was the lower extremity for 62% of patients, the upper extremity for 30%, the head and neck for 25%, the chest for 25%, and the abdomen for 16%. Among 52 patients with orthopedic injuries evacuated during OEF between December 2001 and January 2003, 15 (29%) had suffered traumatic amputations, of which 5 (33.3%) were below-knee.(6) All amputations were caused by land mines or exploded ordinance.

Twenty-eight percent of all individuals medically evacuated to the Walter Reed Army Medical Center (WRAMC) due to combat injuries during OEF/OIF had a TBI, according to a report in 2006.(4) By contrast, 12 to 14% of all combat casualties in the Vietnam War had a brain injury.(7) In the current conflicts, Kevlar body armor and helmets have

improved overall survival rates and reduced the frequency of penetrating head injuries.(7) Because mortality from substantial brain injuries among U.S. combatants in Vietnam was 75% or greater, soldiers with recognized brain injuries made up only a small fraction of the casualties. Between January 2003 and February 2005, 59% of all patients who were exposed to a blast and admitted to WRAMC were given a diagnosis of TBI.(7) Closed TBI accounted for 88% of all TBI. Moderate to severe TBI accounted for 56% of TBI cases. Nineteen percent of TBI patients sustained concomitant amputation.

Brain injuries from blasts may go undiagnosed and untreated in patients with polytrauma because of the attention focused on more visible injuries. Commonly overlooked pain-related conditions in patients with polytrauma may include soft-tissue damage, PTSD, nerve damage, hearing loss and tinnitus, chronic infections, vision changes, lung injury, vestibular problems, and undiscovered shrapnel fragments.(8) In addition to the direct effects of blasts, injuries can result from the structural collapse and fragmentation of buildings and vehicles, and may include crush injuries and compartment syndrome.(9)

Under a new system established by the VHA in 2005, severely injured soldiers with TBI are being referred early in their treatment to one of four VA medical centers in Richmond, VA; Tampa, FL; Palo Alto, CA; and Minneapolis, MN) designated as Polytrauma Rehabilitation Centers (PRCs). The four PRCs approach treatment of polytrauma patients using a mechanism-of-injury approach to provide a comprehensive, efficient, and interdisciplinary system of care.(8) Each of the four PRCs has been identifying six to 10 cases of TBI per month that were missed in military hospitals.(10)

METHODS

Topic Development

This topic was nominated by Michael Clark, PhD, Clinical Director of the Pain Program, James A. Haley VAMC. The scope and key questions for the review were further refined in consultation with representatives from the VA HSR&D Service, the VA Evidence Synthesis Program, and technical experts in pain, polytrauma, or traumatic brain injury (Robert Kerns, PhD; Nina Sayer, PhD; Marti Buffum DNSc, APRN, BC, CS; Michael Clark, PhD; Henry Lew, MD, PhD; Nancy Carney, PhD; Ron Gironda, PhD; Martin Schreiber, MD).

1. Have reliable and valid measures and assessment tools been developed to measure pain intensity and pain-related functional interference among patients with cognitive deficits due to TBI? Which measures and tools are likely to be most useful in assessing pain in polytrauma patients with cognitive deficits due to TBI?

2. A. Which treatment approaches are most likely to be effective in improving pain outcomes (pain intensity and functional interference) in polytrauma patients?
   B. Which pain treatment approaches are most likely to enhance overall rehabilitation efforts?

3. A. Does blast-related headache pain differ in terms of phenomenology and treatment from other types of headache pain?
   B. Which treatments are best for persistent blast-related headache pain?

4. What patient factors are associated with better and worse pain-related clinical outcomes among polytrauma patients? Have interventions been developed to specifically address these factors?

5. What are unique provider and system barriers to detecting and treating pain among polytrauma patients? Have interventions been developed to effectively address these barriers?

Polytrauma is defined as concurrent injury to two or more body parts or systems resulting in cognitive, physical, psychological or other psychosocial impairments. Combat-related mental conditions co-occurring with injury to at least one other system also constitutes polytrauma.

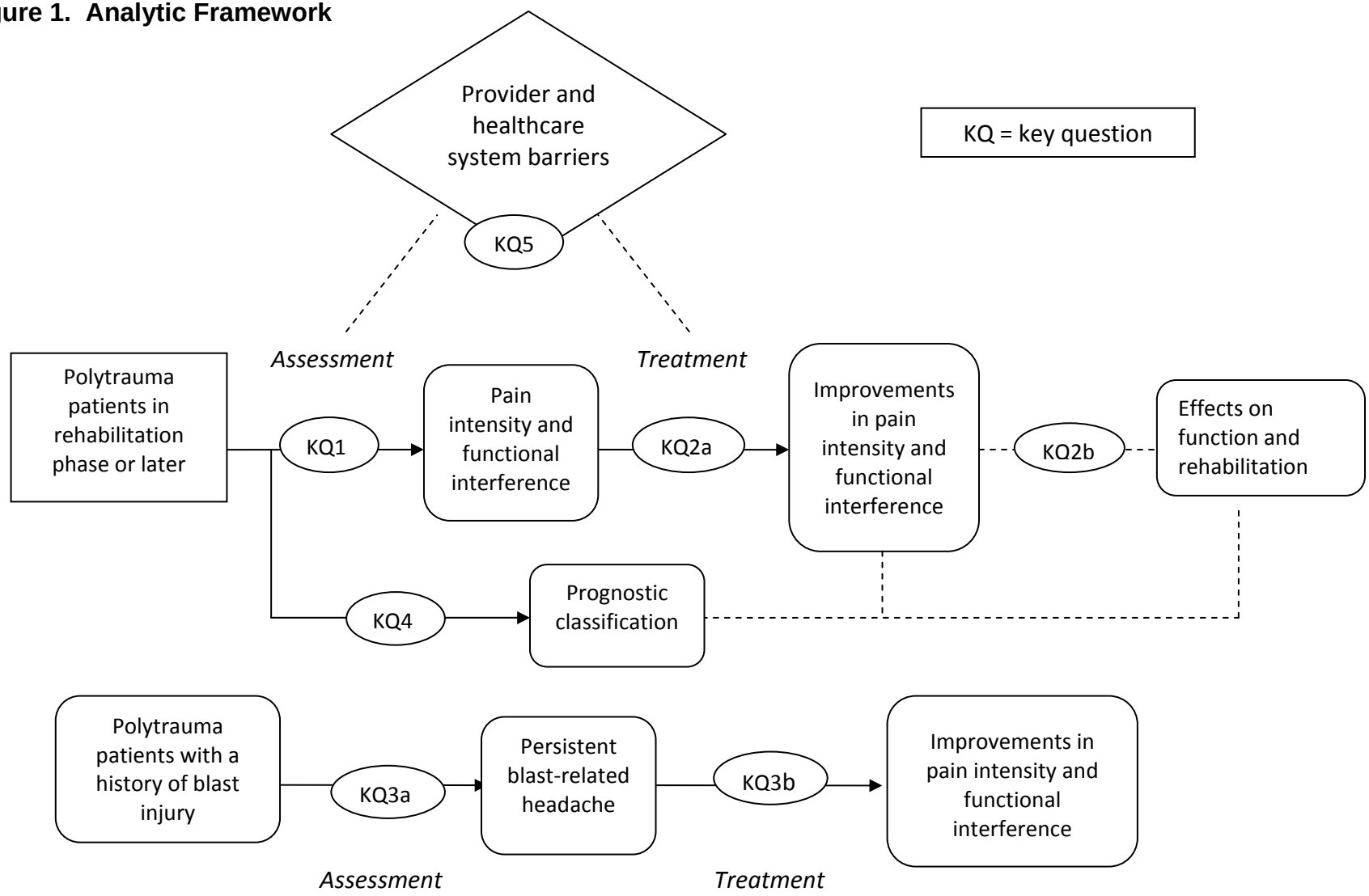
The scope of this review **includes** the assessment and treatment in rehabilitation and post-rehabilitation care settings of persistent pain or exacerbations of pain resulting from polytraumatic injuries. We included studies measuring pain-related outcomes, specifically pain intensity and pain-related function or interference, 3 months or more from the date of injury.

The scope of this review **excludes** the following:

- Short-term (less than 3 months) outcomes following injury. We sought to focus on pain persisting into the rehabilitation phase of treatment or longer, and not battlefield or acute management of polytraumatic injury.
- Unilateral amputation without other concurrent conditions or injuries. Bilateral amputation was considered polytrauma.
- Spinal cord injury without other concurrent conditions or injuries
- Choice of specific surgical strategy or specific procedures for particular orthopedic injuries or perioperative management of traumatic injuries.
- Post-traumatic/post-concussive headache unrelated to blast injury, unless the sample includes patients with moderate or greater TBI.
- Functional outcomes of polytrauma unless pain measures are included as one component of the functional outcome measure or in addition to the functional outcome measure.

Figure 1 illustrates the analytic framework that guided our review and synthesis.

Figure 1. Analytic Framework



Literature Search Strategy

Two research librarians (Rose Campbell and Andrew Hamilton) independently designed search strategies based on the key questions, and conducted searches in Medline of literature published from 1950 through July 2008. Appendix A provides the search strategies in detail. The results of both searches were combined into a single reference library. Additional articles were identified from reference lists of studies, review articles, editorials, and by consulting experts. We also searched for relevant studies in the following databases: PsychINFO; the PILOTS Database (the VA PTSD bibliographic database); REHABDATA, the bibliographic database of the National Rehabilitation Information Center; the DoD Defense Technical Information Center; and the Cochrane Database of controlled clinical trials. All citations were imported into an electronic database (EndNote X1). We also searched for unpublished and ongoing research studies, as described in the section on Active Research to follow.

Study Selection

Three researchers (SD, RC, MF) trained in the critical analysis of literature reviewed the titles and abstracts identified from the searches. Full-text articles of potentially relevant abstracts were retrieved for further review. Each article retrieved was reviewed with a brief screening form (see Appendix B) that collected data on the key question to which the article applied, as well as key words or emerging themes. Reference lists from pertinent articles were reviewed to find additional articles for inclusion.

Study Inclusion Criteria

Eligible articles had English-language abstracts and provided primary data relevant to the key questions. For a study to be eligible for Key Questions 1, 2, 4 and 5, the sample had to have all or a majority of patients with polytrauma, or analyses and findings had to be stratified by whether the patients had polytrauma, such that if a minority of the sample had polytrauma, readers could discern outcomes for the polytrauma group. For purposes of the review, polytrauma was defined as concurrent injury to two or more body parts or systems resulting in cognitive, physical, psychological or other psychosocial impairments. TBI of moderate or greater severity was also considered polytrauma (head injury itself plus associated cognitive sequellae). Combat-related mental conditions co-occurring with injury to at least one other system also constituted polytrauma. This definition is consistent with the VHA Directive 2005-024 describing the policy for the PRCs. Eligible studies examined the assessment and treatment in rehabilitation and post-rehabilitation care settings of persistent pain or exacerbations of pain resulting from polytraumatic injuries.

Eligible study designs included controlled clinical trials, systematic reviews, as well as prospective and retrospective cohort studies, case-control design studies, and qualitative studies using rigorous qualitative research methods. For these types of study designs, we abstracted data as described below. Due to a limited number of studies that included a comparator group, we also considered relevant cross-sectional and case report/case series

studies for inclusion for some of the key questions. For these study designs, data were not formally abstracted nor rated for quality of evidence.

Study Exclusion Criteria

Studies examining battlefield/emergency or assessment and care within 3 months of injury were not included unless they also examined pain outcomes 3 months or more from the date of injury, that is, pain persisting into the rehabilitation phase of treatment or longer. We also did not include studies examining choice of specific surgical strategy, the perioperative management of traumatic injuries (including burn injuries), or use of particular procedures or devices for specific orthopedic injuries. There are numerous case reports and case series describing specific surgical interventions for particular types of wounds; we felt that their inclusion would not yield generalizable information. We excluded studies describing functional outcomes of polytrauma unless a pain measure was included and reported as a component of the functional outcome measure or in addition to the functional outcome measure. Finally, we excluded studies of post-traumatic/post-concussive headache unless the sample included patients with moderate or more severe head injury or included a majority of patients with blast-related head injury. There have been a number of narrative reviews of assessment and treatment of post-traumatic headache among patients with mild-TBI or post-concussive syndrome; we felt that inclusion of these studies was beyond the scope of our key questions.

Secondary Findings

For key questions 1, 2, 3, and 4, the investigators included additional information (labeled *Secondary Findings*) from studies that were formally excluded during the search and abstraction process, but which contained information that seemed pertinent to the key questions and which we felt may be of interest to readers. This additional information does not reflect results of a comprehensive, systematic literature search on the specific secondary findings topics; rather it reflects information derived from manuscripts identified during our main search process.

Data Abstraction

We abstracted the following data from included studies: study design, setting, objectives, eligibility criteria, sample size, intervention or exposure of interest, comparator intervention or control group, outcomes measured, timing of outcome assessment, years of enrollment/observation, duration of follow-up, demographics, potential confounders considered, results, and conclusions.

Quality Assessment

We assessed the quality of studies when applicable, using criteria developed by the US Preventive Services Task Force(11) for rating randomized controlled trials, cohort studies, and case control studies (Appendix C). We did not rate the quality of cross-sectional studies, case reports, or case series.

Data Synthesis

We constructed evidence tables showing the study characteristics and results for all included studies, organized by key question, intervention, or clinical condition, as appropriate. We critically analyzed studies to compare their characteristics, methods, and findings. We compiled a summary of findings for each key question or clinical topic, and drew conclusions based on qualitative synthesis of the findings.

Rating the body of evidence

We assessed the overall quality of evidence for outcomes using a method developed by the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) Working Group, which classified the grade of evidence across outcomes according to the following criteria:(12)

High = Further research is very unlikely to change our confidence on the estimate of effect.
Moderate = Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low = Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very Low = Any estimate of effect is very uncertain.

The GRADE Working Group also suggests using the following scheme for assigning the "grade" or strength of evidence:

Criteria for assigning GRADE of evidence
Type of evidence Randomized trial = high Observational study = low Any other evidence = very low **Decrease GRADE if:** ▪ Serious (-1) or very serious (-2) limitation to study quality ▪ Important inconsistency (-1) ▪ Some (-1) or major (-2) uncertainty about directness ▪ Imprecise or sparse data (-1) ▪ High probability of reporting bias (-1) **Increase GRADE if:** ▪ Strong evidence of association-significant relative risk of >2 (<0.5) based on consistent evidence from two or more observational studies, with no plausible confounders (+1) ▪ Very strong evidence of association-significant relative risk of >5 (<0.2) based on direct evidence with no major threats to validity (+2) ▪ Evidence of a dose response gradient (+1) ▪ All plausible confounders would have reduced the effect (+1)

Active Research

In addition to conducting a formal evidence synthesis, we conducted a survey to identify and describe current or planned research that is addressing or will address the key questions. Specific objectives were to 1) describe the data that are being collected that will help to address the key questions, 2) propose actions needed to address the key questions above within a reasonable time frame.

To identify ongoing or planned research relating to key questions, we began by sending email communications inquiring about active or planned research to groups and individuals. The groups and individuals sent initial email communications were:

- Investigators working in the areas of pain, polytrauma or TBI that were known to the Evidence Synthesis investigators or, as indicated from recent published manuscripts, are currently likely to be conducting studies in these areas. We specifically sent initial emails to several DOD researchers thought to be studying patients with polytraumatic injuries.
- Chairs of active VA workgroups, the Assessing pain in TBI workgroup (Buffum), VA Polytrauma Centers Workgroup (Clark), and the TBI QUERI Workgroup (Sayer). The PI of the current evidence synthesis project is a member of the VHA Pain Research Workgroup and sent an email communication directly to all

members of this workgroup. We also discussed this evidence synthesis project with chairs and members of these workgroups.

- Investigators of projects on polytrauma and pain identified from queries and hand-searches of several VA and non-VA website databases: (National Institutes of Health Clinical Trials data base (http:www.clinicaltrials.gov), the Computer Retrieval of Information on Scientific Projects (CRISP) database (http://crisp.cit.nih.gov/), the Meta-Register of Current Controlled Trials (http://www.controlled-trials.com/mrct/), and the VA HSR&D website (http://www.hsrd.research.va.gov/research/default.cfm).
- Each of the five HSR&D VA portfolio managers.

Email communications described our goals and the task, and asked respondents to also identify other investigators who might be working in these areas (snowball approach). Initial email messages were sent at the end of January 2008; email messages to newly identified investigators and follow-up communications occurred continuously until August 28, 2008.

PEER REVIEW

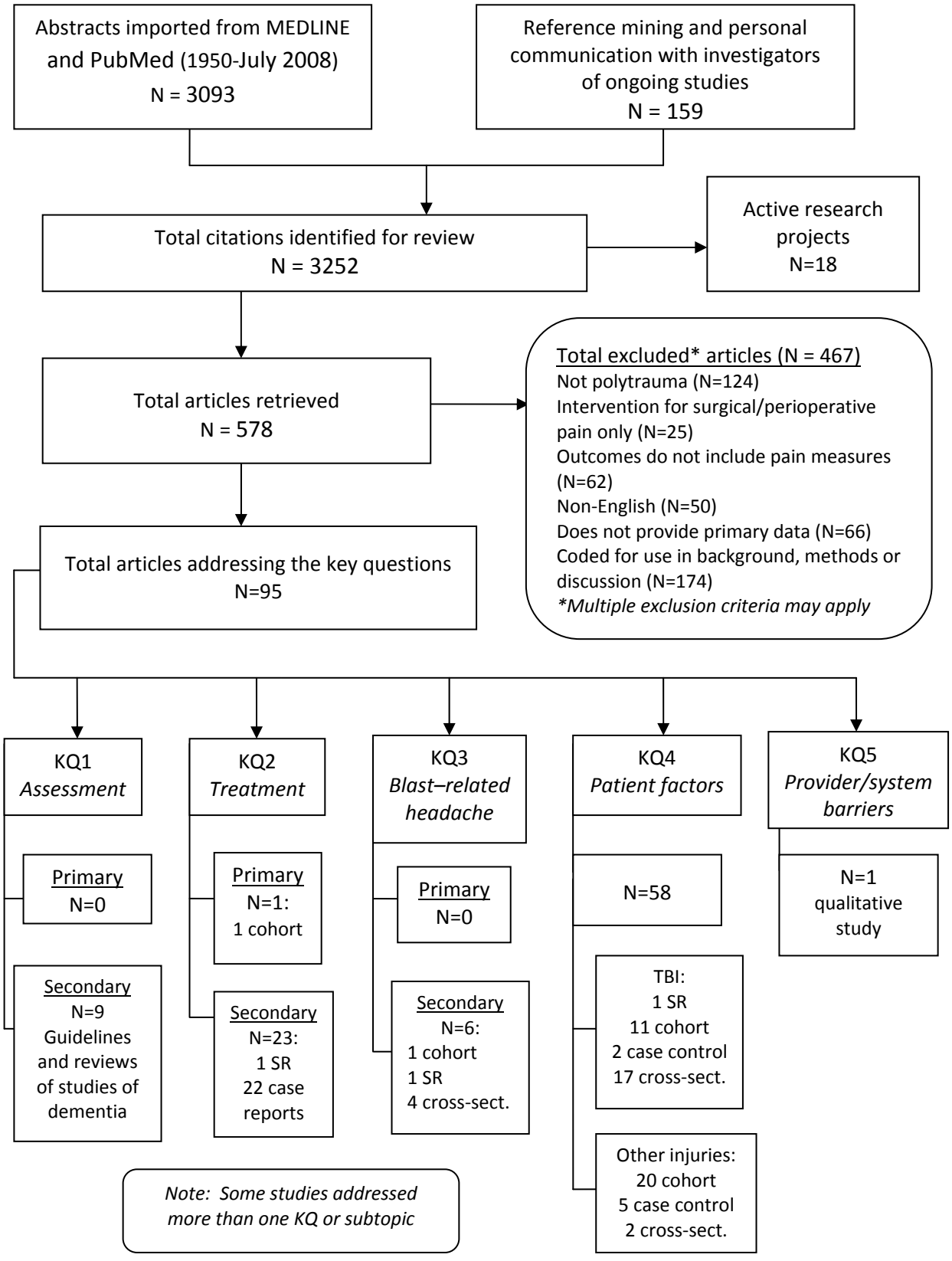
A draft version of this report was sent to the technical advisory panel and additional peer reviewers. Their comments and our responses are shown in Appendix D.

RESULTS

Literature Flow

The combined library contained 3252 citations, of which we reviewed 578 articles at the full-text level. From these, we identified systematic reviews and observational studies that addressed one or more of the key questions. Figure 2 shows the results of the literature search and the organization of themes that emerged for each key question.

Figure 2. Management of Pain in Polytrauma Literature Flow



Results—Key Question #1: Have reliable and valid measures and assessment tools been developed to measure pain intensity and pain-related functional interference among patients with cognitive deficits due to traumatic brain injury (TBI)? Which measures and tools are likely to be most useful in assessing pain in polytrauma patients with cognitive deficits due to TBI?

Summary of findings

There were no published studies that assessed reliability and validity of measures of pain intensity or pain-related function among patients with cognitive deficits due to TBI.

Secondary findings

- A number of primarily cross-sectional and case-control studies suggest that pain may interfere with neurocognitive functioning among TBI patients. Only some of these studies adjusted for potential confounders of the relationship between pain and neurocognitive performance.

- Several studies suggest that most individuals with cognitive impairment due to dementia can understand at least one pain self-assessment measure.

Details of Studies—Secondary Findings

Pain may interfere with neuropsychological assessment among TBI patients
We identified several narrative review articles that addressed this topic in depth.(13-15) These review articles include a number of primarily cross-sectional and case control studies that found negative associations between headache pain and cognitive functioning among TBI and non-TBI patients. Most TBI patients in these studies had mild TBI. Most of these studies support that acute or chronic pain irrespective of whether a patient has TBI, is associated with worse cognitive performance. While cognitive effects associated with pain may be quite variable, attention, memory, speed of processing and executive control may be most strongly affected.(13) Of note, investigators have identified factors other than pain that have the potential to confound or modulate the relationship between pain and neurocognitive performance. Such factors include psychological distress, mood, or anxiety disorders,(16-18) somatic complaints and concerns,(19) and sleep deprivation.(20) Thus, it remains unclear to what extent pain remains negatively associated with neurocognitive functioning when potentially confounding factors are considered.

Assessment of pain in patients with cognitive impairment due to dementia
The recently published VA Evidence Synthesis Report entitled, "Assessment and management of acute pain in adult medical inpatients: A systematic review"(21), four additional published reviews (22-25), and a guideline for assessing pain in the elderly(26) have addressed assessment of pain in patients with cognitive impairment due to dementia. Together, these reviews indicate that there is limited evidence that most individuals with mild to moderate cognitive impairment due to dementia can understand at least one self-assessment pain measure. Among the existing scales of nonverbal behavioral pain

indicators, none have been demonstrated to be substantially more reliable or valid than others for patients with cognitive impairment due to dementia. However, several of the reviews indicate that the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) may be especially promising or useful (27), and that the Discomfort Scale may have especially desirable psychometric properties.(28) To date, these self-assessment measures have not been specifically tested with TBI patients. Guidelines for assessing pain in patients with dementia who cannot understand any of the self-assessment measures suggest that multiple assessment methods may be best. Specific options include the use of an observational assessment measure, input from family, friends, or staff who know the patient well, and empiric pain treatment if the impaired patient has diagnoses usually associated with pain.(29-32)

Key Question #2: A. Which treatment approaches are most likely to be effective in improving pain outcomes (pain intensity and functional interference) in polytrauma patients? B. Which pain treatment approaches are most likely to enhance overall rehabilitation efforts?

Summary of findings

2A: There were no randomized controlled trials, systematic reviews, prospective cohort, case-control, or systematic observational studies that tested the efficacy or effectiveness of specific pain treatment approaches among patients with polytrauma.

2B: One fair-quality retrospective cohort study of patients who had undergone amputation at an urban trauma center demonstrated that after controlling for demographic factors, injury characteristics and other medical morbidity, inpatient rehabilitation was marginally associated with increased likelihood of return to work and decreased likelihood of reduced hours of work. (GRADE: Very Low)

Secondary Findings

- One fair-quality systematic review of primarily case reports on patients with causalgia (now known as complex regional pain syndrome II) due to war-related injuries suggests that sympathetic blocks and sympathectomy are frequently effective treatments.
- A number of manuscripts presented cases or case series describing pain treatment approaches and pain outcomes among patients with polytrauma including TBI.

Details of Studies—Primary Findings

One fair-quality retrospective cohort study of patients who underwent amputation at an urban trauma center between 1984 and 1994 examined factors that predicted whether a patient would receive inpatient rehabilitation and the success of treatment.(33) Seventy-eight patients (68% of eligible respondents) who had undergone trauma-related amputation at one hospital between 1984 and 1994 were contacted and interviewed an average of 7

years after their injuries. The study excluded amputation for non-injury reasons (e.g. diabetes), spinal cord injury or TBI. Many patients in the sample had multiple injuries. After controlling for demographic factors, injury characteristics and other medical morbidity, inpatient rehabilitation was marginally associated with increased likelihood of return to work (p=0.09) and decreased likelihood of reduced hours of work (p=0.05).

Details of Studies—Secondary Findings

One fair quality systematic review on causalgia (now known as complex regional pain syndrome II) was published in 2003.(34) In this review, MEDLINE and Index Medicus were searched using the terms, *causalgia* and *neuralgia*. All references including new cases of causalgia were included. One hundred ten manuscripts describing a total of 1,528 cases of causalgia were identified. No information about any experimental or longitudinal observational studies beyond individual cases or case series was reported. Overall, 57% of cases were war-related and 67% of cases were due to high-velocity missiles. It is unclear to what extent the overall group had polytrauma, but we infer from the traumatic nature of the injuries that polytrauma was likely common. The median nerve and sciatic trunk were the nerves most commonly involved and the most prominent clinical manifestations were burning pain (86%) diaphoresis (73%), paresthesias (96%), and sensitivity to stimuli (98%). Response to sympathetic blocks was observed in 88%, and 94% of patients undergoing sympathectomy were described as cured.

A number of manuscripts presented cases or case series describing pain treatment approaches and pain outcomes among patients with polytrauma including TBI. This information is summarized in Table 1 below. Several case reports support that intrathecal baclofen may be helpful for spasticity associated with TBI and related injuries. Despite supplemental hand-searches within our reference library for manuscripts on the use of opioids in patients with polytrauma including TBI, we found only one case report documenting (positive) specific effects of opioids in a TBI patient (included in Table 1)

Table 1—Secondary Findings pertaining to Key Question 2: Case Reports/Case Series*

Study	Study Design/ Sample	Condition(s)	Treatment Approach	Results
(35)	Single case	Severe TBI with brainstem seizures and pain	Mesothalamic electrode stimulation	Attenuated brainstem generated seizures and relieved chronic pain
(36)	Single case	TBI plus other injuries	Acupuncture	Decreased pain and anxiety
(37)	100 consecu-tive referrals	SCI (includes 15 TBI patients)	Botulinum injections and physical therapy	Clinician-reported global improvement in 90% of patients
(38)	Single case	Complex regional pain syndrome I (formerly known as Reflex sympathetic dystrophy) post-amputation	Topical capsaicin	Associated with disappearance of pain and autonomic changes
(39)	4 cases, one with TBI	Spasticity	Divalproex sodium (DVS)	Marked improvement in pain. One patient could not tolerate DVS
(40)	12 cases, 6 with missile head injury	Anxiety and headache	Fluphenazine	Reductions in headache and anxiety
(41)	2 cases, one with TBI	Central Pain	Gabapentin	*Increased* anxiety
(42)	Single case (OEF/OIF veteran)	Knee pain due to explosion, mild TBI, substance use disorder and PTSD	Multidisciplinary care including cognitive processing therapy	Decreased knee pain interference
(43)	7 cases (veterans) (5 received comparator intervention)	SCI and neuropathic pain	Healing Touch	Variable response; overall improvement in pain and satisfaction with life
(44)	Single case	Heterotopic ossification in TBI	Indomethacin and Radiation therapy	No response to indomethacin, but decreased pain with radiation therapy
(45)	Single Case	TBI with heterotopic ossification	Intense physiotherapy after surgery	Improvements in pain and behavioral symptoms
(46)	11 cases (8 with TBI)	Refractory spasticity	Intrathecal baclofen	Clinican-reported global improvement in all cases
(47)	19 patients (4 with TBI)	SCI-related spasticity	Intrathecal baclofen	Spasticity and pain improved in 14 pts.
(48)	9 cases (1 with TBI	Severe spasticity	Intrathecal baclofen	Most pts. improved, but no change in pain in TBI patient
(49)	14 cases (5 due to trauma	Spastic hypertonia	Intrathecal baclofen	Decreased pain
(50)	3 cases with TBI	Spasticity	Intrathecal baclofen	Decreased painful spasms
(51)	Single Case	TBI with unilateral central pain	Motor cortex stimulation	VAS change from 75-85 to 20-30; 50%-95% improvement in neuropathic symptoms
(52)	Single case	Severe TBI Schizophrenia	Opioid (oxycodone)	Increased interaction with others, decreased anxiety
(53)	Single case	Multiple medical conditions incl. polytrauma	Qigong Therapy	Decreased pain, weight loss, discontinuance of several medications

Study	Study Design/ Sample	Condition(s)	Treatment Approach	Results
(54)	Single case	TBI with severe headache	Sphenopalatine Ganglion pulsed radiofrequency lesioning	Long term relief of intractable headaches
(55)	10 consecutive cases (7 due to trauma)	Complex regional pain syndrome I	Spinal Cord Stimulation	Mean Numeric Rating Scale (NRS) pain score decrease of 6.2; decreased opioid use
(56)	Single case	Blast-related headache	Urea and chorionic gonadotropin	Headache free

*Subjects with TBI had moderate or severe TBI or TBI plus other injuries/complications

Key Question #3: A. Does blast-related headache pain differ in terms of phenomenology and treatment from other types of headache pain? B. Which treatments are best for persistent blast-related headache pain?

Summary of findings

There were no randomized controlled trials, cohort studies, case-control studies, or other systematic observational studies that compared patients with blast-related headache to patients with other types of headache or that specifically addressed treatments for blast-related headache pain.

Secondary findings

- Three studies (57-59) addressed the prevalence of headache among patients reporting head injuries. In a cross-sectional study of Army infantry soldiers post-deployment to Iraq with mild-TBI, most related to blast, 32% of soldiers reporting loss of consciousness and 18% of those reporting altered mental status also reported headache.(57) In a cross-sectional study of soldiers with injuries from Iraq and Afghanistan, two-thirds of whom were exposed to blast, 91% reported post-concussive symptoms, and headache was present in 47% of patients in this group.(58) Finally, in a poor-quality cohort study of civilians injured by munitions explosives in Yugoslavia, one year after injury, 30% of patients with blast injuries reported a constellation of symptoms which included headache, vertigo, and psychological and cognitive sequelae.(59)

- Two cross-sectional studies described blast injuries of the ear including hearing deficits, otalgia, and mandibular pain.(60, 61) We include this information because these types of problems have the potential to complicate the assessment and treatment of blast-related headache. In a study of service members at Walter Reed Army Medical Center referred for audiologic testing for follow-up of blast exposure, age-adjusted hearing thresholds were significantly lower than expected, 32% of patients had experienced tympanic membrane perforation, 49% reported tinnitus, and 5% reported otalgia.(60) In a study of civilians from Iran with war-related blast exposure referred to an oral/maxillofacial surgery clinic for evaluation of mandibular problems,

pain was a common complaint and levels of pain were associated with distance from blasts.(61)

- We identified one good quality systematic review of post-traumatic headache in TBI,(62) but blast exposure was not included as a characteristic in any of the studies, nor did the review explore relationships between TBI severity and headache (thus we include the results here as secondary findings). The review showed that most posttraumatic headache resolves within 6-12 months, but headaches persist beyond one year in 18% to 33% of patients. Many patients with posttraumatic headache have clinical presentations similar to tension-type headache or migraine. Many clinicians treat posttraumatic headache as if they are managing primary headache.

Details of Studies—Secondary Findings

In a recent cross-sectional study assessing the prevalence and significance of self-reported history of combat-related mild TBI, soldiers from two US Army combat infantry brigades were surveyed three to four months after a yearlong deployment in Iraq in 2006.(57) Of 4,618 soldiers potentially eligible to participate, 2,714 (59%) completed surveys. The authors note that lack of availability to complete questionnaires was mostly due to normal transfers to other units, trainings or attendance at military schools. Surveys inquired whether soldiers had been injured during their deployments by a blast or explosion, a bullet, a fragment or shrapnel, a vehicle accident, or other means, and whether the injury involved the head. A soldier was considered to have mild TBI if he or she endorsed "losing consciousness," "being dazed, confused or seeing stars," or "not remembering the injury." Multivariate logistic regression analyses were used to identify correlates of a range of self-reported outcomes including general health, missed workdays, medical visits, and somatic and postconcussive symptoms. Of soldiers reporting injuries with loss of consciousness or altered mental status, 75% reported being exposed to blast or explosion. Five percent reported injury with loss of consciousness, 10% reported in juries with altered mental status, and 17% reported other injuries during deployment. Headache was common, present in 32% of those reporting injury with loss of consciousness and 18% of those reporting altered mental status, as compared to soldiers who reported other injuries (12%) or no injury (8%) ($p<0.001$). In models adjusted for demographics, mechanism of injury, blast exposure, post-traumatic stress disorder (PTSD), depression, combat intensity, and hospitalization, the odds of headache remained significantly greater in soldiers reporting loss of consciousness versus other injury: 2.38 (1.12-5.07). The odds of headache were not significantly greater in soldiers reporting altered mental status vs. other injury: 1.63 (0.92-2.90). Overall, the analyses show that, except for in the case of headache when there is loss of consciousness, the associations among TBI and physical health problems are no longer significant when PTSD and depression are included in models.

An abstract from a cross-sectional study described the characteristics of soldiers returning from Iraq or Afghanistan who were injured in a blast, fall, gun shot wound, or motor vehicle accident, and screened for TBI by the Defense and Veterans Brain Injury Center (DVBIC) of Walter Reed Army Medicine Center between January 2003 and April

2005.(58) The sample included the initial 433 patients seen by the DVIBC. The sample was 95% males, modal age 21. Sixty-eight percent reported blast exposure, 79% reported loss of consciousness less than one hour, and 43% reported post-traumatic amnesia less than 24 hours. Ninety-one percent of patients reported post-concussive symptoms. Headache (47%), memory deficits (46%), and irritability/aggression (41%) were the most common post-concussive symptoms.

A poor-quality cohort study of 1,303 civilians who had been injured by munitions explosives in Yugoslavia between 1991 and 1994 and admitted to the US Military Medical Academy in Belgrade assessed the effects of blast exposure within one year of injury.(59) Approximately 30% of patients with 665 blast injuries reported persisting symptoms including headache, vertigo, positive Romberg's sign, retrograde amnesia, mental blockage, apathy/lethargy, psychomotor agitation, and anxiety. The study was limited by inadequate reporting on rates of follow-up, timing of follow-up assessment, or details of the measurement of these symptoms.

An observational study that sought to examine whether blast was related to significant hearing changes collected audiologic data on 258 service members.(60) The investigators also explored whether polytraumatic injuries were associated with hearing loss. Potential subjects were referred for audiologic testing at Walter Reed Army Medical Center as part of a standard protocol for soldiers reporting at least one blast-related exposure. Only 162 out of 258 patients (63%) had hearing test data available for review. The mean age was 29 years and 98% were male. Within this group, age-adjusted actual hearing thresholds were significantly lower than expected, and 32% of patients had experienced tympanic membrane perforation, 49% reported tinnitus, and 5% reported otalgia. There was no association between polytrauma status and other characteristics. A cross-sectional study of 495 civilians with blast exposure who were referred to an oral/maxillofacial surgery clinic from the Medical Services Centre for War Injured Patients in Tehran, Iran between March 1984 and February 1990 reported that pain was a common complaint and that levels of pain were associated with distance from blasts.(61) In 115 patients, pain was localized in the external acoustic meatus and 15 patients complained of total facial pain. Forty-nine percent of the sample "responded" to limiting jaw movement, adopting a soft-diet, and the use of "pain killers," and 77% responded to a combination of "pain killers" and muscle relaxants. Patient characteristics and the timing and methods to measure outcomes were not specified.

Finally, we identified one good quality systematic review of post-traumatic headache in TBI.(62) In this review, the investigators searched MEDLINE for literature on posttraumatic headache published between January 1990 and February 2005. Five studies specifically describing patient characteristics and types of headache were identified.(63-67) The total number of subjects in these studies was 423 patients. Blast exposure was not included as a characteristic in any of the five studies, and the review did not explore relationships between TBI severity and headache. The review showed that posttraumatic headache usually resolves within 6-12 months, but that 18% to 33% of the time, headaches persist beyond one year. Many (37%) of patients with posttraumatic headache had clinical presentations similar to tension-type headache or migraine (29%). Many

clinicians treat posttraumatic headache as if they were managing primary headache. The authors conclude that there is no universally accepted protocol for treating posttraumatic headache, and that randomized controlled trials are needed in this area.

Key Question #4. What patient factors are associated with better and worse (pain-related) clinical outcomes among polytrauma patients? Have interventions been developed to specifically address these factors?

Summary of Findings

There were no randomized controlled trials. One systematic review, 11 cohort, 2 case-control, and 17 cross-sectional studies specifically addressed patient factors associated with outcomes in TBI patients. Twenty cohort, 2 cross-sectional, and 5 case-control studies addressed patient factors associated with outcomes in other polytrauma patients. Evidence Table 1 in Appendix E shows the data abstracted from these studies.

Traumatic Brain Injury

- One recent fair-quality systematic review showed that overall, 58% of patients with TBI have chronic headache, and that brain injury is associated with headache even after adjustment for post-traumatic stress disorder (PTSD).(68) These findings are consistent with our review, which included additional manuscripts, which found that among patients with TBI, headache is present in one-third to one-half of patients up to five years after injury. (GRADE: Low)

- The recent fair-quality systematic review above also found that patients with mild TBI were more likely to have headache than patients with moderate or severe TBI.(68) However, our review showed very mixed findings regarding the association between severity of TBI and pain (GRADE: Very Low).

- Psychological factors, including depression and posttraumatic stress disorder (PTSD), insomnia and fatigue are associated with pain in TBI patients. (GRADE: Low)

Other injuries in polytrauma patients

- Characteristics of injuries (location, severity, and whether they are multiple) are associated with clinical outcomes including persistent pain and functional status. Specific factors associated with worse pain-related outcomes include: multiple injuries, foot injuries or injuries below the knee joint, and concurrent head injury or cognitive disability. (GRADE: Low)

- Other factors associated with better outcomes in some studies of patients with polytraumatic injuries other than TBI were younger age, higher educational achievement, having a white collar job or higher income. (GRADE: Very Low)

Details of Studies—Traumatic Brain Injury

Prevalence of pain and headache among TBI patients

One fair-quality systematic review was published in 2008. In this review, Ovid/MEDLINE, PubMed, and MD consult databases were searched using the terms *brain injury, pain, headache, blast injury, combat, combat disorders, war, military medicine, wounds and injuries, military personnel,* and *veterans*. The Cochrane Collaboration, National Institutes of Health Clinical Trials Database, Meta-register of Current Controlled Trials and CRISP database were searched using the term *brain injury*. Articles were included which were published between 1951 and February 2008 (however one article from 1939 is also included in the review.(69) The search was not limited by language or publication status. Case reports and review articles were cited only if no other data were available. Twenty-three studies (15 cross-sectional, 5 prospective observational, and 3 retrospective observational) including 4,206 patients were identified. No randomized clinical trials were identified. Data were pooled across studies to obtain overall prevalence rates. The review showed that 58% (95%CI 55.5-60.2%) of patients with TBI have chronic headache, and that brain injury is associated with headache even after adjustment for post-traumatic stress disorder (PTSD).(68)

In our review, we found seven prospective and one retrospective cohort studies that report on the prevalence of pain and headache among TBI patients.(70-77) In a good-quality prospective cohort study of 146 patients enrolled in acute inpatient rehabilitation for TBI, 73% reported pain at one year and 55% reported interference from pain.(71) One fair-quality prospective cohort study measured prevalence and type of headache among 109 patients with moderate to severe TBI consecutively admitted to one of four VA Polytrauma Rehabilitation Centers (PRCs) over 12 months.(70) On admission, 38% of patients reported headache. Sixty-four percent of patients with headache reported no to mild levels of incapacitation from headaches. Among patients with headaches at admission, 54% reported persistent headache symptoms at six months, and of this group, 96% still had headaches at 12 months. Of patients without headache at admission, the majority remained headache free over 12 months. In a fair-quality prospective cohort study of 161 patients admitted to a brain injury rehabilitation unit, 62% reported some type of pain and 31% reported daily pain or continuous pain at six months.(72) Headache was the most frequently reported type of pain. In a fair-quality prospective cohort study of 231 patients admitted to three trauma centers in France with severe head injuries reassessed five years after injury, the prevalence of headache was 44 to 54%, significantly greater than 16% in a comparison group with lower limb injury but no TBI.(73) In a poor quality prospective cohort study of patients with TBI consecutively admitted to an inpatient urban rehabilitation program who completed follow-up assessments, headache prevalence increased from 31% 2 years post-injury to 42% 5 years post-injury.(76) In a poor-quality prospective cohort study of 132 patients consecutively admitted to an inpatient TBI rehabilitation center, 10% of patients had co-existing peripheral nerve injuries, and of these patients, 31% reported pain.(77) In a poor-quality retrospective cohort study of 200 patients admitted to an inpatient accident service, headaches persisted in 17 to 18% of cases 6 months after injury.(75) Finally, in another poor-quality retrospective cohort

study, 58% of patients admitted to an Australian teaching hospital had headaches 5 years after TBI.(74)

Two fair-quality case-control studies demonstrated that pain is more common or more severe in TBI patients than other populations.(78, 79) One of these studies showed that overall pain scores were higher in a volunteer community sample of mild to severe TBI patients at least 12-months post-injury compared to a group of non-injured controls (17.2 vs. 10.1, on a scale of 0-78 using the McGill pain questionnaire,p=.013).(78) The other study showed that the prevalence of pain complaints was 59% in a sample of patients with TBI referred for neuropsychological assessment at a medical center versus 22% of non-TBI patients also referred for neuropsychological assessment (p<.001).(79)

Several cross-sectional studies also support that pain and headache are common among TBI patients.(57, 58, 80-86) In these studies, pain was present in 22% to 90% of patients. In one of these studies of young patients admitted to a brain injury rehabilitation ward in London an average of 25 weeks after injury, only 12% reported headache.(82) Headache was the most common type of pain complaint according to two of these studies.(81, 85) Another study found that reflex sympathetic dystrophy (now known as Complex Regional Pain Syndrome I) was present in 13 of 100 patients consecutively admitted to an inpatient brain injury unit.(84) Notably, in several(81, 85, 86) of the above studies, case status was established at the time of outpatient follow-up assessment; thus, patients with persisting pain complaints may be overrepresented in these samples.

Taken together these studies show that pain is common among patients with TBI, present in approximately one-third to one-half of patients up to five years after injury. One prospective cohort, and several cross-sectional studies suggest that headache is the most common pain complaint among TBI patients.

Relationship between severity of TBI and pain in TBI patients

One fair-quality systematic review was published in 2008. In this review, Ovid/MEDLINE, PubMed, and MD consult databases were searched using the terms *brain injury, pain, headache, blast injury, combat, combat disorders, war, military medicine, wounds and injuries, military personnel,* and *veterans*. The Cochrane Collaboration, National Institutes of Health Clinical Trials Database, Meta-register of Current Controlled Trials and CRISP database were searched using the term *brain injury*. Articles were included which were published between 1951 and February 2008 (however one article from 1939 is also included in the review.(69) The search was not limited by language or publication status. Case reports and review articles were cited only if no other data were available. Twenty-three studies (15 cross-sectional, 5 prospective observational, and 3 retrospective observational) including 4,206 patients were identified. No randomized clinical trials were identified. Data were pooled across studies to obtain overall prevalence rates. The review showed that among civilians, the prevalence of chronic pain was 51.5% (95%CI 49.8% - 53.2%) among patients with mild TBI, compared with 32.1% (95%CI 29.3% - 34.9%) among patients with moderate or severe TBI.(68)

Pain in Patients with Polytrauma

In our review, which included a number of studies not included in the systematic review above, one fair-quality prospective cohort study of 109 patients admitted to one of four VA PRCs, no statistically significant relationships were identified between Glasgow Coma Scale (GCS) score, Loss of Consciousness (LOC), or duration of post-traumatic amnesia (all indicators of head injury severity) and posttraumatic headache prevalence.(70) One good-quality prospective cohort study of 146 patients enrolled in a University acute inpatient rehabilitation program similarly found that baseline GCS was not associated with pain status one year after injury.(71) In another fair-quality prospective cohort study of 231 patients admitted to French trauma centers with severe head injuries who were reassessed five years after injury, headache prevalence was not found to be significantly different according to head injury severity.(73) Patients with severe head injury were less likely to complete follow-up assessments due to deaths. In an additional prospective cohort study of 200 consecutive individuals admitted to an urban hospital with head injuries, headache persisting longer than two months was not more prevalent among patients with more severe head injuries than patients with milder head injuries.(87) Finally, a poor-quality retrospective cohort study of 200 patients admitted to an inpatient accident service found no differences in the prevalence of headache when comparing patients with mild head injury to those with moderate to severe TBI three and six months after injury.(75)

In a cross-sectional study of consecutive TBI patients seen in an outpatient brain injury clinic, over half of the sample reported chronic pain (primarily headaches), and there were similar rates of pain reports when comparing patients with mild TBI to patients with more severe TBI.(81) A retrospective review of the records of 200 consecutive cases of head injury admitted to the surgical wards of the Edinburgh Royal Infirmary similarly found no increase in headache prevalence among patients who had presented with milder head injuries.(88) Finally, in a cross-sectional examination of the validity of the SF-36 for characterizing outcome after multiple trauma, there were no differences in the SF-36 bodily pain scale based on severity of head trauma among patients discharged from trauma centers who did not have concurrent orthopedic injuries.(89)

However, one fair-quality retrospective cohort study,(90) one fair-quality case-control study (79) and five studies using cross-sectional designs(82, 85, 86, 91, 92) found a higher prevalence of headache among patients with mild TBI as compared to more severe TBI. In the retrospective cohort study of 228 patients a median of four years after being admitted to a university ICU for major trauma, patients with severe head injury were less likely to report problems with pain/discomfort (OR 0.31, 95%CI 0.15 - 0.64) after adjusting for retrospectively-patient-reported baseline levels of symptoms and functioning. However, patients with severe head injury were less likely to participate in the follow-up surveys. In five of case-control and cross-sectional studies, study samples were established from referrals or attendees of outpatient follow-up clinics for TBI. Generally, patients were seen in these follow up clinics between six months and two years after their injuries. In one of the studies, the sample consisted of patients admitted to a subacute rehabilitation unit on average 25 weeks post-injury,(82) and in the remaining study, it was unclear whether the study cohort was established at the time of injury or time of outpatient follow-up.(92) Overall, this group of studies found that patients with mild TBI who attend outpatient brain injury clinics are two to three times more likely to report headache than patients with

moderate or severe TBI. However, the analyses in these studies were not adjusted for potential confounding factors, and specific reasons why patients were referred to or sought care in these settings were not specified or adjusted for in most of the studies.

In summary, there is very limited evidence showing that patients with mild TBI are more likely to have headache or other pain than patients without TBI. While one retrospective cohort, one case-control, and a number of cross-sectional studies suggest that patients with mild TBI may be more likely to have headache pain than patients with moderate or severe TBI, six prospective cohort studies and additional cross-sectional studies did not find such a relationship. In the single systematic review showing a difference in rates of pain across levels of TBI severity, data were pooled across studies using different patient samples and designs. Most of the studies identified in that review and in our review that found associations between milder head injury and headache were done in outpatient settings, up to several years post-injury, and did not adjust for potential confounders that may influence relationships between TBI severity and pain. On the other hand, most of the samples in the identified cohort studies were assembled at the time of admission to a hospital or inpatient rehabilitation setting. It is therefore likely that differences in sample composition contribute to the differences in findings between the cross-sectional and cohort studies; patients with mild TBI may be more likely to be referred to or attend outpatient follow-up appointments when they have bothersome or persistent symptoms such as headache.

Relationships between other patient factors and pain outcomes in patients with TBI

Demographics: There are mixed findings regarding the association between demographic factors and pain outcomes in TBI patients. In one good-quality prospective cohort study of 146 patients enrolled in a university acute inpatient rehabilitation program, pain one year after injury was significantly associated with being female and non-white; being non-white remained significantly associated with reports of pain at one year in a multivariate regression model (taking other factors into account).(71) However, a fair-quality cohort study of veterans at VA PRCs(70) and a cross-sectional study of outpatients referred for neuropsychological evaluation (93) did not detect significant associations between demographic factors and headache frequency.

Blast exposure: In a cross-sectional study of 188 service members admitted to one of four VA PRCs, blast exposure was not found to be a significant predictor of pain.(80)

Psychological factors: In a fair-quality prospective cohort study of 109 patients admitted to one of four VA PRCs, headache density (a measure combining headache-related incapacitation and frequency) at six and 12 months was associated with higher depression and anxiety levels among patients with persistent headaches, and among patients with delayed onset headaches.(70) In another good-quality prospective cohort study of 146 patients enrolled in a university acute inpatient rehabilitation program, depression one year after injury remained significantly associated with reports of pain at one year (taking other factors into account).(71) Depression was also found to be a significant factor mediating the relationship between pain and community participation. In a fair-quality prospective cohort study of 161 patients admitted to a tertiary care center brain injury rehabilitation unit, frequency but not severity of chronic pain was associated with PTSD ($p<.05$).(72) In

a multivariate model including psychological factors, only avoidant coping style remained significantly associated with pain severity after controlling for PTSD severity. In a fair-quality prospective cohort study of 47 patients admitted to a regional trauma center, pain was found to be highly correlated with depression (r=.81) in post hoc analyses. Finally, in a cross-sectional study of 84 patients from eight outpatient Mid-west rehabilitation centers, in a model including perceived stress, impact of events, and litigation status, pain was significantly associated with depression (partial R^2 = .07, p=.001).(94)

Fatigue and Insomnia: In a poor-quality prospective cohort study of 38 TBI patients admitted to an inpatient rehabilitation service, there were highly significant correlations between levels of fatigue and pain at one and 2 years post-injury (R=.49 and .62, respectively, p<.01).(95) Another fair-quality case-control study of community volunteers showed that fatigue was correlated with the SF-36 bodily pain scale in TBI patients (R=.389, p<.011).(78) In another fair-quality case-control study of patients referred to a university outpatient neuropsychology service, pain was highly associated with insomnia (p<.001).(79) In an additional cross-sectional study of Canadian community volunteers, pain frequency was significantly associated with insomnia in TBI patients; pain remained a significant predictor of insomnia in a multivariate model that included depression, severity of injury and fatigue.(96) Finally, in another cross-sectional study, pain was significantly associated with insomnia in TBI patients admitted to a comprehensive outpatient rehabilitation program; however, pain dropped out of a multivariate model in which presence of insomnia was the outcome.(97)

Taken together, this group of studies provides limited evidence that psychological factors, including depression and posttraumatic stress disorder (PTSD), insomnia and fatigue are associated with pain in TBI patients.

Details of Studies —Other Injuries in Polytrauma Patients

Injury characteristics—amputations: Studies support that injury factors (location, severity, multiplicity) are often associated with pain-related outcomes in patients with amputations. In a fair-quality retrospective cohort study of 78 trauma-related amputation patients, many of whom had multiple trauma, greater initial severity of injury was associated with significantly worse self-reported physical functioning including bodily pain.(33) In another fair-quality retrospective cohort study, investigators studied 326 patients from Belgrade who experienced missile-caused peripheral nerve lesions, some of whom likely had multiple trauma.(98, 99) In multivariate analyses, three factors were significant predictors of pain up to five years after injury: type of pain syndrome (e.g., complex regional pain syndrome II or deafferentation pain), severity of initial nerve injury, and an absence of pain paroxysms. In an additional fair-quality retrospective cohort study examining the long-term results of compartment syndrome, polytrauma patients were compared to those with a single injury.(100) The investigators did not find a difference with respect to strength, pain, or function and concluded that secondary injuries did not negatively impact the outcome of compartment syndrome. A poor-quality retrospective cohort study compared functional outcomes of Vietnam Veterans who had isolated transtibial amputations to those with amputations and at least one other major injury.(101) The polytrauma group scored

significantly lower than the control group on all 8 subscale scores of the SF-36 including bodily pain, whereas quality of life scores from the single trauma group did not differ with those from the control group. A poor-quality quality case-control study compared 23 bilateral Vietnam Veteran amputees to age and gender matched controls from a national registry. Cases were surveyed an average of 28 years after injury. This study showed that while overall physical function was lower in the case group, bodily pain scores were not significantly different.(102) Finally, a cross-sectional study provided descriptive data on stump pain, phantom sensation, and phantom pain in 40 civilians from Sierra Leone who suffered traumatic upper limb amputation in a civil war setting.(103) Interviews were conducted 10-48 months post-injury. All amputees (100%) had stump pain in the last month and 93% had phantom sensations. Phantom pain was less common among patients with bilateral than unilateral amputations (18% versus 38%; no p-value reported). In an additional cross-sectional study of civilian amputees, stump and phantom limb pain were reported by 73% of multiple level amputees as compared to 63% of upper limb and 74% of lower limb amputees (no comparison significance tests reported).(104)

Injury characteristics—orthopedic injuries Studies also suggest that injury factors are associated with pain-related outcomes in patients with orthopedic injuries. A good-quality retrospective cohort study of 389 patients compared long-term functional outcomes among 3 groups, based on the site of fracture: above-knee, below knee, or combined fractures above and below the knee.(105) A mean of 17 years after injury (minimum 10 years), although persistent pain was not significantly more frequent among patients with below-knee fractures compared with above-knee fractures (46% v. 39%, p=0.25), persistent pain was significantly more common in patients with combined injuries as compared to fractures about the knee joint (58.5% vs. 39.3%, p<.001). Two additional small, fair-quality case-control studies compared functional outcomes in small numbers of polytrauma patients with and without foot injuries.(106, 107) In both studies, the outcomes of multiply injured patients with foot injuries were significantly worse than that of patients without foot injuries. Patients with foot injuries had a dramatically lower scores on SF-36 scales of physical function, role physical (perception of physical functioning), bodily pain, and social function compared to controls.(106, 107)

In another fair-quality prospective cohort study, 659 patients with multiple orthopedic injuries were compared to 165 patients with orthopedic injuries plus other types of injuries.(108) Six months post-injury, patients with combined orthopedic and other injuries had greater pain intensity and reported more disability than patients with multiple orthopedic injuries alone. A fair-quality retrospective cohort study compared pain and function in 27 long-term survivors of open pelvic fracture with the experience of 84 survivors of closed pelvic fracture.(109) Subjects were multiple system blunt trauma patients with a pelvic fracture, and associated injuries included head injury, thoracic trauma, abdominal injury, extremity fractures, and spinal fractures. Survivors of open pelvic fracture had non-significantly lower SF-36 bodily pain scores, and significantly lower scores for physical functioning and role physical subscales, indicating worse outcomes. Finally, a fair-quality prospective cohort study of orthopedic injuries was conducted in 830 polytrauma patients with spine injury.(110) Degree of injury severity was

correlated with pain, functional independence, and return to employment one year and two years follow-up.

Injury characteristics—other polytraumatic injuries: A number of additional cohort studies examined relationships between various injury characteristics and functional outcomes including or in addition to measures of pain.(109, 111-120) Pain intensity was not a main outcome in these studies and was often measured using a subscale of a functional status measure. In only some of these studies were potentially confounding factors adjusted for in analyses involving pain outcomes.(113-115, 119) Most of the studies did not have excessive loss to follow-up, and some studies determined that patients lost to follow-up were not substantially different from patients represented in the study.(112, 113, 115, 116, 120) Almost all of the studies that compared multiply and singly injured patients to patients with a single injury, or measured the severity of injury, found an association between multiple or severe single injuries and worse functional outcomes and pain.(111, 112, 114-118) Some studies that included patients with cognitive disabilities or head injuries found associations between head injury or cognitive disability and decreased functional outcome.(112-115, 117) In an additional poor-quality case control study of 49 patients (setting not specified), patients with head injury plus other types of polytrauma were not found to have worse bodily pain at 6 or 12 months after injury compared to patients with TBI alone.(121) Finally, other injury characteristics associated with worse functional and pain outcomes were lower limb injuries,(114, 116, 120)longer hospital length of stay,(115) and admission to intensive care unit (ICU) and length of ICU stay.

In summary, many cohort studies as well as several case-control and cross-sectional studies found that polytraumatic injury characteristics (principally location, initial severity, and multiplicity of injury) are associated with pain and functional outcomes over time. Injuries below the knee joint are associated with worse outcomes compared to injuries above the knee in polytrauma patients. A number of these studies did not adjust for factors that may confound relationships between injury characteristics and pain-related outcomes.

Demographics: A number of manuscripts reported adjusting for demographic variables (mainly age) in multivariate analyses, but did not report whether and to what extent these variables were significantly associated with pain outcomes. One good-quality (115) and three fair-quality (33, 112, 118) cohort studies found associations between younger age and better functional outcomes in polytrauma patients. One good-quality cohort study (115) and one fair-quality cohort study (111) found associations between being male and better functional outcomes. In an additional cross-sectional study of 40 civilians from Sierra Leone who suffered traumatic upper limb amputation, phantom pain was more common in women than men (63% versus 25%, p=0.057).(103) However, in one fair-quality prospective cohort study of 62 patients injured in traffic accidents, there were no significant differences in SF-36 bodily pain scores by gender in bivariate analyses two and eight months post-injury.(122) Finally, in one fair-quality retrospective cohort study of 78 trauma-related amputation patients, being white was associated with better SF-36 PCS and bodily pain outcome scores, higher likelihood of return to work, and lower likelihood of reduced work hours.(33)

Other factors associated with better functional status were higher educational achievement (two good-quality (115, 119) and one fair quality (114) cohort studies), having a professional/white collar job (one good quality (119) and two fair-quality (112, 118) cohort studies) and higher income, job stability, job flexibility and lower physical demands at work (one good quality cohort study).(119) The authors of this latter study also found an association between receiving worker's compensation and lower return to work rate.

Psychosocial Factors: Almost no studies reported on the relationships between psychosocial factors and pain-related outcomes in patients with polytraumatic injuries other than TBI. In one fair-quality retrospective cohort study of 69 patients admitted to an inpatient surgical service, loss of non-work activities was significantly correlated with pain.(112) One cross-sectional study provided descriptive data on stump pain, phantom sensation, and phantom pain 10-48 months post-injury in 40 civilians from Sierra Leone who had suffered traumatic upper limb amputation in a civil war setting.(103) No significant relationships were reported between mood and the prevalence of phantom or stump pain.

To summarize, there is very limited evidence regarding the extent to which demographic factors are associated with pain-related outcomes in patients with polytraumatic injuries other than TBI. Four cohort studies show that younger age is associated with better longer-term outcomes in patients with severe multiple injuries, and three cohort studies and one cross-sectional study show a relationship between male sex and improved outcomes after major trauma. There is almost no information available regarding relationships between race and ethnicity and pain-related outcomes. There is almost no information available regarding relationships between psychosocial factors and pain-related outcomes in patients with polytraumatic injuries other than TBI.

Key Question #5. What are unique provider and system barriers to detecting and treating pain among polytrauma patients? Have interventions been developed to effectively address these barriers?

Summary of findings

There were no randomized controlled trials, cohort studies, case-control studies, or other systematic observational studies that addressed provider and system barriers to detecting and treating pain among polytrauma patients. One qualitative study of providers from four VA Polytrauma Rehabilitation Centers (PRCs) addressed potential provider and system barriers to treating polytrauma patients.(3) In qualitative interviews, providers reported that polytrauma patients are very complex to treat, and that the work with this population is very challenging and emotionally taxing. Increasing use of multidisciplinary and concurrent care, and consultation from experts may be necessary to provide the complex care that is needed.

Details of Study

This study was a qualitative study of provider perspectives on the rehabilitation of patients with polytrauma. This study which used Rapid Assessment Process methodology including semi-structured interviews, observation, and field liaison. The purpose of the study was to describe, from the perspective of providers working or affiliated with one of four VA Polytrauma Rehabilitation Centers (PRCs), 1) patients with combat-related polytrauma and their rehabilitation; 2) polytrauma patient family member involvement in rehabilitation; and 3) the impact on providers of providing polytrauma rehabilitation. Clinicians of various disciplines were selected among the four PRC sites, as well as personnel who work closely with the PRCs, including: 1) clinicians who provide regular consultation to PRC patients, including pain, PTSD, infectious disease, and low-vision specialists; 2) military liaisons who are US Department of Defense (DOD) employees housed at the PRC to help active-duty patients navigate across care systems; and 3) the VA points of contact who help US Service members obtain needed VA services; specific demographics of the clinicians interviewed were not provided. Fifty-six interviews were conducted.

A number of common themes were identified which are pertinent to this key question:

1. Patients with blast-related injuries including TBI have more injuries and more severe injuries than other patient populations. Serious psychiatric disorders, including PTSD and injury-related pain are highly prevalent, and complicate rehabilitation for TBI. These factors make this patient population quite complex to treat.
2. Providers find working with this population very challenging and emotionally taxing.
3. In order to address the level of complexity, providers are increasingly using co-treatment across disciplines, more regular consultation with services outside rehabilitation, such as surgery, amputation care, and psychiatry, and more frequent consultation with colleagues within and across the PRCs. PRC teams are expanding to include experts in areas including pain.
4. Spouses, parents, siblings, and children have become intensely involved in the injured service member's rehabilitation and have their own informational, instrumental, and support needs. Providers must respond to family needs and engage them as collaborators in the rehabilitation process.

Limitations—Literature Review

Heterogeneity and Generalizability

Due to innumerable etiologies and combinations of injuries, there is great heterogeneity among polytrauma patients. For example, within the category of blast-related head injury alone, there are multiple potential mechanisms of brain injury, and injuries may or may not be concurrent with other penetrating head injuries.(123) There is consequent heterogeneity among the study samples described in the literature as well as in the methods used to describe study samples. Many studies were done at single sites or within specialized types of settings. Thus, the conclusions we might draw from a particular study or set of studies

may have limited relevance for other polytrauma patients, and comparisons among studies may be challenging.

Scope

Due in part to the degree of heterogeneity among studies and their descriptions, as well as the lack of precision inherent in the term, "polytrauma", we adopted a fairly stringent operational definition for polytrauma (multiple concurrent injuries in two or more systems) and focused on identifying studies that clearly included majorities of patients with polytrauma in their samples. Thus, for example, some studies of patients with spinal cord injuries or amputations were not included unless there was clear indication at the abstract or full-text level that multiple injuries were (often) involved. It is therefore likely that some manuscripts that might have relevance for the treatment of pain in polytrauma or subgroups of polytrauma patients were not identified. Surgical approaches were excluded due to the heterogeneity of the conditions being treated with specific techniques. We did not feel that information generated from review of specific surgical approaches would be very generalizable to the polytrauma patient population as a whole. We note that we did search more broadly for studies pertaining to TBI and blast since there is particular relevance for a large segment of the OEF/OIF patient population.

Publication Bias

Our search strategies were comprehensive and we evaluated a large number of studies for possible inclusion in the review. Two librarians independently searched the literature and their results were combined to form our reference library. While this process identified many manuscripts for potential inclusion in the review, it is possible that our search terms did not capture some relevant manuscripts, especially for older studies which might not have been indexed in databases as pertaining to polytrauma or multiple injury/trauma. We therefore included additional search terms pertaining to blast, TBI, and war, and relied extensively on reference lists of studies, review articles, editorials, and consulting experts to identify additional manuscripts for review.

Study quality

We did not exclude individual studies based on quality rating alone. Thus the strength of our conclusions is inherently limited by the quality variation among included studies. We did make an effort to note particular methodologic limitations, and each cohort and case-control study was closely reviewed for overall quality using a rigorously developed approach. Although cross-sectional studies were not formally rated, methodologic limitations were often noted.

RESULTS—ACTIVE RESEARCH

Summary of findings

Nineteen relevant active or planned projects were identified and project data were collected on 18 of these projects. Pain measures constitute main outcomes in 8 of the studies, and will be collected as secondary outcomes in 10 of the studies. Fifteen of the studies should generate information regarding patient factors that may contribute to pain-related outcomes among polytrauma patients (Key Question 4), and 4 studies are testing interventions for pain among polytrauma patients (Key Question 2). One study will test the reliability and validity of measures to assess pain in cognitively-impaired TBI patients and another study is using primarily qualitative methods to examine the utility of a CPRS pain assessment template module to assist clinicians in evaluating pain in PRC patients with cognitive impairment (Key Question 1). One study is examining the phenomenology and treatment of blast vs. other types of headache (Key Question 3), and one study is addressing provider and systems barriers to detecting and treating pain in polytrauma patients (Key Question 5).

Details of findings

Email communications were sent to a total of 73 individuals, 4 VA workgroups (via their chairs), and 5 HSR&D portfolio managers, inquiring about possible projects the addressing key questions and inquiring about identifying others who might be doing or planning research relevant to the key questions. Individual email recipients included 41 VA investigators, 5 Department of Defense (DOD) investigators, and 27 non-VA, non-DOD investigators. Responses were received from 47 investigators. Nineteen relevant projects were identified and project data were collected on 18 of these projects. Table 2 on the following pages lists the ongoing studies for which data were available. The characteristics of these studies are described in further detail in Appendix E, Evidence Table 2.

Table 2. Summary of active research studies of pain in polytrauma

Title of Project	Main objective(s) of project	Pain-related variable(s) main or secondary outcome?	Study characteristics	KQ
Concurrent Validity of 4 Pain Intensity Scales in persons with Polytrauma and Cognitive Impairment(124)	Examine the concurrent validity of four pain intensity scales in the traumatic brain injury (TBI) inpatient rehabilitation population	Main	Study design: prospective randomized measurement study Sample: 15 TBI patients	1
Pain Assessment in Polytrauma Rehabilitation Centers (PRCs)(125)	Evaluate utility of CPRS pain assessment templates, modify education materials; develop pain reports for clinicians and pain assessment database; identify best practices for pain care	Main	Study design: Qualitative Sample: Providers and nursing staff in two PRCs	1,5
Evaluation of Stepped Care for Chronic Pain (ESCAPE)(126)	Compare a stepped care intervention vs. usual care in OIF/OEF veterans with chronic and disabling musculoskeletal pain	Main	Study design: RCT Sample: 300 OIF/OEF veterans	2,4
The ViRTICo Trial: Virtual Reality Therapy & Imaging in Combat Veterans(127)	Compare effects of Virtual Reality Exposure Therapy & Imaging compared with Prolonged Exposure (current first-line therapy)	Secondary	Study design: controlled clinical trial Sample: OEF/OIF veterans with PTSD and TBI combined; PTSD alone; TBI alone; neither PTSD or TBI.	2,4
Regional Anesthesia Military Battlefield Pain Outcomes Study(128)	Determine short-term and long-term pain-related outcomes in OEF/OIF veterans with traumatic extremity injuries; evaluate efficacy of early aggressive advanced regional anesthetic interventional techniques 2-yrs post-injury	Main	Study design: prospective cohort Sample: OEF/OIF soldiers with one or more maligned or amputated limbs	2,4
Chronic Headache among OEF/OIF Veterans Exposed to Blasts(129)	Evaluate initial characteristics and treatment of blast-TBI in OEF/OIF veterans; assess feasibility and effectiveness of brief cognitive-behavioral headache management treatment (BCBHMT)	Main	Study design: case series Sample: OEF/OIF veterans	2,3
Headaches in veterans returning from Iraq/Afghanistan: relation to trauma and combat-related injury(130)	To determine the relationship between Post-Traumatic Stress Disorder (PTSD), TBI, self-report of headaches, and combat-related injury in Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) veterans	Main	Study design: Cross-sectional Sample: 343 male and female veterans registering for care	4
Long-term Outcomes in Burned OEF/OIF Veterans (LOBO)(131)	Assess long term outcomes in OEF/OIF veterans with combat burn injury, combat nonburn injury, and in civilian burn patients	Secondary	Study design: Prospective cohort Sample: OEF/OIF veterans	4
Women Veterans Cohort Study(132)	Assess health care utilization, costs, stress, and satisfaction in OEF/OIF veterans	Secondary	Study design: Prospective cohort Sample: OEF/OIF veterans	4

Pain in Patients with Polytrauma

Title of Project	Main objective(s) of project	Pain-related variable(s) main or secondary outcome?	Study characteristics	KQ
Pain and Emotional Disorders in Veterans with and without Polytrauma(133)	Describe the prevalence, types, and course of pain and psychiatric disorders, as well as functional outcomes, among OEF/OIF vets with and without polytraumatic injuries	Main	Study design: Prospective cohort Sample: 150-200 polytrauma and 300-400 non-polytrauma OEF/OIF veterans	4
Multidiscipline Assessment of Blast Victims for Cognitive Rehabilitation(134)	Determine whether blast exposure is associated with neuropsychological deficits and/or psychiatric disorder and identify contributors to blast-related post-concussive syndrome	Secondary	Study design: Prospective cohort Sample: OEF/OIF veterans	4
Telerehabilitation of OEF/OIF combat wounded with TBI(135)	Provide care coordination and monitor functional and cognitive outcomes of 45 veterans discharged from a VA PRC with TBI; monitor for adverse effects of pain medication	Secondary	Study design: Prospective cohort Sample: OEF/OIF veterans with TBI	4
Predicting Rehabilitation Costs for VA Patients with Traumatic Brain Injury(136)	Compare cost for rehabilitation for veterans with combat TBI to veterans with non-combat TBI; compare utility of measures in predicting costs; examine affect of PTSD on outcomes/costs	Secondary	Study design: Retrospective cohort Sample: OEF/OIF patients with TBI	4
Characterization and Care Coordination of Polytrauma Patients(137)	Study & describe characteristics of polytrauma patients, including cognitive, emotional, physical and overall functional impairment	Secondary	Study design: Cross-sectional Population: OIF/OEF patients	4
Pain, mental health, and daily function in OIF/OEF veterans(138)	Describe the pain concerns of OIF/OEF veterans, examine association between pain, comorbid mental health concerns, and daily functioning	Main	Study design: Cross-sectional Sample: 233 OIF/OEF veterans	4
Clinical Characteristics of Patients with Polytrauma and Blast-Related Injuries(139)	Describe clinical characteristics, interventions and outcomes for inpatients with polytrauma and blast-related injuries *(Assessment and treatment = primary)*	Main	Study design: Cross-sectional Sample: Veteran inpatients at 4 PRCs	4
Evaluation of Polytrauma Pain(140)	Retrospectively examine pain experiences of soldiers and veterans with polytraumatic injuries incurred during OIF/OEF	Primary	Study design: Cross-sectional Sample: OIF/OEF veterans	4
Validity and reliability of proton magnetic resonance spectroscopy as a diagnostic and outcome measure in clinical trials involving people with SCI(141)	Determine the validity and reliability of Magnetic Resonance Spectroscopy (MRS) as a diagnostic and outcome measure for clinical trials of SCI chronic pain populations; to improve the management of chronic neuropathic pain following SCI	Secondary	Study design: Measurement study Sample: 60 persons with SCI and chronic neuropathic pain, 25 persons with SCI without neuropathic pain, and 25 healthy controls	4

One study is addressing assessment of pain in cognitively impaired patients due to TBI (Key Question 1) using a prospective randomized measurement study of four pain intensity scales in persons with polytrauma and cognitive impairment.(124) Another study will evaluate the usability and utility of CPRS pain assessment templates in two PRC sites; a

template contains a module designed to assist clinicians in evaluating pain in patients with cognitive impairment.(125)

Four studies are testing interventions in patients with polytrauma (Key Question 2): Bair is using an RCT design to test a stepped care intervention for OEF/OIF veterans with chronic and disabling musculoskeletal pain.(126) It is expected that some enrollees will meet criteria for polytrauma. Gallagher's prospective cohort study will evaluate the efficacy of early advanced regional anesthetic techniques on pain and mental health outcomes two years post-injury.(128) Using a pre-post evaluation design, Gironda is piloting a brief cognitive headache management intervention for OEF/OIF veterans suffering from persistent blast-related headache.(129) In a controlled clinical trial, Roy is testing whether the Virtual Reality Exposure Therapy and Imaging intervention improves measures of functional health and disability compared to prolonged exposure therapy among veterans with PTSD and TBI.(127)

One study is examining clinical characteristics of headache conditions among OEF/OIF veterans referred to a VA Blast Injury Clinic (Key Question 3).(129)
Thirteen studies will provide information about patient factors associated with outcomes in polytrauma patients (Kew Question 4). Six studies utilizing prospective cohort designs (128, 131-135) and one study using a retrospective cohort design (136) will follow samples of OEF/OIF soldiers or OEF/OIF veterans over time; outcomes include measures of pain, functional status, or adverse effects of pain treatments. Two clinical trials (126, 127) and 5 cross-sectional studies (130, 137-140) will also generate information regarding the relationship of patient factors to pain outcomes in polytrauma patients. An additional study is likely to include polytrauma patients and will examine the validity and reliability of Magnetic Resonance Spectroscopy as a diagnostic tool for clinical trials involving SCI patients with chronic pain.(141) A study objective is to determine pathophysiological and psychosocial contributors to pain after SCI.

Finally, in an ongoing study using qualitative and quantitative methods to evaluate the utility of CPRS pain assessment tools, information will be generated regarding provider or system barriers to treating pain among polytrauma patients (Key Question 5).(125)

Limitations—Active Research

Although we made efforts to identify VA and non-VA investigators who are conducting or planning projects that address key questions, it is very likely that potentially relevant projects were not found. Our primary means of surveying was using email; many investigators did not respond to our queries, and we presume that in many of these cases, these investigators were not doing research relevant to the key questions. A snowball approach was used to identify relevant research projects; this approach identified several of the projects included in this review. We note that we communicated with several military/DOD and a number of non-VA, non-DOD investigators during the process. In addition, we searched a number of web-databases to identify funded VA and non-VA projects.

SUMMARY AND DISCUSSION

Pain from polytraumatic injuries poses numerous challenges during and after rehabilitation treatment. Pain assessment and intervention efforts are further complicated when the injuries include TBI. The overall purpose of this project was to identify and synthesize evidence on the assessment and treatment of pain in polytrauma patients.

Overall, the literature provides very limited evidence to guide clinicians in this area. Although some previous investigations indicate that pain may interfere with neurocognitive performance in TBI patients, there have been no published studies examining approaches to assessing pain among patients with moderate to severe TBI. Studies that have been done with patients with cognitive impairment due to dementia indicate that most cognitively impaired individuals can understand at least one self-assessment measure. Guidelines suggest that for patients with dementia who cannot understand any of several self-assessment measures available, an observational assessment measure or input from family, friends, or staff who know patients well, or empiric pain treatment if the patient has diagnoses usually associated with pain, may be helpful. How well these findings and guidelines might apply to younger patients with cognitive impairment due to TBI is currently unknown. One ongoing VA research study is examining the validity and reliability of 4 pain intensity scales in persons with polytrauma and cognitive impairment, and an additional VA study is examining the utility of a CPRS pain assessment template module to assist clinicians in evaluating pain in patients with cognitive impairment in PRCs.

The literature also provides very limited evidence to guide clinicians in selecting among non-surgical pain treatments in patients with polytrauma. Aside from one good quality retrospective cohort study indicating that rehabilitation may improve outcomes among patients with trauma related amputation, no systematic pain intervention studies have been done in the polytrauma population. A number of case reports suggest possible approaches to treating pain in polytrauma patients, ranging from intrathecal baclofen pumps for pain associated with spasticity to alternative therapies including healing touch. These potential treatment modalities have not been rigorously tested with polytrauma patients. Despite potential concerns about adverse effects, we found only a single case report regarding the use of opioids for pain other than for acute care among TBI patients. Several ongoing research projects are testing interventions in patients with polytrauma. These interventions include stepped care for chronic musculoskeletal pain, advanced regional anesthetic techniques, brief cognitive headache management therapy for persistent blast-related headache, and Virtual Reality Exposure Therapy and Imaging for veterans with PTSD and TBI.

Although several studies show that headache (as well as auditory deficits and otalgia) is common among blast injury patients, there are no published studies describing how blast-related headache might differ in terms of phenomenology or treatment from other types of headache pain. One VA study is currently examining clinical characteristics of headache conditions among OEF/OIF veterans referred to a VA Blast Injury Clinic.

Pain in Patients with Polytrauma

From a number of cohort studies, there is moderate evidence showing that injury factors (including location, severity, and the number of different injuries) are associated with pain and functional status over time. TBI itself is associated with worse outcomes when compared to polytrauma patients without TBI, and there is some evidence that pain is common among TBI patients, present in one-third to one-half of patients up to five years post-injury. However, contrary to what is often reported in the literature and reported in a recent systematic review, we found very limited evidence to support that patients with mild TBI are more likely to have headache or other pain than patients without TBI. While predominantly cross-sectional studies suggest that patients with mild TBI may be more likely to have headache pain than patients with moderate or severe TBI, six prospective cohort studies and several additional cross-sectional studies did not find a relationship between TBI severity and headache prevalence. Most of the cross-sectional studies were done in outpatient settings up to several years post-injury, and did not adjust for potential confounders that may influence relationships between TBI severity and pain. In these studies, cases were identified based on who was referred or attended outpatient follow-up visits. It is thus likely that differences in sample composition contribute to the differences in findings between the cross-sectional and cohort studies, in that patients with mild TBI may be more likely to be referred to or attend outpatient follow-up appointments when they have bothersome or persistent symptoms such as headache.

Overall, we found limited evidence regarding other patient characteristics that are associated with pain-related outcomes in polytrauma patients. Factors found to be associated with worse outcomes across at least several studies were: multiplicity of injury, head injury or cognitive disability, and lower limb injuries. Factors associated with better outcomes in a few studies were: younger age, higher educational achievement, and having a white collar job. Among TBI patients, factors found to be associated with pain and pain-related function in several studies included depression, PTSD, insomnia, and fatigue. Fifteen ongoing research studies will provide additional information about patient factors associated with outcomes in polytrauma patients. Seven studies utilizing cohort designs will follow samples of OEF/OIF soldiers or OEF/OIF veterans over time, and should help to identify important correlates of pain-related outcomes among polytrauma patients.

Finally, there is almost no evidence that addresses provider and system barriers to treatment of pain among polytrauma patients. In one rigorously conducted qualitative study, providers reported that polytrauma patients are very complex to treat, and that the work with this population is very challenging and emotionally taxing. In order to provide high quality care to this complex patient population, clinicians have increased their use of multidisciplinary and concurrent care, and consultation from experts. One active study, which is using qualitative and quantitative methods to evaluate the utility of CPRS pain assessment tools, is likely to generate information regarding provider or system barriers to treating pain among polytrauma patients.

CONCLUSIONS

Table 3. Summary of Systematic Evidence Review by Key Question

Key Question	Type of Evidence	Quality (GRADE) of Evidence*	Comments
1. Are pain assessment tools reliable and valid in patients with cognitive deficits due to TBI?	No direct evidence on pain assessment tools in TBI	Very Low*	▪ No particular assessment tool or strategy is known to reliably or validly measure pain intensity or pain-related function in patients with cognitive deficits due to TBI. ▪ Most patients with mild cognitive impairment due to dementia can understand at least one pain self-assessment measure. ▪ Pain may interfere with neurocognitive functioning in TBI patients. ▪ There is no evidence that pain assessment tools for dementia can be reliably applied to persons with cognitive impairment related to TBI
2a. Which treatment approaches are most effective in improving pain outcomes in polytrauma patients?	No direct evidence on effective pain treatment approaches for polytrauma	Very Low	▪ No rigorous studies have been done assessing potential benefits or risks of opioids in patients with polytrauma.
2b. Which pain treatment approaches enhance overall rehabilitation efforts?	1 retrospective cohort study	Very Low	▪ Inpatient rehabilitation may be associated with increased likelihood of return to work and decreased likelihood of reduced hours of work.
3a. Does blast-related headache pain differ from other types of headache pain?	No evidence comparing blast-related headache to other types of headache	Very Low	▪ It is not known how blast-related headache differs from other types of headache in terms of phenomenology or outcome. ▪ Headache and auditory deficits are common among patients with blast-injuries.
3b. Which treatments are best for persistent blast-related headache pain?	No evidence on treatment of blast-related headache	---	▪ Specific treatments for blast-related related headache pain have not been studied.

Table 3. Summary of Systematic Evidence Review by Key Question, continued

Key Question	Type of Evidence	Quality (GRADE) of Evidence	Comments
4. What patient factors are associated with better and worse clinical outcomes among polytrauma patients? Have interventions been developed to address these factors?	Patients with TBI: 1 systematic review, 10 cohort, 3 case-control, and 11 cross-sectional studies	Very Low	▪ There are mixed findings regarding the association between severity of TBI and pain.
		Low†	▪ Psychological factors, including depression and posttraumatic stress disorder (PTSD), and insomnia and fatigue are associated with pain in TBI patients.
	Other patients: 32 cohort studies, 3 cross-sectional studies	Low	▪ Specific factors associated with worse pain-related outcomes include: multiple injuries, foot injuries or injuries below the knee joint, and concurrent head injury or cognitive disability.
		Very Low	▪ Factors associated with better outcomes are younger age, higher educational achievement, having a white collar job or higher income.
5. What are unique provider and system barriers to detecting and treating pain among polytrauma patients? Have interventions been developed to address these barriers?	1 qualitative study of interviews with providers	Very Low	▪ In qualitative interviews, providers reported that polytrauma patients are very complex to treat, and that the work with this population is very challenging and emotionally taxing. Increasing use of multidisciplinary and concurrent care and consultation from experts may be necessary to provide the care that is needed.

***** GRADE: Very low = any estimate of effect is very uncertain.

† GRADE: Low = research is very likely to have an important impact on our confidence in the estimate of effect and may change the effect

FUTURE RESEARCH RECOMMENDATIONS

In order to highlight gaps between the key questions and information available from the literature and information to become available based on current research, Table 4 depicts the results of the literature review of studies that have been published to date, the types of studies necessary to address the key questions, and the research we identified that is currently being done to address the key questions.

Table 5 lists potential study topics and designs as suggested by the investigators and expert reviewers based on the above identified information gaps, and includes their cumulative ratings of the priority of conducting particular studies. Raters were asked to review the research topics and assign them high, medium or low priority, the most important criterion being to achieve the highest possible impact on patient care in the VHA. In rating the suggestions for future research, raters were also asked to consider: 1) the degree to which the proposed research will address information gaps identified in the systematic review, 2) the quantity and quality of the research completed so far including systematic reviews; 3) research currently planned or in progress; 4) the feasibility and timeframe that would be necessary to complete the proposed research; 5) existing barriers that have prevented this research from being undertaken before, and 6) the pros and cons of different research methods that might be appropriate for each research question. Table 5 presents the mean priority ranking for each research topic, based on input from 11 reviewers. Because these are preliminary rankings, a panel or other mechanism to achieve consensus is needed to refine and finalize the recommendations for future research.

We also note the following considerations for conducting and funding research in this area:

- Substantial heterogeneity in the causes and types of polytraumatic injuries, as well as the dynamic nature of recovery from injuries, create challenges for defining and comparing distinct patient populations in research studies, as well as for developing and testing generalizable interventions. In future research it is critical that investigators comprehensively describe polytrauma study samples, settings, recruitment methods, and measurements.
- Due to the level of heterogeneity in the causes and types of polytraumatic injuries, interventions that have the potential to apply, and that are able to be tested among patients with a wide-spectrum of injury patterns may be especially desirable.
- Pilot studies of interventions may be especially helpful to determine feasibility of treatment approaches in the polytrauma patient population before proceeding to larger-scale randomized clinical trials. Enhancement of funding mechanisms that facilitate such pilot work is desirable.
- Battlefield, acute-phase, or early rehabilitation pain interventions may have an important impact on subsequent pain-related outcomes. The DOD may obtain follow-up survey data that could be used or augmented to conduct pain outcome research. Mechanisms that foster improved DOD/VA collaborations including additional data collection may highly desirable. Establishment of a joint DOD-VA pain workgroup might facilitate such collaboration.

Table 4. Summary of Literature Review Findings and Identified Ongoing Research

Key Question or Subquestion	Results of Literature Review	Types of studies needed to answer question	Identified ongoing research
1. Are pain assessment tools reliable and valid in patients with cognitive deficits due to TBI?	No direct evidence on pain assessment tools in TBI or polytrauma.	Qualitative research in rehabilitation patients with polytrauma	▪ Qualitative/quantitative study of clinicians from PRCs regarding pain education & assessment tools(125)
		Prospective observational study of reliability and validity of instruments in rehabilitation patients with polytrauma	▪ Prospective randomized study comparing validity of 4 pain scales in TBI patients(124)
2a. Which treatments improve pain outcomes in polytrauma patients? 2b. Which pain treatment approaches enhance overall rehabilitation efforts?	▪ Case series and case reports of various pain treatments. ▪ Little to no information on use of opioids or integrated care approaches	Exploratory research: feasibility of treatment modalities in case series	▪ Case series pilot of cognitive behavioral intervention for blast headache(129) ▪ Clinical trial of Virtual reality therapy for TBI (pain secondary outcome)(127)
		Effectiveness research: Controlled comparisons of different treatment strategies in patients with polytrauma before or at inception of rehabilitation	▪ RCT of stepped care in OIF/OEF veterans with severe chronic musculoskeletal pain(126) ▪ Prospective cohort study of outcomes of regional anesthesia(128)
3a. Does blast-related headache pain differ from other types of headache pain?	▪ None. ▪ Headache and auditory deficits are common in patients exposed to blast	Prospective, observational studies to determine whether features of injuries, including exposure to blasts, are associated with a different clinical course and outcome.	▪ Case series pilot of cognitive behavioral intervention for blast headache(129)
3b. Which treatments are best for persistent blast-related headache pain?	None.	Exploratory research: feasibility of treatment modalities in case series	▪ Case series on brief cognitive-behavioral headache management treatment (BCBHMT) of blast-TBI(129)
		Effectiveness research: Controlled comparisons of different treatment strategies in patients with blast-related headache	No identified studies using this design

Key Question or Subquestion	Results of Literature Review	Types of studies needed to answer question	Identified ongoing research
4a. What patient factors are associated with better and worse (pain-related) clinical outcomes among polytrauma patients?	▪ Cohort, case control, and cross-sectional studies. ▪ Injury characteristics, insomnia, fatigue, and psychosocial factors are associated with pain-related outcomes (Grade: Low)	Prospective observational study of factors associated with pain-related outcomes among polytrauma patients.	▪ 6 prospective cohort studies examining various (including pain-related) outcomes).(128, 131-135) ▪ 1 retrospective cohort study(136) and 5 cross-sectional studies.(130, 137-140)
		Effectiveness research: Controlled comparisons of different treatment strategies in patients with and without certain characteristics	▪ Clinical trial of Virtual reality therapy in TBI patients (pain secondary outcome)(127) ▪ RCT of stepped care in OIF/OEF veterans with severe chronic musculoskeletal pain(126)
4b. Have interventions been developed to specifically address these factors?	None.	Exploratory research: feasibility of treatment modalities in case series	No identified studies using this design
		Effectiveness research: Controlled comparisons of treatment strategies in patients with comorbid conditions	No identified studies using this design
5a. What are unique provider and system barriers to detecting and treating pain among polytrauma patients?	One qualitative study of interviews with providers.	Qualitative research in rehabilitation patients with polytrauma	▪ Qualitative/quantitative study of clinicians from PRCs regarding pain education & assessment tools (125)
		Prospective observational study of provider and systems factors associated with pain-related outcomes in polytrauma patients.	No identified studies using this design
5b. Have interventions been developed to effectively address these barriers?	None.	Exploratory research: feasibility of treatment modalities in case series	No identified studies using this design
		Effectiveness research: Controlled comparisons of treatment strategies in patients with polytrauma	No identified studies using this design

Table 5: Future Research Topics/Designs – Ratings of Priority

Key Question or Subquestion	Results of Literature Review	Future Research Topic Suggestions	Median rank 1, 2, or 3 *1 = most important*	Interquartile range
1. Are pain assessment tools reliable and valid in patients with cognitive deficits due to TBI?	No direct evidence on pain assessment tools in TBI or polytrauma.	Quantitative measurement study of reliability and validity of existing pain assessment tools among patients with varying levels of communicativeness and brain injury.	1	1, 2
		Examine the discriminant validity of tools for distinguishing pain from other forms of distress and impairment (e.g., restlessness, PTSD symptoms)	1	1, 2
		Examine the validity of assessment tools in the context of a clinical trial of an intervention for a specific pain condition. For example, in trial of opioids for patients with multiple orthopedic injuries and TBI, use tool to measure changes in pain over time.	2	1, 2
		Examine utility, reliability and validity of CPRS Pain assessment modules being used in VA PRCs for assessment of non-communicative patients with pain.	2	1, 3
		Qualitative study to identify pain behaviors in different cognitively impaired TBI states. From this information, develop and test new tool or modify existing tools to match severity and type of cognitive impairment.	2	1, 3
		Qualitative/quantitative research using partnership with family (and staff) to identify key pain behaviors. Develop or modify tool to incorporate information from patient, caregivers, and empiric trials of analgesics (i.e., guideline recommended approaches).	2	2, 3
2a. Which treatments improve pain outcomes in polytrauma pts? 2b. Which pain treatment approaches enhance overall rehab. efforts?	▪ Primarily case series and case reports of various pain treatments. ▪ Little to no information on use of opioids or integrated care approaches.	Trials of non-pharmacological interventions of varying treatment intensity, including psychological interventions and telephone-based interventions.	1	1, 2
		RCTs of integrated treatment approaches including comprehensive interdisciplinary rehab., collaborative care, and treatment involving family members.	1	1, 2
		Compare treatments for common specific core conditions (e.g., TBI; PTSD; Pain) to integrated treatment of these core overlapping symptoms.	1	1, 2
		Systematic prospective observation methods and single case experimental designs with replication to study the relationship between pain control and rehabilitation outcomes.	2	2, 3

Key Question or Subquestion	Results of Literature Review	Future Research Topic Suggestions	Median rank 1, 2, or 3 *1 = most important*	Interquartile range
3a. Does blast-related headache pain differ from other types of headache pain?	▪ None. ▪ Headache and auditory deficits are common in patients exposed to blast.	Cross sectional study describing and comparing characteristics of veterans with headache presumed to be blast-related to veterans with headache not known to be blast-related.	2	1, 2
		Prospective observational cohort study comparing outcomes of veterans with blast-related headache to those without blast-related headache	2	1, 2
		Study associations between comorbid psychiatric conditions and headache among patients with blast-headache; compare to patients with non-blast-headache	2	1, 2
		Perform routine imaging on soldiers exposed to blast to assess for structural abnormalities and correlate with headache symptoms	2	2, 3
3b. Which treatments are best for persistent blast-related headache pain?	None.	Trials of pharmacologic and non-pharmacologic treatments, including patients with blast-related headache in one arm of the trial. Non-pharmacologic interventions to test include cognitive behavioral treatment, hypnosis, relaxation training, and biofeedback.	1	1, 1
4a. What patient factors are associated with pain-related outcomes in polytrauma patients? Have interventions been developed to specifically address these factors? (see 2. above)	Some evidence that injury characteristics, insomnia, fatigue, and psychosocial factors are associated with pain-related outcomes	Prospective cohort study measuring pain outcomes over time. Measuring contributions of patient characteristics and comorbid conditions, while adjusting for injury characteristics including multiplicity of injury, pain type, and location.	1	1, 2
		Prospective cohort study examining relationships between pain, PTSD, and TBI, and pain-related outcomes	1	1, 2
		Collaborate with DOD to collect or obtain existing pre-deployment DOD survey data to adjust for baseline characteristics prior to injuries in prospective or retrospective cohort studies.	2	2, 2
		Use data obtained in collaboration with DOD and/or from Landsthuhl Regional Medical Center to identify long-term effects of battlefield, acute-phase, or early rehab. treatment.	2	2, 2
		Evaluate contribution of partnership with family and other social variables to pain-related outcomes in polytrauma patients.	2	2, 3

Key Question or Subquestion	Results of Literature Review	Future Research Topic Suggestions	Median rank 1, 2, or 3 *1 = most important*	Interquartile range
5a. What are unique provider and system barriers to detecting and treating pain among polytrauma patients? Have interventions been developed to effectively address these barriers?	One qualitative study of interviews with providers.	Establish treatment guidelines for pain in polytrauma based on expert opinion. Disseminate and measure impact of guidelines on care.	1	1, 2
		Evaluate patient perceptions of provider and systems barriers, and the impact of efforts to mitigate those barriers.	2	1, 2
		Evaluate implementation of CPRS pain assessment tools in PRCs. Refine tools and reevaluate.	2	1, 2
		Couple evaluation of site-specific organizational factors with multi-site prospective observational study of patient pain-related outcomes. Identify associations between organizational factors and patient outcomes.	2	1, 2
		Identify adaptations PRCs are making to accommodate diversity among polytrauma patients with pain.	2	2, 3
		Measure the impact of polytrauma pain education on provider behavior.	2	2, 3
		Formative evaluation of implementation of guidelines and education and impact on treatment processes in PRCs.	2	2, 3

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