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Integrative Review: Post-Craniotomy Pain in the Brain Tumor Patient

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Abstract

Aim—To conduct an integrative review to examine evidence of pain and associated symptoms in adult (≥ 21 years of age), post-craniotomy, brain tumor patients hospitalized on intensive care units.

Background—Healthcare providers believe craniotomies are less painful than other surgical procedures. Understanding how post-craniotomy pain unfolds over time will help inform patient care and aid in future research and policy development.

Design—Systematic literature search to identify relevant literature. Information abstracted using the Theory of Unpleasant Symptoms' concepts of influencing factors, symptom clusters and patient performance. Inclusion criteria were indexed, peer-reviewed, full-length, English-language articles. Keywords were 'traumatic brain injury,' 'pain, post-operative,' 'brain injuries,' 'postoperative pain,' 'craniotomy,' 'decompressive craniectomy,' and 'trephining.'

Data sources—Medline, OVID, PubMed and CINAHL databases from 2000 – 2014.

Review Method—Cooper's five-stage integrative review method was used to assess and synthesize literature.

Results—The search yielded 115 manuscripts, with 26 meeting inclusion criteria. Most studies were randomized, controlled trials conducted outside of the United States. All tested

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CONFLICT OF INTEREST STATEMENT

The authors had no conflicts of interest.

Author Contributions:

All authors have agreed on the final version and meet at least one of the following criteria (recommended by the ICMJE*):

1. substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. drafting the article or revising it critically for important intellectual content.

* http://www.icmje.org/recommendations/

pharmacological pain interventions. Post-craniotomy brain tumor pain was well-documented and associated with nausea, vomiting and changes in blood pressure and impacted patient length of hospital stay, but there was no consensus for how best to treat such pain.

Conclusion—The Theory of Unpleasant Symptoms provided structure to the search. Post-craniotomy pain is experienced by patients, but associated symptoms and impact on patient performance remain poorly understood. Further research is needed to improve understanding and management of post-craniotomy pain in this population.

Keywords

Brain tumor; craniotomy; pain; Theory of Unpleasant Symptoms; integrative review; literature review; nurses; nursing

INTRODUCTION

Background

Brain tumor is the seventeenth-most diagnosed cancer worldwide, with 256,000 new cases of brain tumor diagnosed in 2012. Men suffer from brain cancer slightly more frequently than women (Bondy *et al.* 2008, World Cancer Research Fund International 2013, Central Brain Tumor Registry of the United States 2014, Ferlay *et al.* 2015) and incidence rates are higher in developed countries than in lesser developed countries (Bondy *et al.* 2008, World Cancer Research Fund International 2013, Central Brain Tumor Registry of the United States 2014). Scientific advances have resulted in improvements in the diagnosis and treatment of brain tumors (Bondy *et al.* 2008). In fact, one- and five-year survival rates have increased from 7.3% in 1970 to over 18% in 2011 (Informational Services Division of the National Health Services 2010, Cancer Research UK 2014, Ferlay *et al.* 2015, Queen's University Belfast 2015).

Approximately 90% of patients with brain tumors undergo craniotomies for excision and removal of the tumor to increase survival (National Cancer Institute 2014). Surgical procedures are generally understood to be painful (McCaffery & Pasero 1999) but less is understood about post-craniotomy pain. Healthcare providers commonly believe that craniotomies are less painful than other types of surgery due to lack of innervation in the brain (Hassouneh *et al.* 2010, American Brain Tumor Association 2012) and are thus less apt to treat pain. In addition, post-craniotomy pain is often untreated or undertreated due to concerns that it may mask neurological changes in these patients (Talke & Gelb 2005, Durieux & Himmelseher 2007, Lai *et al.* 2012). Pain is often associated with other symptoms including anxiety and depression (McCaffery & Pasero 1999, Rocha-Filho 2015) and nausea and/or vomiting (Dolin & Cashman 2005). Understanding post-craniotomy pain in brain tumor patients is important because post-operative pain is a common cause of delayed mobilization (Saha *et al.* 2013), lengthened hospital stay (Chung *et al.* 1997, Casler *et al.* 2005, Saha *et al.* 2013), disability and decreased quality of life (Andrasik *et al.* 2011, O'Connor & Dworkin 2011). In addition, research has shown that under-treated, generalized post-operative pain is a predictor of the development of persistent pain (Macrae 2001, Dobrogowski *et al.* 2008, Watt-Watson & McGillion 2011, Wu & Raja 2011, Lamacraft

2012). To date, post-craniotomy pain and the symptoms associated with it is poorly understood. Researchers have called for additional studies to understand influencing factors and associated symptoms of post-craniotomy pain and to determine how to best treat it to prevent negative health outcomes (Talke & Gelb 2005, Roberts 2005, Watson 2011, deOliveira Ribeiro Mdo *et al*. 2013, Rocha-Filho 2015).

Definitions and Theory

The International Society for the Study of Pain describes pain as a subjective sensory and emotional experience (McCaffery & Pasero 1999, Watt-Watson & McGillion 2011, Gelinas *et al*. 2013). Pain is a complex symptom comprised of at least four dimensions (intensity, affect, quality and location) (Puntillo *et al*. 2002, Jensen & Karoly 2011). Physical, psychological, social and cultural factors influence the experience of pain (Melzack 1999, Saha *et al*. 2013).

The Theory of Unpleasant Symptoms (TOUS), which suggests that symptoms such as pain are multidimensional and interactive, is commonly used to support pain research because it is relevant to practice and can be used as a framework for making decisions related to patient care (Myers 2009, Lenz *et al*. 2013). The TOUS includes three main concepts: (1) physiological, measureable *symptoms* experienced by the patient; (2) *influencing factors* which alter the patient's experience of the symptom; and (3) patient *performance* (Lenz *et al*. 1997, Lenz *et al*. 2013). *Influencing factors* are physiological, psychological and situational in nature and can catalyze each other affecting patient performance (Lenz *et al*. 1997, Lenz *et al*. 2013). *Performance* is the impact of the symptom on patient outcomes including functional performance (the ability to physically function) and cognitive performance (the ability to think) (Lenz *et al*. 1997, Lenz *et al*. 2013). Researchers using the TOUS have termed groups of associated symptoms as '*clusters*' (Lenz *et al*. 1997). This review will also use the term *cluster* to identify these groups of co-related symptoms.

THE REVIEW

Aim

The aim of this study was to conduct an integrative review using the TOUS as a guiding framework to synthesize and examine what is known about the phenomenon of pain in adult (≥21 years of age), post-craniotomy, brain tumor patients. Specifically, this review sought to answer the following research questions: (1) What is the evidence for post-craniotomy, post-brain tumor pain in adult (≥21 years of age) patients hospitalized on intensive care units?; and (2) What is the evidence for a post-craniotomy symptom cluster associated with pain in adult (≥21 years of age) patients hospitalized on intensive care units?

Design

Cooper's (2010) integrative review method guided the review. This method of integrative review was chosen because it provides a systematic framework to synthesize the current literature regarding post-craniotomy pain in the brain tumor patient (Whittemore & Knafl 2005, Cooper 2010). Cooper's method includes five stages: advance formulation of the problem, data collection, data extraction, evaluation, analysis and interpretation (Cooper

2010). The formulation of the problem, the first stage of the method, was informed by a preliminary literature search and the researchers' clinical experience that suggested a greater understanding of acute post-craniotomy pain was warranted. The authors felt an integrative review was necessary to synthesize the current literature and further the state of the science (Whittemore & Knafl 2005, Cooper 2010).

Search Methods

Data collection, the second stage, consisted of a literature search. Studies were identified for inclusion by purposive searching of electronic databases including Medline, OVID, PubMed and CINAHL. In addition, hand-searching of references and an examination of citations from identified published reviews were conducted. Two experienced reference librarians provided consultation on the search process. Search terms for all databases and searches included traumatic brain injury; pain, postoperative; brain injuries; postoperative pain; craniotomy; decompressive craniectomy; and trephining. Inclusion criteria were as follows: (1) data-based quantitative and qualitative articles focused on post-craniotomy pain in adult brain tumor patients aged 21 or older; (2) published between 1 January 2000 – 12 December 2014; (3) English-language; (4) neurosurgical inpatients; and (5) intensive care unit settings. Abstracts, editorials, dissertations, theses, reviews and articles concerning intraoperative pain control, end-of-life care, or institutional practices were excluded.

Search Outcome

The search strategy generated 115 studies. The studies which were recorded in a Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) diagram. (Figure 1.) A total of 109 potentially relevant studies remained after the initial screening of titles for duplicates, publication in English and publication dates. The remaining abstracts were reviewed for type of study, population, study setting and discussion of pain. After application of the inclusion and exclusion criteria, we eliminated 83 additional articles from review, including five qualitative studies that either did not meet inclusion criteria because they did not focus on pain or the participants were not in-patients. This resulted in a sample of 26 quantitative articles to be reviewed in full-text format (Table 1). Data from eligible studies were abstracted into tables listing general information, level of evidence and concepts defined in the TOUS.

Quality Appraisal

In the third stage, two authors completed a quality appraisal on the 26 articles. Using a 3-point scale (yes, no, unclear) described by Gazarian, they rated the studies on nine criteria including aims, design, methods, sample, ethical considerations, results, limitations, implications and sponsorship (2013). The studies were also appraised for bias using the Cochrane Risk of Bias tool. Twenty-one of the studies used a randomized design. Of the five studies that did not use randomization, two were retrospective (Thibault *et al.* 2007, Ducic *et al.* 2012) and three were prospective trials (Irefin *et al.* 2003, Grossman *et al.* 2007, Nair & Rajshekhar 2011). The team determined that these five studies nonetheless met inclusion criteria and thus all 26 studies are included in the review.

Data Abstraction

The fourth stage includes data analysis and interpretation (Cooper 2010). In this stage, all of the included studies were read in full and relevant data were extracted and tabulated. Table 1 displays the authors' names; dates and countries of publication; purpose and design; sample, setting and intervention; medication tested; and pain prevalence, incidence and intensity. (Table 1).

Data Synthesis

In the fifth and final stage, the tabulated data were synthesized to address the research questions (Cooper 2010). The authors grouped the data into categories suggested by the TOUS including incidence of pain, influencing factors, cluster and patient performance. (Table 2). Two of the authors (RG & DV) reviewed each study and verified the accuracy of data as presented and over several meetings compiled the results.

RESULTS

Description of the Studies

Of the 26 studies included, all were pharmacological pain management trials (pain medications) and most were randomized, controlled trials (RCTs) (n = 21). The studies included 1892 total patients and were originally designed to test local wound infiltration or medications to control pain (intravenous, intramuscular, oral medications, nerve blocks, general anesthesia) (Table 1). The medications that were tested varied but mostly included bupivacaine, ropivacaine, tramadol, parecoxib, paracetamol and morphine.

The mean ages of the participants in the studies ranged from 45 to 55 and approximately equal numbers of men and women were represented. The comprehensive search identified five qualitative studies; however, these did not meet inclusion criteria (focus not on pain or participants not in-patients) and were excluded from final analysis. The majority of trials took place outside of the United States at non-profit, urban, academic medical institutions. Only one study reported racial characteristics of the sample that consisted mostly of Caucasians (52 versus 12 non-Caucasian) (Morad *et al.* 2009). Reports included both supratentorial surgeries and infratentorial surgeries with mean lengths of surgery ranging between 200 and 300 minutes.

Main Results

As previously discussed, we used the TOUS as the guiding framework for describing the experiences and cluster associated with post-craniotomy pain in brain tumor patients, which resulted in five categories: (1) evidence of pain; (2) manner of pain assessment; (3) influencing factors; (4) symptom cluster; and (5) patient performance (Tables 1 and 2).

Evidence of Pain—Fifteen studies reported specific percentages of participants experiencing moderate-severe pain. These percentages were as high as 60–96% within the first two days after surgery, despite the use of analgesics. Participants in eight studies required additional pain medications and in one study, inadequate analgesia in 75% of participants necessitated the removal of one study arm (Verchere *et al.* 2002). In this arm, six

of eight patients experienced inadequate analgesia and multiple infusions of additional pain medication were required to reduce pain intensity scores to below 30 (out of 100) (Verchere *et al.* 2002). An additional study reported the withdrawal of five participants for severe pain in the first post-operative hour (Sudheer *et al.* 2007).

Manner of Pain Assessment—Measures that were used to assess pain varied but most used one-dimensional assessments of intensity including visual analogue scales (VAS), numerical rating scales (NRS), visual rating scales (VRS), or visual numeric scales (VNS). Study authors did not measure other dimensions of pain such as timing, distress, affect and quality. Twenty-one studies (81%) identified inadequate pain relief.

Influencing factors—Table 2 displays the evidence of post-craniotomy pain, factors that may influence its development, an associated symptom cluster and possible impact on patient performance. Many authors did not report all elements of the TOUS. Eleven of the 26 studies (42%) discussed some physiological, psychological, or situational factors influencing post-craniotomy pain.

Several studies examined physiological influencing factors such as included gender and age but findings were inconsistent. One study found that women tended to experience higher pain levels than men (Morad *et al.* 2009) while another study found that men were more likely to ask for pain medication than women (Jellish *et al.* 2006). The impact of age in the development of post-craniotomy pain also was not clear. One study found that older age was associated with less pain (Thibault *et al.* 2007) while another found increased pain levels in older patients (van der Zwan *et al.* 2005).

Psychological influencing factors are the patient's emotional reactions to the disease and can include mood and perceived level of self-sufficiency (Lenz *et al.* 1997, Lenz *et al.* 2013). No studies examined psychological factors that may influence the experience of post-craniotomy pain.

Situational factors are found in the social and physical environment and can include surgical positioning, site of surgery and use of anesthetics. Three studies reported less pain among patients with frontal craniotomies (Thibault *et al.* 2007, Morad *et al.* 2009 Ducic *et al.* 2012) and one study found that perioperative nerve blockade decreased the incidence of post-operative pain (Morad *et al.* 2009). General anesthetics used included sevoflurane and desflurane. The use of sevoflurane resulted in less pain in one study (Magni *et al.* 2005), while in another, patients receiving sevoflurane required additional medication to control their pain (Magni *et al.* 2009).

Clusters—Clusters in the TOUS are groups of co-related symptoms that interact, affecting the patient's symptom experience (Lenz *et al.* 1997, Lenz *et al.* 2013). Although the researchers did not explicitly explore 'symptom clusters,' 21 (81%) studies discussed symptoms related to pain. Symptoms reported include headache nausea and vomiting, shivering, fatigue, dizziness, respiratory depression, constipation, neurologic changes, increased risk of intracranial bleeding and agitation. The top three most common symptoms

described were nausea (15 studies; 58%), vomiting (16 studies; 62%) and changes in blood pressure including, but not limited to, the development of hypertension (9 studies, 35%).

Patient performance—Patient performance is frequently assessed in terms of tangible functional outcomes, such as length of stay, readiness to be discharged and perceived quality of life. Although performance related to post-craniotomy pain was not explicitly examined, almost half of the studies described potential results of post-craniotomy pain (Table 2). However, it was unclear if the impact on patient performance was a direct result of pain, the use of pain medication, or other factors. Other functional performance outcomes reported included increased cost of medication and increased hospital length-of-stay. In two different studies, poorly managed post-craniotomy pain resulted in delayed discharge and altered quality of life (Jellish *et al.* 2006, Ducic *et al.* 2012). Four studies described changes in cognitive performance using the proxy measure of level of conscious assessed by the Glasgow Coma Scale (GCS) (Magni *et al.* 2005, Saringcarinkul & Boonsri 2008, Magni *et al.* 2009, Williams *et al.* 2011). Two studies found changes in level of consciousness due to type and amount of analgesic used (Saringcarinkul & Boonsri 2008, Williams *et al.* 2011) and one identified these changes as being the result of uncontrolled pain (Magni *et al.* 2005).

DISCUSSION

To our knowledge, this is the first integrative review of data-based studies examining: (1) evidence for post-craniotomy, post-brain tumor pain; and (2) the evidence for a post-craniotomy pain symptom cluster in brain tumor patients. Brain tumors affect many worldwide and pain has been identified as a public health priority. Accordingly, most research on post-craniotomy pain has been conducted in other countries. Research to date has focused solely on pharmacological intervention and fails to explore the multidimensional nature of pain through comprehensive assessment (Leslie & Troedel 2002, Nemergut *et al.* 2007, Hansen *et al.* 2011, Guilfoyle *et al.* 2013). Although pharmacological interventions exist, no one therapeutic medication has been identified as most efficacious (National Pharmaceutical Council 2003, Paolino *et al.* 2006, Institute of Medicine Committee on Advancing Pain Research 2011, Saha *et al.* 2013). Our review found that despite the use of 18 different analgesics, moderate to severe pain still occurred among post-craniotomy brain tumor patients and that many patients expressed inadequate pain management resulting in the need for more analgesics. This review provides strong evidence for the existence of post-craniotomy pain and the need for more research to develop evidence-based practice guidelines in this population.

While researchers have begun to study patients' subjective experiences after craniotomy, such as their fears, expectations and satisfaction (Khu *et al.* 2010, Milian *et al.* 2014), these investigations have not yet addressed pain. Patients' experiences of pain will necessarily be affected by amount of pain control and healthcare provider interaction, but the extent to which these influence post-craniotomy, post-brain tumor patient experience has not yet been made clear. Due to the complicated nature of post-craniotomy pain, further research is warranted to provide evidence-based care.

A full understanding of the post-craniotomy pain experience from the patients' perspectives would improve assessment of pain, planning of interventions and evaluation of care (Melzack 1999 andrasik *et al.* 2011, Watt-Watson & McGillion 2011). This review serves as a call to action to describe the context and unfolding of post-craniotomy brain tumor pain from the patient's perspective and provides evidence to challenge the commonly held belief that post-craniotomy pain is not an important problem (Hassouneh *et al*, 2010, American Brain Tumor Association 2012).

The intensity of post-craniotomy, post-brain tumor pain is well-documented. Measures such as VASs are capable of reflecting this intensity and change in pain over time (Jensen & Karoly 2011). However, pain intensity is not necessarily correlated with level of patient distress and resulting patient performance (Melzack 1999, Jensen & Karoly 2011, Turk & Melzack 2011, Turk & Robinson 2011, Watt-Watson & McGillion 2011). Consequences such as the development of dysfunction and disability reflect broader dimensions of pain that cannot be assessed by mere measures of intensity and distress (Turk & Melzack 2011, Watt-Watson & McGillion 2011). Current research fails to explore the pain experience beyond intensity and does not address the cluster of associated symptoms that may magnify pain and/or moderate treatment effects.

The limited and conflicting nature of the evidence concerning physiological factors that influence the development of post-craniotomy pain in the brain tumor patient suggests that additional, more comprehensive description is needed. Increased awareness of the experiences of post-craniotomy pain across age groups is needed (Andrasik *et al.* 2011).

Investigations of the experience of post-craniotomy, post-brain tumor pain by gender could lead to the development of targeted approaches for men and women. Similarly, while incidence of brain tumor is higher in Caucasians than in those of other racial backgrounds (National Cancer Institute 2014), few authors report racial characteristics of the study sample, preventing clear understanding of the manner in which post-craniotomy pain unfolds among different groups.

Psychological factors influencing the development of post-craniotomy, post-brain tumor pain are also thought to be important (McCaffery & Pasero 1999, Melzack 1999 andrasik *et al.* 2011, Turk & Robinson 2011, Lenz *et al.* 2013). None of the studies in the review, however, addressed these factor and thus it is not yet clear what role emotions, mood and perceived level of self-sufficiency play in the unfolding and experience of post-craniotomy pain.

Situational factors that affect the unfolding and experience of post-craniotomy pain also need further clarification. Longer surgical time influences length of intensive care unit stays in cardiac patients (Chu *et al.* 2008) and length of surgery influences the severity of post-operative pain in ambulatory care surgical patients (Chung *et al.* 1997). In post-craniotomy patients, longer surgeries may increase post-surgical pain due to greater time spent in surgical positions, increased duration of muscle retraction, larger incisions and the potential for more involved surgical procedures (Casler *et al.* 2005, Ducic *et al.* 2012). Researchers

should therefore investigate the impact of length of surgery on the development of post-craniotomy pain.

More detailed comparisons could also be made if surgical diagnoses were consistently reported. For example, it is known that post-operative headache in occipital surgeries stems from resulting occipital neuralgia (Ducic *et al.* 2012). Examining the effect of surgical location on development of post-craniotomy headache could lead to better targeted interventions.

The existence of a symptom cluster would call for comprehensive post-craniotomy pain assessment (Melzack 1999 andrasik *et al.* 2011, Saha *et al.* 2013). Little is known, however, about the cluster associated with post-craniotomy, post-brain tumor pain. In the current science, effects of pharmaceutical interventions, post-craniotomy pain, other symptoms such as pain and anxiety and patient performance are often confounded. Research that explicates the nature of symptom clusters in this population is needed.

Literature shows that post-operative pain may affect performance by increasing length-of-stay, cost of hospitalization and delaying discharge (Watt-Watson & McGillion 2011, Saha *et al.* 2013). Some research links post-craniotomy pain to increased length of stay and delayed readiness to be discharged in the traumatic head injury population (Honeybul 2010, Honeybul & Ho 2010). However, only a few studies have examined the impact of post-craniotomy pain on brain tumor patients' functional and cognitive performance.

In the broader pain literature, untreated acute pain has been correlated with the development of long-term pain due to nervous system plasticity (Melzack 1999, Turk & Robinson 2011, Watt-Watson & McGillion 2011, Ducic *et al.* 2012). In addition, researchers of general post-surgical pain have shown that inadequate post-operative analgesia has led to the development of persistent pain (Horn & Munafo 1997, McCaffery & Pasero 1999, Watt-Watson & McGillion 2011). Batoz *et al.* (2009) have shown that improved pain management in post-craniotomy patients during the acute post-operative period decreases the development of persistent pain at two months, but the relationship between post-operative pain management and persistent pain has not been well-studied in post-craniotomy brain tumor patients. Therefore, describing the connection between post-craniotomy pain and patient performance could lead to the development of interventions to prevent or minimize both post-craniotomy pain and its resulting effects.

Over forty years of research have repeatedly illustrated that pain is under-assessed, under-recognized and undertreated. The treatment of post-craniotomy pain is further complicated by a lack of understanding of the manner in which it unfolds over the course of the post-operative period and a reluctance to treat it aggressively for fear of masking neurological changes. The result is an unclear risk-benefit ratio associated with the treatment of post-craniotomy pain in brain tumor patients. Additional research would illuminate the relationship between post-craniotomy pain, influencing factors, associated clusters and patient performance, leading to the development of timely interventions to control pain without increasing risk to patients.

Limitations

This review was limited to examining studies that discussed particular influencing factors, associated clusters and the effect of post-craniotomy, post-brain tumor pain on patient performance. It is possible that studies looking at post-craniotomy pain in a different context were missed. In addition, this review does not represent ongoing or unpublished studies, nor does it include published work that has not undergone the peer review process.

CONCLUSION

Evidence suggests that post-craniotomy, post-brain tumor patients experience significant post-surgical pain but no guidelines have been established to treat this pain. Post-craniotomy pain may influence length of hospital stay, cost of medications, quality of life and development of persistent pain. However, little research has been conducted on the complex nature and experience of post-craniotomy, post-brain tumor pain. Mitigating or preventing post-craniotomy pain in the brain tumor population will likely result in improved patient outcomes. Patient-centered outcomes research should focus on attempting to understand post-craniotomy pain, which will pave the way for the development of timely interventions and standardization of treatment for post-craniotomy pain to improve functional outcomes and quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SUMMARY STATEMENT

Why is this research or review needed?

- Brain tumor patients have long been believed to experience little pain post-craniotomy due to lack of innervation in the brain.
- Understanding symptoms correlated with post-craniotomy pain in brain tumor patients will help healthcare providers provide better treatment.
- Addressing untreated and undertreated post-craniotomy pain will improve patient-centered outcomes and quality of life.

What are the key findings?

- Post-craniotomy patients experience significant levels of pain, but current treatment of post-craniotomy pain lacks evidence-based guidelines.
- Post-craniotomy pain in brain tumor patients may be associated with nausea, vomiting and changes in blood pressure and may play a role in healthcare use such as longer hospital stays.

How should the findings be used to influence policy/ practice/ research/ education?

- Understanding the manner in which post-craniotomy pain unfolds should inform healthcare providers' recognition of the symptom.
- Recognition of the intensity of post-craniotomy pain and its impact should lead to timely treatment of the symptom and improve patient outcomes.

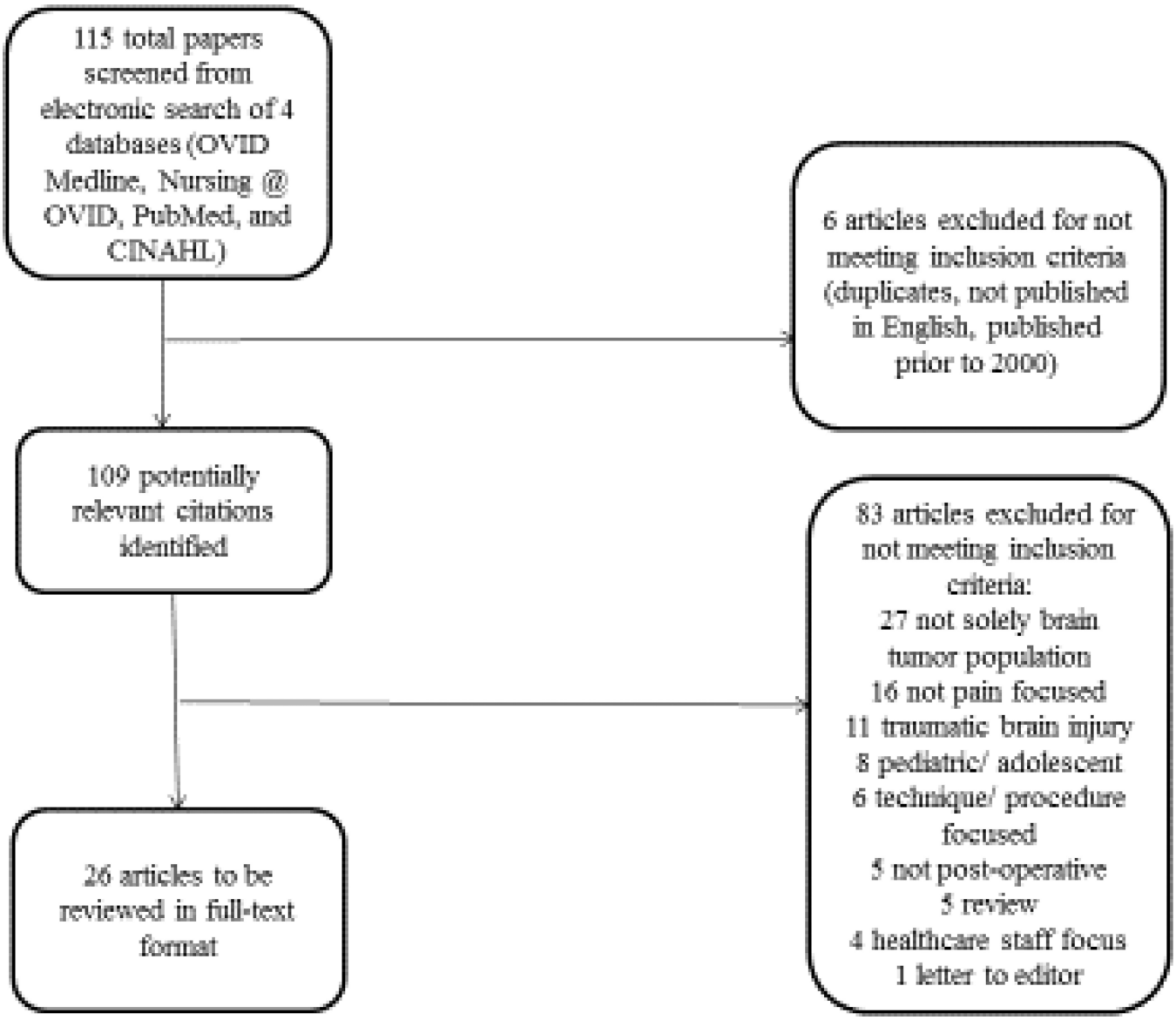

Figure 1.
PRISMA Diagram of Systematic Search

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Table 1

Summarization of Studies

Author, Year, Country	**Design, Sample Size, Medication**	**Existence of Pain and Pain Intensity, Rating Scale Used**
Bala et al. (2006) India	Prospective, double-blind RCT; *N = 40* Medication: Scalp nerve block (bupivacaine)	60% experienced moderate-severe pain in first 12h post-op (control) 25% experienced moderate-severe pain in first 12h post-op (intervention) Rating Scale: NRS; scores 0–22.5 out of 100
Batoz et al. (2009) France	Prospective, single-blinded study; *N = 52* Medication: Incisional infiltration (ropivacaine); nalbuphine post-surgery	VAS scores higher in control group Persistent pain significantly lower in intervention group at 2 months (56% in control group vs. 8% in intervention group) Rating Scale: VAS; scores 0–35 out of 50
Biswas and Bithal (2003) India	Prospective, double-blind RCT; *N = 50* Medication: Incisional infiltration (bupivacaine) vs. fentanyl	Additional medication needed in 60% of bupivacaine group and 57% of fentanyl group Rating Scale: VAS; scores 0–4 out of 10
Ducic et al. (2012) United States	Retrospective interview of patients; *N = 7* Medication: None tested	86% experienced pain greater than 80% on migraine index Rating Scale: VAS; scores 2–10 out of 10
Ferber et al. (2000) Poland	Multi-stage prospective study; *N = 35* Medication: Intravenous tramadol	Pain relief in 50% of patients receiving one dose; in 88% of patients receiving 2 or 3 doses Rating Scale: VRS; scores 0–4 out of 5
Girard et al. (2010) Canada	Prospective, double-blind RCT; *N = 30* Medication: Cervical plexus nerve block (lidocaine and bupivacaine) vs. intravenous morphine bolus	Similar pain scores between nerve block and morphine groups Rating Scale: NRS; scores 2–7 out of 10
Grossman et al. (2007) Israel	Open, prospective, double-blind non-randomized, placebo- controlled study; *N = 40* Medication: Incisional infiltration (lidocaine and bupivacaine); metamizol intra-operatively	13 patients needed additional pain medication Rating Scale: NRS; scores 0–4 out of 10
Irefin et al. (2003) United States	Prospective study; *N = 128* Medication: None tested	No significant difference in pain scores between groups Rating Scale: VAS; scores 0–5 out of 10
Jellish et al. (2006) United States	Prospective, double-blind RCT; *N = 120* Medication: PCA (morphine or morphine plus ondansetron)	Up to 76% experienced post-op pain Administered analgesia was inadequate Rating Scale: VAS; scores 4.5–6.1 out of 10
Jones et al. (2009) Australia	Prospective, double-blind RCT; *N = 50* Medication: Intravenous parecoxib; morphine post-operatively	89% of patients required additional pain medication (morphine) Pain scores significantly lower in parecoxib group only at 6 hours Rating Scale: VAS; scores 0–35 out of 100
Law-Koune et al. (2005) France	Prospective, double-blind RCT; *N = 80* Medication: Incisional infiltration (bupivacaine plus epinephrine) vs. ropivacaine	Placebo group received more morphine than bupivacaine or ropivacaine groups (22.2 mg;12.7 mg; 10.5 mg, respectively) Rating Scale: VAS; scores 0–7 out of 10
Magni et al. (2005) Italy	Prospective, randomized, open-label clinical trial; *N = 120* Medication: General anesthesia (sevoflurane-	10% of ropivacaine group and 6% of sevoflurane group experienced pain at 45 minutes Rating Scale: VAS; scores unclear out of 100

Author, Year, Country	Design, Sample Size, Medication	Existence of Pain and Pain Intensity, Rating Scale Used
	fentanyl vs. propofol-remifentanil)	
Magni et al. (2009) Italy	Prospective, double-blind RCT; *N = 120* Medication: General anesthesia (sevoflurane vs. desflurane)	22% of sevoflurane group and 17% of desflurane group required additional medication for pain Rating Scale: VAS; scores unclear out of 100
Morad et al. (2009) United States	Prospective RCT (unblinded); *N = 64* Medication: as needed intravenous fentanyl vs. PCA (fentanyl)	Patients in PCA group had significantly lower pain scores than PRN group (2.53 versus 3.62, respectively) PCA group received significantly more fentanyl Rating Scale: NRS; scores 2–4.7 out of 10
Nair and Rajshekhar (2011) India	Prospective longitudinal study; *N = 43* Medication: Oral paracetamol	5% had moderate pain in first post-op hour Significant pain reported by 63% of patients during first 48h; severe pain in 12% within first 12h; incidence decreased over first 48h Rating Scale: VAS; not stated out of 10
Nguyen et al. (2001) Canada	RCT; *N = 30* Medication: Scalp nerve block (ropivacaine)	70% of patients in saline group experienced moderate pain in first 48h post-op Rating Scale: VAS; scores 1.6–4.4 out of 10
Rahimi et al. (2006) United States	Prospective, single-blinded RCT; *N = 27* Medication: Oral narcotics vs. oral COX-2 inhibitors	Pain scores significantly higher in narcotics-alone group than COX-2 group (p = 0.003) Rating Scale: VAS; scores 2–5.3 out of 10
Rahimi et al. (2010) United States	Prospective, blinded RCT; *N = 50* Medication: Oral narcotics vs. tramadol	Tramadol group had significantly lower pain scores than narcotics-alone group (p<0.005) Pain scores between groups significantly different (p = 0.001435) Rating Scale: VAS; scores 1–8 (narcotics-along group), 0–7 (tramadol group) out of 10
Saring-carinkul and Boonsri (2008) Thailand	Prospective, double-blind RCT; *N = 50* Medication: Incisional infiltration (bupivacaine)	33% of bupivacaine group pain free at 30 minutes; decreased to 4% at 8 hours 16% of control group pain free at 30 minutes; decreased to 4% at 1 hour Rating Scale: VNS; scores 2.5–3.5 out of 10
Simon et al. (2011) Hungary	Prospective RCT; *N = 90* Medication: Pre-operative oral diclofenac	Significant difference in incidence of pre-operative headache between intervention and control groups (p = 0.0045) 77.7% experienced pain (first post-op day); 69.4% experienced pain (fifth post-op day) Rating Scale: VAS; scores 0–9 out of 10
Sudheer et al. (2007) Wales	Prospective RCT; *N = 60* Medication: PCA (morphine vs. tramadol) vs. intramuscular codeine	4 patients did not require additional medication in first post-operative hour; 5 had severe pain necessitating withdrawal from study Less pain in morphine and codeine groups; significant residual pain noted in tramadol group Rating Scale: VRS; scores 0–10 out of 10
Thibault et al. (2007) Canada	Retrospective chart review; *N = 299* Medication: None tested	24% experienced mild pain, 51.5% moderate pain, and 24.5% severe pain Overall prevalence of pain = 76% Rating Scale: VRS; scores unclear out of 10
Ture et al. (2009)	Prospective RCT; *N = 80*; 75 completed study	Pain scores significantly higher in phenytoin group at 15, 30, and 60

Author, Year, Country	Design, Sample Size, Medication	Existence of Pain and Pain Intensity, Rating Scale Used
Turkey	Medication: Oral gabapentin vs. oral phenytoin	minutes ($p < 0.001$) Total morphine consumption significantly higher in phenytoin group ($p = 0.01$) Rating Scale: VAS; scores 0–4 out of 10
Verchere et al. (2002) France	Prospective, blind, RCT; *N =64* Medication: Paracetamol vs. paracetamol plus tramadol vs. paracetamol plus nalbuphine	Paracetamol-only group stopped quickly due to inadequate analgesia in 75% of patients Rating Scale: VAS; scores 5–30 out of 100
Williams, Pemberton and Leslie (2011) Australia	Prospective, double-blind RCT; *N = 100* Medication: Intravenous parecoxib	70% of control group and 61% of parcoxib group needed additional pain medication Rating Scale: VAS; scores 2–5 out of 10
van der Zwan et al. (2005) The Netherlands	Prospective, double-blind RCT; *N = 50* Medication: Remifentanil vs. fentanyl	No significant difference in pain intensity between groups 13 of remifentanil group (45%) required additional pain medication Rating Scale: VAS; scores 1–4 out of 10

RCT: randomized controlled trial; 4NRS: numerical rating scale; VAS: visual analogue scale; VRS: visual rating scale; VNS: visual numeric scale.

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Table 2

Summarization of Studies Using Theory of Unpleasant Symptoms Concepts

Author, Year	Influencing Factors	Symptom Cluster	Patient Performance
Bala et al. (2006)	• Length of surgery	---	---
Batoz et al. (2009)	---	• Vomiting • Agitation • Shivering • Hypertension	---
Biswas and Bithal (2003)	---	• Change in diastolic blood pressure	---
Ducic et al. (2012)	• Surgical site	• Altered intracranial pressure	• Altered quality of life • Development of persistent pain
Ferber et al. (2000)	---	---	• Change in systolic and/or diastolic blood pressure • Changes in heart rate • Changes in partial pressure of oxygen • Altered intracranial pressure
Girard et al. (2010)	---	• Nausea • Vomiting • Change in systolic blood pressure	---
Grossman et al. (2007)	---	• Nausea • Vomiting • Elevated blood pressure	---
Irefin et al. (2003)	• Gender • Surgical site	• Nausea • Vomiting	---

Author, Year	Influencing Factors	Symptom Cluster	Patient Performance
Jellish et al. (2006)	• Surgical approach • Gender	• Nausea • Vomiting • Headache	• Length of hospital stay • Patient satisfaction • Increased cost of medication used • Delayed discharge from hospital
Jones et al. (2009)	---	• Nausea • Vomiting	• Sedation
Law-Koune et al. (2005)	---	• Nausea • Vomiting • Itching • Change in blood pressure • Bladder dysfunction	• Sedation
Magni et al. (2005)	---	• Nausea • Vomiting • Shivering • Change in blood pressure • Change in heart rate	• Change in Glasgow Coma Scale
Magni et al. (2009)	---	• Change in heart rate • Change in partial pressure of oxygen	• Need for reintubation • Changes in Glasgow Coma Scale
Morad et al. (2009)	• Gender • Age • Surgical site • Surgical approach • Perioperative neural blockade	• Nausea • Vomiting • Change in blood pressure • Change in heart rate • Change in mean arterial pressure	• Neurological deterioration
Nair and Rajshekhar (2011)	---	• Agitation • Sympathetic Nervous System (SNS) stimulation • Altered blood pressure • Brain swelling	• Development of post-operative complications • Increased length of hospital stay • Increased mortality rate

J Adv Nurs. Author manuscript; available in PMC 2017 June 01.

Author, Year	Influencing Factors	Symptom Cluster	Patient Performance
Nguyen et al. (2001)	• Incisional site	---	---
Rahimi et al. (2006)	• Surgical site	• Nausea • Vomiting • Respiratory depression • Constipation • Neurological changes • Constipation	• Altered mental status • Increased cost of medication used
Rahimi et al. (2010)	---	---	• Increased cost of medication used • Increased length of hospital stay
Saringcarinkul and Boonsri (2008)	---	• Nausea • Vomiting	• Sedation • Change in Glasgow Coma Scale
Simon et al. (2011)	• Headache (presence prior to surgery increased post-surgical pain)	---	• Increased length of hospital stay
Sudheer et al. (2007)	• Surgical site (frontal associated with less pain)	• Nausea • Vomiting • Change in partial pressure of oxygen	---
Thibault et al. (2007)	• Surgical site (frontal associated with less pain) • Age (increased age associated with lower pain scores) • Muscle reflection	• Nausea • Vomiting	---
Ture et al. (2009)	---	• Fatigue • Dizziness	---
Verchere et al. (2002)	---	• Nausea • Vomiting • Shivering • Risk of intracranial bleeding	---

Author, Year	Influencing Factors	Symptom Cluster	Patient Performance
		• Agitation • Hypertension	
Williams, Pemberton, and Leslie (2011)	---	• Nausea • Vomiting	• Sedation • Change in Glasgow Coma Scale
van der Zwan et al. (2005)	• Age (increasing age experienced more pain) • Surgical site	• Nausea • Vomiting • Change in partial pressure of oxygen	---
Total Studies Discussing Concept	**11**	**21**	**14**

NRS: numerical rating scale; VAS: visual analogue scale; VRS: visual rating scale; VNS: visual numeric scale.