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

Rebecca Elizabeth Foust Guilkey, BA, BSN, RN, CCRN, Jonas Scholar 2012-2014, T32 STAR Fellow 2014-2015, Indiana University School of Nursing

Diane Von Ah, PhD, RN, Associate Professor, Indiana University School of Nursing

Janet Carpenter, PhD, RN, FAAN, Professor and Associate Dean for Research and Scholarship, Indiana University School of Nursing

Cynthia Stone, DrPH, RN, Associate Professor and Director of Health Policy Management Doctoral Program, Indiana University Fairbanks School of Public Health

Claire B. Draucker, PhD, RN, FAAN, Angela Barron McBride Endowed Professor in Mental Health Nursing, Indiana University School of Nursing

Address correspondence to: Rebecca E. Guilkey, BSN, RN, CCRN, 1111 Middle Drive, NU400, Indianapolis, IN 46202, USA. 317-278-2827. E-mail: refoust@iupui.edu

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Abstract

Context. Patients with brain tumors undergo craniotomies, but craniotomies have been widely believed to be less painful than other surgical procedures. Understanding the experience of post-craniotomy pain will help guide patient care, future research and policy development.

Objective. This integrative review examined prevalence, influencing factors, associated symptom clusters, and consequences of post-craniotomy, post-brain tumor pain.

Methods. A literature search was conducted utilizing Medline, OVID, PubMed and CINAHL using key words "traumatic brain injury," "pain, post-operative," "brain injuries," "postoperative pain," "craniotomy," "decompressive craniectomy," and "trephining." The Theory of Unpleasant Symptoms (TOUS) was used as a guide for abstracting information from each article, including: influencing factors, associated symptom clusters, and consequences of post-craniotomy, post-brain tumor pain. Inclusion criteria were indexed, peer-reviewed, full-length, English-language articles.

Results. The search yielded 115 articles, with 24 meeting inclusion criteria. Hand-searching yielded an additional 2 articles, for a total of 26 articles reviewed. Most studies reviewed (88%) were randomized, controlled trials conducted outside of the United States, and tested pharmacological pain therapies. Although all articles documented the existence of post-craniotomy, post-brain tumor pain, only 12 each discussed influencing factors and associated symptom clusters and 15 reviewed patient performance, while two included information on all four aspects.

Conclusion. The TOUS was helpful in providing structure to our search and can be used to study post-craniotomy, post-brain tumor pain. Further research is needed to improve our understanding and management of post-craniotomy, post-brain tumor pain.

Keywords: brain tumor, craniotomy, pain, Theory of Unpleasant Symptoms, integrative review

Introduction

Brain tumors account for between 85% and 90% of all central nervous system tumors in the United States, with estimates of almost 70,000 new cases diagnosed[1, 2] and 14,300 deaths[3, 4] in 2014. Most new cases (94%) occur in adults [1, 2, 5]. Up to 90% of patients with brain tumors undergo craniotomies for excision and removal of the tumor to increase survival [6]. Though surgical procedures are generally understood to be painful[7], craniotomy, a surgery that entails removal of a section of skull[8], has widely been believed to be less painful than other types of surgery, due to the fact that the brain itself cannot experience pain as it lacks innervation[9, 10]. However, muscle retraction and reflection during surgery result in soft tissue injury that likely contributes to the experience of pain in this population [11-13].

The International Society for the Study of Pain describes pain as subjective in nature and defines it as, "an unpleasant sensory and emotional experience associated with actual or potential tissue damage"[14-17]. Pain is understood as a multidimensional symptom, comprised of at least four dimensions (intensity, affect, quality, and location) [18, 19], influenced by physical [20], psychological [13, 20], social [13], and cultural factors [13], as well as by the patient's previous experiences [13]. The level of intensity of pain is universally described as being whatever that patient states that it is [7, 14, 16, 21], and the presence of pain may or may not be reflected in tissue damage [15, 16, 20, 22].

Consistent with this definition, the Theory of Unpleasant Symptoms (TOUS) suggests that symptoms are unpleasant, complex and interactive, resulting in a multidimensional experience when measured concurrently [23, 24] (See Figure 1). The TOUS includes three main concepts, including *symptoms* experienced by the patient, *influencing factors* which alter the patient's experience of the symptom and affect patient *performance* [24]. *Symptoms* are

described as physiological in nature and encompass the measureable dimensions of intensity, timing, distress, and quality, and are experienced differently by different people [24].

Influencing factors described by the TOUS are physiological, psychological, and situational in nature, are interactive, and can exist in simultaneously occurring groups that can catalyze each other [24, 25]. This catalysis results in a multiplicative effect on patient performance [24]. While Lenz describes the existence of the concept, she does not give it a name. However, other researchers using the TOUS to study heart failure have termed the concept *symptom clusters* [24]. To maintain consistent terminology, we will use the term *symptom cluster* to identify these groups of co-related, co-occurring symptoms.

Finally, the TOUS defines *performance* as the impact of the symptom on patient outcomes in the form of functional performance (the ability to physically function) and cognitive performance (the ability to think) [23, 24]. In particular, the connection between pain and patient performance is of utmost importance because post-operative pain is a common cause of delayed mobilization[13], lengthened hospital stay[13, 26, 27], as well as disability and decreased quality of life[28-30], and when it is under-treated, it is a predictor of the development of persistent pain[15].

This integrative review utilizes the TOUS as a guiding framework to examine what is known about the multidimensional symptom of post-craniotomy pain in the adult brain tumor patient [7, 14, 16, 18, 20]. Specific aims of the literature review were to determine the prevalence of particular influencing factors, to identify the associated symptom cluster, and to determine the resulting effect on post-craniotomy, post-brain tumor patient performance outcomes.

Methods

Analysis methods as well as inclusion/ exclusion criteria were specified in advance of the search process. The search methods were informed by strategies advocated by Cooper [31]. These include advance formulation of the problem, subsequent searching of the literature, data extraction, evaluation, analysis, and interpretation [31].

Studies were identified for inclusion by searching electronic databases including Medline, OVID, PubMed, and CINAHL. Hand-searching of reference noted within articles was also completed to identify additional articles. A second search limited to the years 2010-2014 was also conducted, to ensure that all possible articles were retrieved. Indexed, peer-reviewed, scientific articles discussing pain in the immediate period following craniotomy for the treatment of brain tumor were included. Search terms for all databases and searches were: traumatic brain injury; pain, postoperative; brain injuries; postoperative pain; craniotomy; decompressive craniectomy; and trephining. Search terms were also combined using the terms “and” and “or” in order to identify additional articles (See Figure 2).

Studies were selected if they met pre-determined inclusion criteria: (1) empirical articles focused on post-craniotomy pain in adult brain tumor patients aged 21 or older; (2) published between 1/1/2000 and 7/1/2014; (3) English-language; (4) neurosurgical patients; (5) intensive care unit settings. Excluded were abstracts, editorials, dissertations, theses, reviews, and empirical articles concerning intraoperative pain control or end-of-life care. Titles and abstracts of all records were reviewed to verify eligibility. Data from all eligible studies were abstracted into a series of tables, as guided by the TOUS, in addition to general information and level of evidence of each study.

Results

The search strategy was recorded in a Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) diagram, and generated a total of 115 articles. (See Figure 2.) After removal of duplicates and further reviewing of abstracts, the resulting articles to be reviewed in full-text format totaled 26. Table 1 presents a list of all 26 studies, including author, date, design, sample, pain prevalence, and level of evidence.

Description of Studies

Most articles were reports of randomized, controlled trials of pharmacologic therapies (RCTs; *n = 22*) [11, 32-52]. The remaining articles included two longitudinal descriptive studies [53, 54], and two retrospective studies [12, 28] aimed at understanding the effect of craniotomy location [12, 28, 53] or pain following craniotomy [54]. None of the articles reported qualitative data. The majority of studies (*77%*) were conducted outside of the United States. All studies were conducted within in-patient settings of non-profit, urban medical institutions that were mostly academic medical facilities or teaching hospitals.

Mean ages of study participants in the majority of studies (*n = 19*) were between 45 and 55 years of age [12, 28, 32, 33, 35-38, 42, 43, 45, 47-53]. Most studies included roughly equal numbers of men and women in each study group [11, 12, 32-43, 45, 47-49, 52, 53]. Two studies did not report gender [42, 50]. Interestingly, although incidence of brain tumor is higher in Caucasians than in those of other racial backgrounds [6], only one study reported racial characteristics of the sample [36].

Tumor was listed as a surgical diagnosis in all retrieved articles, with meningioma being the most frequently identified tumor type (*n = 4*) [38, 41, 47, 51]. Additionally, some studies included patients with other acute comorbid conditions including: complex spinal cord injuries (*n*

= 1) [53], aneurysms or other vascular conditions (*n = 6*) [33, 36, 39, 40, 43, 47], epilepsy (*n = 1*) [39], post-traumatic hematoma (*n = 1*) [43], or "other," unspecified conditions (*n = 1*) [40].

Surgical characteristics were reported in some articles. Seven studies reported mean lengths of surgery, with values falling most frequently between 200 and 300 minutes [44-46, 49-52]. Of the eleven studies that reported surgical site, three were classified as supra- or infratentorial in nature [33, 52, 53]. Of note, supratentorial surgeries are assumed to be less painful than infratentorial surgeries [12, 35, 53] because innervation of the head and neck originates in the infratentorial region of the skull [28, 53]. The remaining articles reported frontal (*n = 7*) [11, 12, 34, 35, 38, 39, 49], temporal (n = 6) [11, 12, 35, 38, 39, 49], parietal (n = 6) [11, 12, 35, 38, 39, 49], frontotemporal/pterional (n = 5) [11, 12, 38, 49, 51], or occipital (n = 1) [28] approaches.

All retrieved articles documented post-craniotomy pain in the brain tumor patient. However, all articles measured pain in terms of intensity only. Notably absent were symptom dimensions of timing, distress, affect, and quality. Pain was measured using one-dimensional assessments of severity such as visual analogue scales (VAS, *n = 17*)[11, 28, 32-34, 37-40, 42, 44, 45, 48, 51-54], numerical rating scales (NRS; *n = 4*)[12, 36, 47, 50], visual rating scales (VRS; *n = 3*)[12, 35, 43], or a visual numeric scale (VNS; *n = 1*)[49]. The measurement tool was unclear in one study [41].

Thirteen of the retrieved articles discussed factors purported to influence post-craniotomy pain in the brain tumor patient [12, 28, 33, 35, 36, 39, 42, 45, 46, 48, 51, 53, 55]. According to the TOUS, physiological influencing factors include such categories as age, gender, and race. Two of the retrieved articles noted that gender may have predisposed patients to the development of pain, although the evidence about direction of effect was conflicting [36, 51]. Specifically,

one study found that women tended to experience higher pain levels than men [36], whereas the other found that male subjects asked for more pain medication than females [51]. The role of age in the development of post-craniotomy pain was unclear [12, 33, 36]. Though one study found that older age was associated with less pain [12], another noted increased pain levels in older patients [33].

As defined by the TOUS, physiological factors include emotional states and the patient's reaction to the disease. Physiological influencing factors can also include mood and the patient's perceived level of self-sufficiency. Notably, none of the reviewed studies discussed psychological factors that may influence the experience of post-craniotomy pain in the brain tumor patient.

Included in situational factors are categories such as surgical site, length of surgery, and use of anesthetics. Within six of the retrieved articles, surgical site was cited as affecting the likelihood of post-craniotomy pain [12, 28, 34-36, 56]. Three articles specified frontal craniotomies as resulting in less post-craniotomy pain in the brain tumor patient [12, 28, 36]. Additional potential influencing factors included use of perioperative neural blockade, which decreased incidence of post-operative pain in one study [36].

Symptom clusters are groups of co-related symptoms that interact and affect the patient's symptom experience. Among the retrieved articles, 12 mentioned particular symptoms as related to pain [12, 32-36, 38, 40, 47, 51-53]. Such symptoms included nausea and vomiting (*n = 11*)[12, 32-36, 40, 47, 51-53]; shivering (*n = 2*)[32, 52]; fatigue (*n = 1*)[38]; dizziness (*n = 1*)[38]; respiratory depression (*n = 1*)[34], constipation (*n = 1*)[34], neurologic changes (*n =1*)[34]; increased risk of intracranial bleeding (*n = 1*)[32]; and agitation (*n = 1*)[32].

Patient performance is frequently assessed in terms of tangible outcomes, such as length of stay, readiness to be discharged and perceived quality of life. Within the retrieved articles, there were no studies the focused specifically on patient performance as a study aim. However, almost half of the articles did describe potential results of post-craniotomy pain.

Patient performance encompasses functional and cognitive dimensions. Functional performance is defined by the TOUS as the patient's ability to physically function, and was measured in over half of the articles (*65%*) [11, 28, 32-36, 39-41, 43, 44, 46-49, 51, 52]. Such functional performance included increased blood pressure (*n =6*)[11, 32, 36, 43, 47, 48, 52]; heart rate (*n = 4*)[36, 43, 44, 52]; partial pressure of oxygen (*n = 2*)[33, 35, 43, 44]; mean arterial pressure (*n = 1*)[36]; intracranial pressure (*n = 3*)[28, 41, 43]; itching [48]; and the need for bladder catheterization [48], which all decreased after the administration of an analgesic.

Other outcomes related to functional performance included increased hospital length of stay [39, 42] and increased cost of medication due to type and amount of medication used [34, 39, 51]. Poorly managed post-craniotomy pain also resulted in the development of headache severe enough to affect quality of life (*n = 1*) [28], and lack of readiness for discharge (*n = 1*) [51]. Finally, an additional article specifically asserted that inadequate post-operative analgesia may lead to the development of persistent pain (formerly known as chronic pain) [28].

The TOUS describes cognitive performance as the patient's ability to think. Three of the retrieved articles identified cognitive performance outcomes in the form of decreasing scores on the Glasgow Coma Scale (GCS), indicating deteriorating consciousness, as the result of post-craniotomy pain in the brain tumor patient [40, 41, 49]. Two described this as being a result of analgesics [40, 49], and one identified is as stemming from uncontrolled pain [41]. An

additional article simply reported results of full cognitive emergence from anesthesia, rather than attributing it to analgesic use or post-operative pain [52].

Discussion

To our knowledge, this is the first integrative review of empirical studies examining post-craniotomy pain as a multi-dimensional phenomenon in the brain tumor patient. Using the TOUS as a guiding framework, this review sought to document the existence of post-craniotomy pain in the brain tumor patient, as well as to identify influencing factors, the associated symptom cluster, and the impact of uncontrolled pain on patient performance. Understanding patients' experiences of post-craniotomy pain as it unfolds over the post-operative period will enable healthcare providers to plan strategic interventions that result in improved patient performance. There have been reviews regarding post-craniotomy pain, but they have focused solely on pharmacological intervention and lack both multidimensional assessment and treatment of the symptom [56-59]. Although interventions such as regional anesthesia and the use of various parenteral opioids and non-steroidal anti-inflammatory drugs (NSAIDs) exist, there is currently no consensus on the best way to treat acute post-craniotomy pain [13]. The current review provides significant evidence of the existence of post-craniotomy pain after surgery in adult brain tumor patients and the need for research to investigate the multidimensional nature of pain in this patient population.

All twenty-six retrieved articles reported the existence of moderate to severe pain in the acute, post-craniotomy patient. However, all articles only measured the intensity of this pain, rather than attempting to understand the symptom from a multidimensional perspective. Therefore, this review serves as a call to action for proper assessment and management of post-

craniotomy pain, both of which are noted in the literature to be inadequate[13, 28, 55], as well as providing evidence to challenge the commonly held belief that post-craniotomy pain is not an important problem[9, 10]. This review clearly identified that patients who have had craniotomies have significant pain. In other situations (both post-surgical and other) in which pain is recognized, patients continually report its under-treatment, despite the advances made in the understanding of this symptom [7, 15]. In fact, across all types of pain, researchers have found that less than half of prescribed analgesia is administered, even when patients report moderate to severe pain [7, 15]. Healthcare providers should be aware of the existence of post-craniotomy pain, as well as the necessity of treating this symptom[16], as many remain unsure of its severity and proper management[55]. Education of healthcare providers has been shown to improve patient outcomes [15], and should be pursued with regard to post-craniotomy brain tumor patients. Additionally, little is known about the trajectory of post-craniotomy pain, other than it frequently lessens over the first 48 hours [11, 13, 42, 45, 48, 54]. Therefore, research is needed to make appropriate evidence-based recommendations to address post-craniotomy pain.

Predominant views of the treatment of post-craniotomy pain are based on the Cartesian model of mind-body dualism [16, 20, 60], which separates psychological factors from the "actual" pain, when in fact they are interrelated [7, 16, 20]. Accordingly, none of the studies reviewed examined this pain from a qualitative perspective, attempting to elucidate the *patients' perspectives* of such pain, with the result being that the assessment of post-craniotomy pain in the brain tumor patient has been one-dimensional, which is not in keeping with the knowledge that pain is a multidimensional experience [7, 13-16, 18-20, 30], and best treated by multiple interventions [15, 16, 20, 27]. Focus on the single dimension of pain intensity is not in keeping with the TOUS model, as the latter also discusses the effect of timing, distress, and quality of

symptoms on patient performance [23, 24]. Though measures such as VASs are capable of reflecting intensity of pain and change in pain over time[19], pain intensity is not necessarily correlated with patient distress[15, 19, 20, 22], as physical injury is neither necessary nor sufficient to cause pain[7, 16, 20, 22, 61]. Consequences such as the development of dysfunction and disability reflect broader dimensions of pain that are not encompassed by mere measures of intensity and distress [15, 22]. Pain is subjective, thus the best way to capture its magnitude, location, qualities, and meaning is to obtain the patient's perspective [17, 21, 22]. Therefore, a multidimensional assessment of pain that includes the patient's experience is needed in order to develop interventions and to more effectively evaluate care [15, 20, 30]. Future research should seek to describe the context of post-craniotomy, post-brain tumor pain from multiple perspectives[20] going beyond cursory questioning, which has been shown to be largely ineffective in determining true pain level in critical-care patients[17, 21, 30].

While research on post-craniotomy pain has been conducted in other countries, it is limited in nature, with the most recent research having been conducted in 2012. Therefore, it appears that more timely work is needed to understand the nature of post-craniotomy pain as it affects not only patients worldwide, but those in the United States. Likewise, the limited and conflicting nature of the evidence concerning factors that influence the development of post-craniotomy pain in the brain tumor patient suggests that additional, more comprehensive descriptive research is needed. For example, psychological factors influencing the development of post-craniotomy, post-brain tumor pain are hypothesized to exist [7, 17, 20, 23, 24, 30, 61], yet were entirely absent within the retrieved studies.

In addition, research is needed on a wider age range of patients since the studies reviewed here tended to focus on those ages 45 to 55. The larger literature suggests that increasing age is

linked to decreased perception of pain [7, 16, 27], yet reports of severe pain are more likely to be believed and treated in older adults [7] and endogenous opioids may be less effective in older populations [16]. However, older adults may view pain as a normal part of the aging process, or may be less willing to take opioid analgesics [62], which may confound reports of pain. More research is needed to understand older brain tumor patients' experiences of post-craniotomy pain. [30]

Furthermore, evidence suggests that women may experience pain differently from men [7, 16, 20], receive less thorough clinical assessment of pain [7], and be less likely to receive analgesics [15]. Therefore, studies comparing the experience of post-craniotomy, post-brain tumor pain by gender could lead to recognition and education on the importance of properly assessing pain in female, post-craniotomy brain tumor patients, as well as to the development of interventions targeted to women.

Additionally, the range of surgical encounter time was relatively narrow (mainly 200-300 minutes.) In cardiac patients, longer surgical time significantly increased length of intensive care unit stays [63]. Similarly, length of surgery was a significant predictor of severity of post-operative pain in ambulatory care surgical patients [27]. In the post-craniotomy patients, longer surgeries may exacerbate the perception of pain due to greater time spend in surgical positions, increased duration of muscle retraction, larger incisions, and the potential for more involved surgical procedures[26, 28]. Studies should seek to determine 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 [28]. Therefore, it is likely that research examining the effect

of surgical location on development of post-craniotomy headache could lead to better targeted interventions. Future research should attempt to more clearly identify physiological, psychological, and situational factors that influence the development of post-craniotomy pain in the brain tumor patient.

The existence of symptom clusters confirms the importance of comprehensive post-craniotomy pain assessment [13, 17, 20, 21, 30]. Unfortunately, little is known about symptoms that occur along with post-craniotomy pain in the brain tumor patient. Symptoms may co-occur and co-vary along with post-craniotomy pain in the brain tumor patient, and therefore, may affect the experience of this pain. Indeed, some symptoms have a multiplicative effect on other symptoms, in particular, anxiety and pain [7, 16, 20]. It has been documented that symptoms among cancer patients vary with the stage of illness [7, 64], so it is likely that this variation may be even more profound in the post-craniotomy patient, due to increased patient acuity. However, the extant research confounds co-related symptoms, consequences of post-craniotomy pain, and the impact of such pain on patient performance. To better understand the trajectory and experience of pain in this population and to guide the development of appropriately targeted treatments, consistent use of terminology is important, as are investigations to explicitly identify co-related symptoms.

Some research has been conducted which links post-craniotomy pain to increased length of stay and delayed readiness to discharge in the traumatic head injury population [65, 66]. However, the paucity of information regarding the impact of post-craniotomy, post-brain tumor pain on patient functional and cognitive performance is additional evidence of its under-recognized and under-assessed nature. In fact, none of the reviewed articles attempted to explicitly study the impact of post-craniotomy, post-brain tumor pain on patient performance as a

primary aim. Although some studies listed functional performance outcomes related to pain, such as those related to changes in acute vital signs (increased heart rate, blood pressure, mean arterial pressure, intracranial pressure, and partial pressure of oxygen), or cognitive performance outcomes such as decreased scores on the Glasgow Coma Scale, other listed the same changes as mere outcomes of surgery.

Similarly, few articles recognized that post-craniotomy pain may indeed predict [16] and/or affect [13, 28] patient performance. Current literature shows that post-operative pain may affect performance by increasing length-of-stay, cost of hospitalization, and decreasing readiness for discharge [13, 15, 27]. Though several of the retrieved articles listed performance outcomes such as the development of persistent pain, development of headache severe enough to affect quality of life, increased length of stay, increased cost of medications, and lack of readiness to be discharged, the links between post-craniotomy, post-brain tumor pain and patient performance have not been explicitly studied. Within the broader pain literature, untreated acute pain has been correlated with the development of long-term pain, due to the plasticity of the nervous system [15, 20, 28, 61]. However, this has not been studied in post-craniotomy brain tumor patients. Therefore, explicating 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.

Limitations of This Review

Our review was limited to examining articles that discussed particular influencing factors, associated symptom clusters, and the effect of post-craniotomy, post-brain tumor pain on patient performance. It is possible that studies looking at post-craniotomy pain within 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

Utilizing the TOUS to understand the experience of post-craniotomy pain in the brain tumor patient was useful since this theory postulates the multidimensional nature of symptoms such as pain. Reviewing the existing literature from the perspective of the TOUS allowed identification of numerous gaps in the literature. Namely, there has been limited study of influencing factors, symptom clusters, and the effect of post-craniotomy, post-brain tumor pain on patient performance. Evidence suggests that pain exists, is likely multidimensional, is associated with multiple co-related symptoms, and impacts patient performance by increasing length of stay and costs of medications and hospitalization, as well as decreasing quality of life and potentially leads to the development of persistent pain. Taken together, these findings indicate that mitigating or preventing post-craniotomy pain in the brain tumor population will result in improved patient outcomes and decreased cost, which carries implications for both public health and policy development.

Understanding what causes such pain to develop, what exacerbates the symptom, and what the results of lack of treatment are will pave the way for the development of interventions, optimally including a variety of methods[15, 16, 20, 27], to treat post-craniotomy pain in the brain tumor patient and improve patient outcomes. Thus, comprehending the true nature of post-craniotomy pain in the brain tumor patient will ultimately contribute to improving patients' lives.

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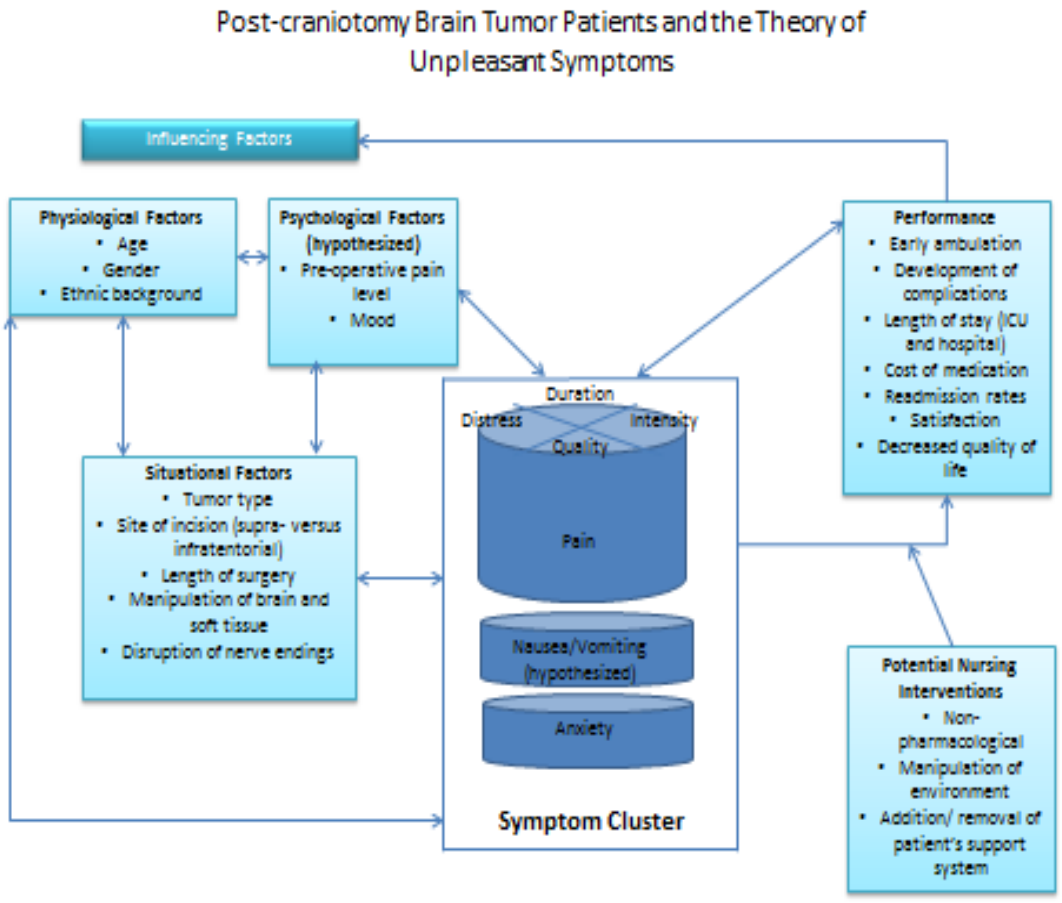
Appendix

Figure 1. Post-craniotomy Pain in Brain Tumor Patients and Theory of Unpleasant Symptoms



Adapted from Lenz's Theory of Unpleasant Symptoms (Lenz, E., Pugh, L. C., Milligan, R. A., Gift, A., & Suppe, F. (1997). The middle-range theory of unpleasant symptoms: An update. *Advances in Nursing Science*, *19*(3), 14-27.)[24]

Figure 2. PRISMA diagram of search strategy.

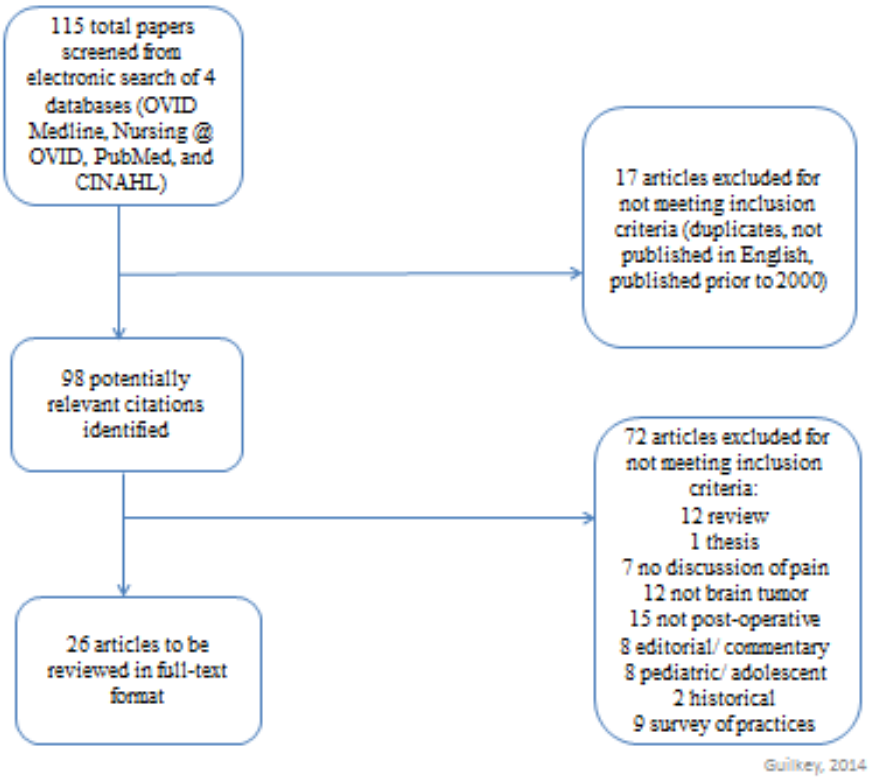


Table 1. Summarization of Studies

Author, Year, Country	**Purpose**	**Design**	**Sample and Setting**	**Pain Prevalence**	**Level of Evidence**
Bala et al. (2006) India	To assess efficacy of scalp block for post-operative pain relief after craniotomy	Prospective, double-blind randomized controlled study	Sample: *N = 40* (elective supratentorial surgery) Tumor patients Setting: Academic institution	60% of patients in control group experienced moderate-severe pain in first 12h post-op (25% in intervention group) More patients in intervention group were pain free (significant only until 4h post-op)	Level II
Biswas and Bithal (2003)	To evaluate effect of preincisional	Prospective, double-blind	Sample: *N = 50* (elective supratentorial surgery); 9	---	Level II

India	scalp infiltration on post-operative pain perception and analgesic requirement	randomized, placebo- controlled study	patients excluded due to poor ventilation = 20 in bupivacaine group, 21 in fentanyl group Resection of tumor Setting: Academic institution		
Ducic et al. (2012) United States	To demonstrate that occipital nerve injury is associated with chronic post-operative headache	Retrospective interview of patients	Sample: *N = 7* (acoustic neuroma resection) Resection of tumor	6 of 7 patients experienced pain greater than 80% on migraine index	Level VI

			Setting: Academic institution		
Ferber et al. (2000) Poland	To evaluate effect of IV bolus of tramadol on post-operative pain, ICP, and CPP	Multi-stage prospective study	Sample: *N = 35* across 3 groups (1: n = 11, 2: n = 13, 3: n = 11) Brain tumor among those groups included Setting: Academic institution	---	Level IV
Girard et al. (2010) Canada	To compare quality of transitional analgesia via superficial	Prospective, double-blind randomized controlled study	Sample: *N = 30* (infratentorial or occipital surgery)	---	Level II

	cervical plexus block or morphine following craniotomy		Tumor among groups of patients Setting: Academic institution		
Grossman et al. (2007) Israel	To evaluate incisional infiltration with metamizol for post-operative pain control	Open, prospective, double-blind non-randomized, placebo- controlled study	Sample: *N = 40* consecutive Resection of tumor Setting: Academic institution Anesthesiology and neurosurgery departments	---	Level III

Irefin et al. (2003) United States	To examine hypothesis that patients who have infratentorial craniotomy experience more severe pain and more frequent nausea than those undergoing supratentorial surgery	Prospective study	Sample: *N = 128* (elective infratentorial or supratentorial craniotomy or spinal surgery) Resection of tumor Setting: Non-profit, academic institution	---	Level IV
Jellish et al. (2006) United States	To examine effectiveness of PCA with combination	Prospective, double-blind randomized,	Sample: *N = 120* (elective infratentorial –posterior fossa – surgery)	Up to 67% of acoustic neuroma patients experienced post-op pain	Level II

	morphine/ondansetron for analgesia and emesis control	placebo- controlled study	Resection of primarily acoustic tumor Setting: Non-profit, academic institution PACU	Evidence that inadequate analgesia administered	
Jones et al. (2009) Australia	To evaluate effect of preincisional scalp infiltration on post-operative pain perception and analgesic requirement	Prospective, double-blind randomized, placebo- controlled study	Sample: *N = 50* (elective supratentorial surgery); 9 patients excluded due to poor ventilation = 20 in bupivacaine group, 21 in fentanyl group Reason for surgery not discussed	---	Level II

			Setting: Non-profit, Catholic institution		
Law-Koune et al. (2005) France	To determine analgesic effect of scalp infiltration with bupivacaine or ropivacaine	Prospective, double-blind randomized study	Sample: *N = 80* (elective supratentorial surgery); 4 patients excluded post-operatively due to complications Resection of tumor Setting: Non-profit institution	---	Level II
Magni et al. (2005)	To compare early post-operative recovery and	Prospective, randomize, open-label clinical trial	Sample: *N = 120*	---	Level II

Italy	cognitive function in patient undergoing craniotomy		(craniotomy for supratentorial intracranial surgery) "Expanding lesions" Setting: Academic institution		
Magni et al. (2009) Italy	To compare post-operative recovery and cognitive function in patients receiving sevoflurane and	Prospective, double-blind randomized, placebo- controlled study	Sample: *N = 120* (elective supratentorial surgery) "Expanding lesions" Setting: Academic institution	---	Level II

	desflurane anesthesia				
Morad et al. (2009) United States	To determine efficacy of PCA in treating supratentorial craniotomy pain	Prospective, randomized study (unblinded)	Sample: *N = 64* (elective supratentorial surgery) Tumor patients included among others Setting: Non-profit, academic institution Neuroscience ICU	---	Level II
Nair and Rajshekhar (2011)	To study intensity of pain I post-operative period following	Prospective longitudinal study	Sample: *N = 43* (male predominant; supratentorial surgery)	5% had moderate pain in first post-op hour	Level IV

India	supratentorial craniotomy		All patients admitted to neurosurgical ICU; tumor not explicitly mentioned Setting: Non-profit, academic institution Neurosurgical ICU	Significant pain reported by 63% of patients during first 48h; severe pain in 12% within first 12h; incidence decreased over first 48h	
Nguyen et al. (2001) Canada	To assess efficacy of scalp block in decreasing post-operative pain in brain surgery	Randomized controlled experimental	Sample: *N = 30* (supratentorial surgery) Supratentorial mass or aneurysm clipping	At least 70% of patients in saline group experienced moderate pain in first 48h post-op	Level II

			Setting: Academic institution		
Rahimi et al. (2006) United States	To evaluate efficacy of alternative pain management strategies	Prospective, single-blinded randomized, controlled study	Sample: *N = 27* (elective craniotomy) Reason for surgery not discussed Setting: Non-profit, academic institution	---	Level II
Rahimi et al. (2010) United States	To evaluate efficacy of alternative pain management strategies	Prospective, blinded, randomized, controlled study	Sample: *N = 50* (elective supratentorial surgery) Tumor patients included among others	---	Level II

	following craniotomy		Setting: Non-profit, academic institution		
Saringcarinkul and Boonsri (2008) Thailand	To determine effect of scalp infiltration on post-operative craniotomy pain	Prospective, double-blind randomized controlled study	Sample: *N = 50* (elective supratentorial surgery); 9 patients excluded due to poor ventilation = 20 in bupivacaine group, 21 in fentanyl group Reason for surgery not discussed Setting: Academic institution	---	Level II

Simon et al. (2011) Hungary	To assess incidence of post-craniotomy headache (PCH); to test efficacy and safety of diclofenac	Prospective, randomized controlled study	Sample: *N = 90* Tumor resection Setting: Academic institution	Headache present in 48.8% pre-operatively (different in two groups: 21/54 in intervention group, 25/36 in control group; p = 0.0045) HA of any severity 89% on day of surgery (intervention), 75% (control)	Level II
Soliman et al. (2011) Egypt	To assess perioperative effect of intraoperative dexmedetomidine	Prospective, double-blind randomized, placebo-controlled study	Sample: *N = 40* (elective supratentorial surgery) Tumor patients	---	Level II

			Setting: Academic institution		
Sudheer et al. (2007) Wales	To compare 3 analgesic regimens during first 24h post-op	Prospective, randomized study	Sample: *N = 60* (various surgical sites) "Expanding lesions" Setting: Academic institution	---	Level II
Thibault et al. (2007) Canada	To assess intensity of post-operative pain in relation to location of craniotomy	Retrospective chart review	Sample: *N = 299* All craniotomy patients (tumor not explicitly listed) Setting: Academic institution	Within study: 24% mild pain, 51.5% moderate pain, 24.5% severe pain Overall prevalence of pain = 76%	Level IV

Ture et al. (2009) Turkey	To evaluate effectiveness of gabapentin on acute post-operative pain	Prospective, randomized, controlled study	Sample: *N = 80* (supratentorial surgery); 75 completed study Tumor resection Setting: Non-profit, academic institution	---	Level II
Verchere et al. (2002) France	To compare analgesic efficacy of three different post-operative treatments	Prospective, blind, randomized controlled study	Sample: *N =64* (supratentorial surgery) Tumor patients Setting: Non-profit institution	---	Level II

Williams, Pemberton, and Leslie (2011) Australia	To determine if IV parecoxib decreases total morphine consumption and side effects	Prospective, double-blind randomized, placebo- controlled study	Sample: *N = 100* (elective supratentorial surgery) Tumor patients included among others Setting: Non-profit institution	---	Level II
van der Zwan et al. (2005) The Netherlands	To investigate the post-operative effect of piritramide	Prospective, double-blind randomized, study	Sample: *N = 50* (elective supratentorial surgery); 9 patients excluded due to poor ventilation = 20 in bupivacaine group, 21 in fentanyl group; 2 patients excluded after randomization	---	Level II

			Resection of tumor Setting: Academic institution		

Levels of evidence range from I: systematic review to VII: opinion of authority or expert committee. Derived from Melnyk's Integrating Levels of Evidence into Clinical Decision Making. (Melnyk, B. (2004). Integrating levels of evidence into clinical decision making. Pediatric Nursing, 30(4), 323-325. [67]

Table 2: Summarization of Studies Using TOUS Criteria

Author, Year	**Existence of Pain**	**Measurement of Pain**	**Influencing Factors**	**Symptom Cluster**	**Patient Performance**
Bala et al. (2006)	X	NRS	X	---	---
Biswas and Bithal (2003)	X	VAS		---	X

Ducic et al. (2012)	X	VAS	X	---	X
Ferber et al. (2000)	X	VRS	---	---	X
Girard et al. (2010)	X	NRS	---	X	X
Grossman et al. (2007)	X	NRS	---	---	---
Irefin et al. (2003)	X	VAS	X	X	---
Jellish et al. (2006)	X	VAS	X	X	X
Jones et al. (2009)	X	VAS	---	---	---
Law-Koune et al. (2005)	X	VAS	X	---	X
Magni et al. (2005)	X	VAS	---	X	X
Magni et al. (2009)	X	VAS	---	---	X
Morad et al. (2009)	X	NRS	X	X	X
Nair and Rajshekhar (2011)	X	VAS	---	---	---
Nguyen et al. (2001)	X	VAS	X	---	---

Rahimi et al. (2006)	X	VAS	---	X	X
Rahimi et al. (2010)	X	VAS	X	---	X
Saringcarinkul and Boonsri (2008)	X	VNS	---	---	X
Soliman et al. (2011)	X	Not reported	---	---	X
Simon et al. (2011)	X	VAS	X	---	---
Sudheer et al. (2007)	X	VRS	X	X	X
Thibault et al. (2007)	X	VRS	X	X	---
Ture et al. (2009)	X	VAS	---	X	---
Verchere et al. (2002)	X	VAS	---	X	X
Williams, Pemberton, and Leslie (2011)	X	VAS	---	X	X

van der Zwan et al. (2005)	X	VAS	X	X	
Totals	**26**		**12**	**12**	**17**

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