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Review Article

The Influence of Race, Ethnicity and Genetic Variants on Postoperative Pain Intensity: An Integrative Literature Review

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ABSTRACT

Objectives: Chronic postsurgical pain is pain that develops and persists for at least 3 months after a surgical procedure. The purpose of this review was to discover what evidence exists regarding the influence of race and ethnicity on postoperative pain intensity and what evidence exists regarding the influence of genetic polymorphisms on postoperative pain intensity.
Design: Integrative literature review.
Data sources: CINAHL, PsychInfo, SCOPUS, and PubMed/Medline databases were searched for entries within the last 10 years. Sources included primary research investigating the relationship among race, ethnicity, and genetics in postoperative pain outcomes.
Review/analysis methods: Studies adhered to a strict inclusion and exclusion criteria. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were utilized to evaluate and assess manuscripts for inclusion.
Results: Twelve manuscripts were included for final review. There are significantly higher preoperative and postoperative pain intensity scores reported between African American and Hispanic individuals compared with non-Hispanic whites. Although some studies identified that non-Hispanic whites consumed more opioids and reported increased pain, there were no significant differences in opioid requirements in Hispanic and non-Hispanic individuals. *COMT* and *OPRM1* were the most identified genetic polymorphisms associated with postoperative pain intensity.
Conclusions: The literature varies with respect to race, ethnicity, and postoperative pain perception. Perioperative pain intensity has been suggested as a significant predictor of chronic postsurgical pain. *COMT* and *OPRM1* may be associated with higher pain perception after surgical procedures.

Background

Chronic postsurgical pain (CPSP) is defined as pain that develops after a surgical procedure and persists for at least 3 months AFTER surgery (Treede et al., 2015). As a classification of chronic pain that was recently highlighted by the International Association for the Study of Pain (2017), there is growing awareness of how many individuals are affected by CPSP in both adult and pediatric populations. After major surgery, CPSP is reported by 10%-50% of adults depending on the type of surgical procedure (Katz & Seltzer, 2009; Kehlet, Jensen, & Woolf, 2006). Adults who undergo orthopedic procedures are at an increased risk of developing CPSP compared with other medical procedures (Simanski et al., 2014). Although CPSP is not often studied in the pediatric population, it is also an issue of concern. A recent meta-analysis determined that CPSP was documented in 20% of children across all surgery types at 12 months postoperatively (Rabbitts, Fisher, Rosenbloom, & Palermo, 2017). Across the lifespan, CPSP is associated with poor health outcomes and greater functional disability (Kristensen,

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Pedersen, Hjortdal, Jensen, & Nikolajsen, 2010; Rabbitts, Zhou, Groenewald, Durkin, & Palermo, 2015).

Although the exact cause of CPSP is not fully known, the biopsychosocial model of pain (Gatchel, 2004) posits that maladaptive pain occurs as a result of dynamic interactions among biological, psychological, and sociocultural factors throughout the perioperative period. Perioperative factors, such as high intensity of preoperative and acute postoperative pain, have been found to increase the risk of CPSP (Batoz, Semjen, Bordes-Demolis, Benard, & Nouette-Gaulain, 2016; Bonnet, Lavand'homme, France, Reding, & De Kock, 2012; Kristensen, Ahlburg, Lauridsen, Jensen, & Nikolajsen, 2012; Kristensen et al., 2010). A deeper understanding of the factors that influence preoperative and acute postoperative pain could lead to the development of indicators for identifying those who are at increased risk for CPSP. Numerous studies have examined the psychosocial characteristics associated with the development of CPSP (Carreon et al., 2011; Connelly et al., 2014; Ferland et al., 2017; Rullander, Lundstrom, Lindvist, Hafflof, & Lindh, 2016; Upasani et al., 2008), but results are inconsistent across studies and may vary based on the developmental stage of the individual (Rabbitts et al., 2017). Psychosocial factors that have been found to affect the incidence of CPSP include pain catastrophizing and social support systems (Katz & Seltzer, 2009). In addition, depressive symptoms and pain beliefs are also vital in understanding the transition to chronic pain (Alcântara, Sampio, Souza, Silva, & Kirkwood, 2013).

Aside from perioperative and psychosocial factors, biological factors also contribute to increased risk of developing CPSP. It has been reported that peripheral and central pain sensitivity may contribute to variability in the intensity of acute postoperative pain and the associated risk of CPSP (Petersen, Arendt-Nielsen, Simonsen, Wilder-Smith, & Laursen, 2015). Theories posit that neuroplasticity and changes to neuronal membrane excitability as a result of inflammatory processes may be responsible for CPSP development. Peripherally, the release of proinflammatory mediators by tissues damaged perioperatively may increase the excitatory threshold, leading to increased perception in the presence of innocuous (allodynia) or painful (hyperalgesia) stimuli. Centrally, stimuli from the periphery may activate intracellular release of protein kinases within the dorsal horn of the spinal cord, thus modifying expression of ion channels and overall neuronal excitability (Kraychete, Sakata, de Oliveira Carvahlo Lannes, Bandeira, & Sadatsune, 2016).

There is evidence to support that there is a fair degree of heritability of CPSP, ranging from 30%-70% (Clarke et al., 2015; Hoofwijk et al., 2016). Candidate gene studies may be potentially useful in determining individuals who are at increased risk of CPSP development (Bruce & Quinlan, 2011). Additional factors have been found to influence pain sensitivity, including genetic variations, such as single nucleotide polymorphisms (SNP). An SNP, or polymorphism, is a variation in the DNA sequence that occurs when a single nucleotide (A, T, C, or G) in the genome sequence is different among individuals. Unlike genetic mutations that are rare and occur in <1% of the general population, SNPs are the most common form of human genetic variation. SNPs occur at a rate of approximately 1 SNP per kilobase of genomic sequence and must occur at a frequency of ≥1% within a population (Brookes, 1999). Although most SNPs have no known effect on health or development, some SNPs within a gene may have a direct role in disease susceptibility or response to certain drugs or toxins or may be associated with a specific trait through altering the gene's activity (U.S. National Library of Medicine, 2018a). These changes can be either advantageous or maladaptive for individuals who possess the SNP, such as decreased or increased pain sensitivity.

Genetic polymorphisms specific to CPSP have been identified, although correlations among race, ethnicity, and CPSP have not been discussed in depth (Hoofwijk et al., 2016). It is important to acknowledge that race and ethnicity are not completely exclusive of each other and contain both social and biological determinants. Throughout this review, self-report of race and ethnicity have been used within identified studies. The definition of *race* includes biological and physical characteristics shared by a group of individuals, such as skin color and hair texture. Emphasis of race relies on geographic region of origin of person's ancestry, such as African American (AA), white, American Indian, and so on (Burchard et al., 2003). *Ethnicity* is defined as a distinct set of claims, including sense of common ancestry based on cultural practices, including religion and rituals. Ethnicity can also encompass common physical traits within a group of people (Cornell & Hartmann, 1998). Despite evidence indicating that there may be a small overall contribution of genetics to racial variance in major chronic health conditions, there is vitality in researching racial differences within the context of health. According to Williams, Mohammed, Leavell, and Collins (2010), researching racial differences within the context of health could be beneficial to understand how social and cultural experiences interact with biological determinants to affect health outcomes.

A recent systematic review of racial and ethnic differences in experimental pain sensitivity published by Kim et al. (2017) reported that AAs, Asians, and Hispanics had higher experimental pain sensitivity compared with non-Hispanic whites (NHWs). In their meta-analysis, they found that AAs had lower pain tolerance and higher pain ratings compared with NHWs. However, whether experimental pain sensitivity is associated with acute postoperative pain intensity and other outcomes is not completely clear (Sangesland, Storen, & Vaegter, 2017; Werner, Mjobo, Nielsen, & Rudin, 2010). Other clinical studies have reported that racial and ethnic minorities, in general, receive lower quality of pain management than NHWs across health care settings (Anderson, Green, & Payne, 2009; Hampton, Cavalier, & Langford, 2015; Kim et al., 2017). However, an integrated analysis of the relationships among race/ethnicity, genetic variants, and increased incidence of CPSP has not been previously reported.

The identification of individuals at risk for experiencing CPSP could help to inform personalized pain management strategies throughout the perioperative period. Whether variability in postoperative pain intensity is due to differential pain sensitization in underrepresented minorities compared with NHWs, inequities in postsurgical pain management or genetics warrants further evaluation because minorities constitute a growing percentage of the overall population (Shavers, Bakos, & Sheppard, 2010). The National Institutes of Health (2000) defines underrepresented minorities as those racial, ethnic, or cultural groups who are disproportionately represented in biomedical research; these include AAs, Hispanics or Latinos, American Indians or Alaskan Natives, and Asian or Pacific Islanders. Therefore this integrative review was performed to provide a synthesis of the literature on the influence of self-identified race and ethnicity, or genetic factors, on postoperative pain intensity and overall perception, which may leave an individual at increased risk of CPSP. The literature review was guided by the following questions:

1. What evidence exists regarding the influence of race and ethnicity on postoperative pain intensity?
2. What evidence exists regarding the influence of genetic variants (single or polymorphisms) on postoperative pain intensity?

To date there are few comprehensive syntheses of the literature that incorporate racial/ethnic differences, genetic differences, and the incidence of CPSP. As a result, the current literature is oftentimes skewed, and definitive conclusions are difficult to make. The purpose of this review is to analyze the existing literature that

addresses the biopsychosocial implications on the development of CPSP with an emphasis on postoperative pain perception, genetics, and racial/ethnic diversity.

Review Methods

The integrative review methodology developed by (Whittemore & Knafl, 2005) was used to conduct the literature search. A thorough search of databases, including CINAHL, PsychInfo, SCOPUS, and PubMed/Medline was conducted. To ensure that the publications were reflective of the current state of pain assessment and management and the current social climate in respect to race and ethnicity, publications were limited to those published within the last 10 years. Search terms included *race, ethnicity, pain, pain sensitivity, postoperative pain, postsurgical pain, chronic postsurgical pain,* and *genetics*. Inclusion criteria of the selected publications included publications from 2006 to present, research studies focused on variability in postoperative pain intensity for surgical procedures performed in the hospital setting, and studies that included analysis of self-reported race and ethnicity variables. Publications were excluded if they included participants who had comorbid pain conditions (i.e., fibromyalgia, cancer pain) or did not include clinical pain (i.e., experimentally evoked pain only). Publications obtained were read several times to ensure accuracy and relevance to the topic. Of the 145 publications identified, very few included analyses of postoperative pain intensity by race or ethnic group. The final search yielded 12 relevant publications for use within this integrative literature review. The search process is detailed in Figure 1 using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Moher et al., 2015). Publications were excluded based on Meline's (2006) systematic review inclusion criteria.

Results

Of the 12 publications included within this integrative review, the study sample populations ranged from pediatric to adults. Although nearly half investigated the role of race and pain in adults (n = 7), the remaining publications explored race and pain in pediatric populations (n = 5). It is important to note differences between pediatric and adult populations because the mechanisms underlying the transition from acute to chronic pain may vary in the postoperative period. Many of the publications focused on AA and Hispanic populations (n = 8), whereas the remaining studies focused on Asian populations (n = 4). The publications originated from two regions of the world, the United States (n = 8) and Singapore (n = 4).

Tables 1 and 2 outline the selected publications and provide a brief synopsis of those analyzed. Although all publications addressed the issue of race, ethnicity, and genetics in postoperative pain, it was done so in varying degrees. Publications within Table 1 mainly provide explanation on racial and ethnic variation on postoperative pain, and the publications presented within Table 2 focus on genetic variation on postoperative pain. The following results section is organized in such a way to address the overarching questions proposed for the integrative literature review.

What Evidence Exists Regarding the Influence of Race and Ethnicity on Postoperative Pain Intensity?

Significantly higher preoperative and postoperative pain intensity scores have been reported by AA and Hispanic populations compared with NHWs (Bhattacharyya & Shapiro, 2014; Lavernia, Villa, Lavernia, & Villa, 2015; Sadhasivam et al., 2012). In a retrospective analysis by Bhattacharyya and Shapiro (2014) in which 79,520 cases of tonsillectomy were reviewed, AA and Hispanic children had an increased risk for acute pain at their follow-up appointments (odds ratio [OR], 1.36; 95% confidence interval [CI], 1.10-1.67; and OR 1.34; 95% CI, 1.14-1.57, respectively) relative to NHW children. In another retrospective study of 105 AA and 1,905 NHW patients who underwent knee or hip arthroplasty, AA patients reported more severe preoperative pain intensity as measured by the visual analog scale (8 ± 1.8 vs. 8 ± 2.0, mean difference = 0.76 [95% CI 0.34-1.1], $p < .001$) compared with NHW patients (Lavernia et al., 2015). AA patients also had worse well-being preoperatively (0.537 ± 0.004 vs. 0.532 ± 0.005, mean difference = −0.01 [95% CI, −0.02 to 0.00], $p = .037$), general health, and disease-specific scores compared with NHW patients. Postoperative scores, measured up to 1 year later, remained significantly different between the two groups. One year later, pain (1 ± 3.1 vs. 1 ± 1.8, mean difference = 0.08; $p = .010$) and quality of well-being scores (0.579 ± 0.09 vs. 0.607 ± 0.11, mean difference = −0.049; $p = .008$) remained statistically different, with worse scores in AA individuals. However, the authors note that the threshold for clinical significance was not met.

Sadhasivam et al. (2012) performed a prospective analysis of postoperative pain among 194 healthy children undergoing tonsillectomy. All patients received the same weight-dependent dose of intraoperative morphine (0.2 mg/kg); however, AA children experienced significantly more postoperative recovery room pain than NHW children. AA children also had significantly higher postoperative opioid requirements ($p = .0011$), maximum postoperative pain scores ($p < .0001$), and analgesic interventions ($p < .0001$) compared with NHW children. In a large retrospective study that examined race (NHW n = 3,841, AA n = 194) and socioeconomic status on postoperative pain among patients undergoing total knee arthroplasty, the mean pain score was worse for AAs compared with NHWs ($p < .001$; Goodman et al., 2016). Although differences in pain intensity at 2-year follow-up was not significant between groups, the authors reported that AAs living in communities with census tract poverty of 40% compared with 10% had significantly higher pain and worse functional outcomes.

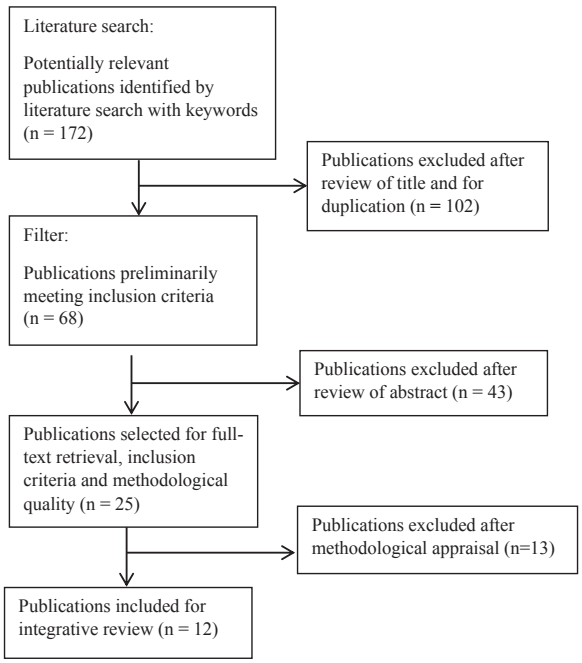

Figure 1. PRISMA flow diagram.

Table 1
Racial Influences on Postoperative Pain Intensity

Title	Year	Author	Country	Purpose	Sample	Design	Demographic Characteristics	Findings
Associations between socioeconomic status and race with complications in children	2014	Bhattacharyya & Shapiro	USA	Examine socioeconomic disparities and outcomes in children undergoing tonsillectomy	N = 79,520 children White (n = 46,917) Black (n = 7,952) Latino (n = 18,289) Other (n = 6,362)	Multisite database, cross-sectional analysis	Race/ethnicity, household income, asthma status	Minority children (black and Hispanic) had a higher risk for pain at follow-up tonsillectomy appointment (OR, 1.36; 95% CI, 1.10-1.67; and OR, 1.34; 95% CI, 1.14-1.57, respectively).
Impact of race on 30-day complication rates after elective complex spinal surgery (>5 levels)	2017	Elsamadicy et al.	USA	Determine the effects of race on postoperative complication rates after spinal fusion surgery	N = 490 adults White (n = 438) Black (n = 52)	Retrospective chart review	Age, gender, race, BMI	Thirty days after surgery, black and white adults experienced similar pain levels (15.8% vs. 14.1%, respectively; $p = .74$).
Disparities in TKA outcomes: Census tract data show interaction between race and poverty	2016	Goodman et al.	USA	Understand the associations between race and socioeconomic factors with pain after TKA postoperatively	N = 4,035 adults White (n = 3,841) Black (n = 194)	Retrospective, surgical registry study	Age, gender, BMI, race, ethnicity, educational level, insurance payer, comorbidities	MCID was 7. WOMAC pain at 2 years' post TKA were different between blacks or whites but did not reach the MCID (estimate, 3.55; SE 1.42; $p = .01$). WOMAC function scores worsened when tract poverty levels were included. Increased poverty decreases WOMAC pain scores at 2 years (i.e., 40% poverty level; black vs. white [79 (3) vs. 85 (2); $p = .03$]).
Is ethnicity associated with morphine's side effects in children? Morphine pharmacokinetics, analgesic response and side effects in children having tonsillectomy	2012	Jimenez et al.	USA	Examine whether genetic polymorphisms and/or morphine pharmacokinetics aid in analgesic response and pain scores	N = 68 Latino (n = 33) Non-Latino (n = 35)	Prospective cohort study.	Age, gender, ethnicity.	No statistically difference between Latino and non-Latino pain scores postoperatively; Latino vs. non-Latino mean pain scores (SD) 2.9 (2.9) vs. 3.0 (2.6); $p = .84$.
Pain prevalence, intensity, assessment and management in a hospitalized pediatric population	2014	Kozlowski et al.	USA	To examine pediatric opioid consumption in hospitalized children based on demographic characteristics	N = 124 children White (n = 59) Black (n = 16) Other (n = 16)	Prospective design	Age, gender, race, weight, admitting diagnosis	White children reported higher pain scores and had higher opioid consumption than children of other racial backgrounds ($p = .014$).
Does race affect outcomes in total joint arthroplasty?	2015	Lavernia & Villa	USA	Examine the differences in race after joint arthroplasty	N = 2,010 adults White (n = 1,905) Black (n = 105)	Retrospective study	Age, gender, race, ethnicity, BMI, ASA physical status classification system, CCI, preoperative diagnosis	Black patients had more severe preoperative and postoperative pain intensity ($p < .001$; $p = .01$); and worse well-being scores ($p = .037$; $p = .008$, respectively).
Race and unequal burden of perioperative pain and opioid related adverse effects in children	2012	Sadhasivam et al.	USA	Determine the effect of race on analgesia and opioid adverse events postoperatively in black and white children	N = 194 children	Prospective clinical observational study design	Age, weight, gender, BMI	Black children had more postoperative pain than white children ($p < .0001$), greater need for intervention ($p = .029$), and greater morphine requirement ($p = .0011$). White children had increased opioid-related complications ($p = .039$).

BMI = body mass index; CI = confidence interval; OR = odds ratio; TKA = total knee arthroplasty; MCID = minimum clinically significant difference; SE = standard error; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SD = standard deviation; ASA = American Society of Anesthesiologists; CCI = Charlson Comorbidity Index (CCI).

Table 2
Genetic Influences on Postoperative Pain Intensity

Title	Year	Author	Country	Purpose	Sample	Design	Genotype	Findings
Genetics of pain perception, *COMT* and postoperative pain management in children	2014	Sadhasivam et al.	USA	Understand the vitality of *COMT* SNPs in postoperative pain management in children	N = 149 adults White (n = 121) Non-white (n = 28)	Prospective, genotype-blinded observational study	*COMT* gene SNPs rs6269 rs4633 rs4818 rs4680	Maximum FLACC scores associated with rs4633, rs6269, rs4680 (p = .01, 0.04, 0.05). Postoperative morphine requirement increased in those with CC genotypes of rs4818 (p = .07).
Influence of mu-opioid receptor variant on morphine use and self-related pain following abdominal hysterectomy	2013	Sia et al.	Singapore	To understand the differences of morphine effects in various racial groups in relation to *OPRM1* gene	N = 973 children Chinese (n = 755) Malays (n = 136) Asian Indian (n = 82)	Prospective clinical study	*OPRM1 118AG* SNPs Genotyping AA (n = 354) AG (n = 474) GG (n = 145)	Pain scores were associated with *OPRM1* genotypes in Chinese; total morphine was associated with *OPRM1* in Chinese and Asian Indians.
Ethnicity-dependent influence of innate immune genetic markers on morphine PCA requirements and adverse effects in postoperative pain	2016	Somogyi et al.	Singapore	Investigate the role of genetic variability and polymorphisms in opioid requirements and signaling pathways in the postoperative period	N = 1,066 adults Chinese (n = 598) Malay (n = 230) Indian (n = 133)	Prospective observational study	20 SNPs in 14 genes involved in: - Glial activation - Inflammatory signaling - Neuronal regulation	No between group difference of pain perception were identified related to genotypes (p > .05). *COMT* SNP rs4680 causes increased pain in Chinese individuals (p = .0007) but not in other ethnic groups.
Ethnicity and *OPRM* variant independently predict pain perception and patient-controlled analgesia usage for post-operative pain	2009	Tan et al.	Singapore	Understand the influence of *OPRM* polymorphisms on postoperative pain and morphine use	N = 994 adults Chinese (n = 620) Malay (n = 241) Indian (n = 137)	Prospective, observational study	*OPRM A118G* SNPs rs1799971 rs6912029 (promoter) AA (n = 389) GG (n = 170) AG (n = 435)	No significant difference in pain scores among the groups. Significance in association morphine usage in Chinese individuals within the 118A<G SNP (p = .0039). With each additional G allele, morphine usage increased by 0.025 mg (95% CI: 0.012-0.038; p = .00017)
Common variants of catechol-O-methyltransferase influence patient controlled analgesia usage and postoperative pain in patients undergoing total hysterectomy	2016	Tan et al.	Singapore	Evaluate postoperative pain and morphine use in women who underwent hysterectomy	N = 973 adults Chinese (n = 755) Malays (n = 136) Indians (n = 82)	Prospective observational study	*COMT* gene SNPs rs4680 rs4818 rs4633	No notable differences were identified between ethnic groups in relation to pain threshold and/or tolerance. Researchers found that rs4818 was associated with increased postoperative pain.

COMT = catechol-O-methyltransferase; SNP = single nucleotide polymorphism; FLACC = Faces, Legs, Arms, Crying and Consoloability Scale; *OPRM* = opioid receptor mu; PCA = patient-controlled analgesia; CI = confidence interval.

However, not all the studies reported increased pain intensity in AA and Hispanic patients compared with NHWs. To identify the prevalence in and demographic characteristics of hospitalized children experiencing pain, a prospective descriptive study was conducted by Kozlowski et al. (2014) in which pain intensity scores were tracked among 199 children (124 NHW and 75 minority) who were hospitalized over a period of 5 days. Self-reported pain scores were recorded with the use of either a numeric 0-10 scale or the Wong-Baker FACES scale [Wong-Baker FACES Foundation (2018)], and daily pain scores reported corresponded to the highest pain score reported by the participant on each study day. NHW children reported higher pain scores than did children of other races. In addition, NHW children consumed more opioids than children of any other racial background (NHW 0.33 ± 0.05 to 0.53 ± 0.09 mg/kg per day; minority 0.06 ± 0.04 to 0.28 ± 0.18 mg/kg per day; p = .014).

In relation to ethnic minority differences (Hispanic vs. non-Hispanic) another prospective study that examined the morphine requirements in Latino (n = 33) and NHW (n = 35) children undergoing tonsillectomy found no differences in pain scores or need for rescue analgesia (Jimenez et al., 2012). A retrospective study of 490 adults (AA n = 52; NHW n = 438) was conducted to examine complication rates after elective complex spinal fusion in a single institution (Elsamadicy et al., 2017). This study also found no differences between postoperative pain intensity or 30-day complication rates as a result of pain among different racial groups.

What Evidence Exists Regarding the Influence of Genetic Polymorphisms on Postoperative Pain Intensity?

From the studies identified, polymorphisms within catechol-*O*-methyltransferase *(COMT)* and opioid receptor mu 1 *(OPRM1)* were found to be associated with individual's unique response to postoperative pain intensity. Several polymorphisms within these two genes have been found to contribute to differential pain responses

among individuals of different racial or ethnic backgrounds, whereas others did not (Sadhasivam et al., 2014; Sia et al., 2013; Somogyi et al., 2016; Tan et al., 2009, 2016). Table 2 outlines the negative or null associations between varying polymorphisms and individual's postoperative pain response. Tables 3 and 4 outline the function and frequency of SNPs, *COMT* and *ORMP1*, respectively.

In a genotype-blinded observation study of 149 children undergoing surgery, relationships were assessed among pain perception, morphine consumption, and four candidate *COMT* polymorphisms, rs6269, rs4633, rs4818, and rs4680 (Sadhasivam et al., 2014). Intraoperatively, children received the same dose of anesthetic (0.2 mg/kg or morphine), and pain was assessed within the postanesthesia recovery unit using the Faces, Legs, Activity, Cry, and Consolability (FLACC) Scale at specified intervals. The maximum FLACC scores were significantly associated with three of the four *COMT* polymorphisms: rs4633 ($p = .01$), rs6269 ($p = .04$), and rs4680 ($p = .05$). These *COMT* SNPs were responsible for increased pain perception as evidenced by the FLACC scale. However, none of the SNPs accounted for prolonged postanesthesia recovery unit stay as a result of inadequate analgesia. There was no analysis of racial or ethnic differences in relation to differential pain response (Sadhasivam et al., 2014).

In several other studies that enrolled primarily individuals of Asian descent, there were no phenotypic differences in postsurgical pain among ethnic groups (Chinese, Malay, and Asian Indian); however, there were significant differences in allelic frequencies of several polymorphisms within *COMT* and *OPRM1* (Sia et al., 2013; Somogyi et al., 2016; Tan et al., 2009, 2016). A prospective clinical study conducted by Sia et al. (2013) evaluated allelic frequencies within *OPRM1* in 973 children in Singapore of varying ethnic backgrounds and found no significant difference in the frequency of the minor allele: Chinese (0.372), Malay (0.463), and Asian Indian (0.438). An association was found between morphine consumption and allelic frequency in Chinese patients when adjusted for age, weight, and pain threshold ($p = .027$). Total morphine use was also significantly higher in Asian Indians ($p = .019$); however, there was no association with the selected polymorphisms in the Malay ethnic population. Tan et al. (2016) also conducted an analysis among these three ethnic groups and found no differences in relation to pain tolerance or threshold. Morphine consumption in Chinese individuals was significantly associated with genetic variants rs4680 ($p = .030$) and rs4633 ($p = .041$). Although Asian Indians who were rs4818 carriers had increased total morphine requirement, this finding was not statistically significant.

OPRM1 has been found to influence opioid consumption and clearance rates but also contributes to modulation of pain perception. Tan et al. (2009) investigated two *OPRM1* SNPs, rs1799971 (*OPRM A118G*) and rs6912029 (-172T>G promoter), in relation to postoperative pain throughout the perioperative period and associated morphine use. A total of 994 women undergoing elective caesarean delivery were genotyped. Pain scores were influenced by morphine use, ethnicity, age, and socioeconomic status. Within the population assessed, individuals of Indian descent and those who were younger reported higher pain scores ($p = .0004$, $p < .01$), whereas those who were socioeconomically stable presented with lower mean pain scores ($p = .048$). A well-studied genetic mutation is in the *OPRM1* gene, which involves a substitution of nucleotide adenine (A) with guanine (G) at the position 118 of the gene. Within the initial 24-hour postoperative period, there was a significant association with *OPRM1* 118A>G mutation and self-rated pain scores ($p = .024$). Those who were homozygous for the 118G (rare allele) experienced higher pain intensity scores than 118A carriers. In addition, there was a significant association between the 118G SNP in Chinese individuals and morphine use ($p = .0039$), but no associations were identified among the other ethnic groups (Malays and Indians). These findings are consistent with results found within the observational study conducted by Sia et al. (2013).

Somogyi et al. (2016) assessed 961 Asian women (Chinese, Malay, and Indian) who were undergoing elective caesarean section with epidural anesthesia. Pain intensity was included in outcome measurement alongside 26 SNPS in 14 genes. These SNPs were specific to glial activation, inflammatory signaling, and neuronal regulation. The frequency of SNPs varied among the ethnic groups, although there were no differences in pain scores. However, among Chinese women who experienced significantly higher pain ratings, they found significant differences in the allelic distribution of *COMT* variant rs4680.

Discussion

Understanding differences in individual pain perception may aid in the development of individualized care plans. Currently the literature provides inconclusive and conflicting results of pain perception and management within racial and ethnic communities. The purpose of this integrative review was to provide a synthesis of the literature on the influence of race, ethnicity, and genetic factors on postoperative pain intensity, a risk factor for CPSP (Batoz et al., 2016; Bonnet et al., 2012; Kristensen et al., 2012). The literature search identified three retrospective studies that reported significantly higher self-reported postoperative pain intensity scores among AAs and Hispanic populations compared with NHWs (Bhattacharyya & Shapiro, 2014; Goodman et al., 2016; Lavernia et al., 2015). Only one prospective study was identified that was designed to investigate racial and ethnic differences in postoperative pain intensity, which found that AA children experienced significantly higher postoperative pain intensity than NHW children (Sadhasivam et al., 2012). This study included a protocol for weight-based analgesic (morphine) dose in children receiving

Table 3
Catechol-*O*-methyltransferase *(COMT)*

	SNP Consequence	Alleles	MAF*	ASW	CEU	Function
rs6269	5′ UTR variant	A/G	0.36 (G)	G: 0.41† A: 0.59	G: 0.49† A: 0.51	Intron in promoter region
rs4633	Non-synonymous variant	C/T	0.37 (T)	C: 0.663 (2918)‡ T: 0.337 (1486)	C: 0.477 (4103)‡ T: 0.523 (4497)	No change to amino acid structure
rs4818	Non-synonymous variant	C/G	0.30 (G)	C: 0.804 (3542)‡ G: 0.196 (864)	C: 0.605 (5204)‡ G: 0.395 (3396)	No change to amino acid structure
rs4680	Missense variant	A/G	0.37 (A)	G: 0.685 (3019)‡ A: 0.315 (1387)	G: 0.478 (4115)‡ A: 0.422 (4485)	Exon; Val158Met

SNP = single nucleotide polymorphism; MAF = minor allele frequency; ASW = African ancestry in Southwest United States; CEU = Utah residents with Northern and Western European ancestry.
* 1000 Genome Project.
† Applied BioSystems.
‡ National Heart, Lung, and Blood Institute Exome Sequencing.

Table 4
Opioid Receptor Mu 1 (*OPRM1*)

	SNP Consequence	Alleles	MAF*	AA	CEU	Function
rs1799971	Missense Variant	A/G	0.22 (G)	A: 0.969 (3862)† G: 0.031 (122)	A: 0.871 (7238)† G: 0.129 (1070)	Exon; Asn40Asp *OPRM1 A118G*
rs6912029	Missense Variant	G/T	0.07 (T)	G: 0.893 (1236)† T: 0.107 (148)	G: 0.959 (3052)† T: 0.041 (130)	5′ UTR variation, Intron

SNP = single nucleotide polymorphism; MAF = minor allele frequency; AA = African American; CEU = Utah residents with Northern and Western European ancestry.
* 1000 Genome Project.
† National Heart, Lung, and Blood Institute Exome Sequencing.
From Ensembl (2017). Retrieved June 13, 2017 from http://useast.ensembl.org/index.html.

tonsillectomy. Because questions could be raised regarding whether the difference was due to variability in morphine metabolism potentially associated genetic polymorphisms (De Gregori et al., 2012), further research on this topic is warranted. Two prospective studies and one retrospective study were identified that did not find any differences in postoperative pain intensity among racial and ethnic groups compared with NHWs (Elsamadicy et al., 2017; Jimenez et al., 2012; Kozlowski et al., 2014). Thus reports remain inconsistent, given mixed results and lack of consensus among studies.

Although the evidence to date is unclear on whether race and ethnicity influence postoperative pain intensity, these findings reveal some important gaps in knowledge as well as future directions for research. Additional prospective studies designed to detect differences in postoperative pain among diverse populations are clearly needed. These will require well-planned clinical studies using a standardized surgical procedure to account for differences in surgical time and extent of tissue damage and anesthetics and analgesic dosing. Because pain sensitization is thought to be an underlying mechanism of higher postoperative pain intensity, prospective studies should consider using quantitative sensory testing during the perioperative period. Although not commonly performed in clinical practice, studies using quantitative sensory testing as their means of evaluation have consistently found differential responses to elicited experimental pain among different racial and ethnic groups (Angst et al., 2012; Boissoneault, Bunch, & Robinson, 2015; Grewen, Light, Mechlin, & Girdler, 2008; Kim et al., 2017; Rahim-Williams et al., 2007). In addition, as identified by Goodman et al. (2016), additional factors that may influence pain sensitization, postoperative pain intensity, and possibly the risk of CPSP, such as socioeconomic factors, adverse childhood experiences, and perceptions of discrimination, may be considered in the design of future studies. This is particularly important because, as posited by the biopsychosocial model, the social environment exerts a powerful influence on the individual's experience of pain and its management.

In support of this notion, studies assessing provider perceptions of pain among racial groups have found that providers often assume that Asians and NHWs are more sensitive to pain than AA or Hispanic individuals (Green et al., 2003; Wandner et al., 2012). Stereotypes based on phenotypic characteristics and self-report of race and ethnicity can also lead to misplaced judgment against particular racial groups seeking relief for their pain. These implicit biases can have negative consequences on patient outcomes. As an example of these biases, Sabin and Greenwald (2012) found that pediatricians perceived NHW individuals as being more compliant with their pharmacologic regimens and, as such, felt more comfortable prescribing opioids postoperatively to their NHW patients despite minority individuals' pain levels. AA and Hispanic individuals are often viewed as having drug-seeking behaviors, despite evidence against higher risk of prescription abuse (Tait & Chibnall, 2014). A study investigating medical professionals' knowledge of racial differences in pain perception found that physicians were more likely to underestimate the incidence of AA patient's pain, although this was not done intentionally as a result of racist beliefs (Hoffman, Trawalter, Axt, & Oliver, 2016). Thus provider biases and misconceptions about pain may contribute to the disproportionate amount of analgesics prescribed to different racial groups (Burgess et al., 2014; Krieger, 2014; Williams & Mohammed, 2009). These studies support the need to examine sociocultural factors, such as perceptions of discrimination, in clinical pain research.

Publications identified through the literature review support a role of the *COMT* and *OPRM1* genes on variability in postoperative pain intensity (Sadhasivam et al., 2014; Sia et al., 2013; Somogyi et al., 2016; Tan et al., 2009, 2016). In particular the *COMT* SNPs rs6269, rs4633, and rs4680 were associated with postoperative pain intensity (Sadhasivam et al., 2014). In addition, patients who were homozygous for minor allele *OPRM 118G* (rs1799971) experienced higher pain intensity scores than 118A carriers (Tan et al., 2009). As discussed in a recent systematic review by Hoofwijk et al. (2016), these polymorphisms have been studied for the associated with CPSP across different surgical procedures and populations. Future investigations that evaluate genetic variability in CPSP may consider associations with postoperative pain intensity to examine its validity as a predictor of CPSP.

In addition, recent pharmacogenetics studies have identified many polymorphisms that influence drug metabolism and clearance, which may also influence postoperative pain intensity. A significantly higher percentage of AA children compared with NHWs were found to carry SNPs in the glucuronosyltransferase-2B7 *(UGT2B7)* gene, rs7668258 and rs743966 (Sadhasivam et al., 2012). The SNPs were associated with increased rate of morphine clearance and increased need for analgesia within the postoperative period. In addition, NHW patients were found to be more common carriers of defective organic cation transporter 1 *(OCT1)* alleles compared with AAs, which was correlated with low morphine clearance and increased adverse opioid-related events (Fukuda et al., 2013). As more knowledge is generated regarding genetic variability of individual response to analgesics, practitioners will be better equipped to meet the needs of individuals experiencing pain.

Implications for Nursing

Currently there is a high research interest in advancing personalized nursing care that is based on the individual's genomic architecture, guided by their unique sociocultural background and personal preferences. Precision health care and symptom science will contribute to a deeper knowledge base so that health care providers may further optimize strategies of individualized prevention, symptom, and disease management for acute and chronic conditions, such as pain (National Institute of Nursing Research, 2015). This personalized nursing care initiative has a foundation in genomics, with emphasis on using the individual's risk profile to improve the delivery of health care, effectiveness of nursing interventions, and quality of life. One way of doing this is via whole exome or genome sequencing. Whole exome sequencing sequences

the protein coding regions of DNA (exons), which comprises 1% of an individual's entire genome. It is important to note that variations may occur outside of the exome that may affect gene activity and protein regulation (U.S. Library of Medicine, 2018b). Sequencing of these regions, in conjunction with the exome, is referred to as whole genome sequencing. Using whole exome or whole genome sequencing provides a comprehensive representation of the individual's genetic blueprint. However, health care providers must be aware that whole exome or genome sequencing, like many diagnostic health care tests, comes with its own set of unintended risks, such as incidental findings (Prows, Tran, & Blosser, 2014). Therefore those who are providing educational counseling for genetic findings must have education and training in disseminating such sensitive results. Nurses and nurse scientists may be an integral part of the everchanging landscape of genomics and health care research. As the costs of genome sequencing decreases, its clinical relevancy is increasing. Taylor, Wright, Hickey, and Housman (2017) explicate the role of nurses in genetic testing as being beneficial for the individual. Because of nurses' inherent systems approach to education, care planning, and advocacy for their patients, nurses are excellently positioned to spearhead genomic sequence screenings. Results found within these screenings have the potential to provide therapeutic, personalized interventions ultimately leading to positive health care outcomes throughout the lifespan.

Conclusions

Perioperative pain intensity has been suggested as a significant predictor of CPSP. Previous studies have identified variation among racial and ethnic populations, which may influence the severity of postoperative pain and subsequent development of CPSP. This literature review focused on integrating current knowledge regarding the influence of race, ethnicity, and genetics on postoperative pain intensity and found some evidence suggesting that AA and Hispanic individuals are more vulnerable to experiencing increased postoperative pain intensity compared with NHW patients. However, very few studies in the broader pain literature have examined racial and ethnic differences during the acute stages after surgery. In addition, some evidence supports an association between genetic polymorphisms of *COMT* and *OPRM1* and higher postoperative pain intensity; however, replication is needed to validate these findings. Further research on the influence of race, ethnicity, and genetics on postoperative pain intensity and the risk of CPSP will require well-designed clinical research studies that evaluate pain sensitivity and perioperative pain management. As posited by the biopsychosocial model, sociocultural factors are also important to consider, including socioeconomic status and perceptions of racism or discrimination. A deeper understanding of the mechanisms underlying variability in postoperative pain intensity will enable the development of nursing strategies to improve perioperative pain management and address the biological, psychological, and sociocultural aspects of the pain experience.

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