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Highlights

- The opioid crisis has sparked much attention on policy and practice changes related to opioid prescribing and stewardship across settings. There are myriad related implications that continue to evolve for clinicians and researchers related to opioid and analgesic use. However, little is known about how patients make decisions to use analgesics for cancer pain.
- Pain is one of the most common and burdensome symptoms impacting patients throughout the cancer trajectory, with over one-third of patients endorsing their pain as “moderate” or “severe”. Cancer pain guidelines recommend opioid use as foundational to moderate to severe cancer pain treatment plans. Many patients deviate from recommended analgesic regimens for a number of reasons.
- The purpose is to clarify the concept of analgesic nonadherence for cancer pain and its use within the literature with respect to the US opioid crisis. There are few studies that link analgesic use to health outcomes and little empirical research on cancer pain.
- Given both the sociopolitical implications of the opioid crisis and a number of literature gaps related to this concept, there is insufficient evidence to claim a value judgment on analgesic nonadherence in cancer pain treatment. Additional empirical research is urgently needed in this domain to ensure safe and effective cancer pain management for patients.

Analgesic Nonadherence for Cancer Pain in a Time of Opioid Crisis:**A Concept Analysis**

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Introduction

According to the Centers for Disease Control and Prevention (CDC; 2018), an estimated 68% of the 70,200 drug overdose deaths in the United States (US) in 2017 involved the use of an opioid. In fact, the number of drug overdose deaths that implicated opioids increased six-fold between 1999 and 2017 (CDC, 2018). In the current climate of the opioid addiction epidemic, various stakeholders are calling for tighter opioid access policies, more rigorous prescribing standards, and increasingly tailored patient and community education mechanisms (Christie et al., 2017; National Academies of Sciences [NAS], 2017; National Academy of Medicine, 2017). While there has been robust focus on clinician implications related to responsible opioid stewardship, we still lack clear empirical understanding about the factors that correlate with patients' use of analgesics.

Opioids remain a keystone of moderate to severe cancer pain management (National Comprehensive Cancer Network [NCCN], 2019; Paice et al., 2016; World Health Organization [WHO], 2018), despite discrepant pain management guidelines that complicate prescribing practices (Meghani & Vapiwala, 2018). According to these guidelines, many patients with moderate to severe cancer pain require complex analgesic regimens, at times including a combination of nonopioids, short- and long-acting opioids, and adjuvant prescriptions, to effectively alleviate pain and improve overall function. Even though such medication treatment plans are often warranted, many patients deviate from recommended analgesic regimens or stop taking them altogether.

Patient nonadherence to prescribed analgesics for cancer pain may compromise a number of pain-related, health, and safety outcomes (Lee et al., 2015; Manzano, Ziegler, & Bennett,

2014; Meghani & Knafl, 2016). Cancer patients demonstrate nonadherent behaviors for a variety of reasons, ranging from individual and family factors (Lee et al., 2015; Meghani & Bruner, 2013; Meghani, Chittams, Hanlon, & Curry, 2013; Meghani & Knafl, 2017) to provider and system level barriers (Bryan, De La Rosa, Hill, Amadio, & Wieder, 2008; Schumacher et al., 2014a; Wieder, Delarosa, Bryan, Hill, & Amadio, 2014; Xu, Luckett, Wang, Lovell, & Phillips, 2018).

The purpose of this concept analysis is to clarify the meaning of analgesic nonadherence for cancer pain and its use in the literature with respect to the US opioid crisis. We employ the Walker and Avant (2019) method to deconstruct this concept and articulate future implications for practice, research, education, and policy. To these authors' knowledge, this is the first conceptual analysis of nonadherence specific to analgesics for cancer pain. A clearer understanding of analgesic nonadherence is crucial in order to streamline pain management plans and best assist patients in effectively mitigating their cancer pain burdens in the future.

Background & Significance

The Pain Experience

Pain is a burdensome symptom affecting patients across the cancer trajectory. A recent systematic review and meta-analysis of 112 studies on pain (n=63,533) and pain severity (n=32,261) suggests an estimated two-thirds of patients with advanced cancer report "some" pain, and up to 38% of patients report their pain as "moderate" or "severe" (van den Beuken-van Everdingen, Hochstenbach, Joosten, Tjan-Heijnen, & Janssen, 2016). In a longitudinal study exploring cancer survivors' symptom burden at one-year postdiagnosis (n=4,903), Shi and colleagues (2011) noted that pain was rated as one of the top three symptoms negatively impacting health-related quality of life. The authors of several literature syntheses and landmark

reports conclude that cancer pain control may be suboptimal for many populations and call for enhanced mechanisms to improve equitable access and delivery of pain care services (Institute of Medicine [IOM], 2003; Meghani, Byun, & Gallagher, 2012; NAS, 2017; Xu et al., 2018).

Analgesic Use

A number of factors influence analgesic use. Individual beliefs, preferences, and values are likely to inform nonadherent behaviors. For instance, patients' beliefs about analgesics may act as barriers to adherence, such as worries that these medications will cause physiological or immune system harm or will lead to addiction (Liang, Tung, et al., 2013; Simone, Vapiwala, Hampshire, & Metz, 2012; Ward et al., 1993). Patient affective factors, such as emotional distress or anxiety, have been shown to correlate with nonadherence choices (Jacobsen et al., 2014). In addition to patients, their families and caregivers also play a significant role in determining analgesic use and the level of demonstrated adherence (Valeberg, Miaskowski, Paul, & Rustoen, 2016). In fact, distinct family dynamics and family member hesitancy to use analgesics may mediate patient adherence behaviors (Lee et al., 2015; Schumacher et al., 2014). The evidence points to several other considerations required to grasp the full breadth of the concept, such as the quality of clinician-patient communication and analgesic accessibility (Thinh et al., 2018). Other elements include socioeconomic status and structural barriers, including insurance coverage (Bryan et al., 2008; Valeberg et al., 2008; Wieder et al., 2014).

The Sociopolitical Milieu

The opioid crisis compounds the phenomenon of analgesic taking behaviors throughout the national healthcare system. Across the United States, opioid-related events led to a 64.1% increase of inpatient hospital stays and a 99.4% increase in emergency department visits between 2005 and 2014 (Rudd, Seth, David, & Scholl, 2016); and in 2015, opioid-related deaths led to

overall economic costs estimated at \$504 billion or roughly 2.8% of gross domestic product (The Council of Economic Advisors, 2017). The crisis marks an era of policy flux, rigorous scientific debate, and multi-agency collaboration to balance the dual loyalties of reducing the individual burden of cancer pain while minimizing the mounting social sequelae of opioid use in America (Johnson et al., 2018; Lamar, 2018; NAS, 2017; National Institutes of Health [NIH], 2018; US Department of Health and Human Services, 2017). An additional complicating feature is the recent identification of the critical divide between cancer pain management guidelines of leading pain organizations (Meghani & Vapiwala, 2018). These inconsistent standards are due to the daunting lack of accumulated empirical evidence related to cancer pain management (Meghani & Vapiwala, 2018; NIH, 2014). The concept of analgesic nonadherence is likely to be best understood by accounting for both the context of the opioid crisis and the above noted paucity of empirical cancer research.

Method

Walker and Avant's (2019) approach to concept analysis (Box 1) is employed to construct a precise conceptual definition of analgesic nonadherence for cancer pain for future theoretical and empirical consistency. This method was selected due to its inclusion of example cases, offering a pragmatic application of the conceptual aspects, which is essential given the sociopolitical background previously mentioned. Additionally, this method stresses an iterative approach, promoting continuous exploration and clarification throughout the process. Finally, since concepts are tentative in nature, it is crucial to be aware of the cultural, contextual, and social factors that contribute to the current understanding of the concept at hand (Walker & Avant, 2019). Therefore, this method allows the reader to relate analysis findings directly to the health and policy dynamics of the US opioid crisis.

The initial search in PubMed used the MeSH search ('neoplasms' OR 'cancer' OR 'cancer pain' OR 'cancer related pain') AND ('treatment adherence and compliance' OR 'medication adherence' OR 'patient compliance') AND ('analgesics' OR 'analgesics, opioids' OR 'narcotics'). Further searches in CINAHL, PsycINFO, and Scopus used the above terms as keywords. Search terms were defined in collaboration with a librarian at the University of Pennsylvania Biomedical Library, Philadelphia, Pennsylvania. The search yielded 418 individual records; duplicates, articles in languages other than English, and those without an abstract were excluded. Empirical articles using quantitative and qualitative methodologies and pertaining to analgesic nonadherence for cancer pain in adult inpatient and outpatient settings, written in English, with an abstract, and published between 2010 and 2018 were considered. This time period was chosen because it spans the current opioid crisis in the United States according to related literature that emerged during its peak in 2010.

Relevant internationally gathered evidence was employed if it contributed distinct considerations regarding the concept not addressed in US-based literature. Organizational pain management guidelines and recommendations, as well as seminal documents outside of the proposed time frame that continue to influence current analgesic policy and practice were included. Non-empirical sources included records from Merriam Webster dictionary (n=2); WHO (n=3); NCCN (n=1); and previous related concept analyses (n=2). After applying exclusion criteria (Figure 1), a total of 33 records were selected for detailed review.

Results

Uses of the Concept

The terms *adherence* and *nonadherence* are often used interchangeably in the literature and are facets of the same phenomenon. Other terms such as *noncompliance* and

nonconcordance have been employed synonymously with nonadherence. The Merriam-Webster dictionary defines *nonadherence* as “a lack of adherence” (Merriam-Webster, n.d.-b). It is, therefore, essential to grasp the meaning of *adherence*. *Adherence* is “the act, action or quality of adhering” or “steady or faithful attachment” (Merriam-Webster, n.d.-a). Previous concept analyses of *adherence* define it as a “complex, multidimensional concept impacted by essential elements such as autonomy, self-determination, self-efficacy, and communication” (Gardner, 2015, p. 100). Other authors emphasize the concept should be considered through a patient-centered lens, incorporating an individual’s context in how it is evaluated (Alikari & Zyga, 2014). The WHO (2003) identifies patients’ *active* participation in medical plan development as a primary factor that differentiates *adherence* from the historical notion of *compliance*. The WHO (2003) defines *adherence* as “the extent to which a person’s behavior – taking medication, ... executing lifestyle changes, corresponds with agreed recommendations from a health care provider” (p. 3).

Analgesics are classified using the WHO (1986, 1996, 2018) cancer pain ladder and includes step 1 - nonopioids (e.g., nonsteroidal anti-inflammatories); step 2 - weak opioids (e.g., codeine, tramadol); and step 3 – strong opioids (e.g., morphine, Fentanyl). Opioids are further classified as long-acting, used to obtain background analgesia for chronic cancer pain, and immediate-release, taken to treat breakthrough pain and deliver a quicker onset but shorter duration of pain relief (NCCN, 2019). Some studies include a patient’s use of *coanalgesics*, such as antidepressants, anticonvulsants, or corticosteroids, in understanding predictors of overall nonadherence to pain management recommendations (Schumacher et al., 2014b). Researchers may focus on adherence related to one particular step of the cancer pain ladder, such as strong opioids (Chancellor, Martin, Liedgens, Baker, & Muller-Schwefe, 2012); assess differences in

rates of adherence between nonopioids and opioids (Oldenmenger et al., 2017); focus primarily on short- or long-acting opioids (Yoong et al., 2013); or include a broad range of analgesic types (Simone et al., 2012).

Analgesic nonadherence has been recognized as “a heterogenous construct that lends itself to varied results and interpretations based on the measures used or dimensions studied” (Meghani & Bruner, 2013, p. e23). How analgesic nonadherence is empirically represented varies. For example, some studies define analgesic nonadherence using subject self-report (Meghani & Bruner, 2013); computed rates of adherence based on proportions of prescribed doses taken during a given time period (Meghani, Thompson, Chittams, Bruner, & Riegel, 2015; Rhee et al., 2012); or the number of patients found to be taking medications as recommended during follow-up appointments (Wieder et al., 2014). Other researchers study the proportion of doses taken correctly across a given number of days and within given time intervals per day in relation to medical recommendations (Oldenmenger et al., 2017) or the amount of opioid taken in comparison to the amount of opioid prescribed (Nguyen et al., 2013).

Defining Attributes

Attributes are the qualities or features most commonly associated with a concept (Walker & Avant, 2019). The primary defining attribute of analgesic nonadherence is a behavior that establishes deviation from a prescribed regimen and may be the result of both conscious and unconscious influences (Meghani & Bruner, 2013; WHO, 2003). Such behaviors include filling prescriptions, taking medications as prescribed, attending scheduled appointments, adopting health behavior change, etc. (WHO, 2003). These behaviors have been identified as intentional, unintentional, and/or temporal. *Intentional* nonadherence is a deliberate choice not to follow a given recommendation; an active decision reflects a patient’s desire to stop taking their analgesic

(Morisky, Green, & Levine, 1986). *Unintentional* nonadherence is an unconscious, relatively passive process that results in similarly noted behavior (Morisky et al., 1986). Temporality is an important attribute (Meghani & Knafl, 2016). While some nonadherent behaviors were found to be habitual, many were influenced by temporal choices and priorities, fluctuating in accordance with changes to patients' daily, weekly, or monthly schedules (Manzano et al., 2014).

Antecedents of Analgesic Nonadherence

Per Walker and Avant (2019), antecedents are events that must be in place prior to the occurrence of the concept whereas consequences reflect the outcomes of the concept. For clarity, antecedents have been categorized as individual/family level, provider level, and system level.

Individual/family level. Identifying patients' main anchors for decision-making is central to understanding the driving forces of nonadherent behaviors. In a study of 207 outpatient oncology subjects, about 41% maintained an expectation of pain relief that primarily determined analgesic decision-making; 11% were most concerned with the type of analgesic used; roughly 28% were driven by multifactorial determinants including pain relief and the type and severity of side-effects; and 21% were influenced predominantly by the type of side effects experienced (Meghani & Knafl, 2017). Longitudinal qualitative findings echo that the extent to which side effects interfere with a patient's life directly coincides with nonadherence behaviors (Manzano et al., 2014). Researchers using a phenomenological method to elicit the illness narratives of cancer patients (n=18) suggested that self-perceived benefits of following an analgesic regimen, subjective self-efficacy, and trust in healthcare providers improved adherence; denial of pain as a symptom of the disease process posed a barrier (Torresan et al., 2015).

Such concerns, in addition to beliefs and preferences have been well-documented predictors of nonadherent behavior to analgesic regimens, particularly to opioids (Chancellor et

al., 2012; Rhee et al., 2012). This includes patients' concerns about the physiological effects of opioids and worry about dependence or addiction (Jacobsen et al., 2014; Liang, Chen, et al., 2013; Simone et al., 2012), as well as a belief that doctors should focus on cancer treatment rather than pain (Rhee et al., 2012). Families and caregivers play a pivotal role in this phenomenon. Family hesitancy to use analgesics has been found to mediate patients' barriers and patients' adherence (Lee et al., 2015). Furthermore, family characteristics directly impact the home environment in which patients live and anchor their analgesic decision-making processes (Schumacher et al., 2014b).

Various sociodemographic variables have been identified to play a predictive role in opioid nonadherence. Studies disagree whether males or females demonstrate nonadherent behaviors more frequently (Liang, Wu, Tsay, Wang, & Tung, 2013; Liang, Wang, et al., 2013; Nguyen et al., 2013). The same empirical variation occurs in reference to age, with some investigators noting increased nonadherence among younger cancer patients (Koyyalagunta et al., 2018); however, older patients may be more likely to intentionally stop taking medications when they feel better (Meghani & Bruner, 2013). Other predictors, including income, education and health literacy levels, and level of prescription coverage have been identified as significant (Meghani & Knafl, 2017; Wieder et al., 2014). It appears challenging for patients to take scheduled analgesics at the correct time intervals due to scheduling issues, forgetfulness, and the complexities of daily life (Oldenmenger et al., 2017). Of note, increased use of complementary and alternative medicine for cancer pain management was positively correlated with unintentional nonadherence (Meghani & Bruner, 2013).

Perhaps one of the most glaring sociodemographic antecedents is race - even when controlling for insurance and socioeconomic status (IOM, 2003). African-Americans are found

to experience increased severity of pain more frequently than White counterparts (Martinez, Snyder, Malin, & Dy, 2014). Additional studies have shown that African-Americans are more likely to make nonadherence choices based on the “type of side effects” experienced rather than “pain relief” (Meghani et al., 2013; Meghani & Knafl, 2017), which means nonadherence may be more common in African-American patients due to a higher rate of side effects from inappropriately prescribed analgesics (Meghani et al., 2014).

Provider Level. Prescribing practices are a major aspect of provider level antecedents. Patients prescribed around-the-clock (ATC) analgesics other than long-acting opioids were more inconsistently adherent (Meghani & Knafl, 2016). Racial disparity is also a factor at the provider level. African-Americans may receive inconsistent or erroneous pain assessments by healthcare providers (Wandner et al., 2014) and are less likely to be prescribed long-acting opioids for pain relief (Meghani et al., 2015). Meghani et al. (2014) suggest race is a strong predictor of both the type of opioid prescribed and the severity of analgesic side effects incurred. For example, African-Americans have 71% lower odds than Whites of being prescribed oxycodone versus morphine in the setting of chronic kidney disease (CKD) (Meghani et al., 2014). This is crucial as morphine accumulates toxic renal metabolites in the setting of CKD that exacerbate negative side effects and may promote nonadherence. Other minorities, such as Hispanic patients, have also been noted to be prescribed fewer long-acting opioids than Whites (Meghani et al., 2015; Wieder et al., 2014).

System Level. Researchers’ interviews with cancer patients (n=42) and family caregivers (n=20) point to a number of system level antecedents, including complex clinical care, reimbursement, and analgesic regulation processes; obtaining analgesics; and the patient/family burden of coordinating care and assuring effective communication among different providers

(Schumacher et al., 2014a). Insurance and prescription coverage is a substantive predictive factor, with less coverage often afforded racial and ethnic minorities (Wieder et al., 2014).

Consequences of Analgesic Nonadherence

There are notably few studies that actually link nonadherence to patient or health utilization outcomes. This is a significant gap in the literature. Notwithstanding, the consequences identified impact myriad life domains. In a cross-sectional and descriptive study of 176 patient-caregiver dyads, patients with lower adherence levels who lived in settings where families were hesitant to use analgesics reported an increased severity of pain (Lee et al., 2015). Among a sample of 196 outpatient oncology subjects taking around-the-clock analgesics in a three-month prospective observational study, an interaction of strong (WHO step 3) opioids and inconsistent adherence was the strongest predictor of hospitalization (Meghani & Knafl, 2016). Finally, researchers using an exploratory longitudinal design and qualitative research methods found that patients (n=11) who experienced increased pain secondary to analgesic nonadherence sustained negative impacts to both physical and social functioning, as well as overall quality of life (Manzano et al., 2014).

Model Case

Take the case of a 40-year-old male diagnosed with stage III colon cancer. He is prescribed long-acting oxycontin 20mg by mouth twice daily and oxycodone 5-10 mg by mouth every 4 hours as needed for breakthrough spinal pain due to metastatic disease. He is terrified of becoming addicted to opioids despite no relevant family or personal history and he consistently chooses to forego his oxycontin. The patient will take his oxycodone only when his pain is unbearable. His wife is also adamant he not take opioids due to the news of the national crisis and fear her husband may suffer an overdose. His current prescriber insists on him following the

regimen as recommended and provides standardized education in the form of a brochure intended to alleviate his worries. Of note, this is his first time seeing a pain specialist. His oncologist did not think opioids were indicated and suggested nonopioid analgesics to manage the patient's cancer pain since he is not currently receiving active cancer treatment. This patient's intentional nonadherence has led to multiple emergency room visits for pain crises and a rapid deterioration of quality of life since he is unable to eat, sleep, or work secondary to uncontrolled pain.

This case reflects the ways a patients' salient concerns, family hesitancy, prescribers' lack of clarity regarding guidelines, and depersonalized education intersect to impact a patient's nonadherence behaviors (Lee et al., 2015; Meghani & Knafl, 2017; Meghani & Vapiwala, 2018) and subsequent increase in healthcare utilization (Meghani & Knafl, 2016). Additional cases might describe other challenges, such as analgesic access given insurance coverage gaps, ineffective coordination between healthcare services, or how race has been shown to predict nonadherence (Meghani et al., 2014; Schumacher et al., 2014a; Wieder et al., 2014).

Related Case

According to Walker and Avant (2019), a related case may depict some of the attributes of a concept but also differs from them when examined more closely; a particularly relevant approach to this phenomenon. Take the case of a 34-year-old undomiciled African-American woman recently discharged from a public urban hospital for uncontrolled pain secondary to her advanced breast cancer. Her primary insurance is Medicaid. She experienced confusion and nausea to inpatient trials of morphine and then oxycodone for pain control, finally achieving a desirable response to Fentanyl. While admitted to the hospital, she felt her pain was being inappropriately managed and inconsistently assessed. In addition, she has CKD and had been

resistant to taking morphine for this reason. She is ultimately discharged with prescriptions for a 100 microgram/hour transdermal Fentanyl patch to be changed every 72 hours and hydromorphone 8-12mg by mouth every 3 hours as needed for breakthrough pain. She denies side effects and endorses tolerable pain on this regimen. After discharge, she is told by the local pharmacist that Medicaid will not pay the cost of her prescriptions and she must use a cheaper medication, such as morphine. The licensed independent practitioner at her oncologist's office writes the new prescription that Medicaid will cover. The patient uses her remaining Fentanyl and hydromorphone, foregoes taking the morphine due to the adverse effects she previously experienced, and ends up in the emergency room later that week in a pain crisis. It takes an additional week to gain insurance approval for the analgesic regimen that works best for her to ensure a safe discharge – a structural barrier that prevents adherence to the regimen as prescribed.

System-wide challenges, such as analgesic access given insurance coverage issues and ineffective coordination between prescribers and various healthcare services, makes adherence impossible (Schumacher et al., 2014a; Wieder et al., 2014). This case also illustrates how race has been shown to predict nonadherence based on the inappropriate use of opioids and inaccurate assessment of pain (Meghani et al., 2014).

Empirical Referents

Empirical referents are the means through which the concept can be recognized and its defining attributes measured (Walker & Avant, 2019). Assessing the underlying factors that influence nonadherence and determining their basis is essential. For example, eliciting intentional versus unintentional processes that result in nonadherent behavior have suggested distinct correlates and decision-making heuristics for each category (Meghani & Bruner, 2013;

Morisky et al., 1986). Objective measures used in the analgesic adherence literature include the use of an electronic medication event monitoring system, a tool that records the number of analgesic bottle openings as a proxy for adherence, subsequently correlating findings with prescribed analgesic frequency (Meghani et al., 2015; Oldenmenger et al., 2017).

Incorporating self-reported levels of adherence may capture a key element in unraveling how nonadherence presents in the cancer pain setting. It has been noted that subjective analgesic-related beliefs poorly explain objective analgesic taking, which is influenced more strongly by clinical pain variables (e.g., severity of adverse effects, pain relief, etc.) (Meghani & Knafl, 2016; Meghani et al., 2015). However, subjective measures may be helpful to understand medication-taking habits, comparing objective data to self-reported adherence for increased validity of findings, and recognizing the various preferences and behaviors that interact to result in nonadherence (Meghani et al., 2013; Meghani & Knafl, 2017)

Figure 2 provides a model to depict this concept's defining attributes, antecedents and consequences, and empirical referents.

Discussion

This analysis has sought to clarify the concept of analgesic nonadherence for cancer pain and its use in the literature given the current sociopolitical implications of the opioid crisis. In sum, the literature falls short, leaving us with more questions than answers. Only a handful of studies have made the link between analgesic nonadherence and outcomes, which include increased pain severity, higher rates of hospitalization, and decreased overall quality of life (Lee et al., 2015; Manzano et al., 2014; Meghani et al., 2014; Meghani & Knafl, 2016). Ultimately, 'what' defines optimum adherence behavior is not clear. This paucity of evidence combined with the practice and policy shifts resultant of the opioid crisis invite a new commitment to further

empirical studies in this area. Based on this analysis - while also considering the implications of the current national context - a more inclusive definition of analgesic nonadherence for cancer pain is posed: *Patient deviation from a prescribed analgesic regimen for cancer pain, predicted by highly contextual factors within individual/family and societal domains and potentially complicating both one's symptom burden and a variety of health outcomes.*

There is insufficient reliable evidence to denote a value judgment on analgesic nonadherence as “good” or “bad”. However, initiatives and policies aimed at mitigating the crisis are complicating patient access, decreasing the willingness of prescribers to give opioids, and limiting prescription coverage for patients requiring analgesics, ultimately impacting patients' use (Johnson et al., 2018; Lamar, 2018; NAS, 2017). The question of how to balance social welfare while upholding the moral obligation to alleviate pain and suffering is at the center of this crisis (NAS, 2017), as well as inherent to the antecedents of analgesic nonadherence faced by patients.

Current cancer pain management guidelines are limited by a dearth of empirical research on long-term opioid use to support best practices; the result is conflicting recommendations from a number of organizations (Meghani & Vapiwala, 2018; Ranapurwala, Naumann, Austin, Dasgupta, & Marshall, 2018). Although many guidelines identify opioids as foundational to effective relief for moderate to severe cancer pain (NCCN, 2019; Paice et al., 2016; WHO, 2018), the CDC discourages opioid use as a first-line treatment for cancer survivors, who are likely to continue to experience pain long after active cancer treatment has concluded (Dowell, Haegerich, & Chou, 2016; Shi et al., 2011). These competing guidelines are likely to cause confusion among clinicians, placing patients at risk for subpar, ineffective, and/or risky consequences (Meghani & Vapiwala, 2018). In understanding analgesic nonadherence, we must

ask: Adherence toward what end? Adherence based on which guidelines and considering what literature?

Specifically, Meghani and Vapiwala (2018) point out conflicting recommendations regarding the use of long-acting and immediate-release opioids, which may also affect adherence behaviors. For instance, they point out that per the NCCN (2019), long-acting opioids to provide background analgesia should be used in combination with immediate-release opioids for breakthrough pain; however, the CDC (Dowell et al., 2016) discourages long-acting opioid use, particularly when immediate-release opioids are concurrently prescribed. A crucial question is: What does analgesic nonadherence mean in the context of the CDC opioid guidelines, particularly in the absence of empirical data for this patient population? In other words, how do providers ensure timely, effective pain management by addressing adherence concerns for cancer patients at risk for poor pain control, especially in settings that employ inappropriately applied guidelines for the population at hand?

The continued study of analgesic nonadherent behaviors in the cancer pain field given guideline discrepancies and emergent policy debates will be essential to improve care for affected patients. Furthermore, several studies focus specifically on adherence to ATC pain regimens (Meghani & Knafl, 2016; Yoong et al., 2013); which may warrant distinct considerations from those patients prescribed only immediate release analgesics. In the trend toward prescribing fewer long-acting scheduled analgesics and using primarily immediate release medications, the concept of analgesic nonadherence and its consequences becomes vastly unclear. This paradox requires further investigation to determine similarities and differences between adherence to both long-acting and immediate release analgesics. .

Patients' nonadherent behaviors have been observed in the literature using various patient-reported surveys and instruments and technologies (Meghani & Bruner, 2013; Meghani et al., 2013), which makes it difficult to understand and explicate nonadherence and underlying decision-making processes across studies. Further exploration is needed to test the interplay of objective and subjective nonadherence measures, as well as qualitative data that seeks to tease apart the underlying patterns that result in nonadherent behavior. Additional research might further explore how analgesic adherence choices are made and the utilities and tradeoffs employed by patients in the decision-making process.

Tailored education for patients, families, and prescribers regarding safe and effective analgesic use may assist in promoting that the holistic determinants of nonadherence are addressed. This requires attention to patient-centric models that elicit individual preferences and values, mitigate risks, and empower prescribers to correctly apply guidelines. Oldenmenger and colleagues (2018) systematically reviewed 28 randomized controlled trials (n=4,735), showing that standard patient education programs to reduce analgesic nonadherence may be effective but are correlated with a significant pain improvement outcome in less than 20% of all cancer pain patients. These results highlight additional research gaps in this area.

Overall imperatives include the improvement of pain control, function, and quality of life and ultimately determining if heightened scholarly focus on nonadherence has a meaningful role in meeting these outcomes. Furthermore, available evidence is inconclusive about how to best decrease nonadherent behaviors and understand its role in predicting patient outcomes.

Limitations

The findings of this concept analysis should be considered in light of the following limitations. While MeSH terms were used, the diversity of terms chosen to describe nonadherent

behavior may have resulted in the omission of some articles during the literature review. Though a limited number of organizational recommendations prior to 2010 were included in the analysis due to their continued influence on analgesic management of cancer pain and adherence, the selected time frame of the search criteria (2010-2018) may have overtly limited additional meaningful records for this phenomenon which possesses an already extensive literature gap. While this analysis was approached with consideration to the US opioid crisis, broader inclusion criteria in the future might invite a different understanding of the concept when explored through the lens of opioid use and availability in the international arena and across diverse cultures.

Conclusion

Cancer pain impacts patients and families by limiting physical and social function, negatively impacting quality of life, and complicating already taxing oncology treatment plans. Analgesic nonadherence in the current sociopolitical milieu deserves further scholarly dialogue and research to further elicit its relationship to cancer pain; in short, the role of nonadherence in shaping clinical outcomes must continue to be addressed. Ultimately, a more detailed understanding of the physiological mechanisms of analgesic nonadherence may lead to interventions at individual and aggregate levels that support patients in employing pain medication regimens to more effectively meet their needs.

It is impossible to sever the complexities related to the opioid crisis from factors that influence analgesic nonadherence. In fact, the opioid crisis is a crucial and underexplored antecedent of analgesic nonadherence. The context that birthed the addiction epidemic, including the beliefs, preferences, and values of both providers and patients, continues to evolve in an era of stigma and policy fluctuation. The full impact of the role analgesic nonadherence plays in

cancer pain management, particularly within this current sociopolitical milieu, needs further critical understanding.

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References

- Alikari, V., & Zyga, S. (2014). Conceptual analysis of patient compliance in treatment. *Health Science Journal*, 8(2), 179-186.
- Bryan, M., De La Rosa, N., Hill, A. M., Amadio, W. J., & Wieder, R. (2008). Influence of prescription benefits on reported pain in cancer patients. *Pain Medicine*, 9(8), 1148-1157. doi:10.1111/j.1526-4637.2008.00427.x
- Centers for Disease Control & Prevention. (2018). Understanding the epidemic. Retrieved from <https://www.cdc.gov/drugoverdose/epidemic/index.html>
- Chancellor, J., Martin, M., Liedgens, H., Baker, M. G., & Muller-Schwefe, G. H. (2012). Stated preferences of physicians and chronic pain sufferers in the use of classic strong opioids. *Value Health*, 15(1), 106-117. doi:10.1016/j.jval.2011.07.002
- Christie, C., Baker, C., Cooper, R., Kennedy, P. J., Madras, B., & Bondi, P. (2017). The President's commission on combating drug addiction and the opioid crisis. Retrieved from https://www.whitehouse.gov/sites/whitehouse.gov/files/images/Final_Report_Draft_11-1-2017.pdf
- Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. *JAMA*, 315(15), 1624-1645. doi:10.1001/jama.2016.1464
- Gardner, C. L. (2015). Adherence: A concept analysis. *International Journal of Nursing Knowledge*, 26(2), 96-101.
- Institute of Medicine. (2003). *Unequal treatment: Confronting racial and ethnic disparities in health care*. Washington, D.C.: National Academies Press.
- Jacobsen, R., Samsanaviciene, J., Liubarskiene, Z., Sjogren, P., Moldrup, C., Christrup, L., . . . Hansen, O. B. (2014). Barriers to cancer pain management in Danish and Lithuanian patients treated in pain and palliative care units. *Pain Management Nursing*, 15(1), 51-58. doi:10.1016/j.pmn.2012.06.002
- Johnson, K., Jones, C., Compton, W., Baldwin, G., Fan, J., Mermin, J., & Bennett, J. (2018). Federal Response to the Opioid Crisis. *Current HIV/AIDS Reports*, 15(4), 293-301. doi:10.1007/s11904-018-0398-8
- Koyyalagunta, D., Bruera, E., Engle, M. P., Driver, L., Dong, W., Demaree, C., & Novy, D. M. (2018). Compliance with Opioid Therapy: Distinguishing Clinical Characteristics and Demographics Among Patients with Cancer Pain. *Pain Medicine*, 19(7), 1469-1477. doi:10.1093/pm/pnx178

- Lamar, A. (2018). S.2680 - The Opioid Crisis Response Act of 2018. Retrieved from <https://www.congress.gov/bill/115th-congress/senate-bill/2680>
- Lee, B. O., Liu, Y., Wang, Y. H., Hsu, H. T., Chen, C. L., Chou, P. L., & Hsu, W. C. (2015). Mediating Effect of Family Caregivers' Hesitancy to Use Analgesics on Homecare Cancer Patients' Analgesic Adherence. *Journal of Pain and Symptom Management*, 50(6), 814-821. doi:10.1016/j.jpainsymman.2015.06.014
- Liang, S.-Y., Wu, S.-F., Tsay, S.-L., Wang, T.-J., & Tung, H.-H. (2013). Prescribed Opioids Adherence Among Taiwanese Oncology Outpatients. *Pain Management Nursing*, 14(3), 155-160. doi:10.1016/j.pmn.2011.02.001
- Liang, S. Y., Chen, K. P., Tsay, S. L., Wu, S. F., Chuang, Y. H., Wang, T. J., . . . Cheng, S. F. (2013). Relationship between belief about analgesics, analgesic adherence and pain experience in taiwanese cancer outpatients. *Asian Pacific Journal of Cancer Prevention*, 14(2), 713-716.
- Liang, S. Y., Tung, H. H., Wu, S. F., Tsay, S. L., Wang, T. J., Chen, K. P., & Lu, Y. Y. (2013). Concerns about pain and prescribed opioids in Taiwanese oncology outpatients. *Pain Management Nursing*, 14(4), 336-342. doi:10.1016/j.pmn.2011.08.004
- Liang, S. Y., Wang, T. J., Wu, S. F., Chao, T. C., Chuang, Y. H., Tsay, S. L., . . . Lee, M. D. (2013). Gender differences associated with pain characteristics and treatment in taiwanese oncology outpatients. *Asian Pacific Journal of Cancer Prevention*, 14(7), 4077-4082.
- Manzano, A., Ziegler, L., & Bennett, M. (2014). Exploring interference from analgesia in patients with cancer pain: a longitudinal qualitative study. *Journal of Clinical Nursing*, 23(13-14), 1877-1888. doi:10.1111/jocn.12447
- Martinez, K. A., Snyder, C. F., Malin, J. L., & Dy, S. M. (2014). Is race/ethnicity related to the presence or severity of pain in colorectal and lung cancer? *Journal of Pain and Symptom Management*, 48(6), 1050-1059. doi:10.1016/j.jpainsymman.2014.02.005
- Meghani, S. H., & Bruner, D. W. (2013). A pilot study to identify correlates of intentional versus unintentional nonadherence to analgesic treatment for cancer pain. *Pain Management Nursing*, 14(2), e22-30. doi:10.1016/j.pmn.2011.03.003
- Meghani, S. H., Byun, E., & Gallagher, R. M. (2012). Time to take stock: A meta-analysis and systematic review of analgesic treatment disparities for pain in the United States. *Pain Medicine*, 13, 150-174.
- Meghani, S. H., Chittams, J., Hanlon, A. L., & Curry, J. (2013). Measuring preferences for analgesic treatment for cancer pain: How do African-Americans and Whites perform on choice-based conjoint (CBC) analysis experiments? *BMC Medical Informatics and Decision Making*, 13, 118. doi:10.1186/1472-6947-13-118

- Meghani, S. H., Kang, Y., Chittams, J., McMenamin, E., Mao, J. J., & Fudin, J. (2014). African Americans with cancer pain are more likely to receive an analgesic with toxic metabolite despite clinical risks: a mediation analysis study. *Journal of Clinical Oncology*, 32(25), 2773-2779. doi:10.1200/JCO.2013.54.7992
- Meghani, S. H., & Knafl, G. J. (2016). Patterns of analgesic adherence predict health care utilization among outpatients with cancer pain. *Patient Preference and Adherence*, 10, 81-98. doi:10.2147/PPA.S93726Patterns
- Meghani, S. H., & Knafl, G. J. (2017). Salient concerns in using analgesia for cancer pain among outpatients: A cluster analysis study. *World Journal of Clinical Oncology*, 8(1), 75-85. doi:10.5306/wjco.v8.i1.75
- Meghani, S. H., Thompson, A. M., Chittams, J., Bruner, D. W., & Riegel, B. (2015). Adherence to Analgesics for Cancer Pain: A Comparative Study of African Americans and Whites Using an Electronic Monitoring Device. *Journal of Pain*, 16(9), 825-835. doi:10.1016/j.jpain.2015.05.009
- Meghani, S. H., & Vapiwala, N. (2018). Bridging the Critical Divide in Pain Management Guidelines From the CDC, NCCN, and ASCO for Cancer Survivors. *JAMA Oncology*. doi:10.1001/jamaoncol.2018.1574
- Merriam-Webster. (n.d.-a). "Adherence". Retrieved from <https://www.merriam-webster.com/dictionary/adherence>
- Merriam-Webster. (n.d.-b). "Nonadherence". Retrieved from <https://www.merriam-webster.com/dictionary/nonadherence>
- Morisky, D. E., Green, L. W., & Levine, D. M. (1986). Concurrent and predictive validity of a self-reported measure of medication adherence. *Medical Care*, 24(1), 67-74.
- National Academies of Sciences. (2017). *Pain management and the opioid epidemic: Balancing societal and individual benefits and risks of prescription opioid use*. Washington, DC: National Academies Press.
- National Academy of Medicine. (2017). *First, do no harm: Marshaling clinician leadership to counter the opioid epidemic*. Washington, DC: NAS.
- National Comprehensive Cancer Network. (2019). NCCN Clinical Practice Guidelines in Oncology: Adult Cancer Pain V1.2019-January 25, 2019. Retrieved from https://www.nccn.org/professionals/physician_gls/pdf/pain.pdf
- National Institutes of Health. (2014). Pathways to prevention workshop: The role of opioids in the treatment of chronic pain. Retrieved from https://prevention.nih.gov/sites/default/files/documents/programs/p2p/ODPPainPanelStatementFinal_10-02-14.pdf

- National Institutes of Health. (2018). About the NIH HEAL Initiative. Retrieved from <https://www.nih.gov/research-training/medical-research-initiatives/heal-initiative>
- Nguyen, L. M., Rhondali, W., De la Cruz, M., Hui, D., Palmer, L., Kang, D. H., . . . Bruera, E. (2013). Frequency and predictors of patient deviation from prescribed opioids and barriers to opioid pain management in patients with advanced cancer. *Journal of Pain and Symptom Management, 45*(3), 506-516. doi:10.1016/j.jpainsymman.2012.02.023
- Oldenmenger, W. H., Sillevs Smitt, P. A. E., de Raaf, P. J., & van der Rijt, C. C. D. (2017). Adherence to Analgesics in Oncology Outpatients: Focus on Taking Analgesics on Time. *Pain Practice, 17*(5), 616-624. doi:10.1111/papr.12490
- Paice, J. A., Portenoy, R., Lacchetti, C., Campbell, T., Chevillie, A., Citron, M., . . . Bruera, E. (2016). Management of Chronic Pain in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. *Journal of Clinical Oncology, 34*(27), 3325-3345. doi:10.1200/JCO.2016.68.5206
- Ranapurwala, S. I., Naumann, R. B., Austin, A. E., Dasgupta, N., & Marshall, S. W. (2018). Methodologic limitations of prescription opioid safety research and recommendations for improving the evidence base. *Pharmacoepidemiol Drug Saf.* doi:10.1002/pds.4564
- Rhee, Y. O., Kim, E., & Kim, B. (2012). Assessment of pain and analgesic use in African American cancer patients: factors related to adherence to analgesics. *Journal of Immigrant and Minority Health, 14*(6), 1045-1051. doi:10.1007/s10903-012-9582-x
- Rudd, R. A., Seth, P., David, F., & Scholl, L. (2016). Increases in Drug and Opioid-Involved Overdose Deaths - United States, 2010-2015. *MMWR: Morbidity and Mortality Weekly Report, 65*(5051), 1445-1452. doi:10.15585/mmwr.mm655051e1
- Schumacher, K. L., Plano Clark, V. L., West, C. M., Dodd, M. J., Rabow, M. W., & Miaskowski, C. (2014a). Pain medication management processes used by oncology outpatients and family caregivers part I: health systems contexts. *Journal of Pain and Symptom Management, 48*(5), 770-783. doi:10.1016/j.jpainsymman.2013.12.242
- Schumacher, K. L., Plano Clark, V. L., West, C. M., Dodd, M. J., Rabow, M. W., & Miaskowski, C. (2014b). Pain medication management processes used by oncology outpatients and family caregivers part II: home and lifestyle contexts. *Journal of Pain and Symptom Management, 48*(5), 784-796. doi:10.1016/j.jpainsymman.2013.12.247
- Shi, Q., Smith, T.G., Michonski, J.D., Stein, K.D., Kaw, C., & Cleeland, C.S. (2011). Symptom burden in cancer survivors 1 year after diagnosis: A report from the American Cancer Society's studies of cancer survivors. *Cancer, 117*(12), 2779-2790.
- Simone, C. B., 2nd, Vapiwala, N., Hampshire, M. K., & Metz, J. M. (2012). Cancer patient attitudes toward analgesic usage and pain intervention. *Clinical Journal of Pain, 28*(2), 157-162. doi:10.1097/AJP.0b013e318223be30

- The Council of Economic Advisors. (2017). The Underestimated Cost of the Opioid Crisis. Retrieved from <https://www.whitehouse.gov/sites/whitehouse.gov/files/images/The%20Underestimated%20Cost%20of%20the%20Opioid%20Crisis.pdf>
- Thin, D. H. Q., Sriraj, W., Mansor, M., Tan, K. H., Irawan, C., Kurnianda, J., . . . Javier, F. O. (2018). Patient and Physician Satisfaction with Analgesic Treatment: Findings from the Analgesic Treatment for Cancer Pain in Southeast Asia (ACE) Study. *Pain Research and Management*, 2018. doi:10.1155/2018/2193710
- Torresan, M. M., Garrino, L., Borraccino, A., Macchi, G., De Luca, A., & Dimonte, V. (2015). Adherence to treatment in patient with severe cancer pain: A qualitative enquiry through illness narratives. *European Journal of Oncology Nursing*, 19(4), 397-404. doi:10.1016/j.ejon.2015.01.001
- US Department of Health and Human Services. (2017). 5-point strategy to combat the opioid crisis. Retrieved from <https://www.hhs.gov/opioids/about-the-epidemic/hhs-response/index.html>
- Valeberg, B. T., Miaskowski, C., Hanestad, B. R., Bjordal, K., Moum, T., & Rustoen, T. (2008). Prevalence rates for and predictors of self-reported adherence of oncology outpatients with analgesic medications. *Clinical Journal of Pain*, 24(7), 627-636. doi:10.1097/AJP.0b013e31816fe020
- Valeberg, B. T., Miaskowski, C., Paul, S. M., & Rustoen, T. (2016). Comparison of Oncology Patients' and Their Family Caregivers' Attitudes and Concerns Toward Pain and Pain Management. *Cancer Nursing*, 39(4), 328-334. doi:10.1097/ncc.0000000000000319
- van den Beuken-van Everdingen, M. H., Hochstenbach, L. M., Joosten, E. A., Tjan-Heijnen, V. C., & Janssen, D. J. (2016). Update on Prevalence of Pain in Patients With Cancer: Systematic Review and Meta-Analysis. *Journal of Pain and Symptom Management*, 51(6), 1070-1090 e1079. doi:10.1016/j.jpainsymman.2015.12.340
- Walker, L. O., & Avant, K. C. (2019). *Strategies for theory construction in nursing* (6th ed.). New York, NY: Pearson.
- Wandner, L. D., Heft, M. W., Lok, B. C., Hirsh, A. T., George, S. Z., Horgas, A. L., . . . Robinson, M. E. (2014). The impact of patients' gender, race, and age on health care professionals' pain management decisions: an online survey using virtual human technology. *International Journal of Nursing Studies*, 51(5), 726-733. doi:10.1016/j.ijnurstu.2013.09.011
- Ward, S. E., Goldberg, N., Miller-McCauley, V., Mueller, C., Nolan, A., Pawlik-Plank, D., . . . Weissman, D. E. (1993). Patient-related barriers to management of cancer pain. *Pain*, 52(3), 319-324.

- Wieder, R., Delarosa, N., Bryan, M., Hill, A. M., & Amadio, W. J. (2014). Prescription coverage in indigent patients affects the use of long-acting opioids in the management of cancer pain. *Pain Medicine, 15*(1), 42-51. doi:10.1111/pme.12238
- World Health Organization. (2003). *Adherence to long-term therapies: Evidence for action*. Geneva, Switzerland: World Health Organization.
- World Health Organization. (2018). *WHO Guidelines for pharmacological and radiotherapeutic management of cancer pain in adults and adolescents*. Geneva, Switzerland: World Health Organization.
- Xu, X., Luckett, T., Wang, A. Y., Lovell, M., & Phillips, J. L. (2018). Cancer pain management needs and perspectives of patients from Chinese backgrounds: a systematic review of the Chinese and English literature. *Palliative and Supportive Care, 16*(6), 785-799. doi:10.1017/s1478951517001171
- Yoong, J., Traeger, L. N., Gallagher, E. R., Pirl, W. F., Greer, J. A., & Temel, J. S. (2013). A pilot study to investigate adherence to long-acting opioids among patients with advanced lung cancer. *Journal of Palliative Medicine, 16*(4), 391-396. doi:10.1089/jpm.2012.0400

Box 1. Concept Analysis Process (adapted from Walker & Avant, 2019).

1. Select a concept.
2. Determine analysis aims and purpose.
3. Identify all discoverable uses of the concept.
4. Describe the concept's defining attributes.
5. Specify antecedents and consequences of the concept.
6. Articulate a model case.
7. Identify a related case.
8. Define empirical referents.

Figure. 1. Inclusion/Exclusion Flowchart.

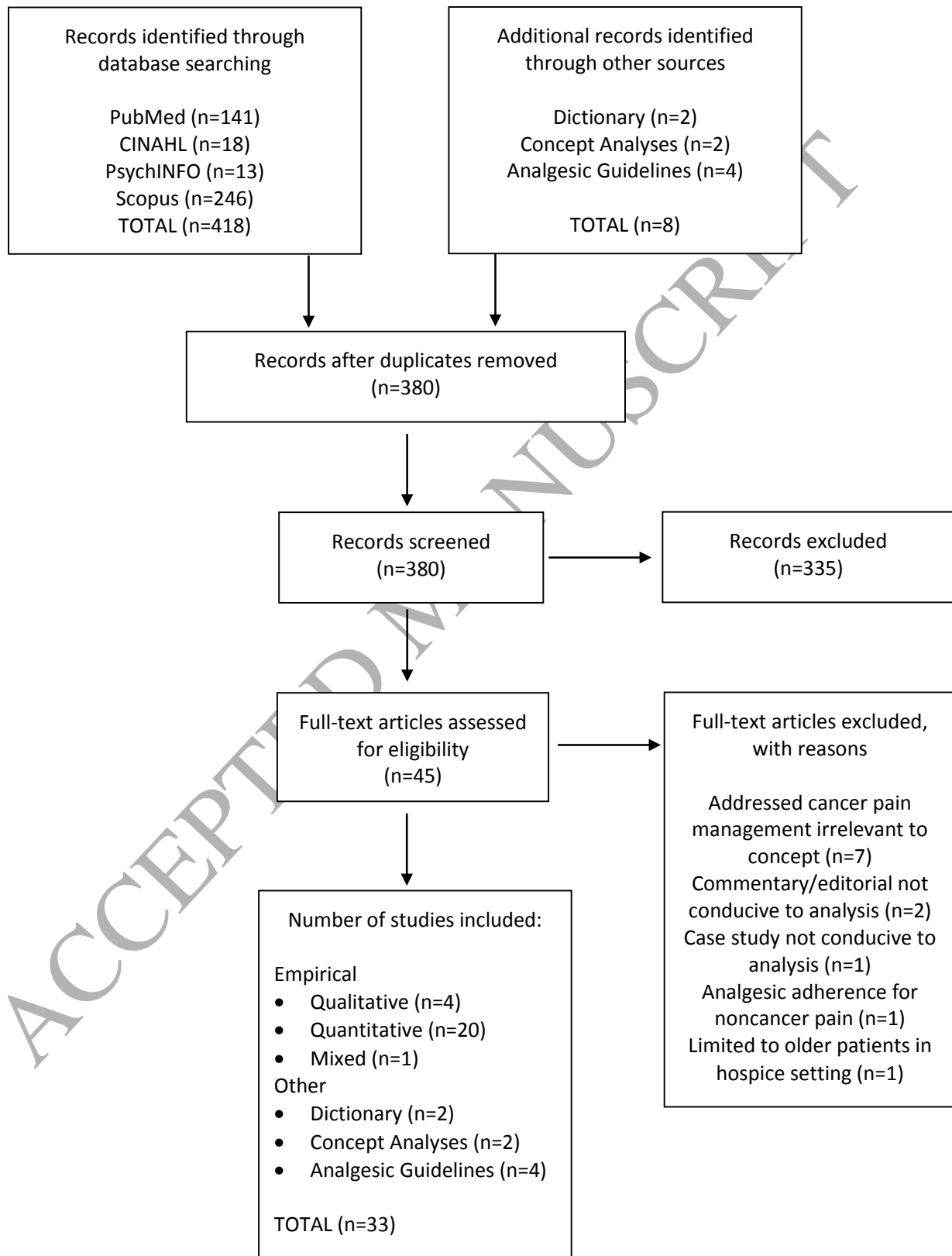
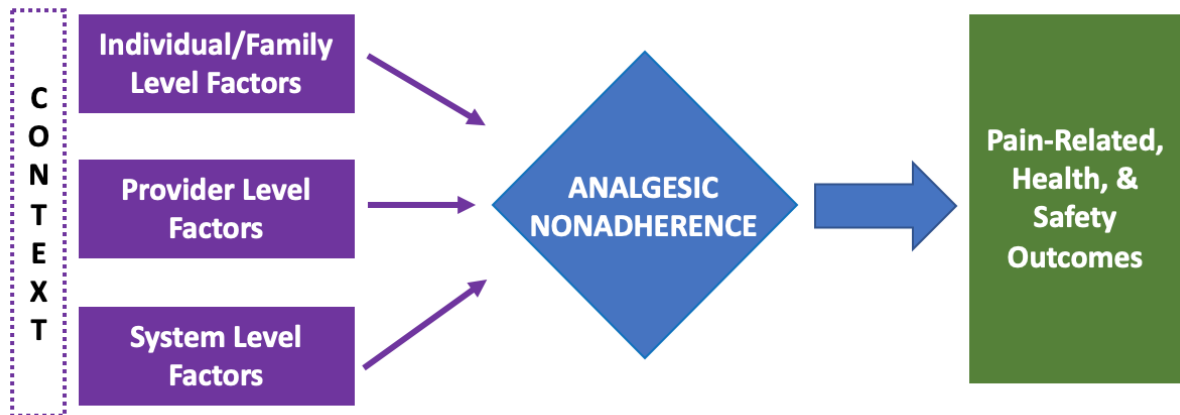


Figure 2. Conceptual Model of Analgesic Nonadherence for Cancer Pain.



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