

Review Article

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Patient beliefs associated with medication hesitancy in palliative care: A systematic review using the theory of planned behavior

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Abstract

Context. The demand of palliative care is increasing due to the aging population and treatment hesitancy or intentional avoidance compromises symptom management.

Objectives. To identify patient beliefs associated with medication hesitancy by using the theory of planned behavior (TPB) namely, attitudes, subjective norms, behavioral intention, and perceived behavioral control associated with medication hesitancy or intentional noncompliance by avoidance.

Methods. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis guideline was followed to conduct a systematic literature search involving the CINAHL, Embase, MEDLINE, and PsycINFO databases from inception until March 2022. Hand-searched articles from reference lists and gray literature were included. Thematic analysis was conducted on qualitative data and triangulated with quantitative data.

Results. About 554 articles were retrieved from the literature search and 17 articles were included based on the eligibility criteria. Three subthemes that were identified under TPB constructs were *attitude*: negative attitude toward medications, passive attitude toward illness and inaccurate information about disease or medication; one subtheme was identified under *subjective norms*: perceived negative opinions from others; and one subtheme was identified under *perceived behavioral control*: perception of manageable symptoms. Quantitative data provided triangulation of qualitative findings related to fear of addiction and side effects, feelings of hopelessness, unclear direction and information, social stigma, endurable symptoms, and illness as determinants for medication avoidance.

Significance of results. This systematic review highlighted some patient beliefs related to medication hesitancy or avoidance. Clinicians should take patient beliefs and concerns into consideration when creating treatment regimens for people receiving palliative care to optimize medication adherence and the quality of care.

Introduction

The demand for palliative care is increasing due to an increased prevalence of life-limiting diseases, as well as the growth of the aging population (Al-Mahrezi and Al-Mandhari 2016). Palliative care aims to improve the quality of life of patients and their family via regular assessment and early intervention of physical, psychosocial, cultural, and spiritual needs. The aims of care include providing symptomatic relief and providing comfort to patients and their families. Challenges include effective provider–patient communication, shared decision-making, education, end-of-life care, and bioethics (Price et al. 2019). Treatment hesitancy or intentional noncompliance by avoidance also compromises patient's symptom management and quality of life. Hesitancy has previously been reported for medications such as opioids (Apolone et al. 2009; Davies et al. 2013) and medicinal cannabis (Zeng et al. 2021). Hence, it is important to address the patient's concern and to consider factors that drive intentional avoidance to promote shared decision-making with patients and optimize patient-centered care.

Qualitative studies in the palliative care setting have highlighted potential barriers to medication adherence including patients' lack of knowledge, side effects of medications, and hesitancy in administering medications (Harasym et al. 2020; Lin et al. 2000). Epidemiological data have determined other factors that affected medication compliance in the overall population such as patient-related factors (such as health literacy), treatment-related factors (such as medication administration route), and disease-related factors (severity and symptoms of disease) (Jin et al. 2008). However, a comprehensive synthesis of evidence of patient perspectives

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in the palliative care setting is scarce. Hence, in the present study, the theory of planned behavior (TPB) framework was adopted to explore medication hesitancy and avoidance in the palliative care setting, which systematically highlights potential factors that influence the occurrence of a certain behavior (medication avoidance and hesitancy in this case). Such factors include personal attitude toward the behavior, subjective norms, and perceived behavioral control (Ajzen 1991) and has previously been widely used in health-care settings to understand patient behavior with respect to medication adherence and other health-related behaviors (Armitage and Conner 2001; Kam et al. 2012; Kopelowicz et al. 2015).

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline (Moher et al. 2009), and the quality of the evidence was critically appraised using the Mixed Method Appraisal Tool (MMAT) (Hong et al. 2018). Synthesis of qualitative and quantitative findings was conducted based on Whittemore and Knaf's integrative methodology (Whittemore and Knaf 2005) with the intention of providing a better understanding of the targeted phenomenon.

Search strategy

Literature was sourced from 4 databases including CINAHL, Embase, MEDLINE, and PsycINFO systematically from inception to March 2022. The search strategy centered around 3 concepts: patient beliefs, medication hesitancy, and palliative care. Specific drug classes and names of medications that have been previously reported to be associated with medication hesitancy such as "cannabis" including its components "cannabidiol" (and "CBD") and "tetrahydrocannabinol" (and "THC"), "benzodiazepines," "midazolam," "clonazepam," "diazepam," "opioids," and "morphine" were also included for the purpose of broadening the search. Subject headings and keywords related to each concept were combined to generate the search. The search strategy was then reviewed and approved by the university librarian. Gray literature such as conference abstracts were also included. Additionally, studies that were recommended and hand-searched from reference lists were included. The detailed search strategies for each databases are shown in [Appendix A](#).

Study selection

The search results were exported to EndNote (EndNote 2013) for deduplication and Covidence (Covidence 2022) was used for the screening process. The title and abstract of the references were reviewed by 3 authors (U.C.L., H.M., and J.L.) independently based on the eligibility criteria. The inclusion criteria were as follows: (1) qualitative and quantitative primary studies, (2) studies that reported avoidance or hesitancy against prescribed medications in the palliative care setting, (3) and studies in which patients had decision-making capacity. We excluded studies that (1) did not include patient-reported outcomes nor patient perspectives, (2) did not report patient attitude toward any prescribed medication, (3) had findings that did not correspond to any TPB constructs, and (4) published in non-English languages. Full-text screening was subsequently conducted to confirm eligibility. Any disagreement was resolved through discussion and consultation with a fourth reviewer (J.A.O.).

Quality assessment

The quality of qualitative, quantitative, and mixed methods studies was assessed by using the MMAT (Hong et al. 2018) for the purpose of examining the strength of evidence and identifying the potential bias and allowing comparison of studies. Affirmation of the first 2 questions was considered as the prerequisites for inclusion (i.e., 1. Are there clear research questions? and 2. Do the collected data allow to address the research questions?), while the remaining 5 questions (i.e., 1. Is the qualitative approach appropriate to answer the research question? 2. Are the qualitative data collection methods adequate to address the research question? 3. Are the findings adequately derived from the data? 4. Is the interpretation of results sufficiently substantiated by data? 5. Is there coherence between qualitative data sources, collection, analysis, and interpretation? for qualitative studies; 1. Is the sampling strategy relevant to address the research question? 2. Is the sample representative of the target population? 3. Are the measurement appropriate? 4. Is the risk of nonresponse bias low? 5. Is the statistical analysis appropriate to answer the research question? for quantitative descriptive studies; or, 1. Is there an adequate rationale for using a mixed methods design to address the research question? 2. Are the different components of the study effectively integrated to answer the research question? 3. Are the outputs of the integration of qualitative and quantitative components adequately interpreted? 4. Are divergences and inconsistencies between quantitative and qualitative results adequately addressed? 5. Do the different components of the study adhere to the quality criteria of each tradition of the methods involved? for mixed-method studies) were used to assess the quality of the study.

Data analysis

TPB constructs served as a theoretical framework to guide data extraction and identification of factors influencing medication hesitancy in patients receiving palliative care. Findings were broadly categorized under factors associated with patient's beliefs and evaluation of their own medication avoidance (attitudes), other people's attitude toward their medication avoidance (subjective norms), their own perception of the extent of medication avoidance (behavioral intention), and their own perception of control or power to avoid prescribed medications (perceived behavioral control). Qualitative data were extracted from the full text and analyzed thematically using NVivo software (NVivo 2020). The data were first read and re-read for familiarity and inductive code generation. During coding, potential ideas were constructed from the data and descriptive themes were developed from these codes. The descriptive themes were analyzed by the TPB constructs (i.e., attitudes, subjective norms, behavioral intention, and perceived behavioral control) served as a priori framework and formed the analytical themes. The codes and themes were developed by 2 authors (U.C.L. and J.A.O.).

Descriptive data from quantitative studies were also obtained and compared with the themes generated from qualitative data. The integration of data allowed the triangulation of findings on patients' perspectives, which influenced medication hesitancy or noncompliance.

Results

A total of 554 references were retrieved from the databases. After deduplication, 455 articles were screened by title and abstract. After title screening, 75 articles remained for full-text review and

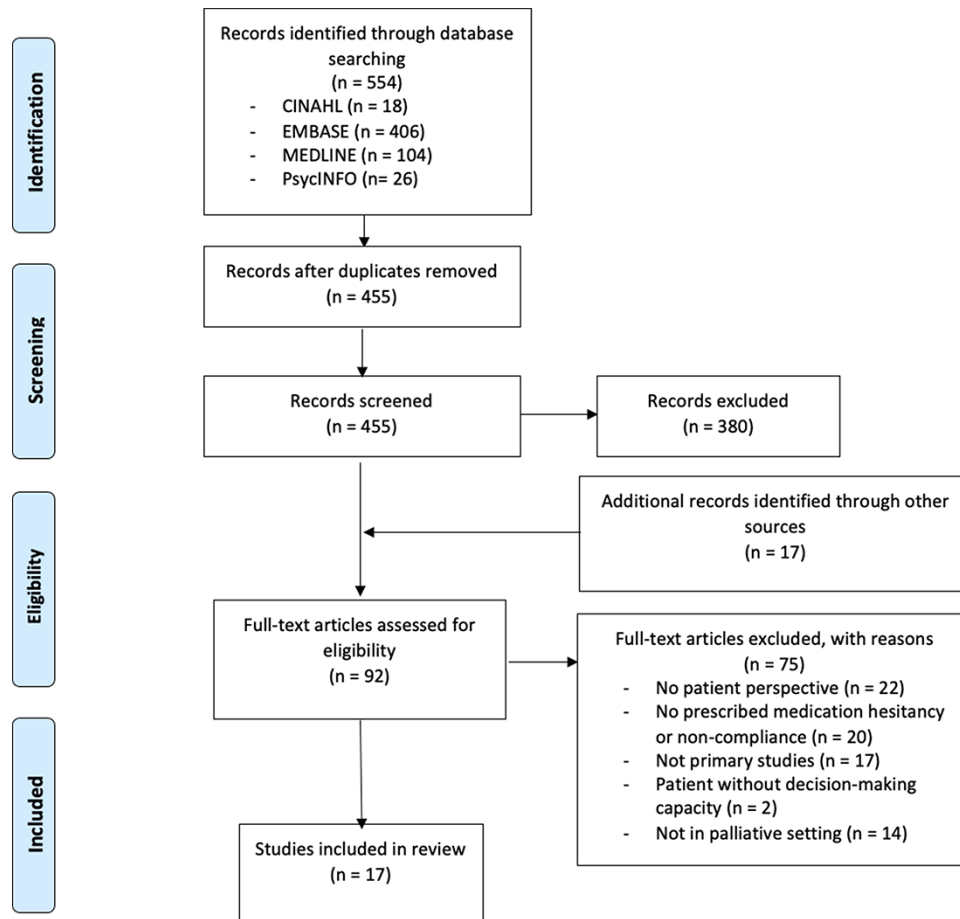


Fig. 1. PRISMA flow diagram.

17 studies were included for this review based on the predefined eligibility criteria for inclusion (Figure 1). Among those studies, 11 were qualitative studies (Adam et al. 2015; Beaussant et al. 2015; Cervantes et al. 2017; Fine 2007; Huijjer and van Leeuwen 2000; Lo and Jonsen 1980; Moran et al. 2019; Persaud-Sharma et al. 2018; Rafii et al. 2021; Reid et al. 2008; Sand et al. 2009), 4 were quantitative studies (Bestvina et al. 2014; Davies et al. 2013; Subramanian et al. 2011; Thongkhamcharoen et al. 2012), and 2 were mixed-method studies (Wright et al. 2019; Xu et al. 2022).

Study characteristics

The included studies were conducted in various countries including Australia ($n = 1$) (Xu et al. 2022), France ($n = 1$) (Beaussant et al. 2015), India ($n = 1$) (Subramanian et al. 2011), Iran ($n = 1$) (Rafii et al. 2021), Malaysia ($n = 1$) (Thongkhamcharoen et al. 2012), The Netherlands ($n = 1$) (Huijjer and van Leeuwen 2000), Norway ($n = 1$) (Sand et al. 2009), the United Kingdom ($n = 2$) (Adam et al. 2015; Reid et al. 2008), and the United States ($n = 5$) (Bestvina et al. 2014; Cervantes et al. 2017; Fine 2007; Persaud-Sharma et al. 2018; Wright et al. 2019). One study was conducted in multiple countries including Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, The Netherlands, the Republic of Ireland, Spain, Sweden, and the United Kingdom (Davies et al. 2013). Two studies did not report the information regarding country or setting (Lo and Jonsen 1980; Moran et al. 2019). There were 1,589 participants who were included in this

review and among them 1,536 were patients. The remainder were either health-care professionals or caregivers. The included studies ranged from the year 1980 to 2022. Among all the included articles, most (15 out of 17) articles included patients diagnosed with cancer (Adam et al. 2015; Beaussant et al. 2015; Bestvina et al. 2014; Davies et al. 2013; Fine 2007; Huijjer and van Leeuwen 2000; Lo and Jonsen 1980; Persaud-Sharma et al. 2018; Rafii et al. 2021; Reid et al. 2008; Sand et al. 2009; Subramanian et al. 2011; Thongkhamcharoen et al. 2012; Wright et al. 2019; Xu et al. 2022). One article focused on end-stage renal disease (Cervantes et al. 2017) and another on chronic obstructive pulmonary disease (Moran et al. 2019). The medications that were most frequently mentioned in the studies were opioids. Other medications involved were paracetamol, cortisone, antibiotics, chemotherapy medications, hormonal therapy, antiemetics, and sedatives. Other information including study objectives, setting, study design, participant characteristics, and drug class or name associated with hesitancy or avoidance and findings are shown in Table 1.

Quality appraisal

All studies fulfilled the prerequisites for inclusion; however, the quality of the included studies varied. For qualitative studies, 6 studies (Adam et al. 2015; Beaussant et al. 2015; Cervantes et al. 2017; Rafii et al. 2021; Reid et al. 2008; Sand et al. 2009) satisfied all 5 MMAT criteria. Three studies (Fine 2007; Lo and Jonsen 1980; Persaud-Sharma et al. 2018) fulfilled 4 criteria but not the

Table 1. Characteristics of included studies

Author (year)	Country and setting	Objective	Design/tools	Patient characteristics	Class or name of medication reported to be associated with hesitancy or noncompliance
Davies et al. (2013)	Austria, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, The Netherlands, Republic of Ireland, Spain, Sweden, and the United Kingdom; Specialized palliative care or pain units	To characterize breakthrough pain in a diverse population of cancer patients	Quantitative Questionnaire	n = 1,000 patients; Median age (range), 62 (23–93); Male, 51%; Female, 49%; Cancer diagnosis: breast (125), gastrointestinal (264), gynecological (72), hematological (35), head and neck (65), lung (172), melanoma (25), neurological (8), sarcoma (34), urological (160), unknown (16), and not stated (24)	Analgesics (opioids, paracetamol, and nonsteroidal anti-inflammatory drugs)
Rafii et al. (2021)	Iran; Oncology wards and palliative medicine clinics in hospitals	To explore barriers to pain management at home from the experiences of family caregivers and patients	Qualitative in-depth interviews	n = 20 patients; Mean age (range), 42 (18–79); Male, 12; Female, 8; Cancer diagnosis: breast (2), lung (1), colon (3), leukemia (5), brain tumor (1), pancreatic (1), prostate (2), ovarian (1), adenocarcinoma (2), sarcoma (1), and bone (1)	Opioids
Fine (2007)	United States; University medical center	To review basic pain assessment, including the concept of total pain; the ethical foundation of pain management strategies; distinctions between tolerance, dependence, and addiction; and a rational, evidence-based approach to analgesia with an emphasis on opioid pharmacology	Case study	n = 1 patient; Age, 68; Sex, female; Cancer diagnosis: breast	Hydrocodone with paracetamol
Lo and Jonsen (1980)	No country or setting reported	To discuss the relevant ethical, legal, and medical considerations, set forth the management options, and describe the psychological and social factors affecting the decision	Case study	n = 1 patient; Age, 62; Sex, Male; Cancer diagnosis: colon	Antibiotics
Persaud-Sharma et al. (2018)	United States; No specific setting mentioned	To highlight the importance of elucidating how a patient understands their own medical condition and reconcile their belief system and cultural practices early in the management and treatment process	Case report	n = 1 patient; Age, 37; Sex, female; Cancer diagnosis: cervical	Chemotherapy medications; Opioids

(Continued)

Table 1. (Continued.)

Author (year)	Country and setting	Objective	Design/tools	Patient characteristics	Class or name of medication reported to be associated with hesitancy or noncompliance
Beaussant et al. (2015)	France; University hospital, general hospital, cancer center and private hospital	To explore the frequency of the questioning about the pursuit, the limitation, or the withholding of specific therapies in advanced cancer patient and the determinants and modalities of the patients' perspectives, with a focus on the patients' involvement	Qualitative; Semi-directed interviews	$n = 29$ patients; Mean age (range), 65.4 (43–80); Male, 12; Female, 17; Cancer diagnosis: gastrointestinal and pancreatic (6), breast (5), respiratory and ear, nose, and throat (4), other solid tumor (5), leukemia (5), lymphoma (3), and myeloma (1)	Chemotherapy medications
Sand et al. (2009)	Norway; Day-care center in a palliative clinic	To explore the experiences of using medicines in patients with far-advanced cancer and short life expectancy	Qualitative; Semi-structured interview	$n = 15$ patients; Mean age (range), 62.4 (39–92); Male, 5; Female, 10; Cancer diagnosis: breast (3), lung (3), oesophagus (1), stomach (2), pancreatic (1), rectal (2), ovarian (1), kidney (1), and skin melanoma (1)	Analgesics (morphine and paracetamol); Cortisone; Hormone therapy; Sedatives
Reid et al. (2008)	United Kingdom; Oncology center	To explore factors affecting decision-making of using morphine when first offered to cancer patients	Qualitative study; In-depth interview	$n = 18$ patients; Mean age (range), 66.6 (55–82); Male, 9; Female, 9; Cancer diagnosis: breast (5), prostate (8), sarcoma (1), lung (2), cholangiocarcinoma (1), and ovary (1)	Morphine
Moran et al. (2019)	No country reported; Tertiary metropolitan hospital	To explore perceptions toward opioid for severe chronic breathlessness management in patients with advanced cardiorespiratory disease	Qualitative; In-depth interview	$n = 10$ patients; Diagnosis: advanced chronic obstructive pulmonary disease; Not reported: age, sex distribution	Opioids
Huijter and van Leeuwen (2000)	The Netherlands; Department of medical oncology at an academic hospital	To explore reasons for patients refusing chemotherapy and the way oncologists respond and communicate to the patients	Qualitative; Semi-structured interview	$n = 3$ patients; Mean age (range), 59.3 (49–73); Male, 0; Female, 3; Cancer diagnosis: breast (2) and ovarian (1)	Chemotherapy medications; Hormonal treatment
Cervantes et al. (2017)	United States; Outpatient hemodialysis facilities	To explore the preferences of symptom management and advance care planning in Latino patients receiving dialysis	Qualitative; Semi-structured interview	$n = 20$ patients; Mean age (age range), 61 (30–78); Male, 10; Female, 10; Diagnosis: end-stage renal disease	Opioids; Antiemetic

(Continued)

Table 1. (Continued.)

Author (year)	Country and setting	Objective	Design/tools	Patient characteristics	Class or name of medication reported to be associated with hesitancy or noncompliance
Adam et al. (2015)	United Kingdom; Out-of-hours primary care service	To explore the experiences, views, and opinions of patients and caregivers who have used out-of-hours primary care for help with managing cancer pain	Qualitative; Semi-structured interview	n = 11 patients; Mean age (range), 56.5 (49–72); Male, 2; Female, 9; Cancer diagnosis: breast (4), colorectal (2), endometrial (2), urinary bladder (1), prostate (1), and melanoma (1)	Morphine
Thongkhamcharoen et al. (2012)	Malaysia; Community palliative care setting	To illustrate dyspnea management at home and management of that in a community palliative care setting are impacted by cultural context	Case series	n = 5 patients; Age, 55, 31, 74, 75, 60; Male, 1; Female, 4; Diagnosis: motor neuron disease (1), idiopathic pulmonary fibrosis (1), chronic obstructive pulmonary disease (1), metastatic breast cancer (1), and cholangiocarcinoma (1)	Morphine
Bestvina et al. (2014)	United States; Quaternary referral cancer center and rural oncology clinics	To explore the relationship between nonadherence, financial distress, and patient–physician discussions of cancer treatment–related cost	Quantitative; Survey	n = 300 patients; Median age, 60; Male, 157; Female, 143; Cancer diagnosis: breast (53), colorectal (81), oesophageal and gastric (10), kidney (4), lung (52), pancreas (39), prostate (22), sarcoma (9), testicular (4), uterine (4), and other (22)	Chemotherapy medications
Subramanian et al. (2011)	India; Hospital	To identify reasons for declining palliative care treatment in the hospital	Quantitative Questionnaire	n = 61 patients; Cancer diagnosis: lung (61); Not reported: age, sex distribution	Chemotherapy medications
Xu et al. (2022)	Australia; Cancer care center and palliative care unit of public hospitals, Chinese cancer patient support groups	To explore Chinese migrants' cancer pain experiences and cultural factors influencing their perceptions and responses to cancer pain and its pharmacological management	Mixed method; Focus groups and short version of Barrier Questionnaire-Taiwan (S-BQT)	n = 24 patients; Mean age: 59.4; Male, 2; Female, 22; Cancer diagnosis: breast (12), lung (6), colorectal (2), ovarian (1), nasopharyngeal (1), bowel (1), and pancreatic (1)	Analgesics (opioids and paracetamol); Chemotherapy medications
Wright et al. (2019)	United States; Hospital cancer center	To explore patient approaches to managing chronic cancer pain with long-acting opioids	Mixed method; Prospective study of adherence and semi-structured interview	n = 17 patients; Median age (range), 65 (34–76); Male, 7; Female, 10; Cancer diagnosis: gastrointestinal (11), thoracic (3), gynecologic (2), and breast (1)	Opioids

Table 2. The perspective of individuals towards medication hesitancy or noncompliance based on the TPB model

TPB constructs	Themes	Subthemes
Attitude	Negative attitudes toward medications	Disease progression (Adam <i>et al.</i> 2015; Rafii <i>et al.</i> 2021; Reid <i>et al.</i> 2008)
		Perceived lack of efficacy (Xu <i>et al.</i> 2022)
		Drug addiction (Adam <i>et al.</i> 2015; Fine 2007; Rafii <i>et al.</i> 2021; Sand <i>et al.</i> 2009; Wright <i>et al.</i> 2019; Xu <i>et al.</i> 2022)
		Drug tolerance (Rafii <i>et al.</i> 2021; Sand <i>et al.</i> 2009; Xu <i>et al.</i> 2022)
		Side effects (Adam <i>et al.</i> 2015; Beaussant <i>et al.</i> 2015; Cervantes <i>et al.</i> 2017; Huijjer and van Leeuwen 2000; Lo and Jonsen 1980; Moran <i>et al.</i> 2019; Rafii <i>et al.</i> 2021; Sand <i>et al.</i> 2009; Subramanian <i>et al.</i> 2011; Wright <i>et al.</i> 2019; Xu <i>et al.</i> 2022)
Passive attitude toward their illnesses	Punishment (Cervantes <i>et al.</i> 2017; Fine 2007)	
	Hopelessness (Lo and Jonsen 1980; Rafii <i>et al.</i> 2021; Subramanian <i>et al.</i> 2011)	
Inaccurate information about disease or medication	False hope of recovery (Rafii <i>et al.</i> 2021)	
	Unclear direction and information (Huijjer and van Leeuwen 2000; Sand <i>et al.</i> 2009; Thongkhamcharoen <i>et al.</i> 2012)	
Subjective norms	Perceived opinions of others	Social stigma (Moran <i>et al.</i> 2019; Subramanian <i>et al.</i> 2011; Xu <i>et al.</i> 2022)
Perceived behavioral control	Perception of manageable symptoms and illness	Endurable symptoms and illness (Davies <i>et al.</i> 2013; Rafii <i>et al.</i> 2021; Sand <i>et al.</i> 2009; Thongkhamcharoen <i>et al.</i> 2012; Xu <i>et al.</i> 2022)

criteria related to the data collection method. Two studies (Huijjer and van Leeuwen 2000; Moran *et al.* 2019) fulfilled only 1 criterion due to ambiguity in the data collection method, the way that the data were analyzed and interpreted, and/or the coherency between the data and results. For the quantitative studies, 2 studies (Bestvina *et al.* 2014; Davies *et al.* 2013) fulfilled 3 criteria. These studies did not specify whether the sample represented the target population, the appropriateness of measurement, and/or the risk of nonresponse bias. One study (Subramanian *et al.* 2011) fulfilled one criterion for indicating a relevant sampling strategy, and one study (Thongkhamcharoen *et al.* 2012) did not fulfil any criterion. For the mixed-method studies, 1 study (Xu *et al.* 2022) fulfilled 4 criteria but did not address the rationale of using mixed method, and 1 study (Wright *et al.* 2019) fulfilled 3 criteria (Appendix Table B1–B3).

Patient perspectives toward medication hesitancy from the result section of the studies were extracted and coded using NVivo software. Across all TPB components, 12 subthemes emerged and were categorized into 5 themes (Table 2).

Attitude

Three themes were identified: negative attitude toward medication, passive attitude toward illnesses, and inaccurate information about disease or medication.

Negative attitude toward medications

Some patients perceived the use of medications, particularly morphine, signaled illness progression (Reid *et al.* 2008), or imminent death (Adam *et al.* 2015; Rafii *et al.* 2021; Reid *et al.* 2008).

If I take quite a lot of this morphine then I – it just means I'm getting worse. And I don't want to get worse. (Reid *et al.* 2008)

Other patients were sceptical about the effect of medications and did not think that they would help alleviate the symptoms or simply accepted that symptoms were unavoidable and preferred not to mask symptoms using medications as a method to track illness progression (Xu *et al.* 2022).

I knew that Panadol was not a strong pain medication and I did not think it had effects. (Xu *et al.* 2022)

Patients feared that taking analgesic medications would lead to addiction or feared tolerance and dependence. Despite receiving a poor prognosis, the potential for addiction was still an expressed concern for patients who were prescribed opioids (Adam *et al.* 2015; Fine 2007; Rafii *et al.* 2021; Sand *et al.* 2009; Wright *et al.* 2019; Xu *et al.* 2022).

I am afraid to take all these tablets. Will I become addicted? (Sand *et al.* 2009)

I am afraid of becoming addicted to medicines. I have seen my sister and her battery of tablets for her chronic illness, which she eats greedily. I am not keen on tablets. (Sand *et al.* 2009)

What is my maximum tolerance of morphine? Will I need more and more at the end and still it will not ease the pain? Maybe I will die due to the morphine and not due to the cancer. (Sand *et al.* 2009)

Side effects was a frequently reported concern that made patients hesitant to use medications (Adam *et al.* 2015; Beaussant *et al.* 2015; Cervantes *et al.* 2017; Huijjer and van Leeuwen 2000; Lo and Jonsen 1980; Moran *et al.* 2019; Rafii *et al.* 2021; Sand *et al.* 2009; Wright *et al.* 2019; Xu *et al.* 2022). Some patients believed that all medications were “toxins” that would accumulate and do “damage to the body” and that the disadvantages outweighed the benefits (Beaussant *et al.* 2015; Huijjer and van Leeuwen 2000; Sand *et al.* 2009; Xu *et al.* 2022). In fact, 1 patient perceived paracetamol did more harm than good (Sand *et al.* 2009).

This stemmed from an awareness or previous experience of known side effects including constipation, sedation, dizziness, nausea, vomiting, respiratory depression, and cognitive impairment (Beaussant et al. 2015; Cervantes et al. 2017; Rafii et al. 2021; Wright et al. 2019). Some patients were deterred from medication adherence by psychological effects, mentioning fears of “losing control” or “sense of self,” or peculiar and unusual effects such as their “face [becoming] bigger,” which the patient associated with cortisone use, and could not tolerate (Sand et al. 2009) significant sweating, which led to the avoidance of paracetamol by another patient (Sand et al. 2009).

I got frustrated with how I was feeling and I stopped taking all of the opioids. (Wright et al. 2019)

I don't feel well. I cannot sleep. But I am not sure whether I can use these tablets any longer because they make me so passive. I sit in a chair all day and night. Using the tablets makes me feel physically better, but they make me very passive. (Sand et al. 2009)

Passive attitude toward their illnesses

Some patients were fatalistic or believed that they deserved to suffer from their illnesses (Cervantes et al. 2017; Fine 2007). They considered their illnesses were a type of punishment for their parents or their own past behaviors (Cervantes et al. 2017).

I do believe that everything happens for a reason. I have no choice. This is it. This is as good as it gets. (Cervantes et al. 2017)

Other patients experienced feelings of hopelessness with the diagnosis of their life-limiting illnesses, which was demotivating for treatment adherence (Lo and Jonsen 1980; Rafii et al. 2021).

I know that I am not going to survive, so what is the point of suffering this much pain? I can't bear it anymore, what is the point of these drugs and injections? (Rafii et al. 2021)

I forget to take my medication ... I think the reason is that I don't want to admit that I am ill. The tablets remind me of my cancer. (Sand et al. 2009)

Inaccurate information about disease or medication

Patients preferred lifestyle modifications and practicing healthy lifestyles, which led to decreased interest in using medications (Xu et al. 2022), while some patients had false hope about their disease prognosis; therefore, they did not take prescribed medications (Rafii et al. 2021).

I always think that our bodies also have the ability of self-healing. We should take care of ourselves in all aspects of our diet and daily life. Paying attention to doing the exercises may be helpful. You may help yourself in pain management. (Xu et al. 2022)

Unclear direction and information also appeared to lead to medication hesitancy or noncompliance. More specifically, some patients did not take medication due to feeling confused and unsure about the indications of medication (Sand et al. 2009), while other questioned the need for adjuvant treatment in chemotherapy during periods of wellness (Huijjer and van Leeuwen 2000).

When I see all the different pills prescribed for me, I think, “Must I take all of them?” What does it do to me? (Sand et al. 2009)

Subjective norm

This theme was associated with the perceived opinions of others.

Perceived opinions of others

Patients were hesitant to use medication due to social stigma (Moran et al. 2019). In particular, male patients were noted to be less likely to mention to have experienced pain as they held beliefs that bearing pain was more socially acceptable and had negative perceptions about medications due to cultural reasons, to the extent where people with a Chinese cultural background were highlighted to be more likely to endure pain and avoid taking medications for relief than people with a Western cultural background (Xu et al. 2022).

(They) pay more attention to the quality of life; while our Chinese people are used to enduring the great hardship for more important tasks. The local people would think if I can get relief and why I have to suffer. (Xu et al. 2022)

Perceived behavioral control

The patient's perception of their own control of symptoms and illness was identified under this theme.

Perception of symptoms and illness as manageable

Strong perceived behavioral control was noted as patients described their ability to endure the symptoms and, as a result, actively avoided taking medications (Rafii et al. 2021; Xu et al. 2022). In extreme cases, patients believed their illness could be managed without medications entirely (Sand et al. 2009). However, some patients preferred to avoid opioids and tolerate the symptoms as much as they can until the late stages of illness (Xu et al. 2022).

I feel that if my health condition is so serious, I should take it and accept it. Because I heard from my friend that if the pain is unbearable, we must take it. Only pain medications, like morphine, may stop that kind of pain so that we may sleep well at night ... So, I would take it, because I do not want to have this kind of pain and I do not want to suffer. (Xu et al. 2022)

Behavioral intention

Medication avoidance or reservation for severe or unbearable symptoms only were the behavioral intentions reported by the majority of patients in the included studies (Rafii et al. 2021; Reid et al. 2008; Sand et al. 2009; Xu et al. 2022).

Quantitative findings

The quantitative data from the included studies showed some varying degrees of medication adherence (Bestvina et al. 2014; Davies et al. 2013; Subramanian et al. 2011; Thongkhamcharoen et al. 2012; Wright et al. 2019; Xu et al. 2022). Other than taking medications for symptom alleviation, patients also adopted non-pharmacological interventions (Davies et al. 2013; Xu et al. 2022). Medications associated with nonadherence included opioids (including morphine), non-opioids analgesics (Davies et al. 2013; Thongkhamcharoen et al. 2012), and chemotherapy medications (Bestvina et al. 2014; Subramanian et al. 2011). In a study that included cancer patients from European countries, only 53% of patients were reported to take their opioids for breakthrough pain (Davies et al. 2013). Concerns about side effects and addiction were reported as reasons for medication avoidance (Subramanian et al. 2011; Wright et al. 2019; Xu et al. 2022). Feelings of hopelessness due to poor illness prognosis were also reported (Xu et al. 2022). Other patients claimed that they were unclear about the direction and information of medication (Thongkhamcharoen et al. 2012).

Some patients also reported not taking their medications due to perceived negative opinions from others (Subramanian *et al.* 2011). A few patients mentioned that they could endure the symptoms (Davies *et al.* 2013; Thongkhamcharoen *et al.* 2012). Financial distress (Bestvina *et al.* 2014) and potential disruption to sleep schedule (Wright *et al.* 2019) were also identified as issues associated with nonadherence to medications.

Integrative analysis

The triangulation of both qualitative and quantitative data showed that medication hesitancy and avoidance were related to the negative attitude toward medications, passive attitude toward their illness, inaccurate information about disease or medication, perceived negative opinions from others, and perception of symptoms as manageable, which altogether corresponded with all the TPB constructs (attitude, subjective norms, and perceived behavioral control).

Discussion

This systematic review focuses on medication hesitancy or avoidance as the behavior of interest. The data regarding patient perspective toward medication hesitancy or avoidance were extracted and were deductively analyzed using the TPB constructs. Most studies reported patient concerns were related to medication side effects, and they made their decision based on self or others' experiences. This finding is similar to a previous study exploring older patients' perspectives on cancer treatment (Puts *et al.* 2015). Moreover, perceiving that medications had more risks than benefits and negative medication experiences were found to be associated with poor adherence (Marshall and Given 2018). Another systematic review identified that cancer treatment adherence correlated with multiple factors, such as patient-related factors, therapy-related factors, condition-related factors, health system factors, and socioeconomic factors (Puts *et al.* 2014).

Besides patient attitude, subjective norms, perceived behavioral control, and behavioral intention, there are also background factors that were not captured by the TPB framework, which would indirectly affect the intention and behavior of taking medications. In another systematic review, multiple factors were identified to influence adherence to cancer treatments, including patient-related factors, therapy-related factors, condition-related factors, health system factors, and socioeconomic factors (Puts *et al.* 2014). In the present review, some patients expressed preference for using complementary or natural medications rather than those that were prescribed by health-care professionals, which was in alignment with their cultural values. Other patient-related factors that have previously been reported include life values, demographic characteristics, personality traits, and intelligence (Ajzen 2020).

In terms of existential perspectives on life, patients were reported to be satisfied with their lives and ready for death (Huijter and van Leeuwen 2000). In fact, some patients were noted to express other priorities such as spending more quality time with their families and doing things that they enjoyed, while others preferred distractions from their disease management (Cervantes *et al.* 2017; Huijter and van Leeuwen 2000), and therefore, they preferred not taking medications. In addition, other barriers such as the cost of medications (Bestvina *et al.* 2014; Subramanian *et al.* 2011), skills or equipment for administering medications (Rafii *et al.* 2021), and adverse effects on sleep schedule (Wright *et al.* 2019) have been

previously reported to be associated with medication hesitancy (Ajzen 1991).

Previous studies have also suggested that gender, marital status, race, stage of disease, and performance status can be used to predict treatment refusal in older patients with cancer (Dias *et al.* 2021; Puts *et al.* 2014). Although some patients simply felt wearied of trying medications based on their past experience (Beaussant *et al.* 2015), the importance of social learning in palliative care also emerged in this review as patients associated the experiences of other people with their own hesitation to take medications (Adam *et al.* 2015; Cervantes *et al.* 2017; Huijter and van Leeuwen 2000; Rafii *et al.* 2021; Reid *et al.* 2008; Sand *et al.* 2009). This included others' experiences of developing drug addiction (Adam *et al.* 2015; Rafii *et al.* 2021; Sand *et al.* 2009) or witnessing other's experiences of deterioration caused by opioids (Reid *et al.* 2008). The significance of social learning was also highlighted by patients as they applied others' experiences as part of their own decision-making process (Okuboyejo *et al.* 2018). Medication avoidance was further compounded by inaccurate information or assumptions held about their disease prognosis and/or medication-related issues (such as complex dosing regimen or adverse effects). This has been associated with the lack of or poor communication between patients and health-care professionals and potentially remedied by training in provider-patient communication skills as well as delivering interventions that are tailored to the individuals' reasons for nonadherence and facilitates shared decision-making (Butow and Sharpe 2013; DiMatteo *et al.* 1994; Zolnieriek and Dimatteo 2009).

According to our findings, patients still wished to use medications judiciously and did not want to develop tolerance or dependence even during the end-of-life phase. Some patients bore false hope of recovery to the detriment of their health-related quality of life, which may be remedied by improving communication between patients and health-care professionals and addressing ethical issues surrounding the withholding of information about survival (Back 2020). The noncompliant behavior that is associated with acceptance of death by patients may signal that care toward the end of life may be over-medicalized, which is a finding that has previously been supported by a review that explored the prescribing of potentially inappropriate medications in palliative cancer patients (Lindsay *et al.* 2014).

The strength of this review includes triangulation data from themes that have emerged from qualitative studies with quantitative studies, which enhanced the validity of the results. Our review also involved studies from different countries that capture a variety of patient perspectives. However, the majority of included studies involved people diagnosed with cancer; therefore, our findings may not be broadly generalizable to other people with different life-limiting illnesses. Future research could include the investigation of other factors that are not captured by the TPB framework beyond attitude, social norms, and perceived behavioral control.

Conclusion

This review highlighted that patients in the palliative care setting will intentionally avoid medications for a variety of reasons related to their attitudes toward the medication and illness, which reinforce the importance of discussing medication regimens, the trajectory of illness, and shared decision-making. Furthermore, some patient decisions appear to be made based on "false hope" despite the absence of a favorable prognosis; hence, clear and accurate information should be provided to the patient wherever possible to facilitate informed decision-making.

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Appendix

Appendix A. Search strategy in electronic databases

CINAHL

1. “drug*” (1021627)
2. “medication*” (183866)
3. “opioid*” (48393)
4. “morphine” (12637)
5. “cannabis” (16299)
6. “CBD” (1894)
7. “THC” (1359)
8. “benzodiazepine*” (9835)
9. “midazolam” (4202)
10. “clonazepam” (777)
11. “diazepam” (2272)
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (1128359)
13. “refus*” (19335)
14. “hesitan*” (2277)
15. “barrier*” (109230)
16. “non-complian*” (2344)
17. “noncomplian*” (3189)
18. “non-adheren*” (3591)
19. “nonadheren*” (3906)
20. 13 or 14 or 15 or 16 or 17 or 18 or 19 (140706)
21. 12 and 20 (26728)
22. “palliat*” (59434)
23. Hospice* OR (MH “hospice care”) (34457)
24. “end of life care” (48023)

25. (MH “terminal care”) (19707)
26. 22 or 23 or 24 or 25 (83134)
27. “patient autonomy” (7901)
28. “patient preference*” (5831)
29. “patient decision making” (8051)
30. “patient perspective*” (2843)
31. 27 or 28 or 29 or 30 (23,398)
32. 21 and 26 and 31 (18)

Embase

1. (cannabis or CBD or THC or benzodiazepine* or midazolam or clonazepam or diazepam or opioid* or morphine or medication* or drug*).mp. (12546154)
2. (refus* or hesitan* or barrier* or non-complian* or noncomplian* or non-adheren* or nonadheren*).mp. (616871)
3. palliat*.mp. (185163)
4. hospice/ or hospice*.mp. (30624)
5. “end of life care”.mp. or Terminal care/ (43955)
6. (patient and (autonomy or preference* or decision making or perspective*)).mp. (385360)
7. 1 and 2 (237382)
8. 3 or 4 or 5 (222460)
9. 6 and 7 and 8 (406)

MEDLINE

1. (cannabis or CBD or THC or benzodiazepine* or midazolam or clonazepam or diazepam or opioid* or morphine or medication* or drug*).mp. (6620256)
2. (refus* or hesitan* or barrier* or non-complian* or noncomplian* or non-adheren* or nonadheren*).mp. (468561)
3. palliat*.mp. (107971)
4. hospice/ or hospice*.mp. (19563)
5. “end of life care”.mp. or Terminal care/ (35915)
6. (patient and (autonomy or preference* or decision making or perspective*)).mp. (188351)
7. 1 and 2 (120273)
8. 3 or 4 or 5 (137882)
9. 6 and 7 and 8 (104)

PsycINFO

1. (cannabis or CBD or THC or benzodiazepine* or midazolam or clonazepam or diazepam or opioid* or morphine or medication* or drug*).mp. (484408)
2. (refus* or hesitan* or barrier* or non-complian* or noncomplian* or non-adheren* or nonadheren*).mp. (113686)
3. palliat*.mp. (18323)
4. hospice/ or hospice*.mp. (6198)
5. “end of life care”.mp. or Terminal care/ (5373)
6. (patient and (autonomy or preference* or decision making or perspective*)).mp. (47955)
7. 1 and 2 (17878)
8. 3 or 4 or 5 (21630)
9. 6 and 7 and 8 (26)

Appendix B

Table B1. Critical appraisal tool for qualitative studies using Mixed Method Appraisal Tool

Author (year)	Are there clear research questions?	Do the collected data allow to address the research questions?	Is the qualitative approach appropriate to answer the research question?	Are the qualitative data collection methods adequate to address the research question?	Are the findings adequately derived from the data?	Is the interpretation of results sufficiently substantiated by data?	Is there coherence between qualitative data sources, collection, analysis, and interpretation?
Rafii et al. (2021)	Y	Y	Y	Y	Y	Y	Y
Fine (2007)	Y	Y	Y	N	Y	Y	Y
Lo and Jonsen (1980)	Y	Y	Y	N	Y	Y	Y
Persaud-Sharma et al. (2018)	Y	Y	Y	N	Y	Y	Y
Beaussant et al. (2015)	Y	Y	Y	Y	Y	Y	Y
Sand et al. (2009)	Y	Y	Y	Y	Y	Y	Y
Reid et al. (2008)	Y	Y	Y	Y	Y	Y	Y
Moran et al. (2019)	Y	Y	Y	UKN	UKN	UKN	UKN
Huijjer and van Leeuwen (2000)	Y	Y	Y	N	N	N	N
Cervantes et al. (2017)	Y	Y	Y	Y	Y	Y	Y
Adam et al. (2015)	Y	Y	Y	Y	Y	Y	Y

Note: Y, yes; N, no; and UKN, unknown.

Table B2. Critical appraisal tool for quantitative descriptive studies using Mixed Method Appraisal Tool

Author (year)	Are there clear research questions?	Do the collected data allow to address the research questions?	Is the sampling strategy relevant to address the research question?	Is the sample representative of the target population?	Are the measurements appropriate?	Is the risk of nonresponse bias low?	Is the statistical analysis appropriate to answer the research question?
Davies et al. (2013)	Y	Y	Y	Y	N	UKN	Y
Thongkhamcharoen et al. (2012)	Y	Y	N	N	N	N	N
Bestvina et al. (2014)	Y	Y	Y	N	N	Y	Y
Subramanian et al. (2011)	Y	Y	Y	UKN	UKN	UKN	UKN

Note: Y, yes; N, no; and UKN, unknown.

Table B3. Critical appraisal tool for mixed methods studies using Mixed Method Appraisal Tool

Author (year)	Are there clear research questions?	Do the collected data allow to address the research questions?	Is there an adequate rationale for using a mixed methods design to address the research question?	Are the different components of the study effectively integrated to answer the research question?	Are the outputs of the integration of qualitative and quantitative components adequately interpreted?	Are divergences and inconsistencies between quantitative and qualitative results adequately addressed?	Do the different components of the study adhere to the quality criteria of each tradition of the methods involved?
Xu et al. (2022)	Y	Y	N	Y	Y	Y	Y
Wright et al. (2019)	Y	Y	Y	Y	Y	N	N

Note: Y, yes; N, no; and UKN, unknown.