Review Article

Cannabinoids as an Alternative Option for Conventional Analgesics in Cancer Pain Management: A Pharmacogenomics Perspective

Anmi Jose, Levin Thomas, Gayathri Baburaj, Murali Munisamy, Mahadev Rao

Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal, Karnataka, India

Abstract

The global cancer burden is significantly increasing at an alarming rate affecting patients, relatives, communities, and health-care system. Cancer patients require adequate pain relief and palliative care throughout the life course, especially in terminal illness. Although opioid treatment is successful in majority of patients, around 40% do not achieve enough analgesia or are prone to serious side effects and toxicity. The treatment of medical conditions with cannabis and cannabinoid compounds is constantly expanding. This review organizes the current knowledge in the context of SNPs associated with opioids and nonopioids and its clinical consequences in pain management and pharmacogenetic targets of cannabinoids, for use in clinical practice.

Keywords: Cancer pain, cannabinoids, nonopioids, opioids, pharmacogenomics

Introduction

Cancer malignancies are among the primary reasons of morbidity and mortality globally, with new cases reaching 18.1 million and fatality rate to 9.6 million in 2018. The global cancer burden is significantly increasing at an alarming rate affecting patients, relatives, communities, and health-care system.[1] Cancer-related pain is the most frequent and unsolved problem faced by cancer patients. Pain can be due to the cancer itself, where a tumor compressing and destroying nearby tissues or from diagnostic or therapeutic procedures or by immune responses. 55% of patients receiving chemotherapy and 66% of patients in terminally ill stage experience pain, of which one-third of all patients experience moderate-to-severe pain intensity.[2] Frequent reassessment of pain is necessary in cancer patients as pain intensity varies in accordance with disease condition, cancer treatments, and psychosocial status. Suboptimal pain management negatively impacts patients to carry out activities of daily living and reduces the quality of life, thereby causing mental distress to patients.[3] Hence, cancer patients require adequate pain relief and palliative care throughout the life course, especially in terminal illness.

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Pain Management in Cancer Patients

Multidimensional approach interventions in pharmacological and nonpharmacological aspects are essential to treat pain in patients with life-limiting health conditions.[4] In 1986 and 1997, the World Health Organization (WHO) proposed a pain relief ladder approach for cancer patients.[5,6] According to pain severity in patients, ladder model proposes treatment algorithm starting from nonopioids such as nonsteroidal anti-inflammatory drugs (NSAIDs) to weak opioids and ending in potent opioids. In 2018, the WHO has established guidelines for "pharmacological and radio therapeutic management of cancer pain in adults and adolescents" to offer evidence-based guidance in initiating and managing cancer pain.[7] Generally used medications for

Address for correspondence: Dr. Mahadev Rao, Professor and Head, Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal Academy of Higher Education, Manipal - 576 104, Karnataka, India.
E-mail: mahadev.rao@manipal.edu

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treating pain comprise opioids such as codeine, morphine, hydromorphone, oxycodone, fentanyl, and methadone and nonopioids including paracetamol and NSAIDs with adjuvant therapies such as antidepressant and anticonvulsant agents.

NSAIDs, paracetamol, morphine, and other opioids are considered the mainstays for pain management. As per the WHO consideration, patients should have access to a wide range of opioid analgesics, because there are known clinical differences in patient's response to specific analgesics.[7] Although opioid treatment is successful in majority of patients, around 40% do not achieve enough analgesia or are prone to serious side effects and toxicity. Even if opioid rotation is an option, it is highly time consumable which is challenging to hospice patients. As stated by Van Den Beuken-Van Everdingen *et al*., even though universal opioid consumption rate doubled in 2018 in comparison with 2012, one-third of the patients received no pain medication proportional to their rates of pain intensity.[2] This indicates that dose, dosage, or drug that effectively controls pain for one patient will not be the same for others. Among all other reasons of opioid failures, pharmacogenetic interindividual variability significantly affects the analgesic response and toxicity of the drugs.[8]

Genetic variability due to polymorphism in enzyme metabolizers and transporter genes chiefly accounts for drug sensitivity, response, and predisposition to side effects. One such example is the variation in response to codeine among highly polymorphic cytochrome P450 2D6 variants. Based on the genotype with that of phenotype, patients are categorized as poor (PMs), intermediate, extensive, or ultrarapid metabolizers (UMs). Robust evidence of unsatisfactory pain control and serious side effects of morphine in patients taking codeine urged the Clinical Pharmacogenetics Implementation Consortium to make recommendation to avoid codeine in PMs and UMs.[9] Similarly, various other genes in the family of cytochrome P450, cyclooxygenases, opioid receptors, phospholipase, HLA DQB1 have noteworthy role in affecting analgesic response of conventionally used pain medications.[10-22] SNP's associated with opioids and nonopioids and their respective clinical consequences are depicted in Table 1. Because pain relief is considered as a basic human right,[23,24] poor success rate of traditional analgesics and adjuvant therapies throws light on the urgent necessity of alternative therapies, considering pharmacogenetic interindividuality among patients.

Cannabinoids

Cannabis sativa and *Cannabis indica* plants of family *Cannabaceae* contain approximately 100 cannabinoids, in which the active ingredient Delta-9-tetrahydrocannabinol (THC) is effective in the psychoactive properties. Cannabidiol (CBD) is another chief constituent that lacks the psychotropic effects, but carries antiemetics, antiepileptic, as well as other effects.[25,26] Cannabinoid receptors, to date, CB1 and CB2, have been recognized where CB1 is located in the brain region and CB2 in the immune cells.[27]

Cannabinoids in cancer pain management

Cannabinoids produce analgesic effect by activating CB1 receptors present in CNS and nerve terminals. Furthermore, peripheral CB2 receptors facilitate analgesia, by blocking the production of pain and inflammatory mediators, which is important in managing cancer pain.[28] A selective review study by Blake *et al*. included clinical studies performed between 1975 and 2014 that evaluated the effectiveness of THC and CBD and reported that cannabinoids with decreased cancer pain were significantly associated in four out of five trials.[29] A double-blind randomized clinical trial (RCT) measuring the impact of nabiximols, a novel cannabis extract, showed substantial improvements in pain in patients with advanced cancer with opioid refractory pain.[30] In other RCT of 177 cancer patients who have unsatisfactory clinical response to opioids, the authors compared the effectiveness of THC: CBD extract and THC extract with placebo. THC: CBD extract presented statistically significant modification in baseline score in numerical pain rating scale compared with placebo.[31] These evidences supported the use of cannabinoids and their derivatives to use as an alternative or substitute in patients who are unable to take opioids and NSAIDs in cancer pain management.

Palliative Effects of Cannabinoids

Inhibition of nausea and vomiting

Nausea and vomiting are one of the devastating after effects of cancer chemotherapy. Despite the routinely administering antiemetics, the incidence of chemotherapy-induced nausea and vomiting (CINV) is relatively high.[32] Antiemetic property of cannabinoids is well established in animal models. Suggested mechanisms of antiemesis are through cannabinoid-mediated acetylcholine blocking and inhibiting digestive tract motility or through acting on CB1 receptors present in dorsal–vagal complex of the brain stem. Dronabinol and nabilone are already approved to treat chemotherapy-associated nausea and emesis. Moreover, there is evidence that cannabinoids are efficient in reducing nausea and vomiting during the delayed chemotherapy stage that is poorly regulated by the 5-HT receptor antagonist.[33,34]

Appetite stimulation

Anorexia is one of the most disturbing symptoms of patients with advanced cancer that leads to major weight loss. Numerous studies revealed that THC and other cannabinoids at low-to-moderate doses have stimulatory effects on appetite and increase food consumption in animals. Dronabinol has already approved for AIDS wasting syndrome.[35]

Psychological effects

In vivo studies indicate that cannabinoids exert antianxiety effects at low doses. THC and nabilone provide positive psychological effects, reduction in anxiety and depression, and enhanced sleep. These potentially positive effects can impact the medical outcomes of patients with terminally ill cancer.[36]

Antineoplastic effects

In vitro studies showed that THC, synthetic cannabinoid agonists, naturally occurring cannabinoids (CBD and cannabinol), and

Table 1: SNPs associated with nonopioids and opioids and its clinical consequences in pain management

Drug	Genotype/SNP	Clinical consequences	Reference
Metabolizing enzyme: CYP2D6			
Codeine	Poor metabolizer CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6, CYP2D6*7, CYP2D6*8, CYP2D6*11	Lack of efficacy	[9,10]
	Ultrarapid metabolizer CYP2D6*1xn CYP2D6*2xn	Increased toxicity	
Tramadol	Poor metabolizer CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6	Reduced analgesia and increased risk of side effects	[11]
	Ultrarapid metabolizer CYP2D6*1xn CYP2D6*2xn	Increased toxicity	
Oxycodone	Poor metabolizer CYP2D6*3, CYP2D6*4, CYP2D6*5, CYP2D6*6	Decreased response and lack of efficacy	[12]
	Ultrarapid metabolizer CYP2D6*1xn CYP2D6*2xn	Increased metabolism and high risk of toxicity/side effects	
Methadone	CYP2D6*10, CYP2D6*87, CYP2D6*89, CYP2D6*90, CYP2D6*93, CYP2D6*95, CYP2D6*97, CYP2D6*98	Decreased analgesia and/or increased toxicity	[13]
Metabolizing Enzyme: CYP2C9			
NSAIDs, celecoxib, diclofenac	CYP2C9*2 CYP2C9*3	Increased risk of GI bleeding	[14]
Cyclooxygenases 1: PTGS1			
NSAIDs	PTGS1 (4331 A>T) PTGS1 4331T variant allele	Increased risk of acute coronary syndrome	[15]
Cyclooxygenases 2: PTGS2			
Rofecoxib	PGTS2 (−765G>C) PGTS2-765C variant allele	Poorer pain relief	[16]
Opioid receptor μ: OPRM1			
Morphine	OPRM1 118A>G Mutant 118G allele	Needs larger doses of morphine for pain control	[17]
Opioid receptor kappa: OPRK1			
Morphine	OPRK1 (36 G>T)	Increased dose escalation of morphine is required in cancer related pain	[18]
Opioid receptor delta: OPRD1			
Opioids	OPRD1 921T>C	Increased risk of opioid dependence in variant allele of OPRD1	[19,20]
Others: Phospholipase C gamma 1 (plus strand)			
Acetaminophen and diclofenac, aspirin, propionic acid derivatives or pyrazolones	PLCG1 Ser 279 Gly	Increased risk of angioedema	[21]
HLA-DQB1			
Acetaminophen	HLA-DQB1*02:02	Increased risk of cutaneous adverse reactions	[22]

SNP: Single-nucleotide polymorphism, CYP2D6: Cytochrome P450 2D6, CYP2C9: Cytochrome P450 2C9, NSAIDs: Nonsteroidal anti-inflammatory drugs, PTGS: Prostaglandin-endoperoxide synthase, HLA-DQB1: Major histocompatibility complex, class II, DQ beta 1, GI: Gastrointestinal

endocannabinoids have anticancer effects in case of lung cancer, gliomas, skin cancer, lymphomas, breast cancer, prostate cancer, uterine cancer, neuroblastoma, and thyroid epithelioma. *In vivo* studies also showed that natural and synthetic cannabinoids exhibit anticancer effects in xenografts of lung cancer, thyroid, skin cancer, epitheliomas, lymphomas, and gliomas.[37,38]

Cannabinoid-based pharmaceuticals

Nonimportance in medical field and risk of misuse restricted the use of cannabis and its derivatives until recently. Rapidly changing policy leads cannabis to be given for medicinal purpose in many countries. This paves the way for novel treatment openings for patients although it should be weighed up against risk factors.

Inhalation of smoke is the common route of administration of cannabinoids as the active components are absorbed by lung alveoli and delivered to CNS.[39] However, due to problems caused due to improper delivery and variable absorption of drug, other routes of administration are considered by pharmaceutical companies.[26] Cannabinoid derivatives of THC, CBD, or its combinations are used for therapeutic purpose. An oral spray containing THC and CBD (1:1 ratio) nabiximols (Sativex®) is approved for spasticity therapy in multiple sclerosis in many European nations.[40] Epidiolex®, an oral CBD solution, is currently approved in the USA for the treatment of Lennox–Gastaut syndrome and Dravet syndrome.[41]

Synthetically produced products such as dronabinol and nabilone typically mimic THC. Nabilone has more related structure to THC and more potent when compared to dronabinol. They are approved for the weight loss treatment in HIV patients and patients with CINV, who are nonresponders to traditional antiemetics.[42]

Pharmacogenomics of Cannabinoids

Amidst all the benefits of cannabinoids, the patient's response to the drug depends on the individual's genetic background. Cytochrome P-450 (CYP-450) enzymes are involved in the primary metabolism of several exogenous cannabinoids: THC (CYPs 2C9, 3A4); cannabidiol (CBD; CYPs 2C19, 3A4); and cannabinol (CBN; CYPs 2C9, 3A4). Clinical pharmacogenetic data supported cytochrome P450 2C9 as a major contributor to THC metabolism. UDP-glucuronosyltransferases was recognized as capable of catalyzing the cannabinoid metabolism of both primary (CBD and CBN) and secondary (THC) cannabinoid metabolism.[43] The glucuronidation rates of cannabinol was observed at high levels by UGT1A10 and to a lesser extent by UGT1A7, UGT1A9, and UGT2B7 enzymes.[44] Interestingly, majority of the SNPs associated with the cannabinoids metabolism are distinct from the SNPs associated with the conventional analgesics related to pain management.

Conclusion

Despite significant improvements in recent years in cancer pain assessment and management, still significant number of patients with poorly regulated pain are present. A complete, holistic treatment strategy which consists of pharmacological and pharmacogenetic-based precision therapy would be utmost beneficial. The medicinal use of cannabis for the therapeutic management of multiple diseases have been documented in several traditional ayurvedic literatures over different periods of Indian history.

Further pharmacogenomic research examining the heterogeneity of SNPs associated with benefits and failure of conventional analgesics would aid in deriving appropriate directions for potential precision therapy of cannabinoids for pain management in cancer patients.

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Conflicts of interest

There are no conflicts of interest.

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