Aleksander Turczynowicz[1], Karolina Niedźwiecka[2], Dominik Panasiuk[1], Weronika Pużyńska[3], Kacper Luchowski[3], Julia Kondracka[4], Piotr Jakubów[1, 2]

[1]Department of Anaesthesiology and Intensive Care for Children and Adolescents with Postoperative Care and Pain Management Unit, Medical University of Białystok, Białystok, Poland
[2]Clinical Department of Cardiac Surgery, Medical University of Białystok, Białystok, Poland
[3]Medical University of Białystok, Białystok, Poland
[4]Medical University of Gdańsk, Gdańsk, Poland

Single nucleotide polymorphisms as predictors of treatment efficacy and adverse effects of morphine in palliative medicine: a literature review

Abstract

Introduction: Pain has a significant negative impact on the quality of life of cancer patients and implies numerous clinical consequences. Moderate to severe pain is common in patients receiving palliative care. A major issue is the individual variability resulting in different degrees of response to the analgesic effects of opioids, including morphine, and to the occurrence of their adverse effects. According to one of the theories of pharmacogenomics, single nucleotide polymorphisms (SNPs) are associated with opioid metabolism.

Material and methods: A literature review of the PubMed database identified 18 scientific articles concerning SNPs that affect the analgesic effects and adverse effects of morphine or other opioids, per morphine equivalent, from which additional 22 scientific articles were retrieved.

Results: The review identified SNPs in the genes *OPRM1* A118G, *COMT* rs4680, *ABCB1* C3435T, IL-6, IL-8, TNF-α, *TAOK3*, *HTR3B*, *UGT1A1*/*UGT1A8* and *OPRM1* Arg181Cys, which were found to affect both the occurrence of potential adverse effects and the different demand in palliative care patients for a dose of morphine that will effectively relieve pain. SNPs were found to significantly affect morphine metabolism; the determination of this effect is individual-based. Most studies were conducted in small groups of individuals from ethnically diverse populations, which, if mutations are present, may significantly affect the efficacy of opioid-related SNP assays and the response of patients to the analgesic treatment administered.

Conclusions: Findings raise the prospect of the use of SNPs in clinical practice as part of personalised medicine in the future.

Palliat Med Pract 2023; 17, 1: 29–38

Key words: pain, morphine, cancer, palliative care, gene polymorphisms

Address for correspondence:
Aleksander Turczynowicz
Department of Anaesthesiology and Intensive Care for Children and Adolescents with Postoperative Care and Pain Management Unit, Medical University of Białystok, Jerzego Waszyngtona 17, 15–274 Białystok, Poland
e-mail: aleksander.turczynowicz@sd.umb.edu.pl

Palliative Medicine in Practice 2023; 17, 1, 29–38

DOI: 10.5603/PMPI.a2022.0027

Received: 9.09.2022 Accepted: 3.10.2022 Early publication date: 8.11.2022

Introduction

Pain in cancer patients significantly affects patients' quality of life (QoL) and implies numerous clinical consequences. Pain can be caused by cancer as well as related treatment. Moderate to severe pain occurs in 50–80% of cancer patients [1, 2]. The primary tools for pain management in the palliative care setting are opioid analgesics of the second and third step of the WHO's pain relief ladder (PRL), including morphine that is a primary drug but has numerous adverse effects [3]. The lowest possible doses are used for effective analgesia, with as few adverse effects as possible. However, the problem is individual variability among patients, which causes different degrees of response to the analgesic effect of morphine and to the occurrence of potential adverse effects [4]. Opioid metabolism-related single nucleotide polymorphisms (SNPs) are one of the theories to explain this variability [5]. SNPs are the most common type of human genetic variation. This variation involves changing a single nucleotide (adenine, thymine, guanine or cytosine) to another, for example, in the event of the occurrence of a SNP in the *OPRM1* gene, the adenine nucleotide is changed to guanine at position 118 (A118 > G) [6]. Since the discovery of the effect of SNPs on the functionality of various receptor proteins or enzymes, it has been considered how these changes affect the clinical response during the use of opioids for pain management [7]. The search for the ideal "marker" to accurately assess a patient's response to analgesic treatment is still underway. Numerous polymorphisms that may affect the clinical effects of morphine were found in genomic studies [4]. This article discusses the polymorphisms whose effects were described among palliative care patients to answer the question of whether SNPs in genes related to opioid metabolism, opioid receptors or opioid transporters can be considered a marker to personalise analgesic therapy for each patient in order to provide the most effective analgesia and safety in terms of potential adverse effects.

Material and methods

The literature review was conducted in the PubMed database using a MeSH (Medical Subject Headings) search and a text search. The search phrases included "snp", "single nucleotide polymorphism", "genetic polymorphism", "oprm1", "abcb1", "comt", "morphine", "palliative", "palliative care", "palliative medicine" using the conjunction "and" to identify original articles, review articles and meta-analyses that were published up to August 2022 and contained methods to study the effects of selected SNPs on the clinical effect and adverse effects of morphine or other opioids, the doses of which in this article were converted to a morphine equivalent daily dose (MEDD) [7]. Based on the search criteria, 50 articles were identified, of which 32 were rejected due to the use of drugs other than morphine or the use of other opioids without conversion to MEDD, lack of investigation of the effect of polymorphism on adverse effects of morphine and lack of relevance to pharmacological pain management. Additional 22 articles relevant to this review were extracted from references of the remaining 18 articles.

The effect of single gene polymorphisms on demand for morphine in palliative care patients

OPRM1 118A>G

This gene encodes the mu-opioid receptor (MOR). MORs are one of three classes of opioid receptors. The other two classes are delta and kappa receptors. MORs are involved in the transmission and modulation of pain stimuli in the central and peripheral nervous system. Morphine acts mainly on MOR, causing analgesia, miosis, bradycardia and hypothermia, as well as addiction. MOR is the main target of endogenous opioid peptides, such as beta-endorphins, enkephalins, and opioid analgesics. The 118A>G allele is associated with alcohol/opioid dependence and with differences in terms of pain sensitivity but findings to date are inconsistent [8].

In an Italian study conducted among 137 cancer patients treated with morphine for pain, the presence of the A118>G polymorphism was found to significantly reduce pain intensity on the Numeric (Pain) Rating Scale (NRS). It was revealed that A/A homozygous patients experienced less pain intensity compared to G/G homozygous patients during pain management with morphine (ΔNRS = 3.73, SD = ± 1.72 *vs.* ΔNRS = 0.3, SD = ± 1.77, $p < 0.00001$) [9].

In a study conducted among 207 cancer patients in Norway, Reyes-Gibby et al. found that patients who were homozygous or heterozygous carriers of the 118G allele had to receive higher daily doses of morphine to achieve effective analgesia (225 mg in the GG homozygous group *vs.* 97 mg in the group with the wild-type AA allele). Moreover, no factors were found to influence the results [10, 11]. Differences in gene alleles vary according to the environment, including geographic location and race of a patient. In studies conducted in the Asian population, differences in the frequency of mutant allele, i.e. 118G in either homo- or heterozygous form, were observed in patients with a frequency of up to 38.39% among

112 Chinese Han cancer patients, who represent 19% of the world population. In a study by Di Gong et al. [12], similarly to patients in Norway, there was a higher daily demand for opioids, including morphine, in patients with the AG/GG genotype, compared to those with the AA genotype (97.33 mg/152.34 mg *vs.* 72.48 mg, $p < 0.0004$). It was also found that cancer patients who are carriers of the 118G allele had a greater demand for morphine and other opioids for pain management, compared to carriers of the 118A allele, i.e. wild-type allele (120.36 mg ± 79.12 mg/day *vs.* 81,48 ± 66.52 mg/day, $p < 0,001$). Based on this, it was concluded that A118G SNP in the OPRM1 gene may be one of the important factors for individual variability in demand for opioids in the cancer population in China [12].

Similar results were found among patients in the Middle East. Hajj et al. [13] conducted a study among palliative care patients, which assessed not only the dependence of the dose of morphine on the presence of SNPs, among others in the *OPRM1* gene, but also the subjectively assessed QoL by patients. The potential effect of the *OPRM1* SNP on QoL will be described later in this publication. According to a study conducted among 89 palliative care patients in the Middle East, the presence of one 118G allele in the gene for MOR results in a greater demand for morphine in patients with the AA genotype (50 mg/24 h *vs.* 30 mg/24 h, $p < 0.001$). There was a lower demand for morphine with age and an increase in this demand with duration of analgesic treatment; however, the presence of SNP in the *OPRM1* gene was an independent factor in the increased demand for morphine for effective analgesia [13].

COMT rs4680 Val158Met

Catechol-O-methyltransferase (COMT) is an enzyme that metabolises catecholamines and has numerous additional functions that also include involvement in the pathogenesis of many neuropsychiatric diseases, migraine and Parkinson's disease, and, most importantly, include participation in the regulation of pain sensation. A polymorphism that causes substitution of valine by methionine at position 158 (Val158Met) is one of the most extensively studied SNPs in the gene for *COMT*. This polymorphism results in reduced thermostability of the enzyme and a subsequent three- to fourfold decrease in activity. Patients with the Met/Met homozygous genotype reveal the strongest response to experimental pain, i.e. thermal pain or pain induced by electrical stimulation [6, 11].

Most of the available literature on the Val158Met SNP in the *COMT* gene relates to patients' subjectively assessed sensitivity to pain stimuli. Some studies assessed the effect of the presence of polymorphisms in the *COMT* gene (SNP rs4680) on the demand for morphine or other opioids converted to a morphine-equivalent dose (MED). In one of the first studies, a population of 207 cancer patients in Norway was assessed. There was a significant relationship between the presence of the Val/Val genotype and the daily dose of morphine. Patients with the Val/Val genotype received 155 ± 160 mg/24 h on average, patients with one copy of the allele and the Val/Met genotype received 117 ± 100 mg/24 h on average, and Met/Met patients 95 ± 99 mg/24 h on average ($p = 0.025$). Also, in a direct comparison of mean doses in the Val/Val genotype group, these patients were found to have significantly higher doses of morphine compared to the Met/Met genotype group ($p = 0.03$). That study also revealed statistically non-significant higher concentrations of morphine metabolites: morphine-3-glucuronide (M-3-G) and morphine-6-glucuronide (M-6-G). According to the authors, this trend is reflected by the activity of the Val158Met SNP, where the group with the Val/Val genotype, in addition to having the highest demand for morphine, also presents the highest plasma concentrations of morphine and metabolites. Furthermore, no factors were found to clearly affect the results, hence the conclusion that SNPs in *COMT* may be another source of individual variability in the clinical effects of morphine and other opioids [11, 14].

In a genomic study conducted in the same cancer group of 207 patients, genotyping detected 11 SNPs in the *COMT* gene which showed statistically significant correlations, both individually and in haplotypes. In a genomic study conducted in the same cancer group of 207 patients, genotyping detected 11 SNPs in the *COMT* gene. These SNPs showed statistically significant correlations, both individually and in haplotypes. The other SNPs of the *COMT* gene, despite their significant effects on demand for morphine, were a topic beyond the scope of this article concerning the most common SNPs, rs4680 Val158Met, and are thus not discussed further [15].

Although the results negate the independent effect of the previously described gene for the mu receptor, the study by Matic et al. [16] found that SNPs in the *COMT* gene have an effect on the relative increase in morphine dosage during the first three days of treatment. Significant effects were found for both carriers of single SNP rs4680 with the A/G and G/G genotypes ($p < 0.012$) and for the broader spectrum of SNPs that make up the LPS (low pain sensitivity), APS (average pain sensitivity) and HPS (high pain sensitivity) haplotypes; however, no results were significant for

ΔMED ($p < 0.06$). Furthermore, despite the lack of a significant effect of SNPs in the *OPRM1* gene on doses of morphine, there is a strong correlation between the combination of SNPs for *OPRM1* and *COMT* — patients with A118G *OPRM1* SNP and Val158Met SNP in the *COMT* gene had a greater demand for morphine dose modification during the first three days of therapy ($p < 0.001$) [16].

In response to ample evidence suggesting a role for the Val158Met SNP in shaping the response to morphine treatment in cancer patients, a study was conducted in the Japanese population. Fifty patients with histopathologically confirmed malignancies and associated pain, in addition to previously untreated with opioid drugs, were included in an observational study that assessed the doses of morphine administered at which satisfactory analgesia was achieved on days 1 and 8 of therapy. There was a relationship between the presence of SNPs, G/G genotype in *COMT* and a significantly higher dose compared to patients with A/G and A/A genotypes (35.2 ± 11.5 mg *vs.* 29.5 ± 2.3 mg *vs.* 25.0 ± 7.1 mg, $p = 0.013$) on the first day of treatment [17].

The possibility of using SNPs in the *COMT* gene as a marker of response to analgesic treatment with morphine was confirmed by Matsuoka et al. [18], who conducted a study among cancer patients with pain. That study explored the relationship between changes in the expression of beta-arestin 1, *COMT* SNPs and *OPRM1* in the Japanese population. Patients who are carriers of the A/A genotype required lower doses of morphine and had lower serum morphine concentrations compared to patients with the A/G genotype ($p = 0.008$) and G/G genotype ($p = 0.03$), and the *OPRM1* SNP revealed no significant relationship in that study [18].

The aspect of how polymorphisms affect pain sensation and morphine metabolism in children was poorly understood. Lucenteforte et al. [19] investigated a group of 87 cancer children treated with opioids and they conducted a systematic literature review. Similar to adults, children with the G/G genotype were found to have higher pain intensity compared to A/A homozygotes or A/G heterozygotes ($p = 0.042$). For children treated with morphine alone ($n = 60$), patients with the G/G genotype were found to require higher average daily doses of morphine compared to those with the other *COMT* rs4680 SNP genotypes, in order to achieve equal analgesia at Visual Analogue Scale (VAS) = 0 ($p = 0.01$). In a systematic review of five studies conducted among adults, the daily dose of morphine from the first pain measurement was significantly higher in patients with the G/G genotype, compared to A/G and A/A genotypes, indicating that the effect of SNPs in the *COMT* gene is age-independent in terms of cancer pain management [19].

ABCB1/*MDR1* C3435T

A membrane-bound protein encoded by this gene is a member of the ATP-binding-cassette (ABC) transporter superfamily. ABC proteins transport various molecules through extracellular and intracellular membranes. The P-glycoprotein encoded by the *ABCB1 (ATP-binding-cassette B1)* gene, also known as *MDR1 (multidrug-resistance 1)*, is an ATP-dependent pump for various xenobiotics. Among other things, this protein acts as a transporter in the blood-brain barrier (BBB) and is an important part of it, as it affects the bioavailability of many drugs, especially opioids, including fentanyl and its derivatives as well as morphine and its metabolites, namely M-3-G and M-6-G [10]. A trial conducted among 112 patients in Asia, in a study previously described for the *OPRM1* gene, found that the C3435T polymorphism in the *ABCB1* gene results in an increased daily dose ($p = 0.057$) and adjusted daily dose of morphine, relative to body surface area ($p = 0.028$), in patients with CC/CT genotypes compared to the TT genotype [12].

Campa et al. [10] reported on the association of pain treatment with morphine and polymorphisms — the previously described *OPRM1* SNP and *ABCB1* C3435T revealed that 145 SNPs tested for the T/T homozygous genotype showed faster and better pain control with morphine compared to carriers of the wild-type allele homozygote, i.e. C/C (ΔNRS = 4.39, SD = ± 2.21 *vs.* ΔNRS = 2.31, SD = ± 1.73, $p < 0.001$) [9]. It was found that not only a single SNP but also interactions of genotypes of different SNPs may be responsible for the variability in the clinical effect of morphine; patients with both the *ABCB1* C/C genotype and *OPRM1* G/G need significantly more morphine to achieve satisfactory analgesia. Moreover, a statistical analysis revealed a statistically stronger relationship compared to single genes (*ABCB1* $F = 19.8$, $p < 0.00001$ and *OPRM1* $F = 38.5$, $p < 0.00001$) [10].

According to the WHO's PRL, the standard treatment for the management of pain is to include, in addition to opioids and non-opioid analgesics, drugs with no analgesic effect, i.e. co-analgesics, which when combined produce a synergistic and additive effect. Benavides et al. [20] conducted a study among 36 patients with neuropathic pain who were reintroduced with therapy with nortriptyline and morphine and then evaluated in three 2-week treatment phases (6 weeks in total). Patients receiving combined therapy with nortriptyline and morphine improved by 88% compared to no therapy in patients with the C/C genotype ($p < 0.05$) [20].

Others

Two articles were found in which authors described the effect of other, less commonly discussed SNPs on the efficacy of opioid therapy as measured in the difference in terms of pain intensity and doses of prescribed analgesics. These included SNPs for the *IL-6, IL-8, TNF-α* genes or a newly discovered polymorphism in the TAOK3 gene. As mentioned earlier, studies concerning the effect of SNPs on cancer pain and opioid treatment outcomes in children are much less frequent compared to similar studies conducted among adult palliative and oncology patients. Therefore, a study in a cohort of paediatric patients, which examined the response to opioid analgesic therapy by comparing its efficacy in patients with SNPs for the *IL-6, IL-8, TNF-α* genes, seems very interesting. It appears that in the case of the SNP rs1800797 for *IL-6*, patients with the A/G or G/G genotype described their pain intensity significantly higher compared to A/A ($p = 0.017$), while G/G homozygous patients required significantly higher doses of morphine or MED compared to patients with other genotypes ($p = 0.047$) [20]. Interestingly, patients with at least one copy of the A allele had a significantly lower risk of achieving an NRS pain intensity score of more than 4 points. The SNP rs1800795 for *IL-6* may also provide some indication of personal sensitivity to pain stimuli, as the same study revealed that carriers of the G/G genotype in SNP rs1800795 have a higher risk of pre-treatment pain intensity ($PI_{t0} > 4$ and $\Delta VAS > 2$) compared to carriers of even one C allele [21].

A similar relationship was also described for the *TNFα* rs1800629 SNP — daily and total doses of morphine or other opioids per MED were statistically significantly higher ($p = 0.010$ and $p = 0.031$, respectively) in patients with the G/G genotype compared to others. This leads to the conclusion that SNPs for *IL-6* and TNF-α may also, in addition to the more extensively studied SNPs described above, be potential indicators of initial pain intensity in oncology patients and, at the same time, a marker of demand for opioids in a particularly important, but less studied, group of paediatric oncology patients [21].

Another interesting and newly discovered SNP that may be involved in the presence of individual variability in the analgesic effect of morphine may be two SNPs in the *TAOK3* (TAO kinase 3, i.e. serine/threonine protein kinase) gene. These SNPs were discovered in genome-wide association studies (GWAS) as a factor for increased post-operative pain levels and the subsequent greater demand for post-operative opioids converted to MEDD [21]. In a study conducted among 110 hospice patients in Canada, the rs1277441 C/T and rs795484 A/G SNPs in the *TAOK3* gene were analysed. It appears that homozygotes for rarer alleles (C in rs1277441 and A in rs795484, respectively) required a total MEDD of more than 800 mg for satisfactory pain control ($p = 0.013$ and $p = 0.004$, respectively) [22]. This coincides with the study conducted in the postoperative setting and may represent a reason for potentially clinically relevant variability in cancer pain management in the palliative medicine setting but requires further research [22, 23].

Effect of polymorphisms on the adverse effects of morphine in the palliative care setting

OPRM1

The concept of effective and appropriately selected analgesic treatment includes not only the reduction in absolute difference in terms of pain intensity before and after the implementation of treatment but also, as far as possible, the selection of doses of morphine or other opioids so as to minimise treatment-related adverse effects of these drugs.

Some palliative care patients with comorbid chronic renal failure are more likely to experience adverse effects with morphine due to the accumulation of an active metabolite of morphine, i.e. morphine-6-glucuronide (M-6-G). The search for factors that exacerbate or protect against the toxic effects of M-6-G led to the discovery that SNPs in the *OPRM1* gene, particularly A118G SNP, are one of the factors that affects the possible occurrence of toxic effects. These SNPs were previously described in the perspective of morphine sensitivity. A 2002 study described two patients treated with oral morphine for cancer pain with concurrent renal failure. However, patients presented extremely different treatment effects — patients homozygous for the A allele, i.e. wild-type allele, presented numerous adverse effects of morphine use — excessive sedation and dizziness. Interestingly, the patient with the G/G genotype, in contrast to the A/A patient, did not present any adverse effects despite almost twice the serum levels of the morphine metabolite M-6-G (A/A — 941 ng/mL *vs.* G/G — 1735 ng/mL) at slightly different daily doses of morphine (35 mg *vs*. 41.1 mg). This indicates that in patients with A118G SNP A/G or G/G, the potential effect of morphine-6-glucuronidee will be attenuated and thus less severe adverse effects of morphine can be expected; however, a study with a larger sample would need to be conducted to confirm this [24].

Reports regarding the protective effect of carriers of SNP rs1799971 A118G with the G allele support the results of a study that indicates a significantly lower risk of somnolence as an adverse effect of morphine

treatment in G/G homozygous patients compared to carriers of the A allele (0% *vs.* 28.4%, p = 0.005) [25]. The fact that patients are more susceptible to the sedative effects of opioids, especially morphine in carriers of A118G *OPRM1* SNP with the A allele, may be considered as a potential marker of high-risk groups for this adverse effect, given that Hajj et al. [13] found an association between the presence of lower levels of cognitive function in carriers of A118G SNP A/G and A/A, and thus the use of opioids may result in cognitive and sedative impairment in this group, and consequently deterioration of QoL of palliative care patients [13]. A study conducted among 231 patients from a pain clinic found an effect of the *OPRM1* G/G SNP genotype on sleep problems, including difficulty falling asleep and circadian rhythm disruption. This effect was more common in women (p = 0.002) [26].

SNPs in the *OPRM1* gene, other than A118G, can also be very hazardous from the point of view of doctors who care for palliative patients. After a complete absence of any response to opioids was observed in three Norwegian patients, DNA sequencing studies were performed in these patients, which revealed a previously unknown mutation in the mi-receptor gene that causes a conversion of arginine to cysteine at position 181, resulting in a μ-opioid receptor (MOR) that does not conduct any signals related to opioid stimulation. While one of the three patients — homozygous for the mutant allele — was completely insensitive to opioids, the response to the drugs was severely impaired in heterozygous patients. Due to the small sample size, this report can be considered only an interesting fact. However, the possibility of ineffectiveness of opioids should be borne in mind, one reason for which could be a patient just having a SNP in the *OPRM1* gene [27]. The possibility of the use of SNPs in morphine-related genes and their role in individual pain sensitivity and demand for opioids may also be supported by a study by Matthes et al. [28], in which it was observed that laboratory mice lacking the MOR after the use of morphine lacked analgesic effect, reward effect and withdrawal symptoms. At the same time, this effect was not observed for the other types of opioid receptor [28].

COMT

As a result of numerous studies, SNPs in the gene for catechol-O-methyltransferase are primarily associated with an effect on pain sensation — an article by Diatchenko [7] succeeded in identifying three SNP haplotypes of *COMT* — low-pain sensitivity, average-pain sensitivity and high-pain sensitivity [7]. However, the effect of such a SNP on pain sensation in patients receiving chronic opioid analgesic therapy was not investigated until 2019, when it was discovered that patients with chronic pain who received opioids, including morphine or other opioids per MEDD, and were carriers of the Val/Met genotype presented symptoms of hyperalgesia when stimulated with thermal stimuli compared to patients with the Val/Val (p = 0.039) and Met/Met (p = 0.023) genotypes. This agrees with other studies in which heterogeneous research samples of adult patients with chronic pain also revealed an increased propensity for opioid-induced hyperalgesia when stimulated with thermal stimuli [29]. Opioid-induced hyperalgesia is a serious problem, in which a patient chronically taking opioids for chronic pain begins to experience an increase in pain sensation instead of the expected relief. This can be a potential problem in palliative care, where morphine is the primary analgesic to provide comfort to the patient at the end of life. The prospect is raised by the possibility of being able to tailor therapy to patients by using tools to assess genetic determinants, including SNPs in opioid-related genes such as *COMT* rs4680 [30].

In another study on the effect of SNPs involved in the metabolism of morphine and other opioids, which focused on the occurrence of central nervous system (CNS) adverse effects such as dizziness, nausea, confusion and nightmares, the relationship between the occurrence of these symptoms, the total daily dose of morphine or its equivalent and the presence of 15 different SNPs in the *COMT* gene was tested. Interestingly, the study found significantly more CNS adverse effects, however, these were not related to the rs4680 SNP in question but only to the SNP within intron 1. This SNP was an independent factor in the occurrence of adverse effects [31]. Tanaka et al. [25] investigated the two most common SNPs associated with individual variability in response to morphine, namely *OPRM1* A118G and *COMT* Val158Met, and their potential association with opioid-induced adverse effects. As with the *OPRM1* A118G SNP, the polymorphism studied in *COMT* was also found to be a statistically significant risk factor for opioid-induced somnolence [25].

ABCB1

P-glycoprotein is a protein that transports substances encoded by the *ABCB1* gene out of the cell. This protein is largely responsible for the intracellular concentrations of morphine and M-6-G and M-3-G in the nervous system and contributes to the BBB. This activity affects the potential analgesic effect of morphine. However, as it turns out, it can also affect the adverse effects induced by morphine. Fujita et al. [32] found a significant reduction in the risk of experiencing fatigue, nausea and emesis in a Japanese popula-

tion of patients. Patients with the T/T genotype at position 1236 and TT/TT diplotype at positions 2677 and 3435 of the *ABCB1* gene had lower fatigue intensity ($p = 0.012$). Diplotypes within the *ABCB1* gene at positions 2677 and 3435 were associated with a lower risk of emesis during opioid treatment, provided that the diplotype did not contain G/C alleles [32].

Others

Morphine can alter the sensation of dyspnoea associated with lung and heart disease. For morphine-resistant dyspnoea, a SNP was found that turned out to be significant in a group of 2,294 patients. In the European Pharmacogenetic Opioid Study (EPOS), refractory dyspnoea was three times more common in patients with rs7103572 SNP *HTR3B*, which could not be confirmed among patients treated with fentanyl or oxycodone [33]. Another observation is the effect of genetic variation within the SNP for UDP-glucuronosyltransferase (*UGT*) on morphine metabolism, manifested by individual concentrations of morphine metabolites, namely M-3-G and M-6-G, which are responsible for the adverse effects observed during morphine treatment. In the study by Fladvada et al. [34], the *UGT1A1*/*UGT1A8* haplotypes were a predictor of reduced concentrations of morphine metabolites after oral morphine administration in morphine-treated patients of the previously mentioned EPOS ($n = 759$, false discovery rate-corrected $p < 0.1$) [34].

Conclusions

Pain is the primary symptom associated with cancer and is the one which most worsens the QoL, which is a significant clinical problem [1]. There are several challenges faced by pain management clinicians: the lack of effect of morphine, numerous drug interactions, individual variability in the metabolism of morphine and other opioids, as well as the low level of health education of the public and the myths associated with pain management, time constraints, inequality in access to health care [2]. The fact that there is individual variability in the effect of these drugs, which means that the same dose in patient A may have an inadequate effect and cause adverse effects in patient B, raises major clinical difficulties. According to many concepts that aim to explain this situation, pharmacogenomic studies raise the prospect of the development of personalised medicine, in which a medication and dosage can be tailored to the genetic profile of an individual patient. This reflects the need to find analgesics that are both safe and effective; however, it may be necessary to look not for a new substance but use advances in genetics to achieve such a situation [2, 4].

Over the past 20 years, there have been many reports regarding the impact of various SNPs on both the effects of morphine and other opioids or individual sensitivity to pain stimuli; however, there are few reports summarising the available knowledge. In studies involving small groups of patients, the most common SNPs in the gene for MOR (*OPRM1* rs1799971), catechol-O-methyltransferase (*COMT* rs4680 and others) or ATP-binding cassette B1 (*ABCB1* C3435T) presented statistical significance in the dose of morphine needed to achieve effective analgesia in cancer patients and those receiving palliative care. However, findings may vary according to which part of the world a study was conducted. Similar findings were observed in a relatively homogeneous European population in which the presence of polymorphisms altered the analgesic effect of morphine, as expected for a given genotype. However, there was a study from Erasmus University Rotterdam, based on an article by Matic et al. [16] who found that the A118G SNP in *OPRM1* was statistically significant only when combined with the presence of the Val158Met SNP in the *COMT* gene, not reaching the level of significance as a separate marker in palliative care patients [16]. A relationship between the presence of SNPs in the *OPRM1* A118G genes and the demand for morphine in palliative care patients was also found in the Middle Eastern population, however, the findings are not consistent for this population. Chatti et al. [35] published the results of a pharmacogenomic study in which, by genotyping 129 cancer patients for 3 polymorphisms in the *OPRM1* and *COMT* genes (including rs1799971, i.e. A118 > G and *COMT* rs4680), they found that there were no significant differences in relation to morphine doses that are needed to achieve analgesia in individual patient groups. The study was conducted in an ethnically heterogeneous group of patients from 3 Tunisian hospitals. Moreover, the absence of patients homozygous for the 118G allele in the study group is discussed; the authors highlight the possibility of a geographic and ethnic correlation between the occurrence of SNPs in the *OPRM1* gene and variability in response to morphine [35].

Most of the studies were conducted in small group sizes, where usually the number of patients participating in the study was less than 100. No significant relationship was found in a study conducted among 2,294 European patients to examine the association between SNPs and the efficacy of morphine treatment, despite considering 112 SNPs in 25 genes (including the most extensively discussed SNPs for *COMT*, *OPRM1*, *ABCB1*) that were associated with

variability in clinical response to morphine in several smaller studies. Therefore, the authors of that study imply that it is not appropriate to focus solely on the concept of searching for a single candidate gene as a marker for the efficacy of morphine treatment [36].

Similarly, when it comes to determining the relationship between the occurrence of single nucleotide polymorphisms and the timing of adverse effects of morphine, there are also studies that do not support the findings presented in this article which indicate a positive effect of SNPs in the *OPRM1* or *COMT* genes on the occurrence of adverse effects such as sedation, somnolence, dizziness or cognitive impairment. Kurita's study based on data collected in the study by Klepstad (EPOS) [37] indicates that there is no significant association between the 113 SNPs studied and the occurrence of any adverse effects of morphine.

Although there are studies whose results may not confirm the usefulness of morphine-related SNPs, the number of available studies conducted in smaller groups of patients raises the prospect of their use as a marker that is a part of personalised medicine, provided that larger studies are conducted for individual SNPs on a larger population, taking into account the genetic variation that is associated with different ethnic groups. In the future, the pharmacogenomic approach could be adapted to clinical practice as one of solutions to the challenges of opioid treatment [38, 39]. There are also studies showing that the determination of the SNP rs1799971 of *OPRM1* can be performed by a rapid assay using FRET-PCR, raising the prospect of adapting this method in the future as a screening of the population that needs morphine treatment [40].

According to the authors of this review, this study contributes important data and implies that in order to be able to express with certainty about the pharmacogenomic approach as an effective method to determine the response to morphine, it seems necessary to conduct studies involving large groups of patients, taking into account their ethnic and geographical conditions, as the available data indicate differences in the prevalence of polymorphisms in different ethnic groups and thus causing variation in the efficacy of analgesic treatment. A systematic review and meta-analysis of available scientific studies could be a contribution to a larger study. This review is not a systematic review, which is a limitation. However, the amount of evidence available in the literature should encourage the application of the pharmacogenomic approach in palliative medicine and the conduct of further studies, the results of which may represent a breakthrough in the pain management in palliative care patients and reduce the costs of pharmacotherapy and treatment of complications in terms of both ineffective pain management and adverse effects.

Declaration of conflict of interests

The authors declare that there is no conflict of interests.

Funding

None declared.

References

1. van den Beuken-van Everdingen MHJ, Hochstenbach LMJ, Joosten EAJ, et al. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage. 2016; 51(6): 1070–1090.e9, doi: 10.1016/j.jpainsymman.2015.12.340, indexed in Pubmed: 27112310.
2. Bennett M, Paice JA, Wallace M. Pain and opioids in cancer care: benefits, risks, and alternatives. Am Soc Clin Oncol Educ Book. 2017; 37: 705–713, doi: 10.1200/EDBK_180469, indexed in Pubmed: 28561731.
3. Kaye AD, Jones MR, Kaye AM, et al. Prescription opioid abuse in chronic pain: an updated review of opioid abuse predictors and strategies to curb opioid abuse: part 1. Pain Physician. 2017; 20(2S): S93–S9S109, indexed in Pubmed: 28226333.
4. Bugada D, Lorini LF, Fumagalli R, et al. Genetics and opioids: towards more appropriate prescription in cancer pain. Cancers (Basel). 2020; 12(7), doi: 10.3390/cancers12071951, indexed in Pubmed: 32708424.
5. Choi SW, Lam DMH, Wong SSC, et al. Effects of single nucleotide polymorphisms on surgical and postsurgical opioid requirements: a systematic review and meta-analysis. Clin J Pain. 2017; 33(12): 1117–1130, doi: 10.1097/AJP.0000000000000498, indexed in Pubmed: 28379874.
6. MedlinePlus [Internet]. National Library of Medicine. What are single nucleotide polymorphisms (SNPs)? https://medlineplus.gov/genetics/understanding/genomicresearch/snp/ (2.09.2022).
7. Diatchenko L, Nackley AG, Slade GD, et al. Catechol-O-methyltransferase gene polymorphisms are associated with multiple pain-evoking stimuli. Pain. 2006; 125(3): 216–224, doi: 10.1016/j.pain.2006.05.024, indexed in Pubmed: 16837133.
8. Opioid Conversion Calculator. https://www.Oregonpainguidance.Org/Opioidmedcalculator/ (2.09.2022).
9. Decaillot F, Abul-Husn N, Devi L. Mu opioid receptor. xPharm: The comprehensive pharmacology reference. 2007: 1–12, doi: 10.1016/b978-008055232-3.60073-x, indexed in Pubmed: ISBN 978-0-08-055232-3.
10. Campa D, Gioia A, Tomei A, et al. Association of ABCB1/MDR1 and OPRM1 gene polymorphisms with morphine pain relief. Clin Pharmacol Ther. 2008; 83(4): 559–566, doi: 10.1038/sj.clpt.6100385, indexed in Pubmed: 17898703.
11. Reyes-Gibby CC, Shete S, Rakvåg T, et al. Exploring joint effects of genes and the clinical efficacy of morphine for cancer pain: OPRM1 and COMT gene. Pain. 2007; 130(1–2): 25–30, doi: 10.1016/j.pain.2006.10.023, indexed in Pubmed: 17156920.
12. Gong XD, Wang JY, Liu F, et al. Gene polymorphisms of OPRM1 A118G and ABCB1 C3435T may influence opioid requirements in Chinese patients with cancer

pain. Asian Pac J Cancer Prev. 2013; 14(5): 2937–2943, doi: 10.7314/apjcp.2013.14.5.2937, indexed in Pubmed: 23803057.
13. Hajj A, Halepian L, Osta NEl, et al. OPRM1 c.118A>G polymorphism and duration of morphine treatment associated with morphine doses and quality-of-life in palliative cancer pain settings. Int J Mol Sci. 2017; 18(4), doi: 10.3390/ijms18040669, indexed in Pubmed: 28346387.
14. Rakvåg TT, Klepstad P, Baar C, et al. The Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene may influence morphine requirements in cancer pain patients. Pain. 2005; 116(1-2): 73–78, doi: 10.1016/j.pain.2005.03.032, indexed in Pubmed: 15927391.
15. Rakvåg TT, Ross JR, Sato H, et al. Genetic variation in the catechol-O-methyltransferase (COMT) gene and morphine requirements in cancer patients with pain. Mol Pain. 2008; 4: 64, doi: 10.1186/1744-8069-4-64, indexed in Pubmed: 19094200.
16. Matic M, Jongen JLm, Elens L, et al. Advanced cancer pain: the search for genetic factors correlated with interindividual variability in opioid requirement. Pharmacogenomics. 2017; 18(12): 1133–1142, doi: 10.2217/pgs-2017-0060, indexed in Pubmed: 28745577.
17. Matsuoka H, Makimura C, Koyama A, et al. Prospective replication study implicates the catechol-O-methyltransferase ValMet polymorphism as a biomarker for the response to morphine in patients with cancer. Biomed Rep. 2017; 7(4): 380–384, doi: 10.3892/br.2017.963, indexed in Pubmed: 28928973.
18. Matsuoka H, Arao T, Makimura C, et al. Expression changes in arrestin β 1 and genetic variation in catechol-O--methyltransferase are biomarkers for the response to morphine treatment in cancer patients. Oncol Rep. 2012; 27(5): 1393–1399, doi: 10.3892/or.2012.1660, indexed in Pubmed: 22293824.
19. Lucenteforte E, Vannacci A, Crescioli G, et al. Opioid response in paediatric cancer patients and the Val158Met polymorphism of the human catechol-O-methyltransferase (COMT) gene: an Italian study on 87 cancer children and a systematic review. BMC Cancer. 2019; 19(1): 113, doi: 10.1186/s12885-019-5310-4, indexed in Pubmed: 30704436.
20. Benavides R, Vsevolozhskaya O, Cattaneo S, et al. A functional polymorphism in the ATP-Binding Cassette B1 transporter predicts pharmacologic response to combination of nortriptyline and morphine in neuropathic pain patients. Pain. 2020; 161(3): 619–629, doi: 10.1097/j.pain.0000000000001750, indexed in Pubmed: 31738228.
21. Crescioli G, Lombardi N, Vagnoli L, et al. STOP pain project-opioid response in pediatric cancer patients and gene polymorphisms of cytokine pathways. Pharmaceutics. 2022; 14(3), doi: 10.3390/pharmaceutics14030619, indexed in Pubmed: 35335997.
22. Cook-Sather SD, Li J, Goebel TK, et al. TAOK3, a novel genome-wide association study locus associated with morphine requirement and postoperative pain in a retrospective pediatric day surgery population. Pain. 2014; 155(9): 1773–1783, doi: 10.1016/j.pain.2014.05.032, indexed in Pubmed: 24909733.
23. Gutteridge T, Kumaran M, Ghosh S, et al. Single--nucleotide polymorphisms in TAOK3 are associated with high opioid requirement for pain management in patients with advanced cancer admitted to a tertiary palliative care unit. J Pain Symptom Manage. 2018; 56(4): 560–566, doi: 10.1016/j.jpainsymman.2018.07.011, indexed in Pubmed: 30031856.
24. Lötsch J, Zimmermann M, Darimont J, et al. Does the A118G polymorphism at the mu-opioid receptor gene protect against morphine-6-glucuronide toxicity? Anesthesiology. 2002; 97(4): 814–819, doi: 10.1097/00000542-200210000-00011, indexed in Pubmed: 12357145.
25. Tanaka R, Sato J, Ishikawa H, et al. Influence of genetic variants of opioid-related genes on opioid-induced adverse effects in patients with lung cancer: A STROBE-compliant observational study. Medicine (Baltimore). 2021; 100(44): e27565, doi: 10.1097/MD.0000000000027565, indexed in Pubmed: 34871222.
26. Margarit C, Ballester P, Inda MD, et al. OPRM1 gene interaction with sleep in chronic pain patients treated with opioids. Pain Physician. 2019; 22(1): 97–107, indexed in Pubmed: 30700073.
27. Skorpen F, von Hofacker S, Bjørngaard M, et al. The rare Arg181Cys mutation in the μ opioid receptor can abolish opioid responses. Acta Anaesthesiol Scand. 2016; 60(8): 1084–1091, doi: 10.1111/aas.12739, indexed in Pubmed: 27113810.
28. Matthes HW, Maldonado R, Simonin F, et al. Loss of morphine--induced analgesia, reward effect and withdrawal symptoms in mice lacking the mu-opioid-receptor gene. Nature. 1996; 383(6603): 819–823, doi: 10.1038/383819a0, indexed in Pubmed: 8893006.
29. Hooten WM, Hu D, Cunningham JM, et al. Effect of catechol--O-methyltransferase (rs4680) single-nucleotide polymorphism on opioid-induced hyperalgesia in adults with chronic pain. Mol Pain. 2019; 15: 1744806919848929, doi: 10.1177/1744806919848929, indexed in Pubmed: 31041874.
30. Mercadante S, Arcuri E, Santoni A. Opioid-Induced tolerance and hyperalgesia. CNS Drugs. 2019; 33(10): 943–955, doi: 10.1007/s40263-019-00660-0, indexed in Pubmed: 31578704.
31. Ross JR, Riley J, Taegetmeyer AB, et al. Genetic variation and response to morphine in cancer patients: catechol--O-methyltransferase and multidrug resistance-1 gene polymorphisms are associated with central side effects. Cancer. 2008; 112(6): 1390–1403, doi: 10.1002/cncr.23292, indexed in Pubmed: 18257092.
32. Fujita Ki, Ando Y, Yamamoto W, et al. Association of UGT2B7 and ABCB1 genotypes with morphine-induced adverse drug reactions in Japanese patients with cancer. Cancer Chemother Pharmacol. 2010; 65(2): 251–258, doi: 10.1007/s00280-009-1029-2, indexed in Pubmed: 19466410.
33. Currow DC, Quinn S, Ekstrom M, et al. Can variability in the effect of opioids on refractory breathlessness be explained by genetic factors? BMJ Open. 2015; 5(5): e006818, doi: 10.1136/bmjopen-2014-006818, indexed in Pubmed: 25948405.
34. Fladvad T, Klepstad P, Langaas M, et al. Variability in UDP-glucuronosyltransferase genes and morphine metabolism: observations from a cross-sectional multicenter study in advanced cancer patients with pain. Pharmacogenet Genomics. 2013; 23(3): 117–126, doi: 10.1097/FPC.0b013e32835ce485, indexed in Pubmed: 23277092.
35. Chatti I, Creveaux I, Woillard JB, et al. Association of the OPRM1 and COMT genes' polymorphisms with the efficacy of morphine in Tunisian cancer patients: Impact of the high genetic heterogeneity in Tunisia? Therapie. 2016; 71(5): 507–513, doi: 10.1016/j.therap.2016.04.004, indexed in Pubmed: 27288213.
36. Klepstad P, Fladvad T, Skorpen F, et al. Influence from genetic variability on opioid use for cancer pain:

a European genetic association study of 2294 cancer pain patients. Pain. 2011; 152(5): 1139–1145, doi: 10.1016/j.pain.2011.01.040, indexed in Pubmed: 21398039.
37. Kurita GP, Ekholm O, Kaasa S, et al. Genetic variation and cognitive dysfunction in opioid-treated patients with cancer. Brain Behav. 2016; 6(7): e00471, doi: 10.1002/brb3.471, indexed in Pubmed: 27247849.
38. Bond C, LaForge KS, Tian M, et al. Single-nucleotide polymorphism in the human mu opioid receptor gene alters beta-endorphin binding and activity: possible implications for opiate addiction. Proc Natl Acad Sci U S A. 1998; 95(16): 9608–9613, doi: 10.1073/pnas.95.16.9608, indexed in Pubmed: 9689128.
39. Haerian BS, Haerian MS. OPRM1 rs1799971 polymorphism and opioid dependence: evidence from a meta-analysis. Pharmacogenomics. 2013; 14(7): 813–824, doi: 10.2217/pgs.13.57, indexed in Pubmed: 23651028.
40. Grösch S, Niederberger E, Lötsch J, et al. A rapid screening method for a single nucleotide polymorphism (SNP) in the human MOR gene. Br J Clin Pharmacol. 2001; 52(6): 711–714, doi: 10.1046/j.0306-5251.2001.01504.x, indexed in Pubmed: 11736886.