REVIEW

Recent advances in the use of opioids for cancer pain

Joanne Droney
Julia Riley

Palliative Medicine Department, Royal Marsden Hospital, London, UK

Abstract: Opioids are the mainstay of treatment for moderate to severe cancer pain. In recent years there have been many advances in the use of opioids for cancer pain. Availability and consumption of opioids have increased and opioids other than morphine (including methadone, fentanyl, oxycodone) have become more widely used. Inter-individual variation in response to opioids has been identified as a significant challenge in the management of cancer pain. Many studies have been published demonstrating the benefits of opioid switching as a clinical maneuver to improve tolerability. Constipation has been recognized as a significant burden in cancer patients on opioids. Peripherally restricted opioid antagonists have been developed for the prevention and management of opioid induced constipation. The phenomenon of breakthrough pain has been characterized and novel modes of opioid administration (transmucosal, intranasal, sublingual) have been explored to facilitate improved management of breakthrough cancer pain. Advances have also been made in the realm of molecular biology. Pharmacogenetic studies have explored associations between clinical response to opioids and genetic variation at a DNA level. To date these studies have been small but future research may facilitate prospective prediction of response to individual drugs.

Keywords: opioids, cancer, pain, pharmacogenetics, constipation, breakthrough pain

Introduction

Most patients with cancer experience pain at some stage in their illness and many of these require opioid analgesia. For the past 20 years cancer pain has been managed according to the World Health Organization (WHO) analgesic ladder. This three-step ladder recommends sequential increases in the strength of analgesia, starting with paracetamol (step 1), adding in a weak opioid (step 2) if the pain persists and finally progressing to a strong opioid (step 3) if pain is still not controlled.[1] The use of the analgesic ladder has been validated in numerous studies and can result in over 80% analgesic control.[2,3]

There have been a number of developments in the use of opioids for cancer pain in recent years including:

- Choice and availability of opioids
- The use of alternative opioids to morphine and opioid switching
- Advances in the methods of delivery of opioids for cancer pain
- Advances in the methods of managing opioid-induced side-effects, particularly with the advent of opioid antagonists
- An increased knowledge and awareness of the molecular basis for opioid effect including pharmacogenetics

Correspondence: Joanne Droney
Palliative Medicine Department, Royal Marsden Hospital, London, UK
Tel +44 20780 82761
Email jodroney@hotmail.com

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Much of the research on opioids has initially been carried out in a non-malignant setting, often involving experimental pain studies. Some of these data however can be extrapolated to a certain degree to cancer patients. Most of these studies influence the direction of research in the use of opioids for cancer pain. All of these advances have improved individualized pain management and pave the way for the future of pain medicine ie personalized prescribing.

Recent advances in the use of opioids for cancer pain: opioid availability and choice

Morphine is the WHO first line strong opioid of choice for cancer pain.[1,4] This recommendation is based on availability and cost rather then evidence of superior efficacy or tolerability. Despite this recommendation, however, until relatively recently morphine was unavailable or not commonly used in many countries. In 1991 twenty countries accounted for 86% of morphine consumption.[5] In 2006 Europe and North America accounted for 89% of global morphine consumption with developing countries, which account for 80% of the world's population only consuming 6% of worldwide morphine.[6] Reasons for this inequality in morphine use/availability include:

- Inadequate health care infrastructures or pain control as a low priority item in a country's national health agenda
- Lack of knowledge/skills in pain treatment. Even in the US, in a survey of 897 physicians, reluctance to prescribe opioids for cancer pain was cited by 61% of respondents.[7]
- Legal and regulatory issues surrounding the use and availability of opioids.[8]
- Fear of addiction and misuse or re-direction of opioids into the illegal drug trade.[9]

In 1984 the WHO Cancer Pain Relief Programme was established in which a country's morphine consumption was considered to be an indicator of progress to improve cancer pain relief.[1,5] Between 1984 and 1992, global consumption of morphine increased by nearly 300%.[5,10] Since then morphine availability has increased worldwide and it has been introduced to many more countries. Other alternative opioids have also become more widely available, although as with morphine, availability and consumption is not uniform worldwide, eg, 94% of oxycodone is consumed by USA, UK, Canada, Germany, and Australia.[6]

There have been very few large randomized controlled trials comparing different opioids thus there is little

evidence suggesting superiority of one opioid over another.[4] Some opioids differ in their mode of metabolism and therefore some are recommended as being safer in some circumstances than others, eg, alfentanil in renal failure. Table 1 details some of the common opioids used in the management of cancer pain. In a recent survey of 3030 cancer patients across Europe, morphine (oral or systemic) was the most commonly used strong opioid (50%), followed by fentanyl (14%), oxycodone (4%), methadone (2%) and hydromorphine (1%).[11] There are marked differences in the choice of 1st line strong opioid in different countries, eg, in Belgium it is fentanyl while in Finland it is oxycodone.[11] The differences in choice of opioid and opioid consumption was also shown in a study comparing opioid consumption in Denmark, Finland, Germany, Iceland, The Netherlands, Norway, and Sweden.[12]

Recent advances in the use of opioids for cancer pain: opioid switching

As more opioids have become available for use and as familiarity and knowledge about these different opioids increases, opioid switching has become a therapeutic maneuver which has become widespread in recent years.

Most patients who are prescribed morphine for cancer pain achieve good pain control without problematic side-effects. These patients are known as "morphine responders". A significant proportion of patients however (up to 30%) do not respond well to morphine.[13] These "morphine non-responders" present in a number of different ways:[14]

- Patients who achieve good analgesia but with intolerable side-effects
- Patients who do not achieve good analgesia because of dose-limiting side-effects
- Patients who do not achieve good analgesia but do not experience side-effects either, despite escalating morphine doses

Morphine "non-responders" often benefit from changing to an alternative opioid in a practice known as "opioid switching". The same principle applies for patients who do not respond well to any other opioid also. When used carefully the practice of opioid switching is a powerful therapeutic tool in the individualization of cancer pain management.

The terms "opioid switching" and "opioid rotation" are often used interchangeably in the literature. For the purpose of this review opioid switching refers to the use of an alternative opioid for the purpose of improving analgesia and

reducing intolerable side-effects. Opioid rotation is taken to refer to the use of an alternative opioid because of availability, patient or physician choice or a change in the route of administration of the opioid. In some studies patients undergoing opioid switching and opioid rotation are included together.[15,16]

A Cochrane review in 2004 examined the evidence base for the effectiveness of opioid switching to improve drug tolerability. Fifty-two studies were included in this review, including 23 case reports, 15 retrospective studies or audits, and 14 prospective uncontrolled studies. All studies except one reported opioid switching as a beneficial clinical practice. The numbers of patients included in these studies tended to be small. At that time no randomized controlled trials or prospective controlled studies had been carried out in this area. Therefore the conclusion of the systematic review was that there was no substantial evidence to support the practice of opioid switching. The author called for further research in a number of areas: 1) to establish the true efficacy of opioid switching and 2) to determine which opioid should be used first line and second line.[17]

A further systematic review in 2006 suggested that opioid switching is associated with improvement in response to opioids in at least 50% of patients.[14] A more detailed look at some of the larger studies suggests that careful opioid switching may in fact be associated with much higher response rates. Table 2 details the results of some of the largest studies in this area.

The only prospective case-controlled study of opioid switching was carried out using morphine as the first line strong opioid of choice for cancer pain with oxycodone as second line. The study, which included 186 patients, comprised 2 cohorts. 74% (138/186) were morphine "responders", who had been on morphine for at least 4 weeks and who had good pain control with minimal side-effects. 26% (48/186) were morphine "non-responders" who had either poor pain control and/or intolerable side-effects despite adequate morphine dose-titration. Switching from morphine to oxycodone in the morphine non-responder group resulted in an overall 96% (179/186) good clinical outcome in terms of pain and side-effect profile.[18]

Two studies have examined the reasons why some patients do not have a successful outcome after opioid switching. In the study by Mercadante et al no association was found with clinical factors (including age of patient, gender), type or dose of opioid, pain type, the use of adjuvant medications or renal impairment. Patients in this study who had both poor pain control and adverse opioid effects were more likely

to be unsuccessful in switching ($P = 0.004$). However the numbers of patients who did not respond to opioid switching in this study was small (N = 15/118) therefore it is difficult to extrapolate these data into meaningful clinical practice. Eight patients in this study required intrathecal pain management.[16] In the study by Riley et al 5/48 patients did not have a successful outcome after opioid switching. One of these required an epidural and the authors suggest that for 3 others anesthetic intervention would have been appropriate.[18]

If a switch from one opioid to another is unsuccessful a number of factors should be taken into consideration:

- A further opioid switch may be indicated. More than 1 opioid switch is sometimes required to achieve an optimum balance between analgesia and side-effects.[16,18,19]
- The pain may not be opioid responsive
- Central delivery of opioids may be required (via the epidural or intrathecal route)
- Other factors may be contributing to the side-effects experienced, eg, renal impairment, concurrent medications, factors related to the underlying disease.

After on opioid switch is undertaken it usually takes a few days to achieve a good outcome. Time to stabilization on the second opioid may be slightly longer if the patient was switched because of both pain and side-effects.[16]

The dose of the original opioid at which an opioid switch is required varies widely. In 1 study in which 54 patients were switched from morphine to methadone, the median daily morphine dose was 200 mg (range 30 to 1000 mg).[20] In another study the morphine equivalent daily dose was 577 ± 1535 mg.[19] In the prospective controlled study in which morphine non-responders were switched to oxycodone, the median dose of morphine at time of switching was 70 mg (range 15 to 580 mg).[18]

Similarly the duration of the initial opioid therapy is variable. In one study patients were on the initial opioid for a median of 44 days (range 20 to 240 days).[20] In another study the mean duration of the previous opioid therapy is reported as 25.8 weeks (180.6 days) (range 1 to 104 weeks).[21] These data may suggest that there are 2 broad groups of patients which undergo opioid switching. The first group require switching shortly after initiation of the initial opioid, when the opioid dose is relatively low. The second group appear to become non-responsive to the initial opioid at either higher doses or after some time has elapsed, perhaps due to changes in the underlying painful state, disease, tolerance or some other contributing factor.

One of the most challenging aspects of switching from one opioid to another is deciding on the starting dose of

Table I Weak and strong opioids commonly used in cancer pain

Opioid (route of administration)	Metabolic pathway	Metabolites	Main receptors	Bioavailability	Relative potency to oral morphine[a]	Specific comments
Weak opioid (Step 2 WHO analgesic ladder)						
Codeine PO, PaR	Hepatic metabolism by cytochrome p450 (CYP2D6)	Norcodeine, morphine, Morphine-3-glucuronide (inactive) Morphine-6-glucuronide (active)	Mu-opioid receptor agonist	40% (variable)[166]	0.1	Prodrug of morphine. Up to 10% of Caucasians experience no analgesia from codeine because they are CYP2D6 poor metabolizers[32]
Tramadol PO, PaR	Hepatic metabolism via cytochrome p450 (CYP2D6)	O-desmethyltramadol (active)	Mu-opioid receptor agonist. Also action on adrenergic/serotonergic pathways	68%–100% (higher after multiple dosing due to saturation of first pass effect)[167]	0.1–0.25 PO 0.1 PaR[167]	Risk of serotonin toxicity if used with other drugs which increase serotonin levels
Strong opioid (Step 3 WHO analgesic ladder)						
Morphine PO, PaR, R	Hepatic metabolism by the enzyme UGT (UDP-glucuronosyltransferase)	Morphine-3-glucuronide (analgesically inactive) Morphine-6-glucuronide (analgesically active)[168]	Mu-opioid receptor agonist	20%–30% oral bioavailability[169,170]		Morphine and its metabolites are excreted in the urine and accumulate in renal failure[171,172]
Oxycodone PO, PaR, R	Hepatic metabolism by cytochrome p450 (CYP3A4 and 2D6)[173,174]	Oxymorphone (active) but metabolites do not contribute to central action[173]	Mu-opioid receptor agonist Kappa-opioid receptor agonist (controversial)[175,176]	60% oral bioavailability[177]	1.5–2.0[178,179]	Reduced clearance in renal impairment[180]
Fentanyl PaR, TD, IN, TM	Metabolized in the liver	Inactive norfentanyl	Mu-opioid receptor agonist	Poor oral bioavailability due to high first-pass metabolism	70–100 when using TD fentanyl formulation[181]	Highly lipid soluble, taken up into fatty tissues. Less than 10% excreted unchanged in urine[182]
Methadone PO, R, PaR	Hepatic metabolism via cytochrome p450 (CYP 3A4)[183]	Inactive metabolites	Mu-opioid and delta-opioid receptor agonist. NMDA (N-methyl-D-aspartate) receptor antagonist. Amine reuptake inhibitor	80% oral bioavailability[169]	Considerable inter-individual variation in pharmacokinetics[169,184] influenced by dose[185] and dosing schedule. Long plasma half-life, therefore higher potency ratio with repeated dosing	Highly protein bound.[183] Fecal excretion.[186] Safer in renal impairment
Buprenorphine PO, TD, TM	Hepatic metabolism via cytochrome p450 (CYP 3A4 and 2C8)	Norbuprenorphine	Partial mu-opioid receptor agonist. Kappa- and delta-opioid receptor antagonist Partial opioid-receptor-like 1 agonist	Poor oral bioavailability due to extensive first pass presystemic elimination[187]	100–115 when using TD buprenorphine formulation[188–190]	Fecal excretion of buprenorphine.[187] High receptor affinity therefore higher doses of naloxone are required to antagonize effects[191]

Hydromorphone PO, PaR, R	Hepatic metabolism	Hydromorphone-3-glucuronide (H-3-G)[192] which is not analgesically active but is neuroexcitatory[193]	Mu-opioid receptor agonist	50%–60%[194,195]	5–7.5[196]	H-3-G accumulates in renal failure[197]
Alfentanil PaR, IN	Hepatic metabolism via cytochrome p450 (CYP 3A4)[198]	Inactive metabolites	Mu-opioid receptor agonist		30	Rapid onset of action[199] Short elimination half-life (90 minutes)[200] Less than 1% excreted unchanged in urine.[200] Safer in renal failure. Dose reduction in liver failure and elderly[201]

[a]For guidance only, as discussed in text.
Abbreviations: TM, transmucosal (buccal, sublingual); PO, oral; PaR, parenteral (SC/IV); TD, transdermal; R, rectal; IN, intranasal.

the second opioid. Although equianalgesic dose ratios are available, these are merely guidelines to the relative potencies of different opioids. These ratios were derived largely from single dose studies and do not take into account individual patient factors which may contribute to effect, such as previous opioid therapy, opioid tolerance or underlying disease.[22,23] The reported equianalgesic dose ratios between opioids also may be quite variable depending on the study. The generally accepted equianalgesic dose ratio for oral morphine: oxycodone lies between 1:1 and 1:2.[22] In 1 study the median dose ratio of morphine: oxycodone was 1.7 with a broad range from 0.25 to 12.[24] To make matters even more complicated the equianalgesic dose ratios may change according to the initial opioid dose, as has been proposed when switching morphine to methadone.[20] One of the major factors contributing to the difficulties in determining the dose of the alternative opioid is the phenomenon of opioid tolerance. This is defined as a reduction in response to a drug after repeated administration. Tolerance to both opioid induced analgesia and side-effects may occur, although not necessarily in tandem together.[25] Incomplete cross tolerance to different opioids exists, which may be explained in part by differing pharmacodynamic and pharmacokinetic factors. There appears to be no defined relationship between the dose of the initial opioid dose at time of switching and the final stable opioid dose after switching.[14,16] In some cases opioid switching facilitates upward dose titration to achieve good analgesia.[26] In others the final equivalent dose of opioid required was reduced.[19] These data demonstrate the importance of individualized dose titration when switching opioids.[14] Most authors recommend deciding on the dose when opioid switching in the context of a) the individual patient experience (ie, whether switching because of uncontrolled pain or side-effects) and b) the type of opioid used. Conservative dose ratios[22] and an initial dose reduction of the equianalgesic dose by 25% to 50%[22,23] are recommended with subsequent careful individualized dose titration.

Recent advances in the use of opioids for cancer pain: pharmacogenetics

To date no clinical factor has been identified which can fully explain inter-individual variation in response to opioids. One of the most recent advances in the use of opioids for cancer pain is the interest in pharmacogenetics: how an individual's genetic makeup may influence variability in opioid response. The hypothesis held by many researchers is that changes at a molecular level in opioid's pharmacokinetic

Table 2 Efficacy of opioid switching

Author	Type of study	Number of patients undergoing opioid switch	Successful outcome after opioid switching	Reason for switching	Comment
Mercadante[a,16]	Prospective uncontrolled study	118	87%	Uncontrolled pain 15.2% Adverse effects 28.8% Uncontrolled pain and adverse effects 50.8%	More than 1 opioid switch required in 7 patients (6%)
Riley[18]	Prospective case-controlled study	48	87%	Morphine responders compared to morphine non responders: Confusion and drowsiness ($P = 5 \times 10^{-12}$) Pain relief ($P = 2.4 \times 10^{-6}$) Nightmares ($P = 5 \times 10^{-5}$) Nausea ($P = 7.3 \times 10^{-3}$)	More than 1 opioid switch required in 4 patients (8.5%)
Wirz[21]	Prospective uncontrolled study	50	64%	Uncontrolled pain 60% Sedation 4% Itch 2% Gastrointestinal effects (nausea, constipation) 40%	
Mercadante[20,2]	Prospective uncontrolled study	52	80%	Uncontrolled pain 20% Adverse effects 16% Uncontrolled pain and adverse effects 64%	
Kloke*[15]	Retrospective uncontrolled study	103	65%	Uncontrolled pain 43% Adverse effects 20% Uncontrolled pain and adverse effects 15%	
De Stoutz[19]	Retrospective uncontrolled study	80	73%	Uncontrolled pain 16% Cognitive failure 39% Hallucinations 24% Myoclonus 11% Nausea 9% Local irritation 1%	More than 1 opioid switch required in some patients

[a]Studies included changing from one opioid to another in order to improve pain and side-effect profile (ie, opioid switching) and also for other reasons (opioid rotation).

and pharmacodynamic pathways may be responsible for altered opioid response.[27] These changes may be brought about by genetic variation at a DNA, RNA, or protein level. Pharmacogenetics is used in a number of areas of medicine including oncology and hematology to prospectively predict an individual's response to certain drugs including warfarin and irinotecan.[28–30] In cancer pain management pharmacogentics may potentially allow prospective prediction of response to different opioids and facilitate choosing the correct dose of the correct drug for the correct patient, ie, personalized prescribing.

DNA variation: single nucleotide polymorphisms

DNA is made up of two opposing strands of nucleotides, with each nucleotide consisting of 1 of 4 bases (adenine [A], guanine [G], thymine [T], and cytosine [C]), a sugar and a phosphate bond. The most common type of genetic

variation at the DNA level consists of a single change in a nucleotide at a particular position along the DNA strand: a single nucleotide polymorphism (SNP). SNPs may occur at any point in a gene and may be associated with a change in the amino acid sequence produced because a) they are located in a coding area of the gene b) through influence on transcription activity or c) because they are in linkage disequilibrium (in a non-random association) with another significant polymorphism.

One of the best characterized pharmacogenetic phenomena involves codeine. Codeine is metabolized to morphine via the genetically heterogenous enzyme CYP2D6 (debrisoquine/spartenine hydroxylase).[31] Up to 10% of Caucasians (and varying proportions of other populations) lack CYP2D6 activity. These are known as "poor metabolizers" and thus experience little analgesia from codeine, as compared to "extensive metabolizers.[32] CYP2D6 gene duplication on the other hand is associated with ultra-rapid metabolism

of codeine to morphine, found in 3% of Caucasians.[33] There is a case report of fatal neonatal opioid toxicity in a child who was being breastfed by a CYP2D6 ultra-rapid metabolizing mother.[34,35] Variation in at least 16 alleles has been shown to influence CYP2D6 activity.[36] Recent data suggest that CYP2D6 phenotype also plays a role in response to tramadol.[37] CYP2D6 gene duplication has been described as playing a role in development of respiratory depression on tramadol.[38]

The association between opioid response in cancer pain and a number of other SNPs in different genes has also been studied (see Table 3). In most of these studies morphine has been the predominant opioid used, with sparse data on the genetics of response to other opioids.[39] To date the numbers of patients in these studies have been small and the number of SNPs studied has been limited.

Most genes are chosen for genetic association studies on the basis of the biological role which they play in the pharmacokinetic or pharmacodynamic pathways for the drug. The most frequently studied candidate gene involved in morphine analgesia is OPRM which codes for the mu-opioid receptor. Two hundred fifty-eight validated SNPs have been identified along the OPRM gene.[40] The most commonly studied polymorphism in OPRM is rs1799971, also known as A118G. This SNP which occurs in exon 1and results in an amino acid change (asparagine to aspartate) in the extracellular N-terminus of the receptor. This in turn results in loss of a potential N terminus glycosylation site which theoretically may alter ligand binding and receptor dimerization.[41,42] This SNP occurs with a frequency of 0% to 48.9%, depending on the population being studied.[43] The actual functional consequences of this polymorphism are unclear. One study examined mRNA expression in human brain tissue and reported a reduction in mRNA and OPRM protein (receptor) levels associated with the variant.[44] A further study demonstrated altered receptor binding affinity.[45] Another study however reported no difference in binding affinities between wild type receptor and the mu-opioid receptor coded for by this variant.[46]

Clinical genetic association studies, although somewhat inconsistent, suggest that rs1799971 A118G does play a role in morphine response. The details of association with morphine response in cancer pain are found in Table 3. Generally these studies suggest that carriage of the G allele (variant) of this SNP is associated with a poor response to morphine for cancer pain. Patients with the G allele tend to require higher doses of and experience less pain relief from morphine.[47–49]

This polymorphism was also been associated with differential central effects from morphine and M6G in a single blind two-way crossover study of 12 healthy volunteers who were administered IV morphine and IV M6G. The concentration of drug required to achieve 50% pupil constriction was used as a measure of drug potency. Serum concentrations of morphine and M6G were measured at regular set intervals using liquid chromatography tandem mass spectrometry. Subjects with carrying the variant (ie, genotype AG or GG) required larger doses of M6G to achieve 50% pupil constriction than subjects with AA (wild-type) genotype. There was no difference in the effects of morphine on pupil constriction between the genotypes.[50]

RNA variation: spice variants

A single stretch of DNA can result in a number of different protein products, mainly through RNA modification. Recent work into genetic variation at an RNA level has proposed the concept of multiple mu-opioid receptor subtypes through a process known as alternative splicing. Splicing refers to a process of post-transcription modification in which intronic material is removed and exons are joined together to form messenger RNA (mRNA). mRNA is subsequently translated into the protein product, which in the case of OPRM is the mu-opioid receptor. Different splicing products with potentially different functions can be formed through different arrangements of the exons in the mRNA.

The concept of multiple receptor subtypes is not new, suggested by a) incomplete cross tolerance between various mu-opioid receptor agonists[51] and b) differential actions of mu-opioid receptor agonists and antagonists.[52] Sophisticated rodent studies using inbred strains and knockout strains have further strengthened this concept. Mu-opioid receptor knockout mice demonstrate a complete loss of all mu-opioid receptors from the brain, suggesting that is mu-opioid receptor subtypes exists, they must be derived from the same gene.[53] The CXBK mouse is an inbred strain which is poorly responsive to opioids. When administered morphine, these mice experience reduced analgesia. CXBK mice have reduced levels of OPRM1 mRNA, with subsequent reduced expression of mu-opioid receptors and less signal transduction.[54] CXBK mice, however, retain analgesic sensitivity to morphine-6-glucuronide (M-6-G), heroin and fentanyl, all mu-opioid receptor agonists, suggesting that M-6-G, heroin, and fentanyl act via a different mu-opioid receptor than morphine.[55]

The structure of the human mu-opioid receptor has been cloned.[56] OPRM was initially thought to be made

Table 3 Summary table of pharmacogenetics and response to morphine in human patients with cancer pain[a]

SNP/s	Clinical response	Strongest P value	Method of phenotype definition	Type of study	Study population
Single gene effect					
OPRM (mu-opioid receptor gene) Main site of action for morphine and other opioids					
OPRM A118G (rs1799971) and others	G allele associated with higher daily morphine dose required to achieve adequate pain control. No difference in side-effects scores	0.006	Total daily morphine dose. Average pain score, 11-point NRS (0–10). Side-effects scored on 4 point verbal rating score. Metabolites measured using liquid chromatography mass spectrometry	Prospective observational study. Single time point	99 cancer patients with controlled pain (average pain ≤4)[47]
OPRM A118G (rs1799971)	G allele associated with lower change in pain scores (NRS) between baseline and 7 days of morphine treatment	0.0001	5-point verbal rating scale and 11-point NRS (0–10). Change in NRS between baseline and 7 days of morphine treatment	Prospective observational study. Multiple time points with 8 week follow-up	137 patients starting morphine for cancer pain[48]
OPRM A118G (rs1799971)	G allele associated with higher daily morphine dose. No differences in pain scores	0.012	Total daily morphine dose. Average pain score, 11-point NRS (0–10)	Prospective observational study. Single time point	207 cancer patients on morphine[49]
OPRM A118G (rs1799971), rs589046 and others	Not associated with differences between morphine responder and non-responder	NS	Morphine responders were taking morphine for at least 1 month with good pain control and minimal side-effects Morphine non-responders had inadequate pain control and/or intolerable side-effects	Prospective observational study Single time point	186 cancer patients taking morphine[203]
COMT (Catechol-O-methyltransferase gene) COMT codes for an enzyme which is involved in catecholamine metabolism					
COMT Val158Met (rs4680) and others	>1 allele associated with differences between morphine responder and non-responder	0.003	Morphine responders were taking morphine for at least 1 month with good pain control and minimal side-effects. Morphine non-responders had inadequate pain control and/or intolerable side-effects	Prospective observational study. Single time point	228 cancer patients taking morphine[204]
COMT Val158Met (rs4680) and others	>1 allele associated with differences in central side-effects of drowsiness and confusion/hallucinations	0.003	Side-effects scored on a 4-point subjective categorical scale	Prospective observational study. Single time point	228 cancer patients taking morphine[204]

Gene/SNP	Finding	Value	Study type	Population
COMT Val158Met (rs4680)	Val allele associated with higher daily morphine dose requirements. No differences in serum morphine and metabolites and side-effect scores	0.025	Prospective observational study. Single time point	207 patients on morphine for cancer pain[205]
rs4818, COMT Val158Met (rs4680), rs6269, rs740603 and others (haplotype construction)	>1 haplotypes and alleles associated with differences in daily morphine dose requirements. No differences in serum morphine and metabolites and side-effect scores	0.006 (haplotype analysis)	Prospective observational study. Single time point	207 patients on morphine for cancer pain[206]
COMT Val158Met (rs4680)	Val allele associated with higher daily morphine dose requirements. No differences in pain scores	0.02	Prospective observational study. Single time point	207 cancer patients on morphine[49]
MDR (Multi-Drug Resistance gene) This gene codes for p-glycoprotein which is involved in drug transfer across the blood brain barrier				
rs1128503, rs2032582, MDR C3435T (rs1045642) and others	>1 allele associated with differences in central side-effects of drowsiness and confusion/hallucinations	0.0003	Prospective observational study. Single time point	228 cancer patients taking morphine[204]
MDR1 C3435T (rs1045642)	C allele associated with lower change in pain scores (NRS) between baseline and 7 days of morphine treatment	0.001	Prospective observational study. Multiple time points with 8 week follow-up	137 patients starting morphine for cancer pain[48]
ARRB2 (B-arrestin-2) This gene codes for a protein which is involved in intracellular receptor trafficking and degradation[207,208]				
T8862C (rs1045280), G1143A(rs2036657) and others	>1 allele associated with difference between morphine responder and non-responder	0.013	Prospective observational study. Single time point	186 cancer patients taking morphine[203]
STAT6 (signal transducer and activator of transcription gene)				
C-174T(rs167769), C9065T(rs841718) and others	T allele associated with differences between morphine responder and non-responder	0.026	Prospective observational study. Single time point	186 cancer patients taking morphine[203]

Side-effects scored on a 4 point subjective categorical scale

5-point verbal rating scale and 11 point NRS (0–10). Change in NRS between baseline and 7 days of morphine treatment

Morphine responders were taking morphine for at least 1 month with good pain control and minimal side-effects. Morphine non-responders had inadequate pain control and/or intolerable side-effects

Morphine responders were taking morphine for at least 1 month with good pain control and minimal side-effects. Morphine non-responders had inadequate pain control and/or intolerable side-effects

Total daily morphine dose. Average pain score, 11-point NRS (0–10). Side-effects scored on 4-point verbal rating score. Metabolites measured using liquid chromatography mass spectrometry

Total daily morphine dose. Average pain score, 11-point NRS (0–10). Side-effects scored on 4-point verbal rating score. Metabolites measured using liquid chromatography mass spectrometry

Total daily morphine dose. Average pain score, 11-point NRS (0–10)

Table 3 (*Continued*)

SNP/s	Clinical response	Strongest P value	Method of phenotype definition	Type of study	Study population
Single gene effect					
UGT2B7 (UDP glycosyltransferase 2 gene). This enzyme is involved in the hepatic metabolism of morphine					
A2098T(rs7438284), C2099T(rs7439366)	Not associated with differences between morphine responder and non-responder	NS	Morphine responders were taking morphine for at least 1 month with good pain control and minimal side-effects. Morphine non-responders had inadequate pain control and/or intolerable side-effects	Prospective observational study. Single time point	186 cancer patients taking morphine[203]
UGT2B7 H268Y and others	Not associated with differences in serum morphine and metabolite levels	NS	Metabolites measured using liquid chromatography mass spectrometry.	Prospective observational study Single time point	175 cancer patients taking morphine[209]
UGT1A1*28, UGT2B7 H268Y	Not associated with differences in serum morphine and metabolite levels	NS	Metabolites measured using liquid chromatography mass spectrometry.	Prospective observational study Single time point	70 cancer patients taking morphine[210]
Combined effect of >1 gene					
OPRM/COMT					
COMT Val158Met (rs4680) OPRM A118G (rs1799971)	OPRM AA/COMT Met/Met associated with lowest daily morphine dose requirements	0.012	Total daily morphine dose. Average pain score, 11-point NRS (0–10)	Prospective observational study. Single time point	207 cancer patients on morphine[49]
COMT/MDR					
COMT Val158Met (rs4680), MDR C3435T (rs1045642) and others	Combination of COMT/MDR associated with reduced central side-effects of drowsiness and confusion/hallucinations	<0.0001	Side-effects scored on a 4-point subjective categorical scale	Prospective observational study. Single time point	228 cancer patients taking oral morphine. Morphine responders and non-responders[204]
OPRM/MDR1					
OPRM A118G (rs1799971) MDR1 C3435T (rs1045642)	OPRM AA/MDR1 TT associated with greatest change in pain scores (NRS) between baseline and 7 days of morphine treatment	<0.00001	5-point verbal rating scale and 11-point NRS (0–10).	Prospective observational study. Multiple time points with 8 week follow-up	137 patients starting morphine for cancer pain[48]

aStudies involving >1 gene/clinical outcome are presented separately here. Only studies examining response to opioids for cancer pain are included here.
Abbreviations: NRS numeric rating scale; NS not significant.

up of 4 exons (although more recent work suggests that it is in fact much more complex).[57] Each exon is thought to be important for expression of different parts of the mu-opioid receptor. Exon 1 codes for the amino-terminal of the receptor and exons 1, 2 and 3 code for the transmembrane domains and intra/extracelluler loops.[58] Exon 4 codes for the distal portion of the carboxyl chain of the receptor which is important in coupling the receptor to intracellular signalling systems and events. Knockout animals and antisense probes have been used to examine the impact of blocking expression of parts of a gene of interest. Rodents without expression of exon 1 express significantly reduced morphine analgesia but retain sensitivity to M-6-G.[59,60] Conversely, rodents with loss of exon 2 expression exhibit decreased M-6-G and not morphine analgesia.[59] These data suggest that morphine and M-6-G may act on different mu-opioid receptor subtypes, which may be brought about through variation at an RNA level. Even more intriguing is that although antisense blockade of exon 1 expression inhibited supraspinal morphine analgesia, it did not have any effect on spinal morphine analgesia, suggesting that perhaps different mu-opioid receptors are involved in both processes.[61] Antisense blockade of exon 4 inhibited all morphine effects.[59,61] Immunohistochemical labelling of mu-opioid receptor splice variants demonstrated differential distribution in the brain and spinal cord suggesting region specific processing of OPRM into different mu-opioid receptor subtypes.[62]

Practical challenges of examining human brain RNA means that most research in this area has been carried out in vitro using cell lines expressing mu-opioid receptors.[63] 10 human splice variants have been identified resulting from alternative splicing at exon 4.[63,64] Since exons 1 to 3 remain conserved, all of these splice variants bind mu-opioid agonists, but there are differences in terms of function, eg, receptor internalization and regional distribution.[61] One study examining human brain tissue resected at time of temporal lobectomy for epilepsy demonstrated the presence of mu-opioid receptor splice variants though real time reverse transcriptase polymerase chain reaction.[65]

Alternative splicing of delta- and kappa-opioid receptors has also been demonstrated.[66]

Some human data support the role of splice variants in pain perception. A recent study by Diatchenko et al analyzed patterns of genetic material between mice and humans. Although there are differences in the structure of mouse and human OPRM, this study demonstrated that a) most mouse OPRM exons (of which there are 20) also exist in humans and b) the architecture of the human OPRM is probably more complex than previously thought. A SNP, rs563649, was identified which was associated with altered pain response and which was also associated with differential translation of splice variants of mu-opioid receptor. This SNP was not however statistically associated with morphine analgesic response to experimental ischemic pain. This study does suggest an association between genetic variation at a DNA level (SNPs) and variation at an RNA level.[57]

To date no studies have been carried out examining the association between opioid receptor expression/splice variants and response to morphine in cancer patients in the clinical setting.

Protein variation: receptor dimerization

Finally, even after the genetic code is translated into a protein product, modifications and variation in function may occur through the process of receptor dimerization.

Morphine acts primarily through the mu-opioid receptor. Animal studies have demonstrated that disruption of the mu-opioid receptor gene abolishes the analgesic effect of morphine despite the presence of functional delta- and kappa-opioid receptors.[67] However binding studies suggest that morphine does bind to delta and kappa receptors, albeit with less affinity than to mu-opioid receptors.[68,69] Although the role of delta- and kappa-opioid receptors in morphine response is not entirely clear, there is a suggestion that opioid receptors interact with each other and influence function.[70–73] For example delta-receptor knockout mice do not develop analgesic tolerance to morphine.[74] Opioid receptors can form homo and hetero-dimers, thus producing novel functional properties through altered ligand binding and differential intracellular receptor trafficking.[75–77] Opioid receptor dimerization adds further to the complexity of inter-individual variation in opioid response. There have been no clinical studies examining the role of opioid receptor dimers on analgesic response to morphine for cancer pain.

Recent advances in the use of opioids for cancer pain: alternative routes of opioid administration for breakthrough pain

Breakthrough pain is defined as "a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain".[78] There is some controversy surrounding the definition of this phenomenon but the reported prevalence is as high as 51% to 89%.[79–81]

A number of issues arise when oral opioids are used to treat episodic breakthrough pain:

- Increasing the regular dose of opioids in a patient with stable background pain may result in intolerable side-effects.
- Breakthrough pain often peaks to maximum intensity within minutes.[82] The time to peak plasma concentration of oral morphine is 15 to 60 minutes.[83] Therefore the effect of even immediate release (short-acting) oral opioids may last longer than the episode of breakthrough pain, making these drugs less suitable for pains which have a short duration/onset of action.[84]

In recent years there has been considerable interest in the development of alternative routes of opioid administration for the management of breakthrough pain, with particular emphasis on the oral transmucosal/buccal and also intranasal routes.

The oral mucosa has a rich blood supply and this route of drug administration avoids hepatic first-pass metabolism.[85] Thus the onset of action of drugs administered transmucosally is potentially very rapid.[86] Absorption is affected by lipophilicity of the drug, the fraction of drug which is ionized, the length of time with which the drug is in contact with the oral mucosa and also the pH.[85] Lipophilic drugs such as fentanyl and buprenorphine are more rapidly absorbed than more hydrophilic drugs such as morphine.[87]

There have been a number of studies examining the use of oral transmucosal fentanyl citrate (OTFC) for the management of breakthough cancer pain. OFTC is available as a lozenge on a stick which is rubbed on the inside of the cheek over an approximately 15 minute period.[88] Approximately 25% of OFTC is absorbed via the buccal mucosa with the remaining 75% being swallowed. Overall the bioavailability of OFTC is approximately 50%.[89] The medium time to maximum plasma concentration is approximately 20 to 40 minutes.[88,90] T_{max} is similar regardless of dose.[91] A study of 92 cancer patients demonstrated larger reductions in pain intensity and better pain relief with OTFC compared to placebo.[92] A randomized double-blind dose titration study involving 65 cancer patients with breakthrough pain demonstrated a faster onset of analgesia with OFTC compared to the patient's usual rescue analgesia ($P < 0.0001$). In this study up to two episodes of breakthrough pain per day were treated with OTFC and all other episodes were treated with the patient's usual rescue opioid.[93] Another double-blind double-dummy randomized cross-over study was carried out comparing OTFC and morphine sulphate immediate release (MSIR). Pain intensity and pain relief scores were noted at

15, 30, 45 and 60 minutes post dose. OTFC was associated with lower pain intensity and higher pain relief scores at all time points. A greater than 33% change in pain intensity at 15 minutes was seen in 42.3% of episodes of pain treated with OFTC compared to 31.8% of episodes treated with MSIR ($P < 0.0001$). In this study however only 69% (93/134) of patients were titrated to an effective OFTC dose, with 31% (41/134) withdrawing during the OFTC titration phase. Only 75/93 patients used both OFTC and MSIR and thus were included in the efficacy analysis.[94]

Interestingly there appears to be no relationship between the effective dose of OFTC and the stable background opioid dose.[93–95] Dose titration to an effective dose has been shown to be successful in 67 to 74% of patients.[93,94,96] The usefulness of OFTC is limited if the patient has xerostomia[97] or if the patient cannot manage the technique of applying it to the buccal mucosa.

More recently a novel effervescent transmucosal fentanyl buccal tablet (FBT) has been launched. This medication is designed to dissolve in 10 minutes when placed between the upper gum and cheek above a molar tooth.[98] In a healthy volunteer open label cross-over study (N = 26) comparing OFTC and transmucosal FBT, the latter was found to have a higher absolute bioavailability (0.47 and 0.65 respectively). The time to maximum plasma concentration was shorter for transmucosal FBT compared to OFTC (47 and 91 minutes respectively).[98] Of note the T_{max} for OFTC in this study was actually considerably longer than reported in previous data, as discussed above.[88,90] Transmucosal FBT appears better than placebo for the management of breakthrough pain in cancer patients[99] It appears to be well tolerated in patients with mucositis, although the numbers involved in this study were small and the patients only experienced mild oral symptoms.[100]

Sublingual and intranasal fentanyl preparations have also been studied for breakthrough cancer pain.[101–103] Sublingual and intranasal sufentanil is also used although this drug is not available in some countries. The data on sufentanil in cancer-related breakthrough pain consists of case series and small studies.[104,105]

Recent advances in the use of opioids for cancer pain: opioid antagonists for opioid-induced constipation

Constipation is one of the most common and troublesome side-effects of opioid medication. The published prevalence

of constipation amongst patients taking opioids ranges from 50% to 100%.[106,107] Although the pathogenesis of constipation in cancer patients is multi-factorial,[108] opioid medication plays a key role.[106] There appears to be no dose-response relationship between opioids and constipation and unlike other side-effects such as drowsiness it is thought that for many patients tolerance to constipation is less likely to occur.[109,110]

Unlike opioid-analgesia, opioid-induced constipation is thought to be mediated predominately by peripheral rather than central mechanisms:[111]

- In vitro experiments have demonstrated inhibitory effect of opioids on isolated gut muscle preparations.[112]
- The constipating effects of centrally administered morphine are abolished in animals in which the intestine has been rendered refractory to central influences through vagal resection. In the same animals however, subcutaneous morphine still produced anti-diarrheal action.[113]
- Peripherally restricted opioid agonists such as loperamide which do not cross the blood-brain barrier also cause a reduction in gut transit.[114]

Mu-, delta-, and kappa-opioid receptors are found throughout the gastrointestinal (GI) tract. Mu- and delta-opioid receptors are found in both the myenteric and submucosal neurones while kappa-opioid receptors are predominately localized to the myenteric plexus.[115] Morphine is thought to act directly on these peripheral opioid receptors in the bowel. Morphine administered either intravenously or intra-peritoneally accumulates in the GI lumen.[116] Mu-opioid receptor knockout mice studies demonstrate a key role of mu-opioid receptors in the role of opioid-induced constipation.[117]

Opioid receptor activation by opioid agonists causes a reduction in synaptic neurotransmitter release through activation of potassium channels,[118] inhibition of calcium channels[119] and a reduction in cAMP production.[120] The overall effect is a reduction in acetylcholine release.[106] Opioids increase gut transit time and reduce the amount of fluid in the gut lumen. Forward propulsive contractions are inhibited, the stool spends a longer time in the gut lumen thus more fluid is reabsorbed and the stool becomes hard and dry. Opioids also have an indirect inhibitory effect on luminal fluid secretion via a complex mechanism involving 5-HT2 receptors, α2-adrenoceptors and noradrenaline release.[121]

The management of constipation has traditionally been based around oral and rectal laxative use. A number of different agents are available but to date there is no evidence to suggest that any one laxative is superior to another, mainly because there have been few studies in this area.[122] In recent years there has been a growing interest in the use of opioid receptor antagonists for the management of opioid-induced constipation. Theoretically opioid receptor blockade by an agent which does not cross the blood brain barrier would inhibit peripherally mediated GI side-effects without interruption of centrally mediated opioid analgesia. Three opioid receptor antagonists have been studied for this purpose: naloxone, methylnaltrexone, and alvimopan.

Naloxone

Naloxone is a pan-opioid receptor antagonist with a high affinity for mu-opioid receptors. Systemically administered naloxone is used to reverse life-threatening opioid toxicity and acts both peripherally and centrally. Oral naloxone however undergoes significant hepatic first pass glucuronidation to produce inactive metabolites,[123] resulting in a very low (2%) oral bioavailability.[124] The role of oral naloxone as a peripheral opioid antagonist in cancer patients has been examined in a number of small early studies with good effect.[125–127] These studies however all demonstrated that the risk of precipitating pain or opioid withdrawal is substantial. The study by Sykes (N = 17) investigated the relationship between the dose of morphine and naloxone recommended a daily naloxone dose of 20% of the daily morphine dose, to a maximum of 5 mg.[127] Another study in 22 cancer patients examined the relationship between morphine and effective naloxone dose when naloxone was titrated up to a maximum of 36 mg/day over a 4-day period to laxative use and opioid withdrawal (measured using a modified Himmelsbach withdrawal scale). 23% (4/17) patients who completed the study experienced withdrawal symptoms. There was no relationship demonstrated between morphine and effective naloxone dose.[128] A further study in 9 patients demonstrated again that reversal of analgesia can still occur even when using lower doses of oral naloxone (6 to 12 mg/day).[129]

Recently there has been increased interest in the use of fixed dose combination of prolonged release (PR) oral oxycodone/naloxone as a method to provide analgesia while preventing opioid-induced constipation. A multicentre prospective placebo-controlled randomized double-blind parallel group phase II trial of 202 patients with severe chronic pain concluded that a 2:1 oxycodone:naloxone ratio was optimal in terms of safety and efficacy. Only 2.5% of study participants in this study had a cancer diagnosis.[130] There was no significant difference in the mean pain intensities between treatment groups but there was an improvement in bowel function according to naloxone dose ($p < 0.05$). Opioid withdrawal was not formally assessed in this study.

Similar studies with 12 week follow-up periods comparing oxycodone/naloxone (2:1 ratio) PR with oxycodone PR alone demonstrated a significant improvement in bowel function in those taking the oxycodone/naloxone combination ($P < 0.0001$).[131,132] The maximum oxycodone dose (as part of the oxycodone/naloxone combination) in these studies was 80 mg/day. Studies involving higher opioid doses with longer follow-up are warranted. This efficacy of this combination of oxycodone/naloxone combination in a predominately cancer population has not yet been reported.

Methylnaltrexone

Methylnaltrexone is a quaternary opioid antagonist which does not readily cross the blood brain barrier because of its reduced lipid solubility and increased polarity.[133] It is a non-selective opioid antagonists with preferential mu-opioid receptor binding.[134]

Methylnaltrexone was originally studied in healthy volunteers who were given intravenous placebo, placebo + morphine or methylnaltrexone + morphine. Methylnaltrexone significantly prevented morphine-induced decrease in oral-cecal transit but did not affect morphine analgesia.[135] A randomized placebo-controlled trial was carried out involving 22 subjects who were enrolled on a methadone maintainance programme. All subjects who received methylnaltrexone (intravenous) had a laxation response without opioid withdrawal or significant side-effects.[136]

A large randomized placebo-controlled phase III study using subcutaneous methylnaltrexone in patients with advanced illness has been published recently.[137] Study subjects were administered 0.15 mg/kg methylnaltrexone SC (subcatenous) or placebo every second day for 2 weeks. The primary endpoints of this study were the proportion of subjects who had a rescue-free laxation (without the use of an enema or suppository) within 4 hours of the first dose and the proportion that had a rescue-free laxation within 4 hours after 2 or more of the first 4 doses. Subjects were also assessed for overall pain scores and opioid withdrawal. Forty-eight percent of patients receiving methylnaltrexone had a rescue-free laxation within the first 4 hours after the first dose, compared to 15% who received placebo ($P < 0.001$). Over the course of the first 4 doses, the proportion of patients having a rescue-free laxation within 4 hours ranged from 38% to 48% in patients administered methylnaltrexone and 7% to 15% in those given placebo. Approximately 50% of patients who had a rescue-free laxation within 4 hours had a response within 30 minutes, suggesting a rapid onset of action. There were no differences in pain scores between

the methylnaltrexone and placebo groups and there was no evidence of significant opioid withdrawal. Only 59% (78/133) of study patients had a cancer diagnosis.[137] A similar study in 154 patients with advanced illness receiving a single dose of 0.15 or 0.3 mg/kg SC methylnaltrexone or placebo demonstrated a laxation within 4 hours for 58% to 62% of patients, depending on the dose administered.[138] The authors of both these studies suggest that the reason why there appears to be a substantial proportion of patients who did not have a response to methylnaltrexone is perhaps due to non-opioid causes of constipation or constipation being mediated by central mechanisms.[137,138] SC methylnaltrexone is licensed in the UK for palliative care patients as either 8 or 12 mg depending on body weight.[139]

Oral methylnaltrexone has not been studied in cancer patients to date however there are data to suggest that it may be efficacious. In a small (N = 14) randomized controlled double-blind study of healthy volunteers methylnaltrexone prevented morphine-induced inhibitory effects on gut transit. There was no correlation between plasma concentrations of methylnaltrexone and the gut transit time and less than 1% of methylnaltrexone was excreted unchanged in the urine after 6 hours. Therefore the authors concluded that oral methylnaltrexone has a direct local bowel action.[140] A further randomized controlled trial using an enteric-coated oral formulation demonstrated similarly efficacious results.[141]

Alvimopan

Alvimopan is a large oral peripherally restricted opioid antagonist with high affinity for mu-opioid receptors.[142] It is metabolized in the gut.[143] Systemic absorption ranges from 0.03% in dogs to 6% in humans.[144] Alvimopan reversed morphine-induced GI transit changes (as measured with the hydrogen breath test) in a double-blind, placebo-controlled, randomized, cross-over study in 14 volunteers. As part of the same study 45 patients undergoing tooth extraction were administered IV (intravenous) morphine and either oral alvimopan or placebo. Alvimopan did not alter analgesia and did not affect pupil constriction, confirming a lack of central activity.[145] Oral alvimopan has also been studied with positive effect in post-operative ileus which is thought to be caused by activation of endogenous opioid receptors after bowel handling and also by exogenous opioids administered for pain control.[146–148] Alvimopan was studied in a large trial (N = 522) of patients taking opioids for chronic non-cancer pain. It was associated with an increase in the number of spontaneous bowel movements compared to placebo (p < 0.001). Adverse effects reported in this study included abdominal pain, nausea

and diarrhea.[149] In another large study involving 148 patients on opioids for non-malignant pain and 20 patients on opioid maintenance therapy for opioid abuse, a statistically larger proportion of patients receiving alvimopan than placebo achieved the primary endpoint of having a bowel motion within 8 hours.[150] A large study in patients with cancer pain has been carried out but the final results have not yet been published fully. Concern about cardiovascular side-effects have been raised.[151–153]

Endogenous opioids are thought to play a role in the physiological regulation of gut function.[154–156] Studies with opioid receptor antagonists support this idea. Early studies on isolated pieces of human ileum demonstrated increased muscle contraction when bathed in methylnaltrexone, even in the absence of morphine.[157] Furthermore, in the absence of morphine, repeated intravenous administration in healthy human volunteers demonstrated a significant reduction in gut transit time (as measured by the hydrogen breath test).[158] Oral naloxone has been shown to improve gut function in patients with chronic idiopathic constipation, although the numbers of patients studied was small.[159] In vitro studies using guinea pig ileum demonstrated that alvimopan increases contractions and mechanical activity in morphine-naïve animals.[160]

The development of opioid receptor antagonists is exciting, however a recent Cochrane review urges some caution.[153] These agents have not been directly compared against each other and they have not been compared to best current clinical practice with oral and rectal laxatives. In some of the larger studies, as constipation was a pre-requisite to entering the study, these individuals were clearly on an inadequate laxative regimen from the outset.[137,149] Most data suggest that these agents are more efficacious than placebo in improving opioid-induced bowel dysfunction. Long-term safety data, however, is warranted. Animal studies suggest that chronic use of opioid-receptor antagonists may actually result in an increase in the number of receptors which in turn may lead to increased sensitivity to the constipating effect of opioid agonists and a resultant dependence on opioid antagonists.[161] It has also been suggested that the effects of opioid antagonists may in fact be proportional to the degree of opioid agonist tolerance and that patients on higher doses of opioid agonists may in fact be more at risk of adverse effects from drugs such as naloxone.[162]

Opioids for cancer pain: recent advances and future directions

Opioids are the mainstay of treatment for moderate to severe cancer pain. Unfortunately cancer pain is often managed inadequately. In a recent survey of 5084 cancer patients across Europe and Israel, 56% experienced moderate to severe pain at least monthly.[163] In another European study of 3030 palliative care patients, 32% had moderate or severe pain.[11] Although the variety and availability of different opioids has increased, the greatest advance in the use of opioids for cancer pain is undoubtedly an improved understanding of their mechanism of action. Physicians and researchers have become increasingly aware of marked inter-individual variation in response to opioids for cancer pain in terms of pain and side-effects. Exciting research in the field of pharmacogenomics promises a greater understanding of the mechanisms underlying this variation. Novel modes of administration and the use of peripherally restricted opioid antagonists allow greater pain control while minimizing troublesome side-effects. There have been major advances in the use of functional neuroimaging (such as functional magnetic resonance imaging, fMRI) to identify and measure areas of the brain which are involved in pain perception[164] and also response to opioids.[165] This technology may be of use in the future in furthering our understanding of pain mechanisms and inter-individual variation in opioid response. The future of opioids for cancer pain lies in personalized prescribing ie, the tailored prescription of the correct dose of the correct drug for the individual patient.

Disclosures

The authors declare no conflict of interest.

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