Effects of opioids on immune function in patients with cancer pain: from bench to bedside

Abstract

In patients with cancer, opioids are principally used for the management of acute surgical and chronic cancer-related pain. Opioids have many non-analgesic effects, including direct and indirect effects on cancer cells and on anti-tumour immunity. Direct effects on immune cells are elicited via opioid and non-opioid Toll-like receptors, and indirect effects via the sympathetic nervous system and hypothalamic-pituitary-adrenal axis. Opioids can also decrease/alter immune cell infiltration into the tumour microenvironment. Animal models have shown that this is not a class effect: morphine and fentanyl suppress natural killer (NK) cell cytotoxicity, thereby increasing tumour burden; buprenorphine does not affect NK cell cytotoxicity, whereas tramadol increases NK cell cytotoxicity, thereby reducing metastasis. In healthy individuals, morphine suppresses and fentanyl enhances NK cell cytotoxicity. Although clinical outcomes were not determined, fentanyl has been shown to decrease NK cell cytotoxicity whereas tramadol increases cytotoxicity in patients undergoing surgery. Meta-analyses of opioid-sparing surgical studies have reported an association between improved recurrence-free and/or overall survival with regional/neuraxial anaesthesia compared with systemic opioids. In people receiving opioids for non-surgical cancer-related pain, morphine has variable effects on immunity; clinical outcomes were not assessed. Although there is a potential association between strong systemic opioids and shorter survival in people with cancer and a prognosis of months to years, studies have not been designed to primarily assess survival therefore causality cannot be apportioned. Pain is also immunosuppressive and adequate analgesia is important. The use of opioids for cancer-related pain continues to be recommended, until definitive data is available on the effects of opioids on clinical outcomes in specific patient groups becomes available.

Opioids and the immune system

Opioids are a diverse range of drugs that act on opioids receptors. In patients with cancer, opioids are principally used in the long-term management of cancer-related pain as well as in the shorter term for cancer surgery pain. They can produce a range of undesired effects
(Boland et al., 2013), including effects on the immune system (Grace et al., 2015; Ramaswamy et al., 2016; Wigmore et al., 2016).

In patients with, or developing, cancer, the immune system has a crucial role in controlling and potentially eradicating cancer cells. Many immune cells are involved in anti-tumour immunity including natural killer (NK) cells, T cells, mast cells, dendritic cells and macrophages, as well as cytokines and chemokines (Table 1) (Boland et al., 2014b; Liang et al., 2016; Maghazachi, 2010; Mittal et al., 2014; Nguyen et al., 2014). It has been suggested that NK cell activity is a critical endpoint in the immunotoxicological evaluation of pharmaceuticals (European Medicines Evaluation Agency. Note for Guidance on Repeated Dose Toxicity. CPMP/SWP/1042/99. EMEA: London, 2000) and a consensus statement for opioids for chronic pain in elderly people proposes that the effects of opioids on immune function should be considered (Pergolizzi et al., 2008).

<table>
<thead>
<tr>
<th>Table 1: Role and function of the main immune cells.</th>
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<tbody>
<tr>
<td><strong>Cell</strong></td>
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<tr>
<td><strong>Role</strong></td>
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<tr>
<td><strong>Function</strong></td>
</tr>
<tr>
<td><strong>Arm</strong></td>
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<tr>
<td>Dendritic cell</td>
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<tr>
<td>Antigen presentation</td>
</tr>
<tr>
<td>Presentation of antigenic peptides in the context of MHC class I and II molecules and the delivery of essential co-stimulatory molecules</td>
</tr>
<tr>
<td>Innate</td>
</tr>
<tr>
<td>Natural killer cell</td>
</tr>
<tr>
<td>Anti-tumour</td>
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<tr>
<td>Anti-viral</td>
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<tr>
<td>Release of cytotoxic molecules (granzymes, perforin)</td>
</tr>
<tr>
<td>Innate</td>
</tr>
<tr>
<td>Neutrophil</td>
</tr>
<tr>
<td>Anti-bacterial / fungal</td>
</tr>
<tr>
<td>Phagocytosis and oxidative burst</td>
</tr>
<tr>
<td>Innate</td>
</tr>
<tr>
<td>Monocyte-Macrophage lineage</td>
</tr>
<tr>
<td>Anti-bacterial / fungal</td>
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<tr>
<td>Phagocytosis and oxidative burst</td>
</tr>
<tr>
<td>Innate</td>
</tr>
<tr>
<td>CD4⁺ T cell</td>
</tr>
<tr>
<td>Immune coordination / regulation</td>
</tr>
<tr>
<td>Regulating the activity of other immune cells</td>
</tr>
<tr>
<td>Adaptive</td>
</tr>
<tr>
<td>Regulatory T cell (CD4⁺, CD25⁺, FOXP3⁺, CD127low, plus other markers)</td>
</tr>
<tr>
<td>Immune regulation/ suppression</td>
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<tr>
<td>Immune system modulation, maintaining tolerance to self-antigens, preventing autoimmune disease, potential barrier to the development of protective anti-tumour immunity</td>
</tr>
<tr>
<td>Adaptive</td>
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<tr>
<td>CD8⁺ T cell</td>
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<tr>
<td>Cytotoxicity</td>
</tr>
<tr>
<td>Eradication of virally-infected cells and cancer cells. Induction of apoptosis by i) release of cytotoxins (perforin, granulysin, granzymes) ii) direct cell-cell contact</td>
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<tr>
<td>Adaptive</td>
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<td>B cell</td>
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<tr>
<td>Antibody production</td>
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<tr>
<td>Antibody production</td>
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<tr>
<td>Adaptive</td>
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Adapted with permission from (Boland et al., 2014b)
Given that patients with cancer are also at risk of infection, it is thus important that the anti-infection arm of the immune system to be maintained at an adequate level. There is evidence that opioids could increase the risk of infection in patients with cancer (Dublin et al., 2011; Salimi et al., 2013; Shao et al., 2016; Suzuki et al., 2013), as a retrospective study has shown that patients treated with morphine developed more infections than those treated with oxycodone (Suzuki et al., 2013). Furthermore, the risk of infection risk has been shown to increase by 2% per 10 mg rise in the oral morphine equivalent daily dose; with no difference between opioids (Shao et al., 2016).

Opioids can affect cancer via many mechanisms, including indirect effects on cancer growth via angiogenesis and host immunity (Afsharimani et al., 2011; Gach et al., 2011; Koodie et al., 2014; Yamamizu et al., 2015). Opioids might directly influence the growth of cancer cells as cancer tissue overexpresses mu opioid receptors (MOR) (Lennon et al., 2012; Mathew et al., 2011; Nguyen et al., 2014; Singleton et al., 2014; Zylla et al., 2013). Overexpression of MOR on cancer cells in murine models has been shown to increase the growth of lung cancer (Lennon et al., 2014), and decreasing MOR activity (using MOR small hairpin RNA mice or the opioid receptor antagonist methylnaltrexone) has been shown to reduce the growth of lung cancer (Mathew et al., 2011). Furthermore, MOR overexpression has been associated with metastasis in patients with oesophageal and lung cancer (Singleton et al., 2014; Zhang et al., 2015). Morphine has been shown to have direct effects on cancer cells influencing their proliferation and survival via effects on tumour cell DNA cleavage, mitogen-activated protein kinase, Src, Gab-1, PI3 kinase, Akt and STAT3 signalling pathways (Lennon et al., 2014; Lennon et al., 2012; Mathew et al., 2011).

The remainder of this review will concentrate on the cancer-related immune effects of opioids.

**Mechanisms of immune effects of opioids**

Numerous mechanisms underlying the influence of opioids on immune cells have been described (Figure 1). In vivo, opioids can modulate immune function by direct effects on immune cells, and via indirect effects which involve the central nervous system and its release of immune mediators (Al-Hashimi et al., 2013; Borner et al., 2008; Campana et al., 2010).
For opioids to have direct effects on immune cells, immune cells must express opioid receptors, or opioids must be able to have effects via non-opioid receptors present on immune cells (e.g. Toll-like receptor-4). Although in vitro morphine can directly interact with MORs on immune cells (Borner et al., 2008), the presence of functional opioid receptors on immune cells, as determined using radioligand antibody binding studies, Western blot and polymerase chain reaction analysis continues to be disputed (Al-Hashimi et al., 2016; Al-Hashimi et al., 2013; Borner et al., 2009; Campana et al., 2010; Glattard et al., 2010; Kraus, 2009; Langsdorf et al., 2011; Williams et al., 2007). One possibility for the discrepancy is that MOR expression depends upon immune cell activation - expression of MOR in T cells is non-constitutive (Borner et al., 2008; Kraus et al., 2001). In activated human T cells, MOR mRNA is increased to levels about 1% of those in neurons and can produce functional MORs in T cells (Borner et al., 2007). Many extracellular signals, including the cytokines IL-1, IL-4, IL-6, TNF and IFN-γ, control MOR gene transcription and cell surface opioid receptor expression in immune cells (Kraus, 2009; Langsdorf et al., 2011; Mohan et al., 2010). Toll-like receptor-4 is involved in innate immune system activation. In vitro and in silico techniques have shown that many commonly used opioids activate this receptor and can have direct effects on innate immunity (Franchi et al., 2012; Grace et al., 2015; Hutchinson et al., 2010).

There are two principal pathways via which the central immunosuppressive effects of morphine can be mediated; this is mostly based on animal data and might differ between species (Al-Hashimi et al., 2013; Fecho et al., 1996; Wang et al., 2002). Acute morphine administration acts on the peri-aqueductal grey and sympathetic nervous system (which innervates lymphoid organs) to release immunosuppressive biological amines that can suppress NK cell cytotoxicity (Fecho et al., 1993; Fecho et al., 1996; Gomez-Flores et al., 2000; Hernandez et al., 1993; Irwin et al., 1988; Lysle et al., 1996; Weber et al., 1989). An additional arm to the sympathetic nervous system pathway is the action of acute morphine/diamorphine via D1 receptors in the nucleus accumbens shell. This increases the release of neuropeptide Y from the sympathetic nervous system, which acts on peripheral Y1 receptors to inhibit splenic NK cell cytotoxicity (Saurer et al., 2006a; Saurer et al., 2009; Saurer et al., 2006b). Prolonged use of opioids increases activity in the hypothalamic-pituitary-adrenal axis, thereby increasing the release of immunosuppressive glucocorticoids, and decreasing T cell function and NK cell cytotoxicity (Borman et al., 2009; Hernandez et al., 1993; Mellon et al., 1998; Zhang et al., 2011).
As well as having direct and indirect effects on immune cell activation, MOR activation can inhibit NK cell migration. Fewer NK cells are in the tumours of wild-type compared to MOR knockout mice (Boehncke et al., 2011), morphine has been shown to reduce leukocyte migration in a murine lung tumour model (Koodie et al., 2014), and NK cell infiltration into breast cancer tissue is decreased in women who have received more perioperative systemic opioids (Desmond et al., 2015). For effective anti-tumour immunity, immune cells need to be in the tumour microenvironment, and a lack of immune cell infiltration could therefore be detrimental to anti-tumour immunity.

Not all immune cells are beneficial to the anti-tumour response; regulatory T cells can suppress the immune response (Takeuchi et al., 2016). Meta-analyses have reported increased regulatory T cell infiltration into breast cancers is associated with a poorer survival (Shou et al., 2016; Wang et al., 2016). Regulatory T cells are increased in blood from patients with gastric cancer by in vitro morphine (Hou et al., 2016), in vitro and in vivo by sufentanil and fentanyl in women undergoing breast cancer surgery (Gong et al., 2014); these could inhibit anti-tumour immunity (Takeuchi et al., 2016).

![Figure 1: Peripheral and central mechanisms of opioid-induced immune suppression.](image)

Opioids can have direct effects on immune cells which express appropriate receptors such as mu opioid receptors (MORs) and Toll-like receptor-4 (TLR-4). They can also have immunosuppressive effects via central mechanisms. Acute opioid administration enhances activity in the periaqueductal gray (PAG) matter which activates the sympathetic nervous system (SNS). The SNS innervates lymphoid organs, such as the spleen, and this activation induces the release of biological amines which suppress splenic lymphocyte proliferation and NK cell cytotoxicity (Fecho et al., 1996; Irwin et al., 1988). Second, prolonged use of opioids increases hypothalamic pituitary adrenal (HPA) axis activity and glucocorticoid production, which decrease NK cell cytotoxicity (Fecho et al., 1996; Mellon et al., 1998). Morphine can also act via D1 dopamine receptors in the nucleus accumbens.
shell, increasing the release of neuropeptide Y (NPY) and reducing splenic NK cell cytotoxicity in rodent models (Saurer et al., 2006b). Reproduced with permission from (Boland et al., 2014b).

**Animal studies: NK cells and tumour growth**

NK cells are the principal immune cell involved in tumour immunosurveillance. Suppression of NK cell cytotoxicity has been demonstrated to correlate with increased tumour growth and metastasis in animal models (Franchi et al., 2007; Gaspani et al., 2002; Shavit et al., 2004). The published literature generally reports that morphine (Franchi et al., 2007; Weber et al., 2006; Yeager et al., 1995) and fentanyl (Franchi et al., 2007; Martucci et al., 2004; Shavit et al., 2004) decrease NK cell cytotoxicity, that buprenorphine does not affect NK cell cytotoxicity (Franchi et al., 2007; Martucci et al., 2004) and that tramadol enhances it (Gaspani et al., 2002; Sacerdote et al., 2000) (Table 2). There may be different effects on NK cell cytotoxicity depending on doses, as in pigs low-dose morphine stimulated, and high-dose induced an initial increase followed by suppression (Borman et al., 2009).

There are many studies describing how opioids can affect immunity, and these have mostly using acute administration of morphine. However, the duration of opioid administration (as well as the opioid itself) can lead to different effects on immune function (Liang et al., 2016). The differential effects of opioids on different aspects of immune and how tolerance develops differently is illustrated in a series of murine experiments by Martucci et al (Martucci et al., 2004). In these studies, single dose fentanyl only decreased lymphocyte proliferation, whereas chronic fentanyl reduced lymphocyte proliferation and also splenic NK cell cytotoxicity, IL-2 and IFN-γ production at 24 hours. NK cell cytotoxicity recovered by day 3, whereas lymphocyte proliferation, IL-2 and IFN-γ production recovered by day 7. After the 7 day infusion, the administration of twice the dose of fentanyl for 1 or 3 days to these mice did not affect any immune parameter, thereby suggesting that once immunological tolerance had developed, increasing the dose did not overcome it (Martucci et al., 2004). Buprenorphine did not affect any of the measured parameters at any time point (Martucci et al., 2004).

The effect of the timing of morphine administration on cancer progression has been studied in a murine model of breast adenocarcinoma. If given before the cancer had developed, morphine had no effect on cancer growth. However, once the cancer had developed, morphine, via the MOR, increased cancer progression and decreased survival (Nguyen et al., 2014).
Several surgical studies have assessed how different opioids, and the timing of opioid administration, affect cancer progression. In a series of rodent experiments, (Franchi et al., 2007) showed that morphine and fentanyl decreased NK cell cytotoxicity and increased MADB106 lung metastases, whereas buprenorphine did not. Surgery decreased NK cell cytotoxicity and increased MADB106 lung metastases. In the surgical model, perioperative buprenorphine reversed the suppressive effects of surgery on NK cell cytotoxicity and MADB106 lung metastases, whereas morphine and fentanyl did not (Franchi et al., 2007). Decreased NK cell cytotoxicity correlated with high corticosterone levels, thereby suggesting the involvement of the hypothalamic-pituitary-adrenal axis (Franchi et al., 2007). Fentanyl has been shown to suppress NK cell cytotoxicity in rats, and this suppression correlated to increased tumour load when fentanyl was administered close to the time of MADB106 tumour cell inoculation, but not when fentanyl was administered 6 hours before tumour inoculation (Shavit et al., 2004). Thus, the acute administration of morphine and fentanyl around the time of tumour resection in animals could be detrimental to immune function and cancer outcomes.

In a series of rodent experiments, Gaspani et al demonstrated that tramadol increased and morphine decreased NK cell cytotoxicity in non-operated rats (Gaspani et al., 2002). Surgery reduced NK cell cytotoxicity, and this correlated with increased numbers of MADB106 lung metastases. Morphine did not influence surgery-induced NK cell cytotoxicity suppression, whereas tramadol prevented this and reduced lung metastasis (Gaspani et al., 2002). The (+) enantiomer of tramadol inhibits serotonin uptake and is immunostimulatory – this effect is inhibited by the serotoninergic antagonist metergoline (Sacerdote et al., 1999). It has also been shown that an increased serotoninergic tone stimulates NK cell cytotoxicity (Clancy et al., 1991; Mossner et al., 1998). Thus, the effect of tramadol on NK cell cytotoxicity following surgery might be the summation of stimulation of NK activity, which is also present in non-operated rats, due to serotonin re-uptake inhibition, and the reduction of surgical pain which is itself immunosuppressive (Gaspani et al., 2002; Page, 2003; Page et al., 2001). For potentially immunosuppressive opioids, there is a balance between the immunosuppressive effect of the opioid and the reduction of putative immunosuppression of pain (Figure ) (Page, 2005; Rittner et al., 2008).
Figure 2: Opioids, pain, immunity and cancer.

Pain is immunosuppressive and may worsen rodent cancer outcome (Page, 2003; Page et al., 2001). Opioids, by reducing pain, might have a beneficial effect on immune function and cancer (Gaspani et al., 2002; Page, 2005). However, opioids which suppress immune function, may decrease anti-tumour immunity and promote the development of cancer; the balance of these effects is critical (Shavit et al., 2004; Wang et al., 2008).

A recent study using breast cancer mouse models has shown that perioperative morphine did not affect tumour growth, peripheral blood or tumour-infiltrating immune cells (although NK cells were not assessed), even when surgery was performed (Doornebal et al., 2015). The difference between this and the other presented studies, could be due to orthotopic rather than intravenous inoculation of cancer cells, female mice being used (different species and genders could respond differently) and the 14-day dosing schedule of morphine which was initiated once mammary tumours had developed, or 1 day after mastectomy (Doornebal et al., 2015).

Healthy volunteer studies:

Several studies assessing the effect of opioids in healthy volunteers have been performed (Table 2). These have the advantage of being able to evaluate the effect of opioids on both direct and indirect opioid-immune pathways in humans, as opposed to in vitro studies which can only assess direct pathways, albeit in a very controlled way (Boland et al., 2014a). Healthy volunteer study results cannot be extrapolated to people with cancer, as inflammation and immune cell activation are different.

In a volunteer study, morphine decreased NK cell cytotoxicity, the recovery of which was prolonged beyond 24 hr after the morphine was stopped with higher doses (Yeager et al., 1995). In two volunteer studies, acute administration of intravenous fentanyl increased NK cell cytotoxicity, and this effect was shown to be due to an increase in the proportion of NK cells in the peripheral blood, rather than an increase in the cytotoxicity of individual NK cells (Yeager et al., 2002) (Jacobs et al., 1999). Although these studies suggest that morphine suppresses NK cell cytotoxicity in healthy subjects, with a more prolonged suppression at a
higher dose, and that fentanyl increases NK cell cytotoxicity, we cannot extrapolate healthy volunteer studies to the surgical/clinical setting.

**Human cancer surgical studies**

There is pre-clinical evidence that the immune response at the time of surgical removal of cancer is critical, that some opioids can be detrimental to the immune response and that this can promote cancer progression (Byrne *et al*., 2016; Gaspani *et al*., 2002; Shavit *et al*., 2004). As *in vitro* conditions of most studies do not reproduce the biology of cancer *in vivo*, and that there are differences between opioids (Borner *et al*., 2013), immune response and clinical outcomes to different opioids need to be studied in humans undergoing surgical resection of cancer. During surgery, opioids are just one of many factors that might affect cancer progression/metastasis (Byrne *et al*., 2016). Furthermore, opioids have numerous mechanisms of affecting cancer growth in animal models, with the potential influence on anti-tumour immunity being just one of these (Afsharimani *et al*., 2011; Gach *et al*., 2011; Jaura *et al*., 2014).

In patients undergoing surgery, surgical stress variably reduced NK cell cytotoxicity and different opioids (and the dose used) have different effects on NK cell cytotoxicity. In 30 patients undergoing surgery for uterine carcinoma to whom were administered fentanyl, anaesthetic medications and either morphine or tramadol, NK cell cytotoxicity was not affected by the surgery or by morphine (trend for inhibition only). However, tramadol increased NK cell cytotoxicity at 2 hours post-treatment despite similar analgesia (Sacerdote *et al*., 2000). In a randomised controlled trial of 40 patients undergoing surgery for malignant or benign conditions, post-operative NK cell cytotoxicity was reduced, with high-dose fentanyl delaying the post-operative recovery of NK cell cytotoxicity (Beilin *et al*., 1996). The long-term impact or overall outcome of different opioids and doses were not determined.

The influence of morphine with or without flurbiprofen (the flurbiprofen group consumed less morphine) on immune status has been evaluated in 60 patients undergoing surgery for gastric cancer. In the morphine treated patients, T and NK cell numbers decreased at 2 hours after incision, and NK cell numbers had not returned to baseline at 5 days after surgery. In the flurbiprofen group, NK cells at 2 hours and T and NK cells at 1 day were higher, despite similar levels of analgesia (Shen *et al*., 2014). In a randomised controlled trial of 25 patients undergoing neck surgery, fentanyl suppressed NK cell cytotoxicity more than flurbiprofen on
day 1, but not day 2 postoperatively (Narahara et al., 2013). The difference could either be a beneficial effect of the flurbiprofen or a negative effect of the opioid (Boland et al., 2016; Hooijmans et al., 2015).

Although NK cell cytotoxicity correlates with tumour growth and metastasis in animal models, cancer outcomes have not been assessed in human cancer surgery models (Table 2). Furthermore, the magnitude of change in NK cell cytotoxicity which is needed to produce a clinically relevant effect is unknown. It is therefore difficult to definitively attribute a decrease in NK cell cytotoxicity with poorer outcomes in patients with cancer.

### Table 2: Summary of the effects of opioids on NK cell cytotoxicity and cancer outcomes in the different models

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Animal NK cell cytotoxicity</th>
<th>Animal Cancer</th>
<th>Healthy volunteer NK cell cytotoxicity</th>
<th>Healthy volunteer Cancer</th>
<th>Human cancer surgery NK cell cytotoxicity</th>
<th>Human cancer surgery Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Decrease/no effect on suppressive effects of surgery</td>
<td>Increase</td>
<td>Decrease</td>
<td>No effect/delayed postoperative recovery</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Decrease/no effect on suppressive effects of surgery</td>
<td>Increase</td>
<td>Increase</td>
<td>Delayed postoperative recovery</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>No effect/reversed the suppressive effects of surgery</td>
<td>No effect</td>
<td>Not assessed</td>
<td>No effect/reversed the suppressive effects of surgery</td>
<td>Not assessed</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>Increase/reversed the suppressive effects of surgery</td>
<td>Decrease</td>
<td>Not assessed</td>
<td>Increase/reversed the suppressive effects of surgery</td>
<td>Not assessed</td>
<td></td>
</tr>
</tbody>
</table>

**Systemic opioid sparing surgical studies**

Many studies have assessed the effects of regional analgesia vs. systemic opioids on clinical outcomes. In general, these compare clinical outcomes between pain control with regional/neuraxial analgesia and systemic opioids in patients having cancer surgery.
Meta-analyses for the effect of neuraxial blockade on cancer surgery have generated mixed findings from the included heterogeneous and mostly retrospective studies. One concluded that there was no advantage for overall or progression-free survival (Cakmakkaya et al., 2014), another suggested there might be a benefit for neuraxial blockade for prostate cancer surgery, but not for colonic cancer (Pei et al., 2014). The most recent and largest meta-analysis (21 included studies) reported an association between improved recurrence-free and overall survival with neuraxial anaesthesia (compared to general anaesthetic alone), especially in patients having colorectal cancer surgery (Weng et al., 2016).

There are many reviews assessing the various perioperative factors which might influence cancer-related outcomes. They suggest that although pre-clinical studies indicate a benefit of regional anaesthesia and stress response reduction in cancer formation, there is no clear association between regional/neuraxial anaesthesia for cancer surgery and tumour recurrence and cancer-related survival benefit from the heterogeneous and mostly retrospective studies. However, there might be an association with improved overall survival (Cata et al., 2014; Sun et al., 2015; Vogelaar et al., 2016). This needs confirmation and causality explored in prospective studies.

A randomised controlled trial of 503 patients undergoing abdominal surgery for cancer resection compared the effect of general anaesthesia with either epidural analgesia or postoperative systemic opioids (median 3-day morphine dose: 0mg epidural group; 107mg opioid group). This showed no difference in cancer recurrence and mortality at 2-3 years between the two groups (Myles et al., 2011). In a prospective cohort study of 34,188 cancer survivors who had resections for early stage breast cancer, opioid prescriptions were not associated with breast cancer recurrence (Cronin-Fenton et al., 2015). This echoes previous studies indicating that opioids do not increase de novo cancer risk.

As surgical stress response and increased glucocorticoids can cause immune suppression, some of the benefits from regional anaesthesia may be because of better analgesia (reducing pain-associated immune suppression), along with attenuation of the surgical stress response, decreases in levels of endogenous opioids and the lower doses of systemic opioids (Al-Hashimi et al., 2013; Byrne et al., 2016; Juneja, 2014).

Data on the influence of opioid-sparing techniques for the surgical resection of cancer are mixed, and are primarily derived from retrospective studies. Although the most recent meta-analysis reported an association between improved recurrence-free and overall survival with
neuraxial anaesthesia (Weng et al., 2016), more randomised controlled trials are needed in different cancers to elucidate causation, some of which are underway (Buggy et al., 2015; Byrne et al., 2016; Connolly et al., 2016). In the meantime, there is consensus that there is currently insufficient evidence to change perioperative practice until the results of definitive randomised controlled trials are available (Buggy et al., 2015; Byrne et al., 2016; Connolly et al., 2016).

Effects of opioids on anti-tumour immunity and survival in patients with cancer

Many people receive long-term opioids for cancer-related pain who are not undergoing surgery, and this is a different scenario in terms of the immune effects of opioids and clinical consequences.

Effects of opioids on immunological parameters that are relevant to anti-tumour immune potential in patients with cancer have been reviewed previously (Boland et al., 2014b). Five human studies which assessed the immune effects of morphine in patients with cancer showed variable effects on immunologic end points. Given that none of these studies measured the clinical effects, it is not possible to know the clinical significance of these (Boland et al., 2014b).

Opioids, via immune (and non-immune) effects can influence cancer progression in animal studies and other patient groups. The effect of opioids on prognosis in patients with cancer not undergoing surgery has been systematically reviewed (Boland et al., 2015). In the 13 studies of people in the last days/weeks of life, there were mixed effects of opioids on survival. These studies were short term with poor methodology, sometimes only including patients with a very limited life expectancy such as from hospice admission, or just measured opioids taken in the last day(s) of life (Boland et al., 2015). The best quality end of life study, a secondary data analysis, showed that an intravenous morphine-equivalent dose (IVME) above 20 mg/day was associated with a shorter survival compared with ≤17 mg/ day (the lowest dose group); mean survival: 27 days for patients on ≤17 mg/day IVME vs 12 days for patients on 20-25 mg/day IVME (Portenoy et al., 2006). Studies in patients with a longer prognosis (months to years) tended to be larger and of better quality. Six out of seven studies described an association between strong systemic opioid use or increasing dose and shorter survival. However, these studies did not have survival as a primary, appropriately powered,
endpoint. Furthermore they were limited in that they included variable populations, starting points for opioid use, durations of opioid administration and from when survival was measured. The main confounding factor is that the control groups were not directly matched (i.e. not patients who had refractory severe symptoms, but did not choose opioids), and that greater analgesic requirements and shorter survival is likely to be mediated by painful progressive cancer. As a consequence, these studies cannot show causality, only associations (Boland et al., 2015).

Pharmacogenetic factors are also important. In 2039 women with breast cancer, the A118G MOR polymorphism, which confers a reduced receptor response to opioids, was associated with increased cancer-related survival in invasive breast cancer (Bortsov et al., 2012). Furthermore, Chinese people with the A118G MOR polymorphism had a lower incidence of oesophageal cancer (Wang et al., 2013).

**Future studies**

In view of variable findings between study models, these cannot be extrapolated from in vitro, animal or healthy volunteer to clinical settings, or between the different clinical settings or between opioids (Juneja, 2014; Ramaswamy et al., 2016). Therefore, appropriate studies in each of the clinical settings where opioids are used are needed. These need to focus on long term clinical studies, like those in progress in the surgical setting, and these need to be done in people needing long term opioids for non-surgical cancer-related pain. In vitro, animal and healthy volunteer studies should be used principally to explore mechanisms, as the environments can be carefully controlled. Furthermore, subset analysis of NK cells is needed (as CD56\textsuperscript{bright} and CD56\textsuperscript{dull} NK cells have different function) (Tabellini et al., 2014), and pharmacogenomics, such as the A118G MOR polymorphism, should be taken into account.

People taking opioids for cancer-related pain could be on opioids for a long time, thus tolerance could develop. Given that they might also be on opioids intermittently, it is important to know if regular or intermittent opioids are more immune protective and how this influences clinical outcomes. As pain is immunosuppressive, the effects of pain in patients and how opioids influence immunity and clinical outcomes in these populations need further study. Appropriately designed and powered studies assessing clinical outcomes of opioid use...
in people with cancer are required to inform the optimal use of opioids in these patient groups.

**Conclusion**

Evidence from preclinical, healthy volunteer, clinical and surgical models suggests that different opioids variably influence protective anti-tumour immunity. There are discrepancies in the results of these studies which might be partly explained by differing methodologies, species used, opioid used and the dose and duration of administration. However, in general the literature reports that morphine and fentanyl decrease NK cell cytotoxicity *in vivo* (although short-term *in vivo* exposure to fentanyl in healthy humans increases NK cell numbers and cytotoxicity), buprenorphine does not affect NK cell cytotoxicity and tramadol enhances it. This change in NK cell cytotoxicity correlates with tumour growth and metastasis in rodent models. Opioid dose and duration of administration can influence outcome.

Although clinical evidence is sparse, data suggest that perioperative opioid sparing may lead to better long-term outcomes. However, high-quality perioperative and chronic cancer-related pain studies are needed. Given that current data from patients with cancer are inconclusive, definitive recommendations about how adequate analgesia is best achieved cannot be made and opioids for cancer-related pain continues to be recommended.
References


