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Effects of opioids on immunologic parameters that are relevant to anti-tumour immune potential in patients with cancer: a systematic literature review

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Background: The immune system has a central role in controlling cancer, and factors that influence protective antitumour immunity could therefore have a significant impact on the course of malignant disease. Opioids are essential for the management of cancer pain, and preclinical studies indicate that opioids have the potential to influence these tumour immune surveillance mechanisms. The aim of this systematic literature review is to evaluate the clinical effects of opioids on the immune system of patients with cancer.

Methods: A systematic search of Ovid MEDLINE (PubMed) and Embase, Cochrane database and Web of Knowledge for clinical studies, which evaluated the effects of opioids on the immune system in patients with cancer, was performed.

Results: Five human studies, which have assessed the effects of opioids on the immune system in patients with cancer, were identified. Although all of these evaluated the effect of morphine on immunologic end points in patients with cancer, none measured the clinical effects.

Conclusions: Evidence from preclinical, healthy volunteer and surgical models suggests that different opioids variably influence protective anti-tumour immunity; however, actual data derived from cancer populations are inconclusive and definitive recommendations cannot be made. Appropriately designed and powered studies assessing clinical outcomes of opioid use in people with cancer are therefore required to inform oncologists and others involved in cancer care about the rational use of opioids in this patient group.

The innate and adaptive immune systems provide crucial protection against pathogenic organisms and cancer (Gaspani *et al*, 2002; Shavit *et al*, 2004; Nüssler *et al*, 2007). Cancer immunosurveillance involves natural killer (NK) cells that have an inherent (innate) capacity to recognise and kill tumours via cell surface molecules (Table 1), the secretion of immunoregulatory cytokines and the actions of white blood cell (lymphocyte) subsets, which control and regulate anti-tumour immunity (T 'helper' or $CD4^+$ T cells) or recognise and kill transformed cells ('cytotoxic' T or $CD8^+$ T cells) (Table 1) (Foulds *et al*, 2013).

The importance of immunosurveillance in the context of cancer has been illustrated by a number of findings. High NK cell cytotoxicity and high concentrations of cytotoxic T cells are associated with a reduced progression of disease and better survival in patients with colorectal cancer (Nüssler *et al*, 2007; Pages *et al*, 2009). In contrast, rodent studies using the MADB106

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Table 1. Role and activation pattern of the main immune cells

Cell	Role	Activators	Mechanism of activity	Arm
Dendritic cell	Antigen presentation	Multiple, including bacterial products and cytokines	Presentation of antigenic peptides in the context of MHC class I and II molecules and the delivery of essential costimulatory molecules	Innate
Natural killer cell	Anti-tumour Anti-viral	Multiple, including the lack of MHC class I expression	Release of cytotoxic molecules (granzymes, perforin)	Innate
Neutrophil	Anti-bacterial/-fungal	Opsonisation	Phagocytosis and oxidative burst	Innate
Monocyte–macrophage lineage	Anti-bacterial/-fungal	Opsonisation Antigen presentation	Phagocytosis and oxidative burst	Innate
$CD4^+$ T cell	Immune coordination/ regulation	Antigenic peptides presented by MHC class II plus essential costimulatory molecules	Regulating the activity of other immune cells	Adaptive
$CD8^+$ T cell	Cytotoxicity	Antigenic peptides presented by MHC class I	Induction of apoptosis by (i) release of cytotoxins (perforin, granulysin, granzymes), (ii) direct cell–cell contact, by upregulating surface Fas ligand	Adaptive
B cell	Antibody production	Antigens binding to surface immunoglobulin with help from $CD4^+$ T cells	Antibody production	Adaptive

Abbreviations: CD = cluster of differentiation; MHC = major histocompatibility complex.

(mammary adenocarcinoma) cell line have shown that tumour burden can increase if NK cell cytotoxicity is reduced (Gaspani *et al*, 2002; Shavit *et al*, 2004). Furthermore, the incidence of secondary cancers is higher in patients who have had chemotherapy for a primary cancer (Morton *et al*, 2013). The effect of immune system impairment can also be selective, as there is a higher incidence of non-Hodgkin's lymphoma, lip cancer and melanoma in transplant recipients on immunosuppressive treatment, whereas the incidence of leukaemia, lung, kidney and urinary tract cancers remained the same (Van Leeuwen *et al*, 2010).

The central role that the immune system has in protecting against cancer means that any factors that influence protective anti-tumour immunity are likely to have a profound impact on the course of disease. Although opioids are essential for the management of cancer pain, numerous *in vitro*, animal and volunteer models have reported opioids to have a number of immunoregulatory effects. These are dependent on the opioid being tested, the component of the immune system that is being influenced, the administration schedule and also the experimental model (Van Der Laan *et al*, 1996; West *et al*, 1997; Martucci *et al*, 2004). Given the evidence that opioids have the capacity to influence anti-tumour immunity, it is important to better understand the potential clinical impact of opioid usage in this context.

Although the immune effects of opioids in patients with cancer have been reviewed previously (Budd, 2006; Pergolizzi *et al*, 2008; Sacerdote, 2008), there has been no systematic review of the literature assessing the effects of opioids on anti-tumour immune potential in patients with cancer and how these effects could influence the clinical management. The immunologic consequences of opioids that are administered to patients with chronic cancer pain over a period of several months are likely to be very different to those that are induced by the relatively short treatments that are administered to healthy volunteers or patients post-surgery, because of the differing immunologic phenotypes of these groups (Snyder and Greenberg, 2010; Colvin *et al*, 2012; Heaney and Buggy, 2012; Foulds *et al*, 2013; Galizia *et al*, 2013). We therefore conducted a new systematic review of the literature relating to the effects of a broad range of therapeutic opioids on immunologic parameters that are relevant to protective anti-cancer immunity in non-surgical clinical studies.

It is becoming apparent that an individualised approach to cancer pain treatment is essential, as the analgesic properties and side effects of opioids exhibit great interindividual variability (Ahmedzai, 2013), as do their influence on immune cell function (Thomas *et al*, 1995; Jacobs *et al*, 1999). Furthermore, even if opioids were to have immunomodulatory effects in patients, this would only be of clinical interest and relevant to prescribers if these significantly influenced tumour growth, metastasis, infection and/or other clinical outcomes.

We have identified five studies that evaluated the effect of opioids on immune function in patients with cancer. However, the literature indicates that only the effect of morphine has been evaluated, and none of the studies have reported on relevant clinical end points.

MATERIALS AND METHODS

Search strategy and selection criteria. The aim of this review was to identify all relevant non-surgical clinical studies that have evaluated the effects of opioids on the immune system in patients with cancer. On 8 November 2013, the electronic databases Ovid MEDLINE (PubMed) and Embase (Ovid MEDLINE(R) 1946 to Present and Ovid MEDLINE In-Process and Other Non-Indexed Citations, and Embase 1974 to 2013 Week 29), Cochrane database and Web of Knowledge were searched using the terms and dates listed below. These were devised to be inclusive of all potentially relevant studies and have been extended to include terms relating to other conditions that are mapped to Medical Subject Heading (MeSH) terms as well as searching for these terms as text word searches to increase the search sensitivity. To search for opioids, the search terms used were: opioid OR opiate OR morphine OR codeine OR buprenorphine OR methadone OR tramadol OR tapentadol OR oxycodone OR heroin OR fentanyl OR hydromorphone OR oxymorphone. These were combined with a search for cancer OR neoplasm and immunity: including immune* OR NK cell OR T cell. The limits were English language; clinical trial (any); adults; humans; all adult (MEDLINE) from 1974 to 2013. All titles and abstracts were reviewed to assess their relevance for inclusion. The results of these searches are shown in the PRISMA Flow Diagram (Figure 1; Moher *et al*, 2009).

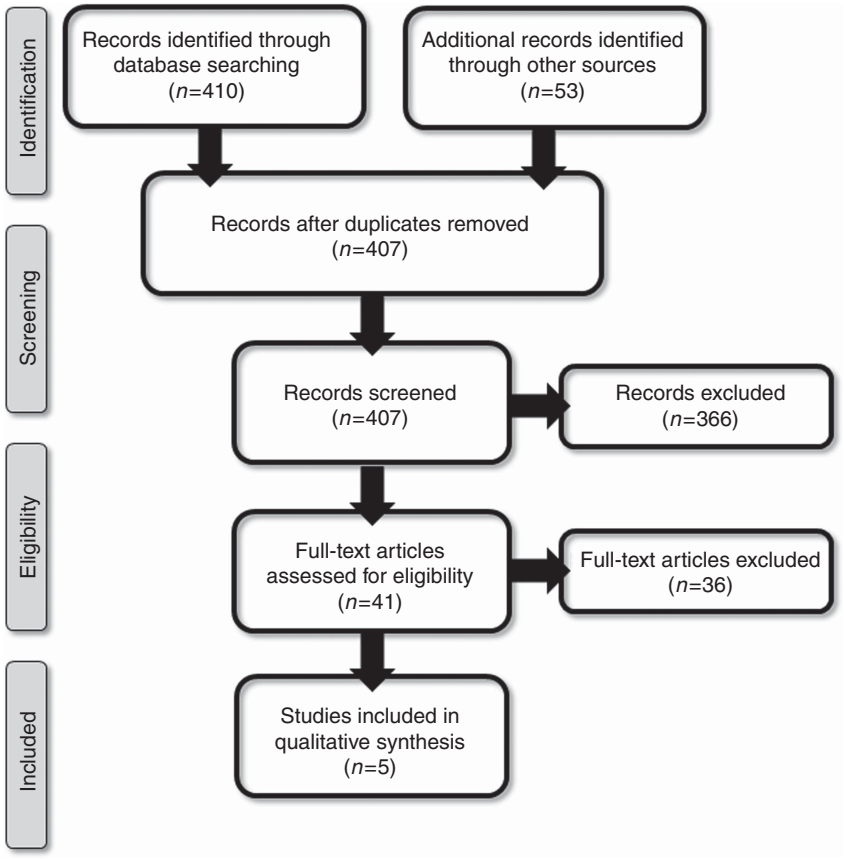

Figure 1. PRISMA flow diagram.

In addition to the electronic search, reference lists from identified reviews and key publications were manually searched. Articles were also identified through searches of the authors' own files, previous reviews on opioid-induced immunosuppression and outputs from prominent researchers in the field. Only papers published as full-text articles in English were reviewed. Surgical studies, patients undergoing cancer surgery, healthy volunteer studies and animal studies were excluded from this systematic review, as these groups have different opioid usage, immune system activation and receptor expression compared with patients on long-term opioids for cancer pain (Snyder and Greenberg, 2010; Colvin *et al*, 2012; Heaney and Buggy, 2012; Foulds *et al*, 2013; Galizia *et al*, 2013). Patients undergoing surgery are also exposed to a range of drugs during the operation, which potentially impact on immune function (Colvin *et al*, 2012; Heaney and Buggy, 2012). Furthermore, the effect of opioids in patients undergoing cancer surgery has been reviewed elsewhere (Colvin *et al*, 2012; Heaney and Buggy, 2012). As the data are only relevant if opioids have significant clinical effects, we specifically looked for articles that assessed clinical effects.

Two authors (JB and KM) undertook independent electronic literature searches and reviewed all titles and abstracts. Full papers were retrieved for those fulfilling the criteria, and also for those publications for which the ability to assess their eligibility could not be assessed on the basis of the titles and abstracts alone. Two review authors (JB and KM) then assessed the full text of all potentially relevant studies. Disagreement at all stages was resolved by consensus and with recourse to a third review author (AGP).

Data extraction, assessment and analysis. JB and KM independently extracted data regarding study design and results and assessed their quality. Data extracted were the type of study, study setting, study population (cancer type, stage, treatment) opioid used, dose and clinical outcome measures (e.g. survival). The methodologic quality of each study was independently assessed by JB and KM using Quality Assessment of Studies of Diagnostic Accuracy included in Systematic Reviews (QUADAS-2) (Whiting *et al*, 2011).

RESULTS

This systematic review of the effects of therapeutic opioids on immune function in patients with cancer identified five studies that were eligible for inclusion (Table 2). All were found to be prospective observational studies and no randomised controlled trials have been undertaken. These clinical studies have focused on the effects of opioids on markers of immune function, rather than on relevant clinical outcomes. All studies examined the effects of morphine – no other opioids have been investigated.

The quality of studies was determined using a QUADAS-2 analysis (Whiting *et al*, 2011). Included studies had a low risk of bias (patient selection, index test and flow and timing) and an unclear risk of reference standard. The two studies by Provinciali *et al* (1991, 1996) had an unclear patient selection risk. All studies had a low risk for applicability concerns (patient selection, index test and reference standard).

Makimura *et al* (2011) attempted to find markers that could predict resistance to morphine treatment by examining the plasma concentrations of 26 cytokines before and after morphine treatment in 44 patients with metastatic cancer (Table 2). They observed interindividual variability in baseline plasma cytokine concentrations and found no significant changes in the levels of

Table 2. Summary of the effect of opioids on immune function in patients with cancer

Author (year)	Research question	Patient population	Study design and method of recruitment	Interventions (opioid and doses) and comparator	Assoc. between opioid and immune function
Makimura *et al* (2011)	Are plasma cytokine levels potential biomarkers for predicting resistance to morphine treatment in opioid-naive cancer patients?	44 Patients Age 69 (40–85) years 50% Men 93% Metastatic cancer PS status 1 (20%), 2 (55%), 3 (23%), 4 (2%)	Prospective observational study Cytokines measured at baseline and compared with samples after 8 days of opioid treatment Morphine titrated as per a standardised protocol (dose not specified)	Morphine – doses not specified Patients acted as own controls, baseline samples compared with day 8	None (except MIP-1a level decreased ($P=0.03$) but multiple comparisons) (baseline: $7.2\pm19.3\,pg\,ml^{-1}$ *vs* day 8 $2.3\pm7.4\,pg/ml^{-1}$) Plasma IL-12 (p40) level decreased nonsignificantly ($P=0.07$) (baseline: $7.0\pm17.4\,pg\,ml^{-1}$, day 8: $2.7\pm7.6\,pg\,ml^{-1}$) No clinical end points measured
Hashiguchi *et al* (2005)	Do morphine and its metabolites modulate immune function in advanced cancer patients?	14 Patients Age 28–76 years 53% Men Mixed-stage IV cancers (including breast, tongue, sarcomas) PS – not documented Group 1: 6 patients, opioid naive Group 2: 8 patients on morphine for 1 month	Prospective observational study Bloods at enrollment (phase 1), 1 week after starting or changing morphine dose/route (phase 2) and 2 weeks after phase 2 (phase 3). Phase 2 was between 10 and 21 days after phase 1 Limitations – 1 patient in group 2 excluded from phase 2 analysis; 2 in group 1, and 4 in group 2 excluded from phase 3 analysis due to deterioration	Group 1, final morphine dose 20–30 mg (routes: oral, intravenous) group 2: starting morphine dose 40–120 mg (oral, 1 rectal); final morphine dose 20–240 mg (routes: oral, intravenous, subcutaneous, rectal) Patients acted as own controls	Negative correlation in Group 1 between morphine, M3G and M6G and immunoglobulin's and PHA-induced lymphocyte proliferation but not NK cell activity or CD4/CD8 ratio Poor correlation for all immunologic markers in Group 2 No clinical end points measured
Provinciali *et al* (1991)	How does morphine affect NK and LAK cell activity in neoplastic patients?	20 Patients with cancers of different origins (including breast, lung, ovarian and prostate) Age, gender, cancer stage, and PS status not reported	Prospective observational study Blood analysed 1 month after starting treatment and compared with healthy volunteers (transfusion centre) Limitations – no baseline analysis	$N=9$ p.o. morphine $\pm$ 30 mg per day $N=6$ i.t. morphine patients 4 ± 1.5 mg per day $N=5$ opioid-naive patients Three patients acted as own controls from p.o. morphine to subsequent i.t. treatment Blood from healthy subjects provided by transfusion centre	Sig reduced NK cell activity ($P<0.05$) NK cell activity reduced further with i.t. than p.o. LAK cell activity significantly increased LAK cell activity higher in p.o. than i.t. ($P<0.005$) No clinical measurements
Provinciali *et al* (1996)	How does short- or long-term morphine administration affect NK/LAK activities?	18 Patients (breast, lung, ovary, prostate, bladder, colon, larynx, stomach and kidney cancer) Age, gender, cancer stage and PS status not reported 10 patients treated with morphine 8 patients had no opioids	Prospective interventional study Short term – 9 patients treated with i.v. 10 mg morphine (4 pretreated with 5 mg p.o. bromocriptine). Blood checked at baseline and after 30 min Long-term p.o. morphine (90 ± 30 mg) for 1 month Limitations – 8 controls low/no pain, 10 active patients had high levels of pain	Morphine:10 mg i.v. in short-term study 90 ± 30 mg per day p.o. for 1 month in long term study $N=8$ opioid naive cancer patients as controls	*Short term*: Cytotoxicity of NK cells reduced 113 ± 62 *vs* $44\pm44\,LU_{20}/10^7$ ($P=0.01$) Increased LAK activity 169 ± 45 *vs* $252\pm62\,LU_{20}/10^7$ ($P=0.02$) No change in the number of peripheral lymphocytes or % $CD3$, $CD4$, $CD8$, $CD16$, $CD56^+$ cells *Long term*: NK cell activity reduced in morphine group *vs* those not treated 89 ± 23 *vs* $171\pm27\,LU_{20}/10^7$ ($P<0.001$) Higher LAK activity in morphine-treated *Daudi*: 1581.5 ± 1325.0 *vs* 408.0 ± 24.15 ($P=0.04$) *K562*: 4420.4 ± 3351.2 vs 1229.0 ± 1643 ($P=0.02$) Higher % of $CD3^+$ and $CD4^+$ increased in morphine-treated CD3 (%): 50 ± 4 vs 44 ± 8 ($P<0.05$) CD4 (%): 31 ± 3 vs 25 ± 5 ($P<0.05$) % $CD8+$ not affected by morphine treatment 12 ± 1 vs 13 ± 3

Table 2. (Continued)

Author (year)	Research question	Patient population	Study design and method of recruitment	Interventions (opioid and doses) and comparator	Assoc. between opioid and immune function
					Decrease % $CD16^+$ cells in morphine treatment 13 ± 3 vs 20 ± 6 ($P<0.05$) No clinical end points
Palm *et al* (1998)	Does prolonged oral treatment with sustained release morphine tablet influence immune function?	10 Patients (3 advanced cancer related pain; 7 non-malignant pain) Age 51.5 (37–65) years 60% Men PS not reported Eight age- and sex-matched healthy controls	Prospective observational study Blood samples before initiation of morphine treatment and after 1, 4 and 12 weeks	Morphine dose 30–240 mg per day Patients acted as own controls from baseline measurements and were also compared with age- and sex-matched healthy controls	Total lymphocyte counts, lymphocyte sub-populations, PHA-induced proliferation of PMC did not differ between patients and controls at baseline or during 12 week study period PMC synthesis of IL-2 increased five-fold after 4 weeks morphine treatment ($P<0.05$) IgM production from PMW cells no longer possible after 4 weeks morphine treatment Impairment of spontaneous and PWM-stimulated IgG production No difference in IgG or IgM between patients and controls at baseline or during treatment No clinical end points

Abbreviations: Ig = immunoglobulin; IL = interleukin; i.t. = intrathecal; i.v. = intravenous; LAK = lymphokine-activated killer; M3G = morphine-3-glucuronide; M6G = morphine-6-glucuronide; MIP-1a = macrophage inflammatory protein 1α; NK = natural killer (cells); PHA = phytohaemagglutin; p.o. = oral; PMC = peripheral mononuclear cell; PS = performance status; PMW = pokeweed mitogen.

any cytokine (including interleukin-2 (IL-2)) after 8 days of treatment with morphine in previously opioid naive patients. This contrasts with the study by Palm *et al* (1998), which showed that the synthesis and secretion of IL-2 by lymphocytes increased significantly after 4 weeks of morphine treatment in 10 patients with chronic pain (including three with cancer). No clinical end points, for example, cancer progression- or disease-free survival were evaluated in either study (Palm *et al*, 1998, Makimura *et al*, 2011). This may suggest that the acute effects of opioids (over days) on the immune system differ from those that are induced following chronic exposure (over weeks).

The possibility that the immunologic consequences of opioids (morphine) depends on the nature of the exposure has been confirmed in a study of 15 patients with advanced cancer by Hashiguchi *et al* (2005) (Table 2), which reported that the impact of opioids on immune function might correlate with the duration of opioid administration. They found a negative correlation between the levels of morphine metabolites and circulating immunoglobulin levels and the *in vitro* proliferation of peripheral blood lymphocytes in response to phytohaemagglutin (a non-specific activator of T cells) in patients who had just commenced on morphine. In contrast, no such effects were observed in patients who had been on morphine for over 1 month. Once again, no clinical parameters were measured.

Patients with a variety of cancers (including breast, lung, ovarian and prostate) on oral or intrathecal morphine have been reported to exhibit a lower NK cell activity and increased lymphokine-activated killer (LAK) cell activity than untreated or healthy controls (Table 2; Provinciali *et al*, 1991). The observation that intrathecally delivered morphine had a more profound effect than oral morphine suggests an important role for a centrally mediated effect. However, only a very small number of patients was studied and no clinical correlates were investigated (Provinciali *et al*, 1991). In a subsequent study, Provinciali *et al* (1996) determined the short-term immune effects (at 30 min) after a single 10 mg intravenous dose of morphine and the long-term effects after 1 month of oral morphine (90 ± 30 mg per day) on NK and LAK cell cytotoxicity in 18 patients with cancer (including breast, lung, ovary and prostate). These cytotoxicity responses were compared with baseline measurements, and those that were present before opioid treatment in the short-term experiments and in cancer patients not on opioids in the long-term study. This study demonstrated that both acute and chronic morphine administration reduced NK cell activity and increased LAK activity. Chronic morphine administration has also been shown to increase the proportion of $CD3^+$ and $CD4^+$ T cells in peripheral blood mononuclear cell preparations, whereas the prevalence of $CD8^+$ T cells is unaffected and the proportion of $CD16^+$ lymphocytes is reduced. CD16 is a member of the Fc receptor family that is instrumental for the induction of antibody-dependent cellular cytotoxicity (ADCC). Antibody-dependent cellular cytotoxicity is a mechanism of cell-mediated immune defence and a decrease in the presence of such cells might therefore negatively impact on tumour surveillance. None of these parameters were affected during acute morphine administration (Provinciali *et al*, 1996). The number of patients in this study was also small, their cancers were different and once again no clinical measurements of tumour progression or survival were measured.

In summary, the studies included here suggest that the influence of morphine on immune potential could be dependent on whether it is administered acutely or chronically, the route of administration and also the immune parameters that are considered. These observations cannot be extrapolated to all opioids due to the heterogeneous physicochemical and pharmacologic properties of this broad class of drugs (Sacerdote *et al*, 1997; Keiser *et al*, 2009). Furthermore, the most important outcome – the clinical impact of these immune influences on cancer progression and patient survival – remains unexplored.

DISCUSSION

The management of pain is essential, as its immunosuppressive properties can influence cancer growth in animal models (Page *et al*, 2001; Gaspani *et al*, 2002; Page, 2003, 2005). Fears of precipitating serious toxicity and the risk of dependence and

tolerance make clinicians commonly reluctant to prescribe opioids, even for patients with significant cancer-related pain (Pergolizzi *et al*, 2008; Breuer *et al*, 2011). This is leading to the greater use of non-pharmacologic methods of pain control such as the delivery of opioids intrathecally, rather than in the form of long-term systemic treatment. Radiation therapy and adjunctive treatments including bisphosphonates and RANK ligand antibodies can also reduce bone cancer pain, and vertebroplasty or balloon kyphoplasty offers good pain relief from vertebral metastases (Terpos *et al*, 2014). The possibility that morphine can directly influence proliferation, apoptosis and metastatic potential of cancer cells and increase tumour growth in animal models raises additional concerns that opioids might promote disease progression (Gaspani *et al*, 2002; Shavit *et al*, 2004; Afsharimani *et al*, 2011; Gach *et al*, 2011). Despite these alternatives and their potential benefits, opioids continue to be essential for the management of cancer pain. Indeed, it is possible that the immunosuppressive effects of pain can be reversed by certain opioids, as tramadol (but not morphine) can overcome the capacity of surgical stress to decrease NK cell activity and enhance tumour metastasis in preclinical models (Gaspani *et al*, 2002).

Immune cells express ORL1 when resting and the mu opioid receptor, which is considered to be critical for immune cells to respond directly to most commonly prescribed opioids, following activation (Williams *et al*, 2007; Borner *et al*, 2008). Opioid receptor activation triggers multiple downstream signalling events, which include decreasing cyclic adenosine monophosphate (cAMP), increasing nitric oxide and cyclic guanosine monophosphate levels, and the stimulation of phospholipase C, mitogen-activated protein kinase (MAPK) and protein kinase C (Kelly *et al*, 2008; Stefano *et al*, 2008). All of these interactions ultimately interfere with immune cell activation pathways, which involve cAMP and MAPK (Borner *et al*, 2008, 2009). Activated immune cells can produce several opioid peptides (such as β-endorphin) in addition to endogenous morphine that can bind to opioid receptors present on peripheral nerves to induce analgesia (Stein and Lang, 2009; Glattard *et al*, 2010). The presence of opioid receptors on activated lymphoid cells suggests that endogenous opioids released by such cells could also contribute to an inhibitory feedback loop (Borner *et al*, 2008). These potential effects are summarised in Figure 2.

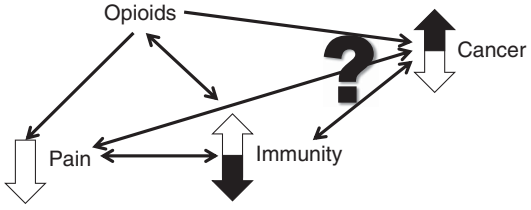

Figure 2. Quadrangulation of the effects of opioids on pain, immunity and cancer. Under normal circumstances opioids inhibit pain, which is itself immunosuppressive (Page *et al*, 2001; Page, 2003). Some opioids also have specific effects on immune function, either suppressive or stimulatory, and the balance of these opioid-mediated effects influences the progression of cancer (in animal models) (Gaspani *et al*, 2002). The immune system, via microglia and cytokines, influences the pain state (Hutchinson *et al*, 2008). Activated immune cells can also produce endogenous opioids, as well as morphine (Stein and Lang, 2009; Glattard *et al*, 2010). Cancer can also cause pain, by nociceptive, neuropathic and inflammatory mechanisms. There is a dynamic interaction of the immune system and cancer with immunoediting and immunosculpting (Reiman *et al*, 2007). Furthermore, there are non-immune effects of opioids on cancer cells (Gach *et al*, 2011). All of these factors combine to create the net balance of cancer cell growth or destruction (Page, 2005). The white arrows indicate a beneficial effect on pain, immunity and cancer, and the solid arrows indicate a detrimental effect on immunity and cancer.

The immunoregulatory effects of morphine and some other opioids can also be elicited by direct effects on immune cells expressing non-opioid receptors such as Toll-like receptor 4 (TLR4) (Wang *et al*, 2002; Borner *et al*, 2008, 2009; Keiser *et al*, 2009; Hutchinson *et al*, 2010; Franchi *et al*, 2012). Opioids can also have indirect effects that manifest via centrally produced mediators such as immunosuppressive glucocorticoids that are released as a consequence of hypothalamic pituitary adrenal axis activation, and via effects on the sympathetic nervous system, which innervates lymphoid organs (Figure 3; Wang *et al*, 2002).

Studies in rats have reported that oral morphine can suppress T- and B-cell proliferation and NK cell activity (Van Der Laan *et al*, 1996; West *et al*, 1997). Conversely, rodent models have shown that tramadol, but not morphine, dose-dependently increases NK cell cytotoxicity. Furthermore, tramadol, but not morphine, reduces lung metastasis following the injection of MADB106 mammary tumour cells into rats (Gaspani *et al*, 2002). The capacity of tramadol to enhance immunity might be because of its coexisting intrinsic serotonergic effect (Sacerdote *et al*, 2000; Gaspani *et al*, 2002). In mice, a single subcutaneous dose of fentanyl, but not buprenorphine, decreases lymphoproliferation in response to the mitogen concanavalin A, but has no effect on NK cell cytotoxicity (Martucci *et al*, 2004). A continuous infusion of fentanyl has been shown to decrease lymphoproliferation and NK cell cytotoxicity at 24 h, with NK cell cytotoxicity normalising by day 3. However, tolerance to the effects on lymphoproliferation did not develop until day 7 in these studies (Martucci *et al*, 2004). Buprenorphine had no such effects. In a rodent surgical model, a

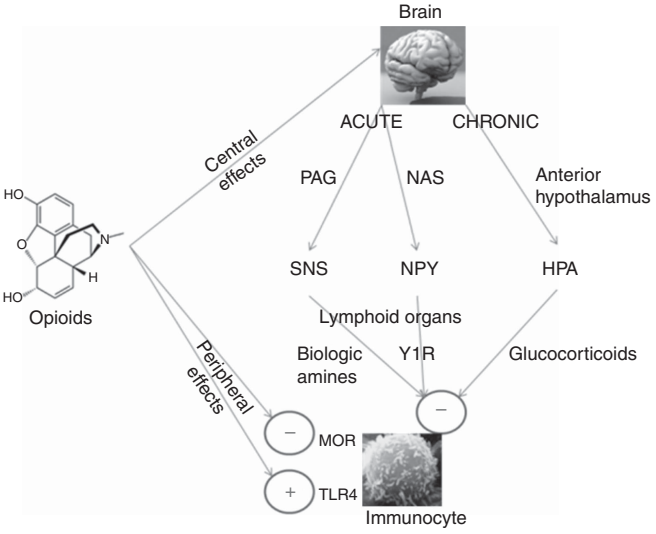

Figure 3. Peripheral and central mechanisms of opioid-induced immune suppression. Different opioids can have direct effects on immune cells, which express appropriate receptors such as mu-opioid receptors (MORs) and TLR4. They can also have immunosuppressive effects on specific immune cells via central 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 biologic amines, which suppress splenic lymphocyte proliferation and natural killer (NK) cell cytotoxicity (Irwin *et al*, 1988; Fecho *et al*, 1996). 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 and Bayer, 1998). Morphine can also act via D_1 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*, 2006).

single dose of fentanyl increased suppression of NK cell activity and resulted in more lung metastasis following the injection of MADB106 tumour cells (Forget *et al*, 2010). Although NK cell cytotoxicity in healthy volunteers is suppressed by morphine (Yeager *et al*, 1995), fentanyl has been shown to increase the number of circulating NK cells and NK cell cytotoxicity (Jacobs *et al*, 1999; Yeager *et al*, 2002).

Although clinically relevant concentrations of morphine and methadone have been shown to inhibit cytotoxicity of NK cells from rats, monkeys and pigs (Molitor *et al*, 1992; Condevaux *et al*, 2001), such effects have not been seen in healthy volunteers, with *in vitro* studies indicating that clinically relevant concentrations of morphine, methadone, fentanyl and diamorphine do not influence NK or T cells (Yeager *et al*, 1992; House *et al*, 1995, Thomas *et al*, 1995; Jacobs *et al*, 1999; Boland *et al*, 2013).

The preclinical data indicate that tramadol might be potentially stimulating of the immune response (Gaspani *et al*, 2002) and buprenorphine to be immune neutral (Martucci *et al*, 2004), however until there are comparative studies with clinical end points, no one opioid can be strongly recommended over another in terms of their immune effects. Furthermore, cancers will have differential effects on the immune status and immune regulatory profiles and responses in one patient might not be broadly applicable to all.

CONCLUSIONS

All studies discussed in this systematic review were prospective and observational. They all used morphine and no study reported the effects on clinical end points. Although the studies included in this review add to the current body of knowledge of opioid effects on the immune system, these findings cannot currently be extrapolated to cancer patients on chronic opioids for pain owing to differences in immune cell activation and opioid receptor expression (Borner *et al*, 2008). As a consequence, there is currently insufficient evidence on which to base a more rational choice of opioids for optimising pain control without negatively impacting on the patient's essential protective immune function. It is therefore hoped that clinically derived data will provide better evidence in the future. In the meantime, judicious doses of opioids should continue to be used as part of a multimodal approach for the management of patients with cancer pain.

AUTHOR CONTRIBUTIONS

JB and KM undertook the literature search and contributed to study design, data collection and data analysis. JB provided the figures. AGP contributed to the study design. All authors were responsible for the writing and approval of the final report.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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