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The use of opioids in cancer patients with renal impairment - a systematic review

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Title: The use of opioids in cancer patients with renal impairment – a systematic review.

Running title: Opioids in renal impairment

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Keywords: Opioids; renal impairment; cancer; pain

Word Count: 3994   Total Number of Pages: 30

Number of Tables: 1   Number of Figures: 1

Abstract

Purpose

Opioids are recommended for moderate to severe cancer pain, however in patients with cancer, impaired renal function can affect opioid metabolism. The aim of this systematic review was to evaluate the current evidence for the use of opioids in cancer patients with renal impairment.

Methods

A systematic review was conducted and the following databases were searched: MEDLINE (1966 to 2015), EMBASE (1980 2015), and Cochrane Central Register of Controlled Trials (up to 2015). Eligible studies met the following criteria: Patients with cancer pain taking an opioid (defined as per the WHO ladder); >18 years; renal impairment (serum creatinine > normal range (study dependent), creatinine clearance (CrCl) or glomerular filtration rate (GFR) measurements <90 ml/min, or as per the study definition); clinical outcome related to renal impairment. All eligible studies were appraised using the Grading of Recommendations Assessment, Development and Evaluations (GRADE) system.

Results

Eighteen studies (n=2422) were eligible but heterogeneity meant meta-analysis was not

possible. Morphine was examined in eight studies (n=1418). oxycodone in two studies (n=325), and fentanyl, alfentanil or sufentanil were discussed in six studies in total (n=442). No recommendations could be formulated on the preferred opioid in patients with renal impairment.

Conclusion

There is lack of consensus within the existing literature on the relationship between morphine, creatinine levels and morphine related side-effects. Based on the current evidence, morphine should be used with caution, however more evidence is needed. Fentanyl, alfentanil and sufentanil are recommended in patients with renal impairment based on pharmacokinetics and clinical experience. However, the present systematic review found very little clinical evidence for this. Overall the quality of the existing evidence on opioid treatment in cancer patients with renal impairment is low. There remains a need for high quality clinical studies examining opioids in patients with renal impairment.

Background

Patients with cancer may have renal impairment due to cancer treatment and/or the disease itself. To illustrate, approximately 60% of patients with cancer have been found to have a creatinine clearance <90 ml/min, and 20% have a creatinine clearance <60 ml/min.(1)

This can present some challenges, as opioids are the mainstay of treatment for moderate to severe cancer pain.(2) Impaired renal function changes opioid metabolism, particularly the half-life, due to several factors. Reduced excretion results in the accumulation of opioid metabolites. This is compounded by changes in hepatic metabolism such as changes in hepatic blood flow, induction of hepatic enzymes, altered protein binding, and altered bioavailability.(3) These alterations in the normal physiological processes mean that using opioids in patients with renal impairment is not straightforward. However it is important that an understanding of opioid metabolism in this setting is appreciated to balance the analgesic effects of opioids with any side-effects.

To date, there has been limited research examining the use of opioids in cancer patients with renal impairment. Although guidelines have been developed, these have been based on known opioid pharmacokinetics and expert opinions, rather than a strong

evidence base.(4) Subsequently there has been a variation in physicians' practise in assessment of renal function and the choice of opioids in accordance to the effect on the renal function.(5) An understanding of the evidence examining opioids in patients with renal impairment is needed. Therefore, the aim of this systematic review was to assess the current evidence for the use of opioids in cancer patients with renal impairment.

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Methods

Ethical approval was not required for this systematic review. The electronic bibliographic databases MEDLINE (1966 to September week 3 2015); EMBASE (1980 to September week 3 2015) and Cochrane Central Register of Controlled Trials (setup to 24th of September 2015) were searched.

Search strategy

An extensive literature search was done, using free text and MeSH/EMTREE search terms. Searches were limited to studies published in the English language. The search strategy is shown in Appendix 1. Hand searching of reference lists of included studies and review articles was also undertaken.

Eligible studies met the following criteria:

- Patients with cancer-related pain, taking an opioid (as defined by the WHO analgesic ladder for cancer pain relief)
- >18 years of age
- Patients with renal impairment, defined as serum creatinine above the normal range (study dependent), creatinine clearance (CrCl) or glomerular filtration rate (GFR) measurements < 90 ml/min, or as per the study definition

- Clinical outcome related to renal impairment

- Primary studies

Excluded studies assessed the longer-term efficacy of opioids during dialysis, case reports on one single patient (n=1), and studies not reported in the English language.

Appraisal

Following the literature search, the titles of all studies were reviewed and studies deemed not relevant were excluded. Then the abstracts of all remaining studies were reviewed, and again non-relevant studies were excluded. Subsequently full text studies were retrieved and evaluated.

Due to variations in study populations, outcome measures and opioid, meta-analysis was not possible. Instead studies were grouped as per primary opioid and discussed thus. Where possible, all studies had their degree of renal impairment classified according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines.(6)

The content and quality of the included studies were assessed by two authors independently (TS and BL), using the Grading of Recommendations Assessment Development and Evaluations (GRADE) criteria.(7) Factors evaluated when applying these criteria included study design; possible study limitations (allocation concealment,

large losses to follow-up, no ITT analysis carried out, early stopping for benefit and failure to report outcomes); participants; setting; and results.(7)

Results

The literature search and appraisal process are shown in Figure 1. The database searches retrieved a total of 640 studies. Removal of 54 duplicates left 586 studies for further evaluation. Hand search of reference lists of included studies, relevant chapters and review articles revealed another 16 studies, making 602 studies in total. Eighteen studies (n=2422) remained after applying the inclusion and exclusion criteria.(8-25) The included studies are shown in Table 1. The most common causes for exclusion were that opioid treatment was not given for cancer related pain; studies on opioid treatment during dialysis; and publications that were case reports.

Morphine

Eight studies assessed aspects of morphine and/or its metabolites.(8, 11, 12, 17-20, 23) Morphine is metabolised in the liver to two major metabolites; morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), both of which are excreted in the urine. M3G is an inactive metabolite, while M6G is active and more potent than morphine itself.(26)

One of the first studies to examine the relationship between morphine plasma concentrations and side-effects in patients with cancer, was published by Somogyi et al. (19) In this small study (n=11) they observed that the average steady state plasma

concentrations of morphine. M3G and M6G were related to the morphine dose per kilogram of bodyweight (p<0.01). They also found that the renal clearance of M3G and M6G were closely related (r^2=0.80; p<0.0005). No relationship was found between renal clearance of morphine. M3G and M6G. and that of creatinine. No relationship was found between plasma morphine and M6G concentrations. and pain relief (only evaluated with visual inspection). On the same theme. Tiseo et al. published a non-randomised cohort study (n=109) in patients with cancer.(20) The relationship between M6G and opioid-related side-effects was assessed and a moderate but significant correlation was demonstrated between M6G/morphine ratio. and blood urea nitrogen (BUN) (r=0.4. p<0.001) and creatinine (r=0.45; p<0.001). These findings were echoed by another study that demonstrated significantly higher concentrations of plasma M3G. M6G. and dose-corrected plasma M3G and M6G in patients with serum creatinine levels above normal range (p<0.001).(8)

Taking this further by assessing how morphine metabolites were related to opioid side effects, Tiseo et al observed that a higher creatinine level did not relate to the likelihood of side-effects: i.e. patients with a high creatinine did not have any more side-effects than those with a low creatinine.(20) This finding was supported by another study which showed no relationship between serum concentrations of morphine, M3G, M6G, and pain intensity or opioid-induced side-effects (nausea, constipation. sedation, and

cognitive failure evaluated).(11) However, other work has demonstrated significant correlations between cognitive function and plasma morphine concentrations (p<0.05), and between higher mean serum creatinine and worse cognitive function in patients with nausea and vomiting adverse effects (p<0.05).(23)

Another important clinical aspect is identifying predictors of morphine intolerance. In 2004, a non-randomised retrospective study compared patients who were morphine-tolerant with those who were morphine-intolerant. Age over 78 years (p<0.03), high white cell count (p<0.002), high platelet count (p<0.003); and poor liver- or renal function were all identified as predictors for higher risk of morphine intolerance. A follow-up study compared patients treated with morphine for at least four weeks with good response (termed "responders") to patients with poor pain control and/or intolerable side-effects on morphine treatment (termed "switchers").(18) Predictors for the need of opioid switch were identified as white cell count (OR: 1.06; 95% CI: 1.01-1.11; p=0.02); body weight (OR: 1.02; 95% CI: 1.00-1.05; p=0.02); concomitant use of antiemetics (5HT3) (OR: 14.81; 95% CI: 2.48-88.46; p=0.003); concomitant use of beta blockers (OR: 4.96; 95% CI: 1.28-19.29; p=0.021); concomitant use of proton pump inhibitors (OR: 0.32; 95% CI: 0.14-0.69; p=0.004); tumour diagnosis of the lower gastrointestinal tract (OR: 4.99; 95% CI: 1.34-18.62; p=0.02); and recent chemotherapy (within 14 days) (OR: 0.38; 95% CI: 0.14-1.01; p=0.05). Interestingly, serum creatinine

was found to not be significantly different between "responders" and "switchers" (no p-value reported), however patients were only included in the study if their creatinine was below 1.5 times the normal range.

Combining all these aspects, the most recent study in this area was published in 2015. The relationship between symptoms and/or adverse effects (fatigue; nausea/vomiting; pain; appetite; constipation; and cognitive dysfunction, assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30], scores transformed into 0-100 scales) and renal function was assessed in 1147 cancer patients on opioid treatment.(12) In this study morphine, oxycodone and fentanyl were all evaluated, and the patients included were exclusively taking one of these three opioids. For morphine, patients with higher serum concentrations were more likely to have severe constipation (OR: 1.73; 95% CI: 1.13-2.65; p<0.001) and severe cognitive dysfunction (OR: 1.77; 95% CI: 1.13-2.78; p<0.01) than patients with lower morphine serum concentrations. Patients with higher M3G serum concentration were more likely to have severe cognitive dysfunction (OR: 1.63; 95% CI: 1.03-2.56; p=0.04) than patients with lower M3G serum concentrations. M6G was not associated with any of the side-effects evaluated. Patients with moderate/severe and mild renal impairment (<90 ml/min/1.73m^2) and being treated with morphine, had significantly higher odds of having severe constipation (OR: 1.91; 95% CI: 1.08-3.37

and OR: 1.80: 95% CI: 1.18-2.75, respectively) compared with patients with normal renal function ($\geq$90 ml/min/1.73 m^2).

Oxycodone

Only two eligible studies examined oxycodone.(15) This was an uncontrolled prospective study published by Narabayashi et al. in 2008. assessing the effect on pain control when rotating from oral morphine to oxycodone in 27 patients with intolerable side-effects on morphine. Overall 21/25 (84%) of the patients achieved adequate pain control on the oxycodone treatment. Acceptability (rated by the patient on a categorical scale 1-5) was significantly improved from study entry when the patients were treated with morphine. to the end of the study when the patients were treated with oxycodone (p<0.0004). No significant correlation was found between creatinine clearance and oxycodone or its metabolites (no p-value reported).

In addition to this study. the retrospective cohort study by Kurita et al. discussed above. also evaluated whether symptoms and adverse effects are associated with renal function in patients treated with oxycodone.(12) The authors found that patients with higher serum concentrations of oxycodone were more likely to report severe fatigue (OR: 1.70; 95% CI: 1.04-2.78; p=0.03) than patients with lower oxycodone serum concentrations. The metabolite noroxycodone was not associated with any of the side-effects evaluated.

Fentanyl

One study exclusively assessed aspects of fentanyl.(25) Mazzocato et al. retrospectively reviewed the records of 53 patients (33 of them were patients with cancer) followed by a palliative care consultant team in a tertiary hospital in Switzerland. The patients had renal impairment (calculated GFR <60 ml/min), and were treated with subcutaneous fentanyl. Pain control was complete in 31/53 (59%) of patients and partial in 14/53 (26%) of patients. In patients that had experienced neurotoxic symptoms thought to be opioid-related, the symptoms resolved completely in 8/26 (31%) and partly in 6/26 (26%) of patients.

In addition to this study, the retrospective cohort study by Kurita et al. discussed above also reported on fentanyl.(12) Neither fentanyl, nor its metabolite norfentanyl were associated with any of the side-effects evaluated.

Alfentanil

Two studies examined aspects of alfentanil.(10, 21) Urch et al. , reviewed therecords of 48 patients treated with alfentanil.(21) The authors investigated the interaction between alfentanil and commonly prescribed inducers and inhibitors of the cytochrome P450 system, which alfentanil is metabolised by. Concomitant prescription of at least one

drug that interferes with cytochrome P450 occurred in 75% of cases. No significant correlation was found between dose escalation and concomitant drugs that interfere with the P450 system.

The study by Kirkham et al. from 1995 reported on four patients with renal impairment, who were intolerant to subcutaneous diamorphine.(10) The authors reported that the patients' agitaton settled after they were switched to subcutaneous alfentanil.

Sufentanil

One of the eligible studies was an editorial letter by White et al. published in 2008.(22) The authors had retrospectively reviewed the records of 48 cancer patients in a hospital palliative care setting in UK. They assessed the use of sufentanil due to difficulties in using other opioids, and generally described the effect on pain control following titrations as "favourable".

Buprenorphine

A prospective parallel group, active-controlled study by Melilli et al. published in 2014 compared use of fentanyl with buprenorphine.(14) Forty-two cancer patients were consecutively enrolled at an outpatient clinic in Bologna, Italy. The patients had uncontrolled pain on NSAIDs and weak opioids, and were unable to take oral opioids.

Patients with renal impairment (serum creatinine ≥ 1.3 mg/dl) were commenced on transdermal buprenorphine, while patients with no renal impairment (s-creatinine ≤ 1.2 mg/dl) were started on transdermal fentanyl (T0). Patients were followed up after 10 days (T1), 30 days (T2) and 90 days (T3). The authors found a significant reduction in NRS-score (0-10) over time in both groups (t-test; T0-T1, T1-T2, and T2-T3; $p<0.0001$, $p<0.001$, and $p<0.05$, respectively). At all times there were no significant differences in pain scores between the groups (T0, $p=0.6225$; T1, $p=0.0639$; T2, $p=0.7838$; and T3, $p=0.9194$). The number of cases with side-effects was similar in both groups, and were reported to decrease over time. At all times no statistically significant association was found between the reported side-effects and the treatment groups (X^2 test: T1, $p=0.2897$; T2, $p=0.4252$; T3, $p=0.2220$). The most common side-effects were somnolence/confusion, nausea/vomiting, constipation and pruritus.

Hydromorphone

Two studies examined aspects of hydromorphone.(13, 16) The study by Lee et al. from 2001 was a retrospective review of records of 55 palliative care patients who had been switched to oral hydromorphone, most often from morphine.(13) The major reason for a change to hydromorphone treatment was found to be side-effects on previous therapy (cognitive, drowsiness, and/or nausea). Following the switch, these side-effects improved in >80% of patients (hallucinations improved in 100%; drowsiness in 85%;

nausea in 89%; pain in 83% (pain only documented in 42 patients)). Patients with renal impairment (urea >10.5 mmol/l and/or creatinine ≥101 mmol/l)) were compared with patients with no renal impairment, and the reasons for a switch to hydromorphone were similar in both groups. There was also an improvement in the side-effect profile in >80% of patients in the renal impairment group.

The study by Paramanandam et al. published in 2011 was a retrospective review of 54 in-patients' records at a hospice in USA.(16) The patients had renal insufficiency (GFR <60 ml/min/1.73 m^2), and were treated with hydromorphone via continuous parenteral infusion. The authors assessed the prevalence of symptoms of neuro-excitation. Tremor had been present in 11/54 (20%) of patients; myoclonus in 11/54 (20%); agitation in 26/54 (48%); and cognitive dysfunction in 21/54 (39%). A strong and graded increase was found in neuro-excitatory symptoms with increasing dose or increasing duration of hydromorphone treatment for agitation (dose, p<0.001; duration, p<0.0001) and cognitive dysfunction (dose, p<0.0002; duration, p<0.002).

Meperidine (pethidine)
One of the studies retrieved was an uncontrolled prospective study by Kaiko et.al published in 1982, where 67 patients (19 of them had cancer) treated with meperidine for pain relief were included from a cancer pain center in New York, USA. The authors

assessed the relationship between signs and symptoms of CNS excitation and plasma levels of meperidine and normeperidine. Patients with symptoms of CNS excitation received meperidine for a longer period (p<0.001) and at a higher rate (p<0.001) than asymptomatic patients. The authors found no difference in the duration or rate of meperidine administration between groups with different intensity of CNS-symptoms. Symptomatic patients also had a higher normeperidine plasma level (p<0.001) than asymptomatic patients. There was an association between high normeperidine-to-meperidine ratios and elevated (>1.7 mg/dl) serum creatinine in symptomatic patients (p<0.05).

Opioids in general

Twomey et.al examined prescribing practice in patients with significant renal impairment (serum urea >10 mmol/l and serum creatinine >150 micromol/l) was assessed.(24) The authors reviewed the records of 40 patients at two specialist palliative care units in UK. Opioids had been prescribed in 34/40 (85%) of patients; codeine/morphine/diamorphine in 18/34 (53%); oxycodone in 9/34 (26%); and a combination in 7/34 (21%). A total of 13/34 (38%) of patients developed opioid toxicity.

Discussion

There is limited evidence upon which to base clinical practice when using opioids in patients with cancer with co-existing renal impairment.(11, 12, 16) However, despite this scarce clinical evidence, several guidelines and recommendations have been published on opioid treatment in cancer patients with renal impairment.(3, 4, 27, 28) These guidelines and recommendations are based on clinical experience and indirect pharmacological evidence, rather than clinical studies.

A previous systematic review undertaken in 2009 echoes the findings of this present review.(29) However, it is important to emphasize that despite of the lack of evidence demonstrated previously, little has been done to move forward the research agenda.

Nevertheless clinicians still use opioids in patients with renal impairment and based on the evidence appraised as part of this review, we present key clinical questions and evidence presented in relation to these.

Should morphine be avoided in patients with renal impairment?
From the studies identified, it is clear that this is a difficult area, with a substantial disagreement within the existing literature. Two of the retrieved studies demonstrated a relationship between an increased creatinine level and higher concentrations of M3G

and M6G(8, 20), while Somogyi et.al. found no relationship between creatinine clearance and clearance of morphine, M3G or M6G.(19) Three studies found a relationship between increased creatinine level and morphine related side-effects (12, 17, 23), while others demonstrated no relationship.(11, 18, 20, 23) The unclear relationship between morphine, creatinine levels and morphine related side-effects raises the question if morphine has got a worse reputation than it deserves. It is clear that more evidence is needed before morphine's role in the treatment of cancer patients with renal impairment is fully understood. Based on the current evidence, morphine should however be used with caution in these patients.

Is oxycodone safe to use in renal impairment?

Oxycodone is metabolised in the liver, and due to a conception that it has fewer effects from accumulating metabolites than morphine, it has been recommended as an effective alternative to morphine in cancer pain.(30-32) However, the situation is not that clear. Other studies have shown that the elimination of oxycodone in renal impairment is significantly prolonged, and excretion of its metabolites is severely impaired.(33) The results from the studies retrieved in the present systematic review were also inconclusive. Narabayashi et.al. did not find any significant correlation between creatinine clearance and oxycodone or its metanolites. On the other hand, Kurita et.al. found that increased serum concentrations of oxycodone were associated with increased

side-effects in form of severe fatigue. Based on this inconclusive picture, caution is recommended for oxycodone in cancer patients with renal impairment.

Are fentanyl, alfentanil and/or sufentanil the drugs of choice in renal impairment?
Both fentanyl, alfentanil and sufentanil have been recommended in guidelines on treatment of cancer pain in patients with renal impairment.(4, 27, 28) These three opioids are metabolised in the liver. Their metabolites have minimal or no pharmacologic effect, and are excreted in the urine (for sufentanil also in the bile).(34-36) The pharmacokinetics of these opioids are largely unchanged in patients with renal impairment, and have therefore been seen as favourable in these patients.(36) It is striking how incorporated this practice seems to be, despite very little clinical evidence. In the present systematic review only two studies were found investigating clinical aspects of fentanyl (12, 25), two studies on alfentanil (10, 21), and one editorial letter on sufentanil.(22) The clinical evidence from these studies are scarce and of very low quality. However, pharmacokinetics and clinical experience point in the direction that these opioids are a recommended alternative in cancer patients with renal impairment.

Is there a role for hydromorphone or methadone in patients with renal impairment?
The primary metabolite of hydromorphone is hydromorphone-3-glucuronide (H3G). Hydromorphone and H3G are primarily excreted by the kidneys, and accumulate in

renal impairment.(37) H3G is believed to have no analgesic effect, but contributes to neuro-excitatory adverse effects as myoclonus, seizures, allodynia, sedation, and cognitive impairment.(37) The limited studies retrieved in the present systematic review found inconclusive data regarding side-effects. Lee et.al found that a switch to hydromorphone (mostly from morphine) improved the side-effect profile in >80% of patients.(13) Paramanandam et.al. found that the prevalence of neuro-excitatory symtoms increased with increased dose or increased duration of the hydromorphone treatment in cancer patients with renal impairment.(16) It is recommended to reduce the hydromorphone dose and monitor the patient carefully if treating cancer patients with renal impairment.

In this systematic review no studies on methadone in cancer patients with renal impairment were retrieved. Methadone is mainly metabolised in liver, but elimination through the kidneys is also observed. The metabolites are inactive or considered of no clinical significance. However, methadone has a very long and unpredictable half-life. After initiation of methadone, or increase of the dose, plasma concentration rises over a prolonged period, which may be associated with a delayed onset of side-effects and potential drug accumulation and toxicity. There is still a debate regarding the equianalgesic dose ratio of morphine to methadone, and the right interval between doses.(38, 39) Due to these factors, methadone is in general recommended to be

prescribed only by experienced clinicians, and with close follow-up of the patients. Patients with renal impairment are in general more complex, and caution is recommended.

What opioid should be used in patients receiving treatment with dialysis?

This systematic review did not include cancer patients receiving dialysis treatment. For these patients, removal of the drug will depend on the opioids' molecular size, water solubility, volume of distribution and protein binding.(40) Hydromorphone has been recommended as an opioid of choice in patients treated with dialysis. It has low protein binding, low molecular weight and a low volume of distribution. Dialysis therefore limits accumulation and side-effects.(41) Fentanyl has also been advocated as a safe option due to its high protein binding, low water solubility, a high volume of distribution, and a moderately high molecular weight.(42) Independent of which opioid, titration is recommended to start at low doses, with an increased dosing interval and with close monitoring for side-effects. Morphine, hydrocodone, and meperidine are not recommended in patients receiving dialysis treatment.

Future studies and design considerations

There are several challenges with carrying out studies in this field. In general conducting trials in patients with advanced cancer is challenging, as patients are often

frail, which makes it more difficult to take part in different assessments. This results in challenges with both recruitment and attrition.

There is a need for high quality randomised controlled trials (RCTs) in this field. An RCT comparing morphine treatment with oxycodone and/or fentanyl/alfentanil in cancer patients with renal impairment is a crucial first step. Cancer patients with renal impairment are complex, and there are several challenges with conducting a study with this patient population. One consideration is classification of renal impairment using glomerular filtration rate (GFR) or creatinine clearance. It is recommended to assess renal function by estimation of glomerular filtration rate (GFR).(43) Another important issue is defining the optimal outcome measure(s). The most relevant as a primary outcome would be opioid toxicity measured by degree of opioid-related side-effects. As secondary end points, both level of achieved analgesia and metabolites quantified from blood samples would be of interest.

Several of the studies in the present review showed some influence from renal impairment on drug and metabolite serum concentrations, but no corresponding influence on symptoms.(11, 18, 20, 23) There might be several design-related explanations for this, as small number of patients included or confounding effects from other patient-related factors as pain mechanisms, anti-tumour treatment, metabolic

status or hydration. However, opioid pharmacology is influenced by genetic variability, which might also be an explanatory factor.(44, 45) Receptor properties or intracellular pharmacodynamic factors might have caused variability in the clinical outcomes.(46-48)

All systematic reviews have got limitations associated with the search strategy. The exclusion criteria can potentially have left out relevant studies. As with all systematic reviews, language bias or publication bias can be present. One of the other main challenges is that there is heterogeneity of both populations studied and classification of renal impairment. We set out to classify all studies as per the KDIGO guidelines, however this was rarely possible, and is a limitation. We would suggest that future studies use this classification.

Conclusion

The present systematic review demonstrates low quality on the existing evidence on opioid treatment in cancer patients with renal impairment. There remains a need for high quality studies to be carried out before any evidence-based guidelines can be established.

Acknowledgements

Funding

Declaration of conflict of interest

The authors declare that there is no conflict of interest

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Appendix 1
Search strategies MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials

MEDLINE

1. Opioid*.mp.
2. Opiate*.mp.
3. Opiate Alkaloids/
4. Analgesics, Opioid/
5. Narcotics/
6. Narcotic*.mp.
7. Morphine/
8. Morphine.mp.
9. Oxycodone/
10. Oxycodone.mp.
11. Methadone/
12. Methadone.mp.
13. Hydromorphone/
14. Hydromorphone.mp.
15. Heroin/
16. Heroin.mp.
17. Diamorphine.mp.
18. Fentanyl/
19. Fentanyl.mp.
20. Buprenorphine/
21. Buprenorphine.mp.
22. Tramadol/
23. Tramadol.mp.
24. Alfentanil/
25. Alfentanil.mp.
26. Codeine/
27. Codeine.mp.
28. Dihydrocodeine.mp.
29. Remifentanil.mp.
30. Sufentanil/
31. Sufentanil.mp.
32. Meperidine/
33. Meperidine.mp.
34. Pethidine.mp.
35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. Renal Insufficiency/
37. Renal impairment.mp.
38. Renal failure.mp.
39. Renal disease.mp.
40. Acute renal impairment.mp.
41. Chronic kidney disease.mp.
42. Kidney Failure, Chronic/
43. Kidney failure, chronic.mp.
44. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. Cancer*.mp.
46. Tumor*.mp.
47. Tumour*.mp.
48. Malignancy.mp.
49. Neoplasms/
50. Neoplasm*.mp.
51. Carcinoma/
52. Carcinoma.mp.

53. 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54. Pain/
55. Pain.mp.
56. 54 or 55
57. 35 and 44
58. 35 and 44 and 53
59. 35 and 44 and 53 and 56
60. limit 59 to (english language and yr="1966 -Current")

EMBASE

1. Opioid*.mp.
2. Opiate*.mp.
3. Opiate Alkaloids/
4. Analgesics, Opioid/
5. Narcotics/
6. Narcotic*.mp.
7. Morphine/
8. Morphine.mp.
9. Oxycodone/
10. Oxycodone.mp.
11. Methadone/
12. Methadone.mp.
13. Hydromorphone/
14. Hydromorphone.mp.
15. Heroin/
16. Heroin.mp.
17. Diamorphine.mp.
18. Fentanyl/
19. Fentanyl.mp.
20. Buprenorphine/
21. Buprenorphine.mp.
22. Tramadol/
23. Tramadol.mp.
24. Alfentanil/
25. Alfentanil.mp.
26. Codeine/
27. Codeine.mp.
28. Dihydrocodeine.mp.
29. Remifentanil.mp.
30. Sufentanil/
31. Sufentanil.mp.
32. Meperidine/
33. Meperidine.mp.
34. Pethidine.mp.
35. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36. Renal Insufficiency/
37. Renal impairment.mp.
38. Renal failure.mp.
39. Renal disease.mp.
40. Acute renal impairment.mp.
41. Chronic kidney disease.mp.
42. Kidney Failure, Chronic/
43. Kidney failure, chronic.mp.
44. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45. Cancer*.mp.
46. Tumor*.mp.
47. Tumour*.mp.
48. Malignancy.mp.
49. Neoplasms/
50. Neoplasm*.mp.
51. Carcinoma/
52. Carcinoma.mp.
53. 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52
54. Pain/
55. Pain.mp.
56. 54 or 55
57. 35 and 44

58. 35 and 44 and 53
59. 35 and 44 and 53 and 56
60. limit 59 to (english language and yr="1980 -Current")

Cochrane Central Register of Controlled Trials

ID	Search
#1	Opioid*
#2	Opiate*
#3	MeSH descriptor: [Opiate Alkaloids] this term only
#4	MeSH descriptor: [Analgesics, Opioid] this term only
#5	MeSH descriptor: [Narcotics] this term only
#6	Narcotic*
#7	MeSH descriptor: [Morphine] this term only
#8	Morphine
#9	MeSH descriptor: [Oxycodone] this term only
#10	Oxycodone
#11	MeSH descriptor: [Methadone] this term only
#12	Methadone
#13	MeSH descriptor: [Hydromorphone] this term only
#14	Hydromorphone
#15	MeSH descriptor: [Heroin] this term only
#16	Heroin
#17	Diamorphine
#18	MeSH descriptor: [Fentanyl] this term only
#19	Fentanyl
#20	MeSH descriptor: [Buprenorphine] this term only
#21	Buprenorphine ·
#22	MeSH descriptor: [Tramadol] this term only
#23	Tramadol
#24	MeSH descriptor: [Alfentanil] this term only
#25	Alfentanil
#26	MeSH descriptor: [Codeine] this term only
#27	Codeine
#28	Dihydrocodeine
#29	Remifentanil
#30	MeSH descriptor: [Sufentanil] this term only
#31	Sufentanil
#32	MeSH descriptor: [Meperidine] this term only
#33	Meperidine
#34	Pethidine
#35	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34
#36	MeSH descriptor: [Renal Insufficiency] this term only
#37	Renal impairment
#38	Renal failure
#39	Renal disease
#40	Acute renal impairment
#41	Chronic kidney disease

#42	MeSH descriptor: [Kidney Failure, Chronic] this term only
#43	Kidney failure, chronic
#44	#36 or #37 or #38 or #39 or #40 or #41 or #42 or #43
#45	Cancer*
#46	Tumor*
#47	Tumour*
#48	Malignancy
#49	MeSH descriptor: [Neoplasms] this term only
#50	Neoplasm*
#51	MeSH descriptor: [Carcinoma] this term only
#52	Carcinoma
#53	#45 or #46 or #47 or #48 or #49 or #50 or #51 or #52
#54	MeSH descriptor: [Pain] this term only
#55	Pain
#56	#54 or #55
#57	#35 and #44
#58	#35 and #44 and #53
#59	#35 and #44 and #53 and #56

Table 1
Included Studies

Author / Year	n	Design	Setting	Primary outcome	Secondary outcome	Opioid used	Summary, main findings	Grade
Ashby M. et.al. / 1997	36	Non-randomised cohort study	Pts with advanced cancer, hospice inpatients receiving morphine orally or subcutaneously. Blood samples collected: s-creatinine, gamma glutamyl transferase, plasma morphine, M3G and M6G concentration. The adverse effects nausea, vomiting, and confusion documented.	No formal outcome measures.		Morphine	Significant associations between plasma morphine, M3G, and M6G concentrations and dose for both routes of administration (p<0.05). Plasma M3G, M6G, and dose-corrected plasma M3G and M6G concentrations were significantly higher in pts with s-creatinine levels above normal range (p<0.001).	D
Tiseo P.J. et.al. / 1995	109	Non-randomised cohort study	Assessment of the relationship between M6G and opioid-related side effects (multifocal myoclonus and cognitive impairment). Pts recruited from a pain service in New York, USA. Cancer pts with chronic pain, treated with morphine. Blood samples: Plasma morphine and M6G, s-creatinine, blood urea nitrogen, total bilirubin, ALP, s-glutamic oxalacetic	Myoclonus and cognitive impairment (present or absent).		Morphine	Moderate but significant correlation between M6G/Morphine ratio, and blood urea nitrogen (r=0.4, p<0.001) and creatinine (r=0.45, p<0.001). No significant difference in creatinine between the group with side effects and the group with no side effects.	C

Somogyi A.A. et.al. / 1993	11	Non-randomised cohort study	transaminase, s-LDH). Assessment of relationship between plasma concentrations of morphine and its metabolites and pain scores. Cancer pts. on oral morphine. Venous blood samples and pain score (NRS 0-100) before dose (0) and after 0.25, 0.5, 0.75, 1, 1.5, 2, 3, and 4 hrs. Quantified Morphine, M3G, and M6G. Creatinine quantified in plasma and urine.	NRS (0-100)	Morphine	Average steady state plasma concentrations of morphine, M3G and M6G were related to the morphine dose per kilogram of bodyweight ($p<0.01$). Renal clearance of M3G and M6G were closely related ($r^2=0.80$; $p<0.0005$). No relationship between renal clearance of morphine, M3G and M6G, and that of creatinine. No relationship between plasma morphine and M6G concentrations, and pain relief (only evaluated with visual inspection).	D
Klepstad P., et.al. / 2003	300	Uncontrolled prospective study	Assess if serum concentrations of morphine, M3G and M6G predict pain intensity, quality of life and cognitive function. Cancer pts. on oral (n=263) or subcutaneous (n=35) morphine.	Pain intensity: BPI (0-10), average pain last 24 hrs. Quality of life: EORTC QLQ-C30 (nausea/vomiting, constipation; tiredness) Cognitive function: MMS	Morphine	No relationship between serum concentrations of morphine, M3G and M6G, and pain intensity or opioid-induced side effects (nausea; constipation; sedation; cognitive failure)	C

Author / Year	N	Study design	Objective / Population	Outcome measure	Drug	Results	Grade
Riley J. et.al. / 2004	177	Non-randomised, retrospective study	Identify predictors for morphine intolerance (demographic, biochemical, and haematological). Tertiary referral cancer center in London, UK. Pts tolerating morphine (n=100) vs. pts. switched (n=77). Haematological and biochemical data: Full blood count, creatinine, urea, electrolytes, calcium, liver function tests. Demographic data: Age, sex, ethnicity, diagnosis, use of cytotoxic meds	Need to switch opioid due to uncontrolled pain and/or intolerable side effects	Morphine	Age over 78 years (p<0.03), high white cell count (p<0.002), high platelet count (p<0.003), and poor liver- or renal function were associated with a higher risk of morphine intolerance	C
Riley J. et.al. / 2006	186	Prospective, observational, controlled clinical study	Identify predictors (demographic, biochemical and haematological) for morphine intolerance. Pts. with cancer pain who required treatment with oral morphine for pain control. Recruited from 2 separate sites at a tertiary cancer centre in London, UK. Responders (n=138): Morphine for at least 4 weeks, good response. "Switchers" (n=48): Poor pain control and/or intolerable side effects (subjective	Brief Pain Inventory (scale 0-10); reason for switching; toxicity scores (4-point scale)	Morphine	Predictors for morphine intolerance: white cell count (OR: 1.06, 95% CI: 1.01-1.11; p=0.02); body weight (OR: 1.02, 95% CI: 1.00-1.05; p=0.02); concomitant use of antiemetics (5HT3) (OR: 14.81, 95% CI: 2.48-88.46, p=0.003); concomitant use of beta blockers (OR: 4.96, 95% CI: 1.28-19.29, p=0.021); concomitant use of proton pump inhibitors (OR: 0.32, 95% CI: 0.14-0.69, p=0.004); tumour diagnosis of the lower gastrointestinal tract (OR: 4.99, 95% CI: 1.34-18.62, p=0.02); and recent chemotherapy (within 14 days) (OR: 0.38, 95% CI: 0.14-1.01, p=0.05). s-creatinine not significantly different between "responders" and "switchers" (no p-value reported) (Obs: Pts. excluded from the study if creatinine >1.5 times normal range).	C

Author / Year	N	Study type	Aim / assessment	Measurement	Drug	Results	Grade
Wood, M. et.al. / 1998	18	Non-randomised cohort study	Hospice inpatients receiving morphine for cancer pain. Assessment of the pharmacokinetics and neuropsychological effects of morphine. Biochemical tests: s-creatinine, s-GGT, plasma morphine, M3G and M6G.	Measurement of cognitive function: National Adult Reading Test. Williams Delayed Recall Test, Immediate Memory for Digits, Trailing Making Test, and the Digit Symbol Substitution Test.	Morphine	Significant correlations between cognitive function (Immediate memory/attention, Symbol Digit Substitution Test), and plasma morphine concentrations ($p<0.05$). Significantly higher mean s-creatinine and worse neuropsychological performance in patients with nausea and vomiting adverse effects ($p<0.05$).	D
Kurita, G.P. et.al. / 2015	1147	Retrospective study	Assessment of whether symptoms/adverse effects are associated with renal function in pts. with cancer on opioid treatment. Pts. taking exclusively one of the three opioids morphine (n=581), oxycodone (n=298), or fentanyl (n=268).	EORTC QLQ-C30 scores (0-100) on fatigue, nausea/vomiting, pain, appetite, constipation, cognitive dysfunction.	Morphine, oxycodone and fentanyl	Moderate or severe low GFR was observed in 11-15% of the pts. treated with morphine; 14-16% treated with oxycodone, and 14-22% of the pts treated with fentanyl. Pts. with higher serum concentrations of morphine were more likely to have severe constipation (OR. 1.73, 95% CI. 1.13-2.65, p<0.001) and severe cognitive dysfunction (OR. 1.77, 95% CI. 1.13-2.78, p<0.01) than pts. with lower morphine serum concentrations. Pts. with higher M3G serum concentration were more likely to have severe cognitive dysfunction (OR. 1.63, 95% CI. 1.03-2.56, p=0.04) than pts. with lower M3G serum concentrations. Pts. with higher serum concentrations of oxycodone were more likely to report severe fatigue (OR. 1.70, 95% CI. 1.04-2.78, p=0.03) than pts. with lower oxycodone serum concentrations. Fentanyl and the metabolites norfentanyl, noroxycodone, and M6G were not associated with	C

	N	Study type	Description	Outcome measures		Drug	Results	Grade
							any of the six symptoms assessed Pts. with moderate/severe and mild renal impairment (<90 ml/min/1.73m^2) on morphine treatment had significantly higher odds of having severe constipation (OR: 1.91; 95% CI 1.08-3.37 and OR: 1.80; 95% CI 1.118-2.75, respectively) compared with pts. with normal renal function (≥90 ml/min/1.73m^2)	
Narabayashi M. et.al. / 2008	27	Uncontrolled prospective study	Assessment of the effect of rotation from oral morphine to oxycodone in pts with intolerable side effects 14 Medical institutions in Japan, cancer in-patients, ≥20 years. Pts with no renal impairment (n=18), s-creatinine ≤1.5 times the upper limit of normal Pts. with renal impairment (n=9), estimated creatinine clearance <60 ml/min.	The rate of pts. who achieved adequate pain control	The acceptability (CAT scale 1-5) and pharmacokinetics of oxycodone, the analgesic efficacy (pain intensity: CAT scale (0-3) + VAS (0-100 mm))	Oxycodone	21/25 (84%) of the pts. achieved adequate pain control Acceptability was significantly improved from the study entry to the end of the study (p<0.0004) In patients with renal impairment there was a significant negative correlation between creatinine clearance and M6G (p=0.0292), and creatinine clearance and M3G (p=0.0038)	C
Mazzocato, C. et.al. / 2006	53 (33 cancer pts.)	Retrospective study	Retrospective assessment of the use of subcutaneous fentanyl in severely ill pts with renal impairment (calculated GFR<60 ml/min) Pts. followed in a tertiary hospital by palliative care	No formal outcome measures		Fentanyl	Pain control was complete in 31/53 (59%) and partial in 14/53 (26%) of pts In pts. with an opioid-related neurotoxicity suspicion, 8/26 (31%) achieved a complete resolution of symptoms, and 6/26 (26%) a partial resolution.	C Published as conference abstract

Study / Year	N	Study design	Context / Patients	Outcome measures	Secondary outcomes	Drug	Results	Grade
Urch, C.E. et.al. / 2004	48 (number of pts. with cancer not given)	Non-randomised retrospective study	consultant team, Switzerland. Retrospective audit over a 21-month period. Investigates the interaction between alfentanil and commonly prescribed inducers and inhibitors of the cytochrome P450 system, and the possible development of tolerance in the long-term subcutaneous use	No formal scoring for efficacy or side-effects.		Alfentanil	Concomitant prescription of at least one drug that interferes with cytochrome P450 occurred in 75% of cases. No significant correlation between duration and dose escalation. No significant correlation between dose escalation and concomitant drugs that either inhibited or induced the P450 system	D
Kirkham, S.R. et.al. / 1995	4	Case (4 pts)	Retrospective assessment of the use of alfentanil. 4 pts. intolerant of diamorphine. Renal impairment.	No formal outcome measures.		Alfentanil	Agitation improved after switching from diamorphine s c to alfentanil s c	D. Published as a letter
White, C. / 2008	48	Retrospective study	Retrospective assessment of the use of sufentanil due to difficulties in using other opioids. Cancer pts, hospital palliative care setting.	No formal outcome measures.		Sufentanil	Effect on pain control following titration generally described as "favourable".	D. Published as a letter
Melili G et.al. / 2014	42	Prospective parallel group, active-controlled study	Cancer pts with uncontrolled pain, unable to take oral opioids, outpatient clinic, Bologna, Italy. Pts. consecutively enrolled. Pts with renal impairment (s-creatinine ≥ 1.3 mg/dl) treated with transdermal buprenorphine. Pts with no renal	Steady NRS score reduction over time in both groups.	Rescue-dose consumption, opioid adverse effects, and study dropouts association with the study's group.	Transdermal buprenorphine compared to fentanyl	A significant reduction in NRS-score over time in both groups (t-test; T0-T1, T1-T2, and T2-T3; $p<0.0001$, $p<0.001$, and $p<0.05$, respectively). At all times there were no significant differences in pain scores between the groups (T0, $p=0.6225$, T1, $p=0.6639$, T2, $p=0.7838$, and T3, $p=0.9194$).	C

			impairment (s-creatinine ≤1.2 mg/dl) started on fentanyl. Follow-up after 10, 30 and 90 days (11-point NRS, KPS (0-100), opioid dose (microgram/hr), rescue dose consumption, occurrence of adverse effects).			
Lee, M.A. et.al. / 2001	55	Retrospective study	No formal outcome measures. Assessment of the efficacy and outcomes of oral hydromorphone therapy. Assessment of the benefit of hydromorphone in palliative care pts with renal impairment. Retrospective review of records of in-patients who had received oral hydromorphone.	Hydromorphone	The major reason for change to hydromorphone was side effects (cognitive/drowsiness/nausea) on previous therapy. Following switch to hydromorphone these side effects improved in >80 % of pts. (hallucinations improved in 100%, drowsiness in 85%, nausea in 89%, pain in 83% (pain only documented in 42 pts.)). The reasons for a switch to hydromorphone were similar in the renal impairment group (urea >10.5 mmol/l and/or creatinine ≥101 mmol/l) (n=29) vs. the group with no renal impairment (n=26). Improvement in the side-effect profile in >80% of pts. also in the renal impairment group.	C
Paramanandam, G. et.al. / 2011	54	Retrospective study	No formal outcome measures. Assessment of the prevalence of neuroexitation (tremor, myoclonus, agitation, cognitive dysfunction, seizures) in in-patient hospice pts. with renal impairment (GFR <60 ml/min/1.73 m²) who were	Hydromorphone	Overall prevalence: Tremor 11/54 (20%), myoclonus 11/54 (20%), agitation 26/54 (48%), cognitive dysfunction 21/54 (39%). A strong and graded increase in neuroexitatory effects with increasing quartile of dose or duration of hydromorphone treatment for agitation (dose, p<0.001, duration, p<0.0001) and cognitive dysfunction (dose,	C

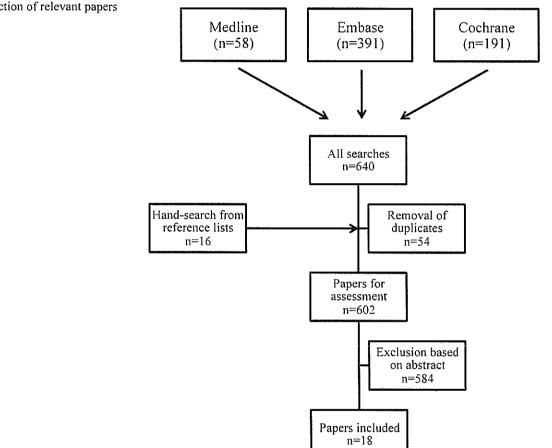| Author / year	n	Study type	Outcome measures	Drug	Results	Quality
					given hydromorphone via continuous parenteral infusion Assessment of factors associated with increased risk of neuroexcitation in this patient group	$p<0.0002$; duration, $p<0.002$).
Kaiko R.F. et.al. / 1983	67 (19 cancer pts.)	Uncontrolled prospective study	No formal outcome measures	Meperidine (Pethidine)	Assessment of the relationship between signs and symptoms of CNS excitation and plasma levels of meperidine and normeperidine. Pts. receiving meperidine for the relief of postoperative (n=48) or cancer (n=19) pain. Cancer pain center, NY, USA	Pts. with symptoms of CNS excitation received meperidine for a longer period ($p<0.001$) and at a higher rate ($p<0.001$) than asymptomatic pts. No difference in the duration or rate of meperidine administration between groups with different intensity of CNS-symptoms. Symptomatic pts. had a higher normeperidine plasma level ($p<0.001$) than asymptomatic pts. Association between high normeperidine-to-meperidine ratios and elevated (>1.7 mg/dl) s-creatinine in symptomatic pts ($p<0.05$)	C
Twomey F. et.al. / 2006	40	Retrospective study	No formal outcome measures	Opioids in general	Assessment of prescribing practice in pts with significant renal impairment (s-urea >10 mmol/l and s-creatinine >150 micromol/l) at two specialist palliative care units, UK.	Opioids prescribed to 34/40 (85%) of pts. Codeine/morphine/diamorphine 18/34 (53%) Oxycodone 9/34 (26%) Combination 7/34 (21%) 13/34 (38%) of pts. developed opioid toxicity	D Published as conference abstract

Figure 1
Selection of relevant papers