Pharmacist educational interventions for cancer pain management: a systematic review and meta-analysis.

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Declarations

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Authorship – Literature searching was assisted by AC and the paper was drafted by ZE with methodological and procedural input from CC and LZ. It was then critically revised by AB and MB. ZE, CC, LZ, AB and MB all made a substantial contribution to the design of the review and the interpretation of the data and approved the paper for publication.

Declaration of conflicting interests – The authors declared no potential conflicts of interest with respect to this research and publication.

Word Count (excluding abstract, tables and figures) 3266

Acknowledgment - We thank Anne Costigan for support with literature searching

Ethical Review – this systematic review and meta-analysis does not require ethical review as it is using previously published and anonymised data.

Abstract

Objectives

Educational interventions by pharmacists for patients with cancer pain aim to improve pain management, but little is known about the different components of interventions and their effectiveness. Our aim was to assess the benefit of pharmacist delivered educational interventions for patients with cancer pain. A systematic review and meta-analysis of experimental trials testing pharmacist delivered educational interventions for cancer pain was carried out to identify the components of interventions and effectiveness at improving pain related outcomes for patients with cancer.

Methods

A literature review was conducted in EMBASE, MEDLINE, CINAHL, PsycINFO, ASSIA, Web of Science and CENTRAL from inception until January 2018 searching for educational interventions involving a pharmacist for patients with cancer pain. Four studies were included involving 944 patients. Meta-analysis was carried out where possible.

Key findings

Meta-analysis of three of the four studies found that mean pain intensity in the intervention group was reduced by 0.76 on a 0-10 scale (95% confidence interval), although only two of the studies used validated measures of pain. Improvements in knowledge, side effects and patient satisfaction were seen although with less reliable measures.

Conclusions

Pharmacist educational interventions for patients with cancer pain have been found to show promise in reducing pain intensity. Studies were few and of varying quality. Further, good quality studies should be carried out in this area and these should be comprehensively reported. Trials measuring patient self-efficacy and patient satisfaction are needed before the impact of the pharmacist delivered interventions on these outcomes can be established.

Keywords

Educational intervention, medicines optimisation, pharmacist, pain, cancer.

Introduction

Cancer is one of the leading causes of death worldwide. In the UK, there were around 357,000 newly diagnosed cases of cancer and 163,000 cancer deaths in 2014 [1]. Life expectancy of people living with cancer patients is increasing and in the last 40 years, the cancer survival[1] rate in the UK has doubled, from 24% to 50% [1].

The World Health Organisation's analgesic three-step ladder is the clinical principle for cancer pain management [2]. It has been used since it was first published in 1986, and it involves a stepwise approach to analgesic prescriptions for cancer pain with non-opioid analgesics for mild pain, weak opioids for moderate pain, and strong opioids for severe pain [3, 4]. Despite the improvement recorded in pain management after using this strategy, evidence indicates that patients living with cancer still experience high levels of pain in situations where it is possible to reduce their suffering [5, 6]. It has been reported that around 25% to 33% of patients living with cancer are receiving insufficient pain management [7, 8]. In addition, two systematic reviews that assessed the quality of pain management in adult patients with cancer revealed modest improvements in pain management, but stated that one third of patients who experience pain continue to be under-treated [9, 10].

Only 18% of patients living in community settings describe their pain as controlled at the end of life compared with 38% and 68% in hospital and hospice settings respectively [11]. The pain experienced can often change rapidly with disease progression and patients have voiced a need for additional support with pain at the end of life [12, 13].
Pain from cancer can be complex. Nociceptive visceral or somatic pain can be caused by the tumour itself and neuropathic pain can be due to treatment.

An educational intervention can be defined as information, behavioural instructions or advice and can be delivered to patients, in this case, with cancer pain, by means of verbal, written, audio- or video-taped or computer aided methods [14].

Educational interventions have been shown to help patients with cancer pain by both improving knowledge and reducing average and worst pain intensity [14]. Mechanisms for this include the positive link between patient knowledge about medicines and adherence to them as well as an association between reduction of barriers to pain relief and adherence [15, 16]. Low adherence to medication has been linked to reduced pain control [17]. A British study found that 61% of patients

[1] People who are diagnosed with cancer and survive their disease http://www.cancerresearchuk.org/health-professional/cancer-statistics#heading-Two .

said they had a significant need for further information about their medicines ten days after it had been prescribed and 25% were non-adherent to medication after four weeks [18].

Community pharmacists in the UK are the most frequently accessed healthcare professional for patients with advanced cancer (along with community nurses) [19]. Community pharmacies are situated in every locality, often opening for extended hours and already offer medicines optimisation services on a walk-in basis for patients. Pharmacists also work in hospitals, family doctor practices, hospices and for external provider organisations all of which could provide a source of medicines advice for a patient with cancer pain. Increasingly, pharmacists are taking on more patient-facing roles including vaccinations, blood testing and symptom management clinics including pain.

Pharmacist interventions for chronic pain have been found to reduce pain and adverse effects however few studies looking at educational interventions by pharmacists for patients with cancer pain have been carried out and this is the first systematic review to be published in this area [20, 21]. There are several systematic reviews focusing on educational interventions by any healthcare professional for patients with cancer pain and these have all found a small reduction in pain intensity in intervention groups [14, 22-24].

We hypothesize that educational interventions by pharmacists for patients with cancer pain might improve pain-related outcomes.

Methods

Search Strategy

We searched the electronic databases EMBASE, MEDLINE, CINAHL, PsycINFO, ASSIA, Web of Science and CENTRAL from inception until January 2018. Reference lists were also screened from papers retrieved. The search strategy is detailed in Appendix 1 and was adapted to meet the needs of each individual database searched.

Initial searches were carried out by ZE and AC and screening of titles and abstracts by ZE. After duplicates were removed the resulting studies were screened by ZE and CC independently and any disagreement was resolved by discussion and consensus.

Eligibility criteria

Studies were included if the following inclusion criteria were met**:**

- Experimental design studies with randomisation against a comparator.
- Reported in English or had an English translation.
- Delivery of any sort of educational intervention (this may have occurred as part of a larger more complex multidisciplinary intervention) by a pharmacist.
- Any setting (home, hospital, primary care etc.).
- Patients were adults with pain from ongoing active cancer of any kind, stage or site.

Studies were included if they had the following outcome measures.

Primary outcome measures:

1. Pain (e.g. self-reported pain intensity expressed on a visual analogue (VAS) or numerical rating (NRS) scale.
2. Patient knowledge, beliefs, attitudes and behaviours
3. Self-efficacy and adherence to medication

Secondary outcomes measures:

4. Patient satisfaction
5. Resolution or reduced risk of side effects or drug interactions
6. Reduced interference from pain in daily activities e.g. functional status or cancer pain specific functional status, social interactions, sleep, quality of life, mood.

Data extraction and reporting

Data was extracted independently by ZE and CC onto a standardised form.

Data was recorded on the following outcomes: knowledge, pain, self-efficacy, side effects, patient satisfaction and quality of life.

Data analysis

The findings of each study with equivalent outcome measures were inputted into RevMan (version 5.3) and meta-analysis was carried out. Other outcome measures were assessed qualitatively.

Quality assessment

Studies were assessed for quality using the Cochrane tool for assessing bias [25]. The tool identifies bias related to the design, conduct, analysis or reporting of the study and helps identify methodological flaws within each study and whether the risk of bias is high, low or unclear. It was decided to use this tool due to its comprehensive nature and clear reporting [25].

Results

In total 989 studies were identified using the database searches, 953 of which were excluded after screening of the titles or abstract (see Figure 1 for flow diagram of study selection). When duplicates (18) were removed, full text screening of 18 individual papers was conducted. After 14 of these were excluded according to eligibility criteria there were 4 unique study papers which met the inclusion criteria for the review.

Figure 1: A flow diagram of study selection for pharmacist educational interventions for patients with cancer pain

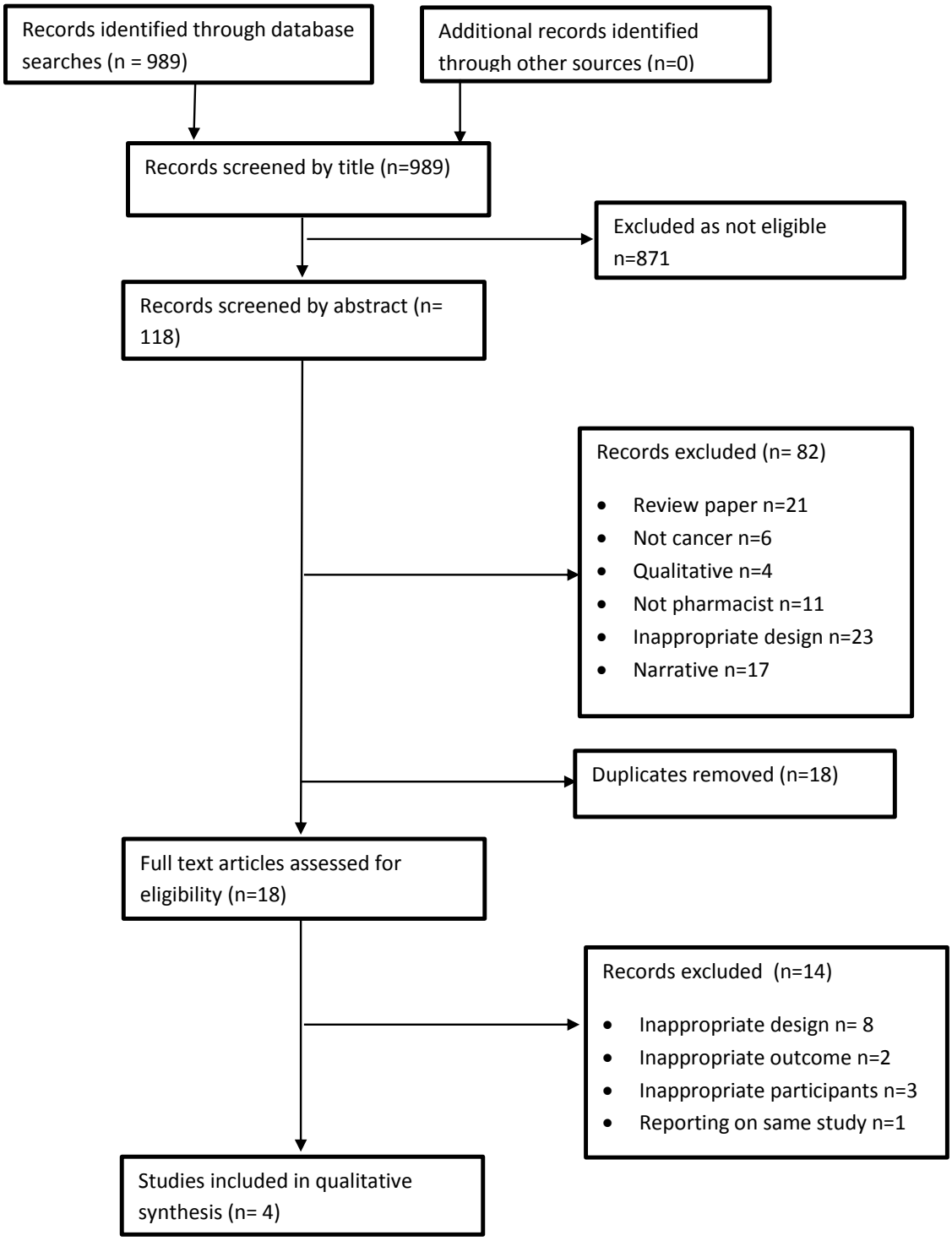

Table 1: Characteristics of included studies

Study	Sample recruited (completed)	Setting	Study design	Follow-up interval	Method of delivery	Dose or quantity intervention	Provision of written material	Pharmacist monitored pain scores	Medication review and adjustment	Findings
1.Powers 1983	16	Community	randomised pre-test/post-test experimental design	8 days	Pharmacist delivered consultations with dosage adjustment, recommendation of over-the-counter medicines and supportive counselling	Daily telephone calls on days 2-7	No	Yes	Review and adjustment	Dosages lowered Improvement in pain scores Fewer side effects Increase in patient satisfaction
2. Wang 2013	237	Hospital and Community	RCT	4 weeks	Face-to-face counselling sessions by pharmacist	Eight 30 minute sessions over 4 weeks	Yes	Yes	Review and recommendations	Improvement in pain scores Increase in pain and analgesic knowledge
3. Chen 2013	542	Hospital and Community	prospective, multicentre, double-arm controlled study	6 months	Assessment of pain control with counselling and liaising with prescriber	Weekly monitoring in hospital and twice a month consultations for six months	No	Yes	Review and recommendations	Standardisation of opioid administration Less frequent prescriptions Improvement in pain scores Increased quality of life Fewer side effects
4. Wang 2015	149	Hospital and Community	prospective randomised controlled study	2 months	Face-to-face counselling sessions	Two sessions a week for 2 months	Yes	No	Medication education	Quality of life increased Improvement in pain scores Increase in knowledge.

Characteristics of included studies are shown in table 1. The four studies included in the review involved a total of 944 participants (individual study populations ranged from 16 to 542). Three of the studies were carried out in China between 2013 and 2015 [26-28] and one in the UK from 1983 [29].

Settings were cross sector in all studies with three studies recruiting from the hospital in-patient population and continuing the interventions in the community [26-28] and one study recruiting from the

hospital out-patient population [29]. All studies consisted of an educational intervention by a pharmacist, one involved dosage adjustment, non-prescription drug recommendation and supportive counselling [29], three involved a series of educational interventions [26-28] of which one involved liaison with the prescriber [26]. Consultations were entirely telephone based in one study [29] with a mixture of telephone and face-to-face in 3 studies [26-28] . The studies ranged from 6 [29] to 16 [28] consultations per patient in total. All studies compared the intervention with usual care.

Components of studies

The Chen et al (2014) study [26] involved a clinical pharmacist-led guidance team which comprised a trained pharmacist, oncology nurses, oncologists and administrators. Pharmacists without prescribing capability, were responsible for educating patients and staff about cancer pain therapy, monitoring medication use and medication drug responses. The team provided a pain consultation at the beginning to select the medicine and dose which was needed. This was then monitored weekly until the patient was discharged from hospital. Consultations were conducted with patients twice a month for six months where pain control and adverse events were assessed and dealt with. Additional communication with prescribers was carried out where any adjustment in medication was necessary. Usual care was described as having no guidance from the clinical pharmacist-led guidance team.

In the Powers (1983) study [29] , patients with chronic cancer pain who were suitable for pain relief by methadone received daily follow-up telephone consultations by the pharmacist after the medicine had been initiated to adjust the dosage, recommend other over-the-counter medicines and deal with side effects. Usual care involved customary medical care including instructions on the administration of methadone.

In the Wang (2013) study [27], patients in the intervention arm received written information and then eight 30 minute face-to-face counselling sessions to provide individualised pain control. Patients were able to contact the pharmacists when required and were able to request extra consultations if they were required. Pharmacists helped patients to complete questionnaires at study entry and after four weeks. The details of usual care were not explained; only that patients had conventional pain control.

In a later study by the same author [28] patients received written information followed by two 30 minute education sessions which were delivered twice a week for two months. Patients were

assessed before and after the intervention for knowledge and quality of life. Usual care was described only as a routine medical service.

Quality of included studies

The quality of included studies is reported in table 2.

Table 2: Cochrane risk of bias summary [25]2

Powers 1983	+	-	-	+	?	-	
Wang 2013	+	?	-	?	?	+	?
Chen 2014	-	-	-	?	-	+	
Wang 2015	+	-	-	?	+	?	
	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias

Three studies [27-29] used adequate methods of randomisation and one study [26] was flawed in how the participants were assigned to the control or intervention groups. Methods of allocation concealment were not adequately discussed in papers and all were unclear, or bias was detected for this.

None of the participants were blinded as to the intervention as this is not possible in a study of this nature.

Outcome assessment blinding was not discussed in Wang (2013), Wang (2015) or Chen (2014) although Powers (1983) stated the pharmacist observer was blinded as to the group patients had been assigned which minimised assessment bias in this study.

2 + denotes low risk
- denotes high risk
? denotes unclear risk

Loss to follow-up was experienced in all studies. None of the authors used intention-to-treat analysis which could have been used to extrapolate findings.

Outcome data was poorly reported in the Chen [26] study. Patients were assigned to either the intervention or control group in order of registration into the study. Loss to follow-up was reported before this allocation making it unclear which group they had been allocated to. There is therefore a large risk of bias in the study. Data is unclear or incomplete in Wang (2013) [27] as 'other reasons' are reported for loss to follow-up. Powers [29] had a very small sample size (with no sample size calculation stated) making the outcome data less reliable. Wang (2015) [28] was assessed as no bias for this measure.

Selective reporting was found in Powers [29] as analysis was not fully described within each group.

Outcome measures

Studies in the review have several different outcome measures (see Table 3).

Table 3: A summary of the different outcome measures reported for the studies in this review **Table 3: A summary of the different outcome measures reported for the studies in this review**

Powers 1983	Wang 2013	Chen 2014	Wang 2015
• Pain intensity • Pain relief • Number of side effects • Patient satisfaction	• Pain knowledge • Analgesic knowledge • Total pain related knowledge • BPI – Usual pain in the last week • BPI - Current pain • BPI – Pain at rest • BPI – Pain with movement • Pain interference – daily activity, mood, walking	• Opioid administration • Pain assessment before therapy • Dose titration before therapy, before slow release formulation, before dosage increase • Inappropriate conversion – change in drug without reason, incorrect conversion	• Knowledge • Attitude • Practice • Quality of life – Global, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning. • Symptom scales – fatigue, nausea and

	ability, normal working, relationships with others, sleep, enjoyment of life	• Opioid – Morphine slow release, Oxycodone SY, Fentanyl patches • Pain score – bone, body, visceral and nerve • Quality of Life score • Gastrointestinal side effects – constipation, nausea, vomiting • Psychological problems – delirium, excess sedation, itchy skin, addiction • Patient feedback – familiarity with clinical pharmacist, how they contributed, satisfaction with outcome, would you request their help in the future.	vomiting, pain, dyspnoea, changes in sleep, appetite loss, constipation, diarrhoea, financial difficulties.

The large quantity of outcome measures used within the four studies contained some validated measures and some less objective measures.

1. PAIN

All studies measured pain intensity in some form. The Chen [26] study measured using numeric or visual rating scales. Wang 2013 [27] used the Brief Pain Inventory which is a commonly used and validated assessment tool for measuring pain. Powers [29] also used a 0-10 scale but invited

participants to place a cross on a 10cm line between 0-10. Wang 2015 [28] used the European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC – QLQ-C30) which includes pain as a measure but using a 1-4 scale. This was then transferred to a 0-100 scale as part of their analysis.

All four studies showed a reduction in pain scores in the intervention group compared with the control. The Chen [26] study was not included in the meta-analysis as the measurement of pain was not comparable with the other three studies although pain was statistically significantly reduced in the intervention group in all pain sites measured.

Figure 2: Change in Pain Intensity

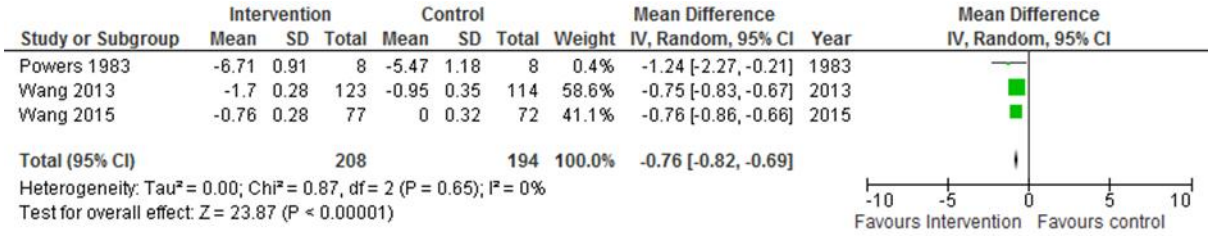

Figure 2 shows the change in pain intensity using the three studies that used 0-10 scales (involving 402 participants). Overall the changes in pain intensity reduced by an extra 0.76 in the intervention group compared with the control group. This was significant at the 5% level and the overall 95% confidence interval suggests the change in pain intensity was reduced by an extra 0.69 to 0.82 points (on a 0-10 scale) in the intervention group compared with the control group. The I^2=0% suggest the studies are not heterogeneous, this is supported by the forest plot which shows studies found fairly consistent results. Though we used the random effects method, which is recommended when there is heterogeneity, using the random effects method would also be an acceptable method to use for all analysis, as long as there are sufficient numbers overall in the samples. This was probably the most appropriate method for us to use also given the differences in the study designs.

2. PATIENT KNOWLEDGE

Both Wang studies [27, 28] looked at patient knowledge of cancer pain before and following the intervention. Both studies found that knowledge increased post intervention in both groups although this was significantly higher in the intervention group at baseline for both studies. Knowledge was measured in Wang 2013 [27] through separate pain and analgesic questionnaires. The questionnaire used was reported as being developed by all authors however it is unclear whether recognised principles of good questionnaire design were used [30]. Questions consisted of poorly

worded and leading statements with the purpose of determining a respondent's knowledge about pain and analgesia with no mention of piloting the questionnaire with patients. The knowledge tested was not always useful for a patient with cancer pain although there may have been changes when the questionnaire was translated into English. The Wang 2015 [28] study questionnaire used a significant amount of technical medical language which patients may have found difficult to understand. It is unclear how useful an increase in this knowledge would be and any change could have been as a result of seeing the questions and investigating their meaning before the second questionnaire.

3. SELF-EFFICACY AND ADHERENCE TO MEDICATION

These were not measured in any of these studies.

4. PATIENT SATISFACTION

Powers [29] and Chen [26] both measured some aspect of patient satisfaction. Chen [26] asked a simple question at the end of the study about satisfaction with the outcome of the treatment which was slightly (but significantly) higher in the intervention group. In the Powers [29] study it is unclear how patient satisfaction was assessed other than by an observer at the end of the study. A substantial increase was seen in the patient satisfaction in the intervention group compared with a small reduction in the control group.

5. SIDE EFFECTS

Side effects were measured in some way in Chen [26], Powers [29] and Wang 2015 [28]. Chen [26] and Wang 2015 [28] broke side effects down into individual symptoms and measured changes over the course of the study. These are not directly comparable as data was collected in different ways but decreases in constipation, nausea and vomiting were seen in both studies. Other side effects collected in these two studies were not comparable. Powers [29] collected data on number of side effects which was found to decrease in the intervention group.

6. QUALITY OF LIFE (QOL)

Chen [26] and Wang 2015 [28] both measured QOL. Chen [26] used the validated European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and found a significant increase in QOL in the intervention group post intervention. Wang 2015 [28] did not go into any detail about how QOL was measured and whether a validated tool was used but also found a significant increase in QOL.

Discussion

The review found that pharmacist educational interventions can have a positive effect for patients with cancer pain in relation to reduction in pain. The difference found in the meta-analysis was in line with that found in meta-analysis of educational interventions by any healthcare professional [14, 22-24]. Some evidence was also found that an improvement in knowledge, patient satisfaction, quality of life and a reduction in side effects can be demonstrated.

This systematic review is the first in this subject area and highlights the paucity of research available. Other studies have been conducted regarding educational interventions by pharmacists for patients with cancer, but these are non-experimental in nature [31-34].

Strengths and Limitations

Three of the four studies reviewed were from China [26-28] and one from UK [29]. The training of pharmacists in China is likely to be different compared with Europe and findings may not be generalizable across the world. The three Chinese studies [26-28] were published from 2013 onwards compared with the Powers [29] study which was published in 1983. The practice of pharmacists throughout the world has changed considerably since 1983 with increasingly more focus on additional medicines optimisation services.

The studies identified were assessed using the Cochrane tool and all were flawed with bias introduced in several ways for each study. Not all elements were clear in the reporting of methods or results and improvements could have been made to study design in all cases [25].

Although pain was assessed by the BPI or with another 0-10 scale with three of the four studies, other outcome measures were not measured in similar ways making comparison and meta-analysis difficult. The heterogeneity of pain measurement was problematic for meta-analysis and due to the necessary conversion of the Wang (2015) [28] data to a 0-10 scale this adds less reliability to our results. This perhaps demonstrates that research on this subject matter is in its infancy and would benefit from learning from educational intervention studies by other healthcare professionals where pain is measured by BPI. Side effects were all measured in different ways from number of side effects (Powers [29]) to changes in symptoms (Chen [26] and Wang 2015 [28]). An alternative way of measuring side effects would be through the Pharmaceutical Care Network Europe (PCNE) classification of drug-related problems [35]. This could be used to compare the problem, its cause, the intervention that followed and whether it was accepted by the physician or patient.

Other outcomes which could be used could focus on follow-up treatment and the number of healthcare consultations or new prescriptions in the time after the intervention. This would perhaps not be an accurate reflection of whether interventions were beneficial for the patient as more consultations or additional prescribing is not necessarily what at patient approaching the end-of-life needs.

The duration and intensity of the reported interventions varied considerably. Only two studies [27, 28] reported how long consultations had lasted (although quantities of consultations ranged from 6 per patient in the Powers [29] study to 16 per patient in the Wang 2015 [28] study. It might be assumed that more contact with a healthcare professional would provide greater benefit for the patient but more contact would also increase the burden on the patient [36, 37]. Finally, the small number of studies and the high risk of bias means the meta-analysis estimate of effect is likely to change with more and better quality studies.

Usual care was not fully described in any study and was lacking any detail in both Wang (2013) [27] and Wang (2015) [28]. It is unclear whether pharmacists were involved in the usual care given in any of the four studies. Usual care is difficult to define but the exact components of the control arm need to be known to differentiate it from the intervention, so this is a limitation of the review.

Recommendations for the future

Very few studies of an experimental nature have been carried out in this area to date. The further research clearly needed would benefit from using Medical Research Council guidance on complex intervention development [38]. Reporting of studies needs to be carried out in a clear and methodological manner to enable comparison and replication. Use of CONSORT and TIDieR guidelines would provide high quality and transparent reporting which would aid informed service design of future studies [39, 40].

Although a positive association was found between educational interventions by pharmacists and cancer pain, it is unclear what the active components of the interventions were. Interventions were all of a complex nature involving different amounts of patient contact over different periods of time, sometimes with additional written information. There was no mention in any of the studies about any feasibility studies the interventions had been informed by and whether the fidelity of interventions had been assessed in any way. Future studies would benefit from evaluation to understand how the different components contributed to the outcomes achieved.

Conclusion

Our systematic review highlights the limited evidence base regarding educational interventions by pharmacists for patients with cancer pain. Although the analysis indicates that these interventions are beneficial and can lead to a reduction in pain intensity and improvements in knowledge, patient satisfaction and side effects, very few RCTs have been carried out. Future research should focus on generating high quality evidence in this area and ensuring it is reported clearly to allow learning and replication for the future. Outcome measures should be considered carefully to ensure potential benefits for patients can be measured and compared easily.

References

1. Cancer Research UK. Cancer Statistics for the UK, http://www.cancerresearchuk.org/health-professional/cancer-statistics#heading-One (2017, accessed 16 April 2017).
2. Raphael J, Ahmedzai SH, Barrie J, et al. The British Pain Society's Cancer pain management: a perspective from the British Pain Society, supported by the Association for Palliative Medicine and the Royal College of General Practitioners, https://www.britishpainsociety.org/static/uploads/resources/files/book_cancer_pain.pdf (2010).
3. Gao W, Gulliford M, Bennett MI, et al. Managing cancer pain at the end of life with multiple strong opioids: a population-based retrospective cohort study in primary care. *PLoS One* 2014; 9: e79266. DOI: 10.1371/journal.pone.0079266.
4. WHO. World Health Organisation: Cancer Pain Relief, http://apps.who.int/iris/bitstream/10665/43944/1/9241561009_eng.pdf (1986).
5. Azevedo São Leão Ferreira K, Kimura M and Jacobsen Teixeira M. The WHO analgesic ladder for cancer pain control, twenty years of use. How much pain relief does one get from using it? *Support Care Cancer* 2006; 14: 1086-1093. 2006/06/08. DOI: 10.1007/s00520-006-0086-x.
6. Ventafridda V, Tamburini M, Caraceni A, et al. A validation study of the WHO method for cancer pain relief. *Cancer* 1987; 59: 850-856.
7. Vuong S, Pulenzas N, DeAngelis C, et al. Inadequate pain management in cancer patients attending an outpatient palliative radiotherapy clinic. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer* 2016; 24: 887-892. 2015/07/27. DOI: 10.1007/s00520-015-2858-7.
8. Mitera G, Zeiadin N, Kirou-Mauro A, et al. Retrospective assessment of cancer pain management in an outpatient palliative radiotherapy clinic using the Pain Management Index. *Journal of Pain & Symptom Management* 2010; 39: 259-267. DOI: 10.1016/j.jpainsymman.2009.07.005.
9. Greco MT, Roberto A, Corli O, et al. Quality of cancer pain management: an update of a systematic review of undertreatment of patients with cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2014; 32: 4149-4154. 2014/11/19. DOI: 10.1200/jco.2014.56.0383.
10. Deandrea S, Montanari M, Moja L, et al. Prevalence of undertreatment in cancer pain. A review of published literature. *Annals of oncology : official journal of the European Society for Medical Oncology* 2008; 19: 1985-1991. 2008/07/18. DOI: 10.1093/annonc/mdn419.
11. ONS OfNS. National Survey of Bereaved People (VOICES): 2014. In: Statistics OfN, (ed.). Office for National Statistics, 2015.

12. Hackett J, Godfrey M and Bennett MI. Patient and caregiver perspectives on managing pain in advanced cancer: A qualitative longitudinal study. *Palliat Med* 2016; 30: 711-719. 2016/02/04. DOI: 10.1177/0269216316628407.
13. Edwards Z BA, Ziegler L, Bennett MI,. How do patients with cancer pain view community pharmacy services? An interview study. *Health and Social Care in the Community* 2018: 1-12. 26th February 2018. DOI: https://doi.org/10.1111/hsc.12549.
14. Bennett MI, Bagnall AM and Jose Closs S. How effective are patient-based educational interventions in the management of cancer pain? Systematic review and meta-analysis. *Pain* 2009; 143: 192-199. DOI: 10.1016/j.pain.2009.01.016.
15. Lowe CJ, Raynor DK, Purvis J, et al. Effects of a medicine review and education programme for older people in general practice. *Br J Clin Pharmacol* 2000; 50: 172-175.
16. Lin CC. Barriers to the analgesic management of cancer pain: a comparison of attitudes of Taiwanese patients and their family caregivers. *Pain* 2000; 88: 7-14.
17. Miaskowski C, Dodd MJ, West C, et al. Lack of adherence with the analgesic regimen: a significant barrier to effective cancer pain management. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* 2001; 19: 4275-4279. DOI: 10.1200/JCO.2001.19.23.4275.
18. Barber N, Parsons J, Clifford S, et al. Patients' problems with new medication for chronic conditions. *Qual Saf Health Care* 2004; 13: 172-175. DOI: 10.1136/qhc.13.3.172.
19. Bennett MI, Closs SJ and Chatwin J. Cancer pain management at home (I): do older patients experience less effective management than younger patients? *Support Care Cancer* 2009; 17: 787-792. DOI: 10.1007/s00520-008-0549-3.
20. Bennett MI, Bagnall AM, Raine G, et al. Educational interventions by pharmacists to patients with chronic pain: systematic review and meta-analysis. *The Clinical journal of pain* 2011; 27: 623-630. DOI: 10.1097/AJP.0b013e31821b6be4.
21. Hadi MA, Alldred DP, Briggs M, et al. Effectiveness of pharmacist-led medication review in chronic pain management: systematic review and meta-analysis. *The Clinical journal of pain* 2014; 30: 1006-1014. DOI: 10.1097/AJP.0000000000000063.
22. Devine EC. Meta-analysis of the effect of psychoeducational interventions on pain in adults with cancer. *Oncology nursing forum* 2003; 30: 75-89. DOI: 10.1188/03.ONF.75-89.
23. Devine EC and Westlake SK. The effects of psychoeducational care provided to adults with cancer: meta-analysis of 116 studies. *Oncology nursing forum* 1995; 22: 1369-1381.
24. Allard P, Maunsell E, Labbé J, et al. Educational interventions to improve cancer pain control: a systematic review. *Journal of palliative medicine* 2001; 4: 191-203. DOI: 10.1089/109662101750290227.
25. Higgins JP, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928. 2011/10/18.
26. Chen J, Lu X, Wang W, et al. Impact of a clinical pharmacist-led guidance team on cancer pain therapy in China: a prospective multicenter cohort study. *Journal of pain and symptom management 48(4)*, http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/149/CN-01072149/frame.html (2014).
27. Wang Y, Huang H, Zeng Y, et al. Pharmacist-led medication education in cancer pain control: a multicentre randomized controlled study in Guangzhou, China. *J Int Med Res* 2013; 41: 1462-1472. 2013/08/23. DOI: 10.1177/0300060513491170.
28. Wang Y, Wu H and Xu F. Impact of clinical pharmacy services on KAP and QOL in Cancer Patients: a single-center experience. *Biomed research international 2015(no pagination)*, http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/725/CN-01128725/frame.html (2015).
29. Powers D, Hamilton C and Roberts K. Pharmacist intervention in methadone administration to cancer patients with chronic pain. *American journal of hospital pharmacy 40(9)*, http://onlinelibrary.wiley.com/o/cochrane/clcentral/articles/333/CN-00343333/frame.html (1983).
30. Stone DH. Design a questionnaire. *Bmj* 1993; 307: 1264-1266.

31. Atayee RS, Best BM and Daniels CE. Development of an ambulatory palliative care pharmacist practice. *Journal of palliative medicine* 2008; 11: 1077-1082. DOI: 10.1089/jpm.2008.0023.
32. Jiwa M, Hughes J, O'Connor M, et al. Field testing a protocol to facilitate the involvement of pharmacists in community based palliative care. *Australian Pharmacist* 2012; 31: 72-76. January 2012.
33. Needham DS, Wong IC, Campion PD, et al. Evaluation of the effectiveness of UK community pharmacists' interventions in community palliative care. *Palliat Med* 2002; 16: 219-225.
34. Hussainy SY, Box M and Scholes S. Piloting the role of a pharmacist in a community palliative care multidisciplinary team: an Australian experience. *BMC Palliat Care* 2011; 10: 16. DOI: 10.1186/1472-684X-10-16.
35. Pharmaceutical Care Network Europe Foundation (PCNE). Classification for Drug related problems V8.02. 2017.
36. White CD, Hardy JR, Gilshenan KS, et al. Randomised controlled trials of palliative care - a survey of the views of advanced cancer patients and their relatives. *Eur J Cancer* 2008; 44: 1820-1828. 2008/06/10. DOI: 10.1016/j.ejca.2008.05.003.
37. White C and Hardy J. What do palliative care patients and their relatives think about research in palliative care?-a systematic review. *Support Care Cancer* 2010; 18: 905-911. 2009/08/25. DOI: 10.1007/s00520-009-0724-1.
38. Medical Research Council. A framework for development and evaluation of RCT's for complex interventions to improve health., https://mrc.ukri.org/documents.pdf/rcts-for-complex-interventions-to-improve-health/ (2000).
39. Boutron I, Altman DG, Moher D, et al. CONSORT Statement for Randomized Trials of Nonpharmacologic Treatments: A 2017 Update and a CONSORT Extension for Nonpharmacologic Trial Abstracts. *Ann Intern Med* 2017; 167: 40-47. 2017/06/20. DOI: 10.7326/M17-0046.
40. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *Bmj* 2014; 348: g1687. 2014/03/07.