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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.

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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 these interventions and their effectiveness. 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 these interventions and their 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

Analysis found that pain intensity in the intervention group was reduced by 0.76 on a 0-10 scale. Improvements in knowledge, side effects and patient satisfaction were also seen although with less reliable measures.

Conclusions

Pharmacist educational interventions for patients with cancer pain have been found to be effective in reducing pain intensity. Studies included were few and of varying quality. Further studies should be carried out in this area and particular attention should be paid to comprehensive reporting and study quality. Trials measuring 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 (Cancer Research UK, 2017). Life expectancy of cancer patients is increasing and in the last 40 years, the cancer survival[1] rate in the UK has doubled, from 24% to 50% (Cancer Research UK, 2017).

The World Health Organisation's analgesic three-step ladder is the clinical principle for cancer pain management (Raphael et al., 2010). 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 (Gao et al., 2014, WHO, 1986). Despite the improvement recorded in pain management after using this strategy , evidence indicates that cancer patients still experience high levels of pain in situations where it is possible to reduce their suffering (Azevedo São Leão Ferreira et al., 2006, Ventafridda et al., 1987). It has been reported that around 25% to 33% of cancer patients are receiving insufficient pain management (Vuong et al., 2016, Mitera et al., 2010). In addition, two systematic reviews that assessed the quality of pain management in adult cancer patients revealed modest improvements in pain management, but stated that one third of patients who experience pain continue to be under-treated (Greco et al., 2014, Deandrea et al., 2008).

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 (ONS, 2015). 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 (Hackett et al., 2016, Edwards Z, 2018).

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 (Bennett et al., 2009a).

Educational interventions have been shown to help patients with cancer pain by both improving knowledge and reducing average and worst pain intensity (Bennett et al., 2009a). 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 (Lowe et al., 2000, Lin, 2000). Low adherence to medication has been linked to reduced pain control (Miaskowski et al.,

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

2001). A British study found that 61% of patients 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 (Barber et al., 2004).

Community pharmacists in the UK are the most frequently accessed healthcare professional for patients with advanced cancer (along with community nurses) (Bennett et al., 2009b). 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. The Medicines Use Review (MUR) is a medicines discussion, usually conducted in person with a patient to discuss medicines understanding and adherence (PSNC, 2017a). MURs have been found to improve patient knowledge and choice of medicine and reduce polypharmacy but unfortunately they are rarely carried out with patients with pain from cancer (Blenkinsopp et al., 2012, Savage et al., 2013). The New Medicines Service (NMS) is a series of usually telephone consultations for patients when they are first prescribed certain medicines from a specified list (PSNC, 2017b). The aim is to help patients manage medicines for long-term conditions and they have been found to improve adherence but cancer is not currently one of the conditions covered by the service (Department of Health, 2014). Pharmacists could therefore be an under-utilised source of medicines advice for patients with pain from cancer living in the community.

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 (Bennett et al., 2011).

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

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 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 (Higgins et al., 2011). The tool identifies bias related to the design, conduct, analysis or reporting of the study and helps identify methodological flaws within each study and how high, low or unclear the risk of that bias is. It was decided to use this tool due to its comprehensive nature and clear reporting (Higgins et al., 2011).

Results

989 studies were identified using the database searches. A flow diagram is shown in Figure 1 of the study selection. 953 of studies were excluded after screening of the titles or abstract. 18 duplicates were removed leading to full text screening of 18 individual papers. 14 of these were then excluded according to eligibility criteria leading to 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

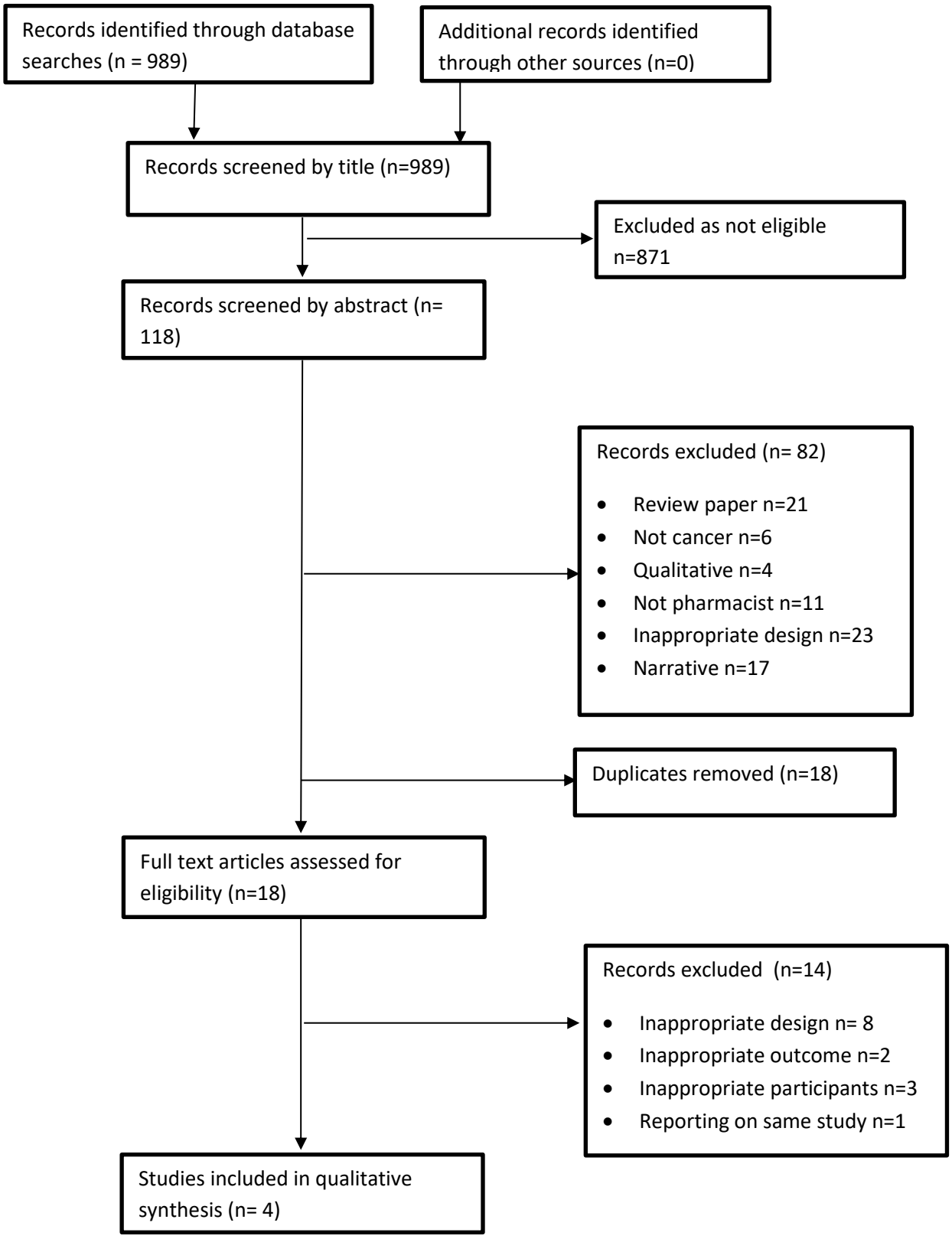

Table 1 Characteristics of included studies

Characteristics of included studies are shown in table 1

Study	Sample recruited (completed)	Follow-up interval	Method of delivery	Dose or quantity intervention	Provision of written material	Pharmacist monitored pain scores	Medication review and adjustment	Findings
Chen 2013(Chen et al., 2014)	542	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
Powers 1983(Powers et al., 1983)	16	8 days	Pharmacist delivered consultations with dosage adjustment, recommendation of over-the-counter medicines and	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

			supportive counselling					
Wang 2013(Wang et al., 2013)	237	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
Wang 2015(Wang et al., 2015)	149	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.

A summary of the studies is shown in Table 1. Four studies were included in the review and these studies involved a total of 944 participants (individually ranging from 16 to 542). Three of the studies were carried out in China and one in the UK. Settings were a mixture of hospital and community although this was not always clear from study reporting. All studies consisted of some sort of educational intervention by a pharmacist, one involved dosage adjustment and one involved liaison with the prescriber. Consultations were entirely telephone based in one study with a mixture of telephone and face-to-face in 3 studies. One study comprised of 6 consultations, one had 8, one had a minimum of 12 and one had 16 consultations.

One study (Chen et al., 2014) involved a clinical pharmacist-led guidance team which comprised a trained pharmacist, oncology nurses, oncologists and administrators. Pharmacists, without prescribing capability, were responsible for training patients and staff, 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 assessing pain control and preventing and dealing with adverse events with additional communication with prescribers where any adjustment in medication was necessary.

A 1983 study (Powers et al., 1983) involved patients with chronic cancer pain who were suitable for pain relief by methadone to receive daily follow-up telephone consultations after the medicine has been initiated to adjust the dosage, recommend other over-the-counter medicines and deal with side effects.

In another study (Wang et al., 2013), patients in the intervention arm were given 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 could have extra consultations if they needed them. Questionnaires were completed with a pharmacist's help at study entry and after four weeks.

Another study by the same author (Wang et al., 2015) involved study patients being given written information and then 2, 30 minute education sessions were delivered twice a week for 2 months. Patients were assessed before and after the intervention for knowledge and quality of life.

All studies compared the intervention with usual care.

Quality of included studies

The quality of included studies is reported in table 2.

Table 2: Cochrane's tool for assessing risk of bias summary (Higgins et al., 2011)

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

Only the Chen study was flawed in how the participants were assigned to the control or intervention groups and Wang 2013, Wang 2015 and Powers used adequate methods of randomisation. 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 and Chen although Powers stated the pharmacist observer was blinded as to the group patients had been assigned which minimised assessment bias in this study.

The questionnaire used in Wang 2013 was felt to be poorly designed and potentially leading which could provide another source of bias.

As is common in studies in this patient group, 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 study as loss to follow up was reported before patients were allocated to the control or intervention group even though they were assigned in order of registration to the control or intervention group. There is therefore a large risk of bias from this study. Data is unclear or incomplete in Wang 2013 as 'other reasons' are reported for loss to follow-up. Powers had a very small sample size making the outcome data less reliable. Wang 2015 was assessed as no bias for this measure.

Selective reporting was found in Powers 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 table showing the different outcome measures reported for the studies in this review

Chen 2014	Powers 1983	Wang 2013	Wang 2015
• Opioid administration • Pain assessment before therapy	• Pain intensity • Pain relief • Number of side effects	• Pain knowledge • Analgesic knowledge • Total pain related knowledge	• Knowledge • Attitude • Practice • Quality of life – Global, physical

• Dose titration before therapy, before slow release formulation, before dosage increase • Inappropriate conversion – change in drug without reason, incorrect conversion • 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	• Patient satisfaction	• BPI – Usual pain in the last week • BPI - Current pain • BPI – Pain at rest • BPI – Pain with movement • Pain interference – daily activity, mood, walking ability, normal working, relationships with others, sleep, enjoyment of life	functioning, role functioning, emotional functioning, cognitive functioning, social functioning. • Symptom scales – fatigue, nausea and vomiting, pain, dyspnoea, changes in sleep, appetite loss, constipation, diarrhoea, financial difficulties.

pharmacist, how they contributed, satisfaction with outcome, would you request their help in the future.			

The large quantity of outcome measures used within the four studies contained some validated measures and some less objective measures. It was felt that the questionnaires used to assess knowledge in both Wang studies did not necessarily reflect knowledge that would be useful for a patient with cancer pain to know and there was little information about how the content of the questionnaires was decided upon. These studies were both from China so it is possible that some changes to meanings of the questions were made in translation to the English language.

Outcomes assessment

PAIN

All studies measured some sort of pain intensity although the Chen study did not measure on a 0-10 (where 0 was no pain and 10 was the worst pain imaginable) scale as the others did. Wang 2013 used the Brief Pain Inventory which is a commonly used and validated assessment tool for measuring pain. Powers also used a 0-10 scale but invited participants to place a cross on a 10cm line between 0-10. Wang 2015 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.

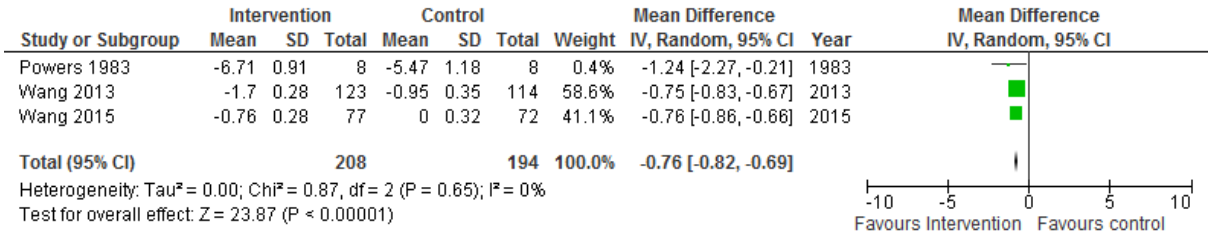

Figure 2 Change in Pain Intensity

Figure 2 shows the change in pain intensity using the studies that used 0-10 scales. 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 have used the random effects method, which is recommended when there is heterogeneity, using the random effects method is also an acceptable method to use for all analysis, as long as there are sufficient numbers overall in the samples. It is probably the most appropriate method for us to use also given the differences in the study designs.

Other outcomes

KNOWLEDGE

Both the Wang 2013 and the Wang 2015 studies looked at knowledge of patients following the intervention. Both studies found that knowledge increased post intervention in both groups although this was significantly higher in the intervention group for both studies. Knowledge was measured in Wang 2013 though separate pain and analgesic questionnaires. The questions asked may not be an accurate representation of the knowledge of patients in the study as they were not validated and comprised questions which could be construed as leading with little insight into useful patient knowledge. The knowledge assessment in Wang 2015 comprised a questionnaire with 19 questions. These questions varied in their usefulness for patients and (after English translation) 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.

QUALITY OF LIFE (QOL)

Chen and Wang 2015 both measured QOL. Chen 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 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.

PATIENT SATISFACTION

Powers and Chen both measured some aspect of patient satisfaction. Chen 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 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.

SIDE EFFECTS

Side effects were measured in some way in Chen, Powers and Wang 2015. Chen and Wang 2015 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 collected data on number of side effects which was found to decrease in the intervention group.

Discussion

The review found that pharmacist educational interventions can have a positive effect for patients with cancer pain in relation to reduction in pain. Some evidence was also found that an improvement in knowledge and patient satisfaction can be demonstrated with a reduction in side effects.

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 (Atayee et al., 2008, Jiwa et al., 2012, Needham et al., 2002, Hussainy et al., 2011, Edwards et al.).

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 (Higgins et al., 2011).

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. 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. Side

effects were all measured in different ways from number of side effects (Powers) to changes in symptoms in Chen and Wang 2015. An alternative way of measuring side effects would be through the Pharmaceutical Care Network Europe (PCNE) classification of drug-related problems (Pharmaceutical Care Network Europe Foundation (PCNE), 2017). 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 interventions found varied considerably. Only one study reported how long consultations had lasted although quantities of consultations ranged from 6 in the Powers study to 16 in the Wang 2015 study. It would be assumed that more contact with a healthcare professional would provide greater benefit for the patient but careful attention should be paid as to how burdensome this could be with research design playing an important part in recruitment success (White and Hardy, 2010, White et al., 2008, Edwards Z et al.).

Recommendations for the future

Very few studies of an experimental nature have been carried out in this area to date. Further research would add to the evidence base already obtained and would benefit from using Medical Research Council guidance in their design (Medical Research Council, 2000). Reporting of studies needs to be carried out in clear and methodological manner to ease 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 (Boutron et al., 2017, Hoffmann et al., 2014).

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. Future studies would benefit from evaluation to understand how the different components contributed to the outcomes achieved.

Strengths and Limitations

Three of the four studies reviewed were from China and one from America. The training of pharmacists in China is likely to be different compared with America and Europe and findings may not be generalizable across the world. The three Chinese studies were published from 2013 onwards compared with the Powers 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.

Conclusion

The review concludes that the few existing studies exploring educational interventions by pharmacists for patients with cancer pain indicate that they are beneficial and can lead to a reduction in pain intensity and improvements in knowledge, patient satisfaction and side effects. As very few RCTs have been carried out in this area, future research should focus on increasing the evidence in this area and ensuring it is reported clearly to allow learning and replication for the future. Outcome measures should be considered very carefully to ensure benefits for patients can be measured and compared easily.

Appendix 1

The following search strategy was employed.

#1	pharmacist OR pharmacists OR pharmacy OR pharmacies
#2	patient education OR educat* OR teach* OR train* OR advi* OR support OR manag* OR instruct* OR information OR guidance OR counsel* OR cope OR coping OR self management OR self care OR self medication OR medicines review OR medication review OR medication counsel*
#3	pain OR headache OR analgesi*
#4	Randomized Controlled Trial [publication type]
#5	Controlled Clinical Trial [publication type]
#6	"randomized"[Title/Abstract]
#7	"placebo"[Title/Abstract]
#8	clinical trials as topic [mesh: noexp]
#9	"randomly"[Title/Abstract]
#10	trial[Title]
#11	"randomised"[Title/Abstract]

#12 #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11

#13 animals [mh] NOT (humans [mh] AND animals [mh])

#14 #12 NOT #13

#15 #1 AND #2 AND #3 AND #14

#16 cancer OR palliative

#17 #15 AND #16

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