A systematic review of the impact of outpatient clinical pharmacy services on medication-related outcomes in patients receiving anticancer therapies – a focus on radiotherapy pharmacy services.

Sam Maleki, B.Pharm, Master Pharmacy Practice, Oncology Pharmacist[1]

sam.maleki@petermac.org

Marliese Alexander, B.Pharm, Grad.Cert. Pharmacy Practice, Master Public Health, Pharmacy Research Manager[1]

marliese.alexander@petermac.org

Tsien Fua, FRANZCR, Radiation Oncologist[2]

tsien.fua@petermac.org

Chen Liu, FRANZCR, Radiation Oncologist[2]

chen.liu@petermac.org

Danny Rischin, MD, FRACP, Director of Medical Oncology[3]

danny.rischin@petermac.org

Senthil Lingaratnam, B.Pharm, Master Public Health, Directory of Pharmacy[1]

senthil.lingaratnam@petermac.org

1. Department of Pharmacy, Peter MacCallum Cancer Centre

305 Grattan Street, Melbourne, Victoria, 3000, Australia.

Tel: +61 (0)3 8559 5202

Fax: +61 (0)3 8559 5203

2. Department of Radiation Oncology, Peter MacCallum Cancer Centre

305 Grattan Street, Melbourne, Victoria, 3000, Australia.

Tel: +61 (0)3 8559 6000

3. Department of Medical Oncology, Peter MacCallum Cancer Centre

305 Grattan Street, Melbourne, Victoria, 3000, Australia.

Tel: +61 (0)3 85597882

Corresponding author:

Address correspondence and reprint request to Sam Maleki, Oncology Pharmacist

Email: sam.maleki@petermac.org

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Title:

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Short title:

Outpatient Oncology Clinical Pharmacy Services: A Systematic Review.

ABSTRACT

Title: A systematic review of the impact of outpatient clinical pharmacy services on medication-related outcomes in patients receiving anticancer therapies.

Background: Patients receiving anticancer therapies are frequently prescribed complex and high-risk medication regimens which at times can result in medication misadventures. The objective of this review was to assess the effect of outpatient clinical pharmacy services on medication-related outcomes in patients receiving anticancer therapies, including patients undergoing radiotherapy.

Methods: A systematic review of original publications indexed in EMBASE, MEDLINE and Cochrane Library from June 2007 to June 2017. Eligible studies evaluated outpatient pharmacy clinic services for cancer patients and reported at least one medication-related quantitative outcome measure. Two authors independently reviewed full-text articles for inclusion, then extracted data and performed quality and risk of bias assessments.

Results: Of 908 identified publications, thirteen met predefined eligibility criteria; one randomised control trial, two controlled cohort studies, and ten uncontrolled before-after studies. Many excluded studies described outpatient pharmacy services but lacked medication-related outcomes. All included studies had informative practice model designs; with interventions for drug-related problems including drug

dose optimisation (*n* = 8), reduced drug interaction (*n* = 6) and adverse drug reaction reporting (*n* = 3). Most studies (*n* = 11) reported on symptom improvement; commonly nausea (*n* = 7) and pain (*n* = 5). Of four studies in radiotherapy cohorts, pharmacist involvement was associated with improved symptoms, satisfaction, and well-being scores.

Conclusion: Few studies have objectively assessed outpatient pharmacy cancer services, even fewer in the radiotherapy settings. Although results support these services, significant heterogeneity and bias in study designs prohibits robust conclusions and further controlled trials are required.

Key words: Radiotherapy, Ambulatory Care, Pharmacy, Medication safety, Medicine Use Optimisation

A systematic review of the impact of outpatient clinical pharmacy services on medication-related outcomes in patients receiving anticancer therapies.

1. Introduction

Cancer treatments are increasingly provided in community and outpatient settings. As cancer care transitions to the outpatient setting, so has hospital pharmacy practice with increasing reports of pharmacy services in outpatient clinics, including cancer supportive care clinics.

Radiotherapy, with or without concurrent chemotherapy, is the cornerstone of many anticancer treatment regimens provided in the outpatient setting. Radiotherapy is fundamental in the treatment of head and neck cancers, lung cancers and upper gastrointestinal cancers. It is also associated with extensive and debilitating adverse effects including mucositis, dysphagia, orofacial pain, nausea, xerostomia, dental issues and weight loss (1-5). Timely management of treatment-related adverse effects and toxicities is essential to reduce patient suffering, prevent treatment discontinuation and reduce unplanned hospital admissions (6). Supportive medications are an integral component of this management process with radiotherapy patients frequently prescribed complex and high-risk medication regimens including systemic chemotherapy or targeted therapies, supportive care medications such as opioid analgesics, and other medications for comorbid

illnesses. Managing medications in this setting is particularly challenging due to the ongoing severe pain, nausea, dysphagia and barriers to verbal communication. From the clinical pharmacy perspective medication formulations must be regularly optimised to manage dysphagic symptoms, with personalised regimens required for the administration of medications via enteral feeding tubes.

The elderly make up a large proportion of the cancer population and with increased comorbid conditions and medication burden, polypharmacy is often problematic (7). In addition, a decreased level of medication adherence has been reported in cancer patients (8) and when combined with other factors such as poor communication of medical information at transition points, can result in high rates of medication-related adverse events and otherwise preventable medication errors (9) with significant economic impact (10).

To date, an extensive body of literature supports the multidisciplinary approach, including pharmacy clinical services, towards ambulatory care (11) and in particular in the cancer setting (12-19). Pharmacy outpatient clinical services provided in relation to chemotherapeutics have been reported to contribute to accurate medication histories, reduced prescribing errors, improved patient adherence and satisfaction with the treatment process (17-24). Similar benefits have been reported for patients undergoing radiotherapy however the evidence for these services in the radiotherapy clinics is less robust (25).

This systematic literature review aimed to assess the impact of outpatient clinical pharmacy services on medication-related outcomes in patients receiving anticancer therapies, including patients undergoing radiotherapy.

2. Methods

2.1 Search strategy

Papers indexed in EMBASE, MEDLINE and Cochrane Collaboration, from June 2007 through to June 2017, were systematically searched. Other articles were identified from the reference lists of the included studies, grey literature and Google platforms. The search strategy was developed using the PICO framework and, broadly, it combined the following search terms: pharmacy/pharmacist/multidisciplinary/interdisciplinary AND outpatient/clinic/ ambulatory AND cancer/oncology/carcinoma/chemotherapy/chemoradiation /radiotherapy/radiation as well as typographic variations; full details reported in **Supplemental Table 1**. Searches were carried out using a combination of Medical Subject Headings (Mesh) terms, keywords and subheadings. Boolean operators as well as relevant truncations were applied to explode and implode result fields.

2.2 Selection criteria

Included studies were required to meet the following criteria: (i) original full-text article published between 2007 and 2017; (ii) evaluated an outpatient clinic pharmacy service; (iii) adult population with a cancer diagnosis; (iv) reported at least one change-over-time quantitative outcome measure; (v) reported at least one medication-related outcome measure; (vi) study design meeting at least criteria for grade III level of evidence according to the Australian National Health and Medical Research Council (NHMRC) (26) Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (27).

Studies of pharmacy services related to chemotherapy day units, clinical trials and community-based cancer services were ineligible for inclusion. Services and the role of pharmacists in these settings were considered to be different to that of a supportive care outpatient pharmacy clinic service, and outside the scope of this review.

2.3 Data collection and analysis

Two authors (S.M. and M.A.) independently reviewed all full-text articles for inclusion, then extracted data and performed quality and risk of bias assessments. Authors rated risk of bias as low, medium, high or critical for individual bias domains ensuing to a final bias assessment. Disagreements were resolved by discussion with escalation to a third author if required (S.L.). For the included

studies the following data was extracted: study location and design, population demographics, cancer diagnoses, nature of pharmacist interventions, patient-related outcome measures and quantitative outcome measures.

2.4 Quality review

A combination of quality assessment tools were used in this review: the Cochrane Collaboration's tool for assessing risk of bias in randomised trials was used for randomised controlled trials (RCT), the Cochrane Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) and study specific tools including the Newcastle-Ottawa Scale (NOS) and the National Institute of Health (NIH) Quality Assessment Tool for Before-After (Pre-Post) Studies With No Control Group were used (28-31).

3. Results

The pre-defined search strategy identified 908 publications, **Figure 1**. Excluding duplicates (n = 314) and non-cancer trials (n = 435), 159 were reviewed by title and abstract. Of these, 136 did not meet eligibility criteria, leaving 23 full text articles for full review; thirteen met eligibility criteria with evidence synthesised for review including one RCT, two cohort studies with control groups, and ten uncontrolled before-after studies. Four studies were eligible for the sub-study in radiotherapy

clinics. A full list of articles and reason for their exclusion is available at **Supplemental Table 2**.

The thirteen studies included 1588 patients with sample size ranging from 15 to 406 and most studies providing a sample size above 50 (n = 9). Aggregate median age was above 60 years and the cancer types were typical of our local patient cohort with breast (n = 7) and lung (n = 6) cancers being the most commonly reported diagnoses in most studies. Characteristics of the 13 included studies are summarised in **Table 1.**

Cohort studies reported change-over-time outcome measures as a comparison of intervention groups with concurrent/historical control groups. The comparative before-after type studies reported symptom improvement on subsequent clinic visits, after intervention by the outpatient clinic pharmacist, and compared this to the patient's baseline scores. Studies reported on a range of pharmacy activities, including (1) various types of pharmacist interventions; (2) routine pharmacy services such as medication reconciliation, patient education, adherence assessments and economic appraisals; and lastly (3) association of these activities and services to direct patient-related outcomes such as improvement in symptoms. Outcome variables are further summarised in **Table 2**.

3.1 Quality of included studies

The level of evidence, quality, and bias risk for each study has been summarised in **Table 3**. Varied study designs were employed meeting criteria for classification of level II or III in the NHMRC evidence hierarchy (26). Notably, one of the included studies (32), although originally presented as a RCT, only reported data for the intervention group necessitating review as a single arm uncontrolled study, and classification as level III evidence. Authors' level of agreeance for risk of bias rating was high and most disagreeance within individual domains was resolved via discussion. On two occasions, the higher bias rating was adopted over individual bias domains; however this did not change the overall bias rating of the implicated studies.

3.2 Pharmacist intervention for drug related problems

All included studies reported on medication-related outcomes with interventions for drug-related problems (DRPs) including drug dose optimisation (n = 8), reduced drug interaction (n = 6), adverse drug reaction (ADR) reporting (n = 3) and adjustment of supportive medications (n = 1). All radiotherapy articles (n = 4) reported on pharmacist intervention for analgesics including opioid dose recommendation, adjustment and monitoring of toxicities.

3.3 Adherence and understanding assessments

Adherence was assessed in five studies, with two out of five demonstrating statistically significant results correlating with pharmacist interventions (33, 34). Ribed *et al*. examined 249 participants and demonstrated a 20% increase in medication adherence ($p < 0.001$) in response to pharmacy services in comparison to a control cohort. Adherence was assessed by the extent of medication procurement by patients by using a dispensing computer software that monitored the rate of medication dispensing to each patient. In contrast, Walter *et al*. used the Morisky adherence tool (35), a structured four-item self-reported adherence measure, to provide a more detailed assessment of adherence. In this study adherence was assessed following the implementation of a clinic pharmacy service. Although higher scores were recorded post-implementation ($p = 0.007$) only 48 patients were recruited and the study lacked suitable controls.

3.4 Symptom assessment

The most commonly used symptom assessment tool was the Edmonton Symptom Assessment System (ESAS) (36). The most commonly reported patient-related outcome measure was nausea symptom scores ($n = 7$), with three of seven studies demonstrating statistically significant improvement in nausea symptoms with pharmacist intervention (37-39). These studies included varied patient populations

and included both acute and delayed chemotherapy induced nausea and vomiting (CINV), described as complete emetic response or partial responses. Pharmacist interventions included pharmacist initiated prophylaxis, education, review and follow-up. The most significant improvement was achieved in a study in breast & ovarian cancers predominantly treated with epirubicin and cyclophosphamide (38). Patients in the intervention group who received pharmacist intervention (education, counselling and medicines review) achieved a cycle 1 complete emesis response rate of 92% compared with 49% in the concurrent control group ($p < 0.001$). Improvements in nausea control for the intervention group were observed to cycle 6, reaching statistical significance to cycle 4. Similar findings were observed in a study of acute and delayed phase complete emetic response rates. Both acute (97% intervention Vs. 71% control, $p = 0.002$) and delayed phase (61% intervention Vs. 52% control, $p = 0.237$) emetic response was improved with pharmacist intervention, but only reaching significance for the acute phase cohort (37). The third study demonstrated significant reductions in nausea score after pharmacist intervention, however using a before-after design without a control, the impact of pharmacist intervention versus time-related change could not be determined (39). All other studies support the positive influence of outpatient pharmacist services in improving patient nausea, although magnitude of impact varied and not all studies

reached statistical significance. Improvement in nausea correlated with improved wellbeing and quality of life (38).

The second most commonly reported outcome measure was pain score ($n = 5$), with four out of five, including two radiotherapy articles, demonstrating significant improvements in pain control with pharmacist intervention (39-43). Pharmacist interventions included modification of opioid dose or formulation, identification of DRPs and drug duplications, direct communication with community care providers, and interventions to improve adherence, patient verbal and written counselling and action/care plans.

Four studies, including three radiotherapy articles, provided composite symptom scores such as improvement in a range of ESAS symptoms including constipation, tiredness, anxiety, depression, drowsiness, dyspnoea and anorexia. Of these only two supported their results with tests of statistical significance ($p < 0.05$) (39, 42).

4. Discussion

This systematic review of pharmacy outpatient services for supportive care oncology clinics identified thirteen eligible studies, with just four within radiotherapy treatment or review clinics, from over 908 studies reviewed. Studies contributed low to moderate level evidence (grade II-III), with significant variation in design and quality. Heterogeneity of design, population and outcomes prevented

aggregation and meta-analyses. Individual study findings provided overall weak but positive evidence that outpatient pharmacy services can improve patient outcomes in this setting. Important lessons for improved study design for the assessment of pharmacy services, including choice of outcome measures and statistical analyses, can be learned from the large volume of excluded studies as well as limitations of included studies. In addition, a large number of abstract only publications were identified, most notably as conference proceedings. Although they described many important facets of outpatient pharmacy services, the lack of clinical data prohibited their utility and they were excluded from this review.

We identified a large degree of variance in quality scores between study-specific tools such as the NOS, the NIH tool for before-after studies and the ROBINS-I tool. In particular, we identified that the NIH tools did not assess for treatment and time-related improvement in symptoms, particularly relevant to our study question. For example, many studies reported improved symptom scores with the pharmacy intervention; however, lacking a control arm improvement in patient symptoms cannot be solely associated with intervention and may instead reflect natural improvement over time i.e. radiotherapy-induced pain usually improve drastically after completion of radiotherapy course. These studies rated with 'critical' levels of bias when assessed using the ROBINS-I tool and although they provided useful

information on the nature of pharmacy service design their results are too problematic to provide any useful evidence on the effect of the intervention (44).

This review identified important information about the evolving nature of pharmacy services. We found that due to a significant degree of heterogeneity in study designs it was not possible to draw any conclusions about the overall effectiveness of these services. In addition, inconsistency in study designs and lack of attention to cofounders has often given rise to substantial bias which further diminishes the strength of such studies. We also discovered inconsistent study titles and key words prohibiting a simple search strategy.

Our results suggest the largest single benefit, of the outpatient clinical pharmacy services for patients, is the improvement in medication safety. Routine medication reconciliation, identification of DRPs, drug interactions and ADRs is often a fulfilling and alerting activity and should be implicated in improving patient safety.

Medication adherence is fundamental for efficacious cancer treatment. Studies frequently report poor rates of medication adherence resulting in treatment failures, failure of supportive medications such as analgesics, laxatives and aperients, reduced patient satisfaction with the treatment process and care providers due to diminished quality of life and decreased overall survival (45). Our results show poor adherence to be a repeating theme and as depicted by Walters *et al.*, simple

adherence tools such as the Morisky's seven point questionnaire can easily be incorporated in many outpatient settings. In addition, in these studies improvement in adherence was co-observed with higher patient satisfaction scores. We believe multi-modal adherence assessment complemented by regular education should be a core component of outpatient pharmacy programs including radiotherapy outpatient clinics.

Patient satisfaction was an important component of many of the included studies and should be considered in any outpatient pharmacy services. The study by Pituskin *et al.* and Fairchild provided a positive patient satisfaction score based on a prospective before-after assessment which could have been biased by design and lack of blind assessment. In the controlled cohort study by Ribed *et al.* the patient satisfaction survey was structured around pharmacy services only and these results were not compared against the overall clinic satisfaction or satisfaction of the control group. While a limited number of studies objectively assessed patient satisfaction we recommend that future trials continue to assess satisfaction.

Most studies provided clear definitions of the nature of the provided interventions. Some defined their intervention as the addition of routine pharmacy services to an existing clinic service. Others provided 'pharmaceutical care' packages including written material and pre-defined verbal pharmacy input. Studies by Caracuel, Hansen & Liekweg narrowed the scope of their pharmacist interventions by limiting

them to anti-emetic drug rationalisation (by protocol) and anti-emetic patient education. Others such as the study by *Ma et al.* explored the interventions by pharmacist as a holistic service looking at all aspects of patient clinic experience. However, this study failed to provide meaningful conclusions on the benefits of pharmacy services across all considered interventions such as (1) determining 'drug efficacies' for analgesics, laxatives or antiemetics and (2) providing advice on drug 'frequency' adjustments.

In the study by Read *et al*. a reduction in total number of supportive medications was associated with a reduction in healthcare costs to the organisation. Similarly, the study by Walters reported a reduction in the rate of unplanned hospital admissions in the intervention arm of an outpatient lung cancer clinic. Although there were financial cost savings from the reduction in unplanned hospital admissions, the result was not statistically significant ($p = 0.265$).

This review has provided informative data relating to the description and utility of outpatient pharmacy clinical services for oncology cancer clinics, however is limited by the quality of informing studies. Data on pharmacy clinical services for radiotherapy clinics are scarce, and although inherently these clinics can benefit from pharmacy services, we cannot make any conclusions and recommendations about their effectiveness and optimum delivery. To enable expanded review and future meta-analyses pharmacy service design studies for supportive care clinics

would benefit from the systematic reporting of common core pharmacy interventions and objective quantifiable outcome measures. Based on studies included in this review, the following outcomes are most broadly applicable: assessment of medication adherence, medication understanding, symptom control favouring pain, nausea and constipation, patient satisfaction and improvement in quality of life. Controlled trials, preferably randomised and informed by consumer feedback, of pharmacy services for outpatient cancer and radiotherapy patient cohorts are required to provide high-level evidence for improved patient outcomes.

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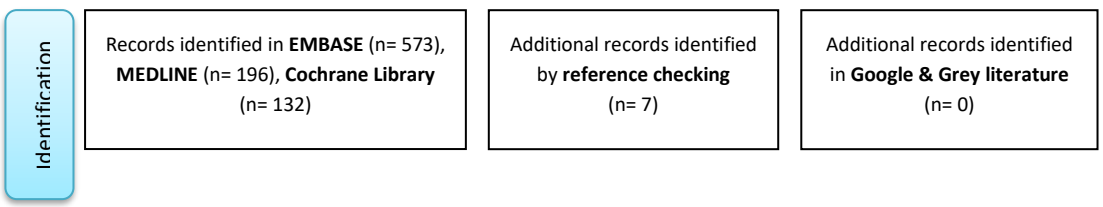

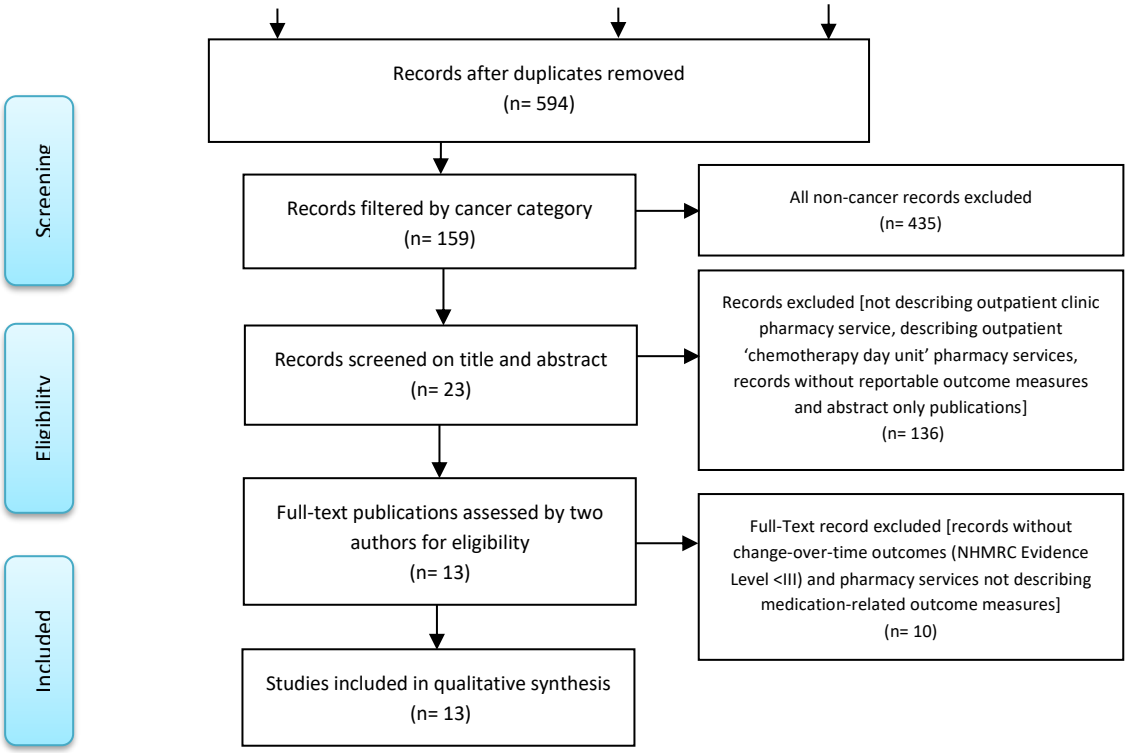

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram (46)

Author, Year	Study Design	Country	Cancer type	Sample size	Median age	Radiotherapy cohort
Pituskin E 2010 (42)	BA*	Canada	Prostate, breast & Non-Small Cell Lung Cancer	82	70	72 received radiotherapy
Valgus J 2010 (43)	BA	USA	Gynaecologic & others (non-specified)	49	NR	24 received radiotherapy
Fairchild A 2009 (40)	BA	Canada	Prostate, breast & lung	71	69.9	Includes radiotherapy population
Walter C 2016 (34)	BA	Australia	Lung	200	67	Includes radiotherapy population
Edwards S 2014 (32)	BA	Canada	Breast, CRC & lung	84	58.7	NR^
Ma J 2016 (41)	BA	USA	Gastrointestinal & Breast	283	51.2	NR
Ribed A 2016 (33)	CWC**	Spain	Lung, multiple myeloma, Renal, hepatic & GIST	138	68.5	NR
H Read 2007 (47)	RCT***	UK	Breast cancer	406	NR	NR
Yennurajalingam S 2011 (39)	BA	USA	Head & Neck & lung	15	59	NR
Arakawa-Todo M 2013 (48)	BA	Japan	Metastatic renal cell carcinoma	102	62.2	NR
Caracuel F 2014 (37)	BA	Spain	Breast, Colorectal cancer & gynaecologic	12	58.5	NR
Hansen E 2016 (49)	BA	USA	Ovarian, endometrial & primary peritoneal	48	NR	NR
Liekweg A 2012 (38)	CWC	Germany	Breast & ovarian	98	49.6	NR
*A comparative before-after (BA) type study **Cohort with control ***Randomised controlled trial						^NR: Not reported

Table 1: Study characteristics (*n* = 13)

		Read	Ribed	Caracuel	Liekweg	Yennurajalingam	Arakawa-Todo	Walter	Pituskin	Valgus	Fairchild	Edwards	Ma	Hansen
Medication-related pharmacist interventions for Drug-Related Problems (DRPs)	Analgesic							*	*	*	*		↓	
	Opioid					*			*		*		*	
	Anti-emetic			*	*	*			*	*	*		*	
	Laxative					*		*	*	*			*	
	Drug Interaction	*	↓^					*	*			*	*	
	Adverse Drug Reaction (ADR)		↓^				↓^						↓	
	Non-specified DRPs		↓^					*	*			*	↓	*
	Supportive medications adjustment								*					
Patient -related outcome measure	Pain scores					↓^			↓^	↓	↓^		↓^	
	Nausea Scores			↓^	↓^	↓^			↓	↓	↓			↓
	Composite symptom score					↓^			↓^	↓	↓			
	Service delays	↓^												
	Patient Satisfaction scores		↑					↑^	↑		↑			
	Quality of Life (QoL)				↑^	↓^			↑^		↑			
Other Pharmacy Services	Medication Reconciliation	*							*		*	↑	*	
	Education/Counselling		*		*		↑^	*			*			*
	Written Education		*	*	*				*					
	Adherence		↔^	*				↑^					↑	*
	Organisational costs	↓^						↓						
ROBINS-I scores:		Low	Low	Low	Low	Mod	Mod	Mod	Critical	Critical	Critical	Critical	Critical	Critical

*Cross-sectional (once-off) data only (no baseline provided)

↑↓ Increase or decrease observed on follow-up/intervention arm compared with baseline/control arm

^Results statistically significant with p value at least less than 0.05

Table 2: Main results: Outcome measures and other reported pharmacy services. All included studies contained at last one change-over-time quantitative outcome measure, denoted by the up or down arrows.

Author, Year	Level of Evidence (NHMRC)	Quality Rating											
		Study specific tools				ROBINS-I							
		Selection	Comparability	Exposure	Score	Bia s due to confounding	Bia s in selection of participants into	Bia s in classification of interventions	Bia s due to deviations from intended interval	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of reported result	Overall bias
Read H 2007	II	Cochrane Risk of Bias for RCTs.				N/A							Low
		1/1	0/2	4/4	5/7								
Ribed A 2016	III-3	New-Castle Ottawa Scoring system.				Low	Low	Low	Low	Low	Mod	Low	Low
		4/4	0/2	3/3	7/9								
Caracuel F 2014	III-2	NIH tool for BA study.				Low	Low	Low	Low	Low	Mod	Low	Low
		5/5	N/A	4/6	9/11								
Liekweg A 2012	III-2	New-Castle Ottawa Scoring system.				Low	Low	Low	Low	Low	Mod	Low	Low
		3/4	2/2	2/3	7/9								
Yennura-jalingam S 2011	III-2	NIH tool for BA study.				Mod	Mod	Low	Low	Mod	Mod	Low	Moderate
		5/5	N/A	3/6	8/11								
Arakawa-Todo M 2013	III-2	NIH tool for BA study.				Mod	Mod	Low	Low	Low	Mod	Low	Moderate
		4/5	N/A	4/6	8/11								
Walter C 2016	III-2	NIH tool for BA study.				Mod	Low	Low	Mod	Low	Mod	Low	Moderate
		5/5	N/A	4/6	10/11								
Pituskin E 2009	III-2	NIH tool for BA study.				Crit	Low	Low	Mod	Ser	Ser	Mod	Critical
		5/5	N/A	3/6	8/11								
Valgus J 2010	III-2	NIH tool for BA study.				Crit	Low	Low	Low	Low	Mod	Low	Critical
		2/5	N/A	3/6	5/11								
Fairchild A 2009	III-2	NIH tool for BA study.				Crit	Low	Low	Low	Ser	Mod	Low	Critical
		4/5	N/A	3/6	7/11								
Edwards S 2013	III-2	NIH tool for BA study.				Crit	Low	Low	Mod	Crit	Mod	Ser	Critical
		5/5	N/A	4/6	9/11								
Ma J 2016	III-2	NIH tool for BA study.				Crit	Low	Low	Mod	Mod	Mod	Mod	Critical
		5/5	N/A	4/6	9/11								
Hansen E 2016	III-2	NIH tool for BA study.				Crit	Crit	Low	Low	Mod	Mod	Low	Critical
		3/5	N/A	4/6	7/11								

Table 3: Level of Evidence and Risk of Bias Assessment

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