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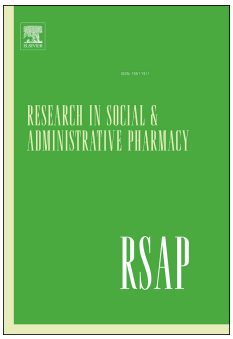

The degree of integration of non-dispensing pharmacists in primary care practice and the impact on health outcomes: A systematic review

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The degree of integration of non-dispensing pharmacists in primary care practice and the impact on health outcomes: a systematic review

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Abstract

Background: A non-dispensing pharmacist conducts clinical pharmacy services aimed at optimizing patients individual pharmacotherapy. Embedding a non-dispensing pharmacist in primary care practice enables collaboration, probably enhancing patient care. The degree of integration of non-dispensing pharmacists into multidisciplinary health care teams varies strongly between settings. The degree of integration may be a determinant for its success.

Objectives: This study investigates how the degree of integration of a non-dispensing pharmacist impacts medication related health outcomes in primary care.
Methods: In this literature review we searched two electronic databases and the reference list of published literature reviews for studies about clinical pharmacy services performed by non-dispensing pharmacists physically co-located in primary care practice. We assessed the degree o integration via key dimensions of integration based on the conceptual framework of Walshe and Smith. We included English language studies of any design that had a control group or baseline comparison published from 1966 to June 2016. Descriptive statistics were used to correlate the degree of integration to health outcomes. The analysis was stratified for disease-specific and patient-centered clinical pharmacy services.

Results: Eighty-nine health outcomes in 60 comparative studies contributed to the analysis. The accumulated evidence from these studies shows no impact of the degree of integration of non-dispensing pharmacists on health outcomes. For disease specific clinical pharmacy services the percentage of improved health outcomes for none, partial and fully integrated NDPs is respectively 75%, 63% and 59%. For patient-centered clinical pharmacy services the percentage of improved health outcomes for none, partial and fully integrated NDPs is respectively 55%, 57% and 70%.

Conclusions: Full integration adds value to patient-centered clinical pharmacy services, but not to disease-specific clinical pharmacy services. To obtain maximum benefits of clinical pharmacy services for patients with multiple medications and comorbidities, full integration of non-dispensing pharmacists should be promoted.

Keywords: clinical pharmacist; integrated care; primary health care; systematic review.

Introduction

The aging of the population results in increasingly complex medication-related needs.[1] To sustain the economic viability of health care the majority of elderly patients should be treated in primary care. To incorporate specific pharmaceutical expertise, some primary care practices have embedded a non-dispensing pharmacist (NDP, also: clinical pharmacist or clinical pharmacy specialist).

NDPs in primary care practice conduct clinical pharmacy services (CPS) that primarily focus on chronic disease management. CPS are usually multifaceted, including medication therapy reviews, counselling and medication education. These services can be aimed at patients with a specific chronic condition such as diabetes, cardiovascular disease or COPD ("disease-specific CPS"), or at a more heterogeneous group of patients at risk of drug related problems, such as patients with multimorbidity and polypharmacy ("patient-centered CPS"). Disease-specific CPS focusses on evidence-based protocolled care, while patient-centered CPS entails a more non-standardized and holistic approach.[2]

Some NDPs are fully integrated into the health care team,[3,4] whereas others only temporarily provide a specific CPS.[5] Common opinion is that integrated care for patients with chronic conditions may improve patient outcomes.[6–8] CPS have been shown to positively affect surrogate outcomes, such as blood pressure, glycemic control and lipid

goal attainment.[9–13] Evidence of the effect of CPS on clinical endpoints, such as mortality, hospitalizations and health related quality of life, is less clear probably due to very heterogeneously defined CPS as well as strongly differing study settings.[12,14]

Both aspects are features of the degree of integration of the NDP who delivers the CPS. The degree of integration of NDPs into the health care team may be a determinant for its success, but this association has never been properly assessed. Therefore, we conducted a systematic review to investigate how the degree of integration of an NDP impacts health outcomes in primary care.

Methods

The protocol of this systematic review has been published in the PROSPERO register. The registration number is: CRD42016017506.[15]

Search strategy

We searched PubMed and Embase from 1966 to June 2016. A trained librarian, in consultation with researchers, developed a search strategy (Appendix Table 1). Also, we manually searched the reference list of systematic reviews and background articles about clinical pharmacy interventions in primary care for additional citations.

Potentially relevant studies were identified by two reviewers (AH and LB) based on predetermined inclusion criteria in a two-step procedure: 1) title and abstract, 2) screening of the full text. In case disagreement about inclusion could not be resolved by discussion between the two reviewers, a third reviewer (AB or MB) was consulted to reach consensus. We used the PRISMA checklist to conduct and report the systematic literature review.[16]

Study selection

Both US and non-US comparative studies of any design that had a control group or baseline comparison were included if they met the following criteria:

The intervention

1. comprised at least one key component of a chronic disease management service aimed at individual ambulatory patients;
2. was conducted by an NDP who had a regular and ongoing relationship with the primary care practice and was at least part-time physically present and at that time not involved in work related to community pharmacy;;
3. measured a relevant clinical or patient reported health outcome or a proxy of a relevant health outcome (e.g. improvement of medication errors).

Studies were excluded if the intervention was delivered in a specialty or off-site clinic without collaboration with the general practitioner (GP), or if it was a pilot of an already included study or a secondary analysis. Also, unpublished studies and studies published in languages other than English were not taken into account for analysis.

Dependant variable: degree of integration

Our main focus was the degree of integration of NDPs, which we assessed via key dimensions of integration from the conceptual framework of Walshe and Smith[17]: organizational, informational, clinical, functional, financial and normative integration (table 1). The financial integration could not be taken into account as most interventions were project funded studies. The key dimensions were scored dichotomous (yes/no). A positive score on zero to two dimensions of integration was defined as "no integration". A positive score on three or four dimensions of integration was defined as "partial integration" and a positive score on all five dimensions was defined as "full integration". Prescriptive authority was taken into account to assess clinical integration, see table 3.

[Table 1]

Primary outcome: health outcomes

The primary outcomes of the intervention were either real clinical health outcomes, such as mortality, or surrogate clinical health outcomes, such as HbA1c, lipids and blood pressure. In addition to clinical health outcomes, we included patient reported health outcomes, such as health related quality of life and proxies of health outcomes, such as quality of care performance indicators.

Data collection process

Other extracted data included the duration of the intervention, study size, primary outcomes, specification of the CPS (disease-specific or patient-centered) and the number of involved practices and NDPs. The primary outcomes of the intervention were categorized as either "positive", "negative" or "no effect". A positive outcome was defined as a statistically significant difference (p value < 0.05) compared to the control group or baseline. A negative outcome being the opposite and no effect as no statistically significant difference between intervention and control group or baseline.

Two authors independently extracted the data and one author cross-checked all extracted data. Differences were resolved in discussion. In case of dissensus, a third researcher was consulted. If we were unable to score the dimensions of integration – despite contacting the corresponding author for additional information and verifying complementary study protocols - the study was excluded for synthesis.

Quality assessment

We used the Effective Public Health Practice Project (EPHPP) Quality Assessment Tool to assess : selection bias, study design, confounders, data collection methods, withdrawals and drop-outs. Given the nature of the included studies, blinding of the participants and outcome assessors was generally not possible. Therefore, this criterion was not included in the quality assessment. Two authors independently assessed each study and resolved disagreement by consensus or by consulting a third reviewer.

Data synthesis

The included studies were heterogeneous regarding the type of CPS, enrolled participants, number of practices, involved NDPs and measured health outcomes. Therefore, it was inappropriate to perform statistical aggregation of findings. To investigate how the degree of integration of an NDP impacts health outcomes we plotted the number of improved primary outcomes against the total number of assessed primary outcomes. We stratified the analysis for disease-specific CPS and patient-centered CPS.

Results

Ninety studies were included for data extraction (Figure 1). For thirty studies we were unable to determine the degree of integration of the NDP and were excluded (Appendix Table 2a/b). We grouped studies by type of CPS: disease-specific CPS (n=43) and patient-centered CPS (n=17).

[Figure 1]

Summary of included studies

The included studies consisted of 35 RCTs, 12 two group cohort studies and 13 one group cohort studies. The median of the study population was 140 patients (interquartile range 76-321). The duration of the interventions ranged from 1 to 60 months. The median of the number of involved practices and NDPs was 1 (interquartile range 1-6) and 2 (interquartile range 1-4), respectively. The majority of the studies were performed in the United Stated of America (USA) (n=43) (Tables 2a and 2b).

Methodological quality

The methodological quality was high in 18 studies (31%), moderate in 34 studies (58%) and low in 8 studies (14%). 35 studies (59%) had a strong design, with described randomization processes. Eight studies (14%) had a high participation rate and were very likely to be representative to the target population. Forty studies (68%) controlled for at least 80% of relevant confounders and 48 studies (81%) used valid and reliable data collection tools. 29 studies (91%) had a follow-up rate of at least 80% (table 3).

[Table 2a and b]

[Table 3]

Synthesis of results

We assessed 89 health outcomes in 60 comparative studies: 54 clinical health outcomes (mainly surrogate health outcomes such as blood pressure or HbA1c), 12 patient reported health outcomes, such as HRQoL and 23 proxies of health outcomes, such as medication errors. CPS conducted by NDPs showed a significant positive effect on 62% (55/89) of assessed health outcomes. The other 34 health outcomes showed no statistically significant difference compared to control group or baseline. None of the included studies measured a negative impact on health outcomes. The effect of CPS on surrogate clinical health outcomes and proxies of health outcomes was high: 67% (36/54) and 78% (18/23) of these outcomes improved. Patient reported health outcomes were less frequently reported (n=12) and showed improvement in one trial.

We related the dimensions of integration to the degree of integration. We found 14 studies (23%) in which the NDPs were not or minimally integrated into the health care team (positive score on 0-2 dimensions of integration). 71% (n=10) of NDPs had shared access to patient medical records (informational integration). Yet, integration on

all other dimensions was low: organizational 14% (n=2), normative 14% (n=2), functional 7% (n=1) and clinical 7% (n=1).

We identified 19 studies (32%) in which the NDPs were partially integrated (positive score on 3-4 dimensions of integration). All but one (95%) had shared access to patient medical records. Integration on the clinical, functional and normative dimension was 68% (n=13) and 47% (n=9) of NDPs were permanently employed within the practice or worked within an umbrella organization or network (organizational integration).

We found 27 studies (45%) in which the NDPs were fully integrated within the primary care practice (positive score on 5 dimensions of integration). This involved permanent employment within the organization, or an umbrella organization or network, shared information systems, shared education or administrative support and a profound clinical role with shared goals and visions, such as a collaborative practice agreement to enhance cooperation in the delivery of CPS.

For each level of integration (none-partial-full), we plotted the number of improved primary outcomes against the total number of assessed primary outcomes (Figure 2). The accumulated evidence from these studies suggests that there is no impact of the degree of integration of NDPs on health outcomes. The percentage of improved health outcomes for none, partial and fully integrated NDPs is respectively 63% (based on 19 assessed health outcomes within 14 different studies), 61% (based on 23 assessed health outcomes within 19 different studies) and 62% (based on 47 assessed health outcomes within 27 different studies). Also, after stratifying the health outcomes into clinical, patient reported and proxies of health outcomes, no association can be identified between the degree of integration of NDPs and an improvement on health outcomes.

Stratification of the results according to type of CPS

We included 43 studies about disease-specific CPS, in which 61 health outcomes, mainly surrogate clinical health outcomes (n=51) were assessed, of which 67% showed a significant positive effect. Five patient reported health outcomes and five proxies of health outcomes were reported, of which 20% (n=1) and 60% (n=3) showed improvement, respectively. Within this subgroup of CPS services, we found 8 studies (19%) in which the NDPs were not or minimally integrated into the health care team, 14 studies (33%) in which the NDPs were partially integrated and 21 studies (49%) in which the NDPs were fully integrated within the primary care team. For disease-specific CPS the percentage of improved health outcomes in studies with not, partial and fully integrated NDPs is respectively 75%, 63% and 59%. Our data suggest a negative association between integration and improvement on health outcomes for disease-specific CPS (Figure 2).

We included 17 studies about patient-centered CPS and assessed 28 health outcomes, mainly proxies of health outcomes (n=18) of which 83% showed a significant positive effect. In total, 7 patient reported health outcomes were reported of which none showed improvement. A small number of surrogate clinical health outcomes was reported (n=3) and 2 were positively affected by the NDP provided services. We found 6 studies (35%) in which the NDPs were not or minimally integrated into the health care team, 5 studies (29%) in which the NDPs were partially integrated and 6 studies (35%) in which the NDPs were fully integrated within the primary care team. For patient-centered CPS the percentage of improved health outcomes in studies with not, partial and fully integrated NDPs is respectively 55%, 57% and 70%. Therefore, our data suggest a positive association between integration and improvement on health outcomes for patient-centeredCPS (Figure 2).

[Figure 2]

[Table 4]

Discussion

We evaluated the impact of the degree of integration of NDPs on health outcomes in primary care. Although we found that the degree of integration of NDPs did not impact health outcomes in the overall group, subgroup analysis suggests that full integration of an NDP may be especially relevant for patient-centered CPS.

An explanation of why full integration of an NDP is more relevant for patient-centered interventions than disease-specific interventions is provided by Weick.[76] Integration enables NDPs to manage interruptions in the care trajectory of an individual patient. Being in close relation with both GPs and patients, NDPs can pick up the small clues that signal lapses in the care trajectory. The degree of integration showed a trend towards a negative association with the health outcomes of disease-specific CPS. The diseases-specific CPS included in this study were based upon a set protocol. Thesestandardized care trajectories are less prone to errors and allowing for variety may not have an added value. Reliability – defined as compliance to the protocols – seems to be more effective.[77]

Almost all studies reported surrogate health outcomes rather than clinical endpoints such as hospitalization or mortality. Disease-specific CPS mainly described surrogate clinical health outcomes (e.g. HbA1c, lipids and blood pressure), while patient-centered CPS often used process outcomes (e.g. quality of care performance indicators) to measure the effect of the intervention. Also, we found a low impact of CPS on health related quality of life.[51,61,65,67,69] The effects of a multifaceted quality improvement service often do not extend as far as to health related quality of life.[78]

Fully integrated NDPs are permanently employed or work within a network or umbrella organization (organizational integration), they usually have shared access to clinical information systems (informational integration), work in multiprofessional teams

with face-to-face collaboration with the GP (clinical integration), have shared education and/or support staff for administrative functions (functional integration) and share a vision on patient care with clinicians (normative integration). Clinical integration into a multidisciplinary primary care team provides greater opportunities for both formal and informal communication, probably enhancing patient care.[63] Also, expanding the clinical role of the NDP by allocating prescribing privileges might be beneficial.[79] Within disease-specific CPS, more than half of the NDPs were authorized to make medication changes within a defined scope of practice. Within patient-centered CPS, only 2 studies showed NDPs with prescribing authority. In these kind of services, with a more holistic approach to pharmaceutical care, prescribing authority would entail the whole spectrum of medications. The current absence of prescribing authority might have restricted the impact of the CPS on health outcomes.

CPS performed in isolation may negatively influence the quality of care.[80] There is one systematic review that described the effectiveness of NDPs co-located in primary care practice.[9] The importance of follow-up and face-to-face communication with the patient's GP (clinical integration) is highlighted. Other available studies described the effectiveness of CPS in different outpatient settings.[10–14] This study is the first to unravel the association between the extent of NDP integration in clinical care and drug related health outcomes.

Limitations

This review has a number of limitations. Similar to most literature reviews, there might have been publication bias. Also, CPS services can like all cognitive interventions be subject to the Hawthorne-effect. The Hawthorne-effect might, at least partly, explain the absence of any negative health outcome in the included studies. The interventions and outcomes assessed in this review were heterogeneous. Also, we were unable to assess the impact of health care systems on the degree of integration of NDPs and on the success of the provided services. Moreover, the study population, duration of the

intervention, number of practices and involved NDPs differed widely, limiting our options to assess the independent effect of integration and to pool data. The problem of heterogeneity in clinical pharmacy intervention studies has been previously addressed.[9,12,14,81–83] Hence, we cannot draw too strong conclusions about the impact of integration – as reflected by the wording we choose. Lastly, the positive association we found between the degree of integration and the effect of patient-centered CPS was based upon a limited number of studies (n=17). Random effects cannot be ruled out. Additional research is required when new studies about integrated clinical pharmacy services in primary care become available.

Implications

This study has several implications for practitioners and policy-makers. Integration on *all* dimensions for *all* types of chronic disease management services performed by NDPs in primary care practice may not be necessary. Integration on *all* dimensions should be promoted for individually tailored, i.e. patient-centered CPS.

Conclusion

To obtain maximum benefits of CPS for patients with multiple medications and comorbidities, full integration of NDPs should be stimulated.

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Table 1. Key dimensions of integrated care for chronic disease management[17], tailored to the setting of an non-dispensing pharmacist in primary care practice

Organizational:	Organizational design and governance arrangements *Measurable element*: an umbrella organization or network, or NDP has permanent position within primary care practice
Informational:	Shared access of clinical information systems *Measurable element*: GP and NDP work with integrated clinical information systems
Clinical:	Delivery of rational and continuous clinical care to patients *Measurable elements*: multiprofessional teams, NDP performs patient counselling and follow-up, face-to-face communication between GP and NDP, patient directed activities outside the scope of the intervention, prescribing authority of the NDP
Functional:	Supportive administrative and functional elements *Measurable element*: shared education or administrative support by primary care practice staff
Financial:	Financial arrangements and payment system *Measurable element*: n/a
Normative:	Shared vision, goals and values *Measurable element*: collaboratively designed protocols with shared goals and visions of the pharmaceutical intervention

Table 2a. Study characteristics of disease-specific clinical pharmacy services (n=43)

DIABETES (n=16)										
Author (year)	**Country**	**No. intervention practices/ No. NDPs**	**Duration intervention (months)**	**No. patients in intervention group**	**Dimension of integration**					**Primary outcomes (effect)**
					Organizational	**Informational**	**Clinical[a]**	**Functional**	**Normative**	
Choe (2005)[18]	USA	1/1	24	41	Yes	Yes	Yes	Yes	Yes	HbA1C (+)
Coast-Senior (1998)[19]	USA	2/4	3-11	23	Yes	Yes	Yes	Yes	Yes	Glycemic control (+)
Heisler (2012)[4]	UK	5/11	14	1797	Yes	Yes	Yes	Yes	Yes	BP (0)
Henry (2013)[20]	USA	1/2	3	93	Yes	Yes	Yes	Yes	Yes	Guideline adherence (0), HbA1C (+)
Ip (2013)[21]	USA	1/1	12	147	Yes	Yes	Yes	Yes	Yes	Baseline changes in HbA1c, LDL-C and BP (+) and goal attainment (+), 10-year cardiovascular risk reduction (+)
Irons (2002)[22]	USA	1/2	32	87	Yes	No	Yes	No	Yes	Glycemic control (0)
Jameson (2010)[23]	USA	13/1	12	52	No	Yes	No	Yes	Yes	HbA1c (0)
McAdam-Marx (2015)[24]	USA	10/3	48	303	Yes	Yes	Yes	No	Yes	Glycemic control (+)
McCord (2006)[25]	USA	1/1	4	316	Yes	Yes	Yes	Yes	Yes	HbA1c (+), BP (0), lipids (+)
McFarland (2012)[26]	USA	4/3	6	36	Yes	No	Yes	Yes	Yes	HbA1c (0)
Mourão (2012)[27]	Brazil	6/2	6	50	No	No	No	No	No	HbA1c (0)
Rothman (2005)[28]	USA	1/3	12	112	Yes	Yes	Yes	Yes	Yes	HbA1c (+),LDL-C (0), BP (+)
Salvo (2012)[29]	USA	1/1	18	69	Yes	Yes	Yes	Yes	Yes	HbA1c (+)
Scott (2006)[30]	USA	1/1	9	76	No	Yes	Yes	Yes	Yes	HbA1c (+)
Shane-McWorther (2005)[31]	USA	1/1	36	176	Yes	Yes	Yes	Yes	Yes	HbA1c (0), lipids (0), BP (0)
Simpson (2011)[32]	Canada	5/2	12	131	Yes	Yes	Yes	Yes	No	BP (+)
Hypertension (n=11)										
Bex (2011)[33]	USA	4/6	18	573	Yes	Yes	Yes	Yes	Yes	BP (+)

Bogden (1998)[34]	USA	1/1	6	49	No	Yes	No	No	No	BP (+)
Borenstein (2003)[35]	USA	1/1	12	98	No	Yes	No	Yes	Yes	BP (+)
Carter (2008)[36]	USA	5/2	9	101	Yes	Yes	Yes	Yes	Yes	BP (+)
Hirsch (2014)[37]	USA	1/2	9	166	No	Yes	Yes	Yes	Yes	BP (+)
Hunt (2008)[38]	USA	9/5	12	230	Yes	Yes	Yes	Yes	Yes	BP (+)
Magid (2013)[39]	USA	10/≥10	6	175	Yes	Yes	Yes	Yes	Yes	BP (+)
Margolis (2013)[40]	USA	16/8	18	228	Yes	Yes	Yes	Yes	Yes	BP (+)
Mehos (2000)[41]	USA	1/1	6	18	No	No	No	No	No	BP (+)
O'Neill (2014)[42]	USA	1/1	1	63	Yes	Yes	Yes	Yes	Yes	BP (+)
Wong (2013)[43]	Hong Kong	1/?	6	92	No	No	No	No	No	BP (0)
Dyslipidaemia (n=5)										
Billups (2005)[44]	USA	16/16-48	12	5550	Yes	Yes	No	No	Yes	LDL-C (+)
Bogden (1997)[5]	USA	1/1	6	47	No	Yes	No	No	No	LDL-C (+)
Smith (2013)[45]	USA	2/1	?	213	Yes	Yes	Yes	Yes	Yes	Lipid profile
Straka (2005)[46]	USA	2/2	6	359	No	Yes	Yes	No	Yes	LDL-C (+)
Tahaineh (2011)[47]	Jordan	1/1	6	73	No	No	No	No	Yes	LDL-C (+)
Metabolic syndrome (n=1)										
Hammad (2011)[48]	Jordan	6/2	6	112	Yes	Yes	No	No	No	Metabolic syndrome status (+)
Heart failure (n=1)										
Lowrie (2012)[49]	UK	174/27	60	1090	No	Yes	Yes	No	No	Composite of death or hospital admission for worsening heart failure (0)

Depression (n=3)										
Adler (2004)[50]	USA	9/5	6	268	No	Yes	Yes	Yes	No	Antidepressant use rate (+). depressions severity (0)
Capoccia (2004)[51]	USA	1/2	12	41	Yes	Yes	Yes	Yes	Yes	Depression symptoms (0)
Finley (2003)[52]	USA	1/?	6	75	Yes	Yes	Yes	Yes	Yes	Adherence to antidepressant (+), patient satisfaction (+), clinical and functional severity (0)
Osteoporosis (n=1)										
Hall (2009)[53]	USA	1/4	?	22	Yes	Yes	Yes	No	Yes	Compliance with treatment guidelines (+)
Cardiovascular disease (n=1)										
Evans (2010)[54]	Canada	1/1	6	176	No	Yes	Yes	No	Yes	10 year cardiovascular risk reduction (0)
Diabetes + hypertension (n=2)										
Edelman (2010)[55]	USA	2/2	12	133	Yes	Yes	Yes	Yes	No	BP (+),HbA1C (0)
Neto (2011)[56]	Brazil	1/4	36	97	Yes	Yes	Yes	Yes	Yes	10 year cardiovascular risk reduction (+)
Diabetes and/or dyslipidaemia (n=1)										
Hetro (2015)[57]	USA	1/?	6	61	Yes	Yes	Yes	Yes	Yes	HbA1C (+), LDL-C (0), BMI (0)
Diabetes, hypertension, dyslipidaemia or asthma (n=1)										
Koenigsfeld (2012)[58]	USA	3/3	13	131+427+299+27	Yes	Yes	Yes	Yes	Yes	Achieving goal levels for DM (0), hypertension (+) and % on asthma controller medication (0)

(+) = positive effect, (0) = no effect, BP = Blood Pressure, HbA1c = glycosylated haemoglobin, LDL-C = low-density lipoprotein cholesterol
A: see Appendix Table 3for specification

Table 2b. Study characteristics of patient-centered clinical pharmacy services (n=17)

Author (year)	Country	No. practices/ No. NDPs	Duration intervention (months)	Study size intervention group (patients)	Dimension of integration					Primary outcome(s) (effect)
					Organizational	Informational	Clinical[a]	Functional	Normative	
Avery (2012)[59]	UK	72/?	12	3812	No	Yes	No	No	No	Three prescribing appropriateness indicators (+)
Berdine (2012)[60]	USA	1/1	36	200	Yes	Yes	Yes	Yes	Yes	Lipids (+), A1C (0) and BMI (+)
Carter (2001)[61]	USA	9/51?	12	523	Yes	Yes	Yes	Yes	No	Patient satisfaction (0), HRQoL (0)
Davis (2007)[62]	USA	6/12	5	79	Yes	Yes	No	Yes	No	MAI (+)
Freeman (2013)[63]	Australia	1/1	0-12	314	Yes	Yes	Yes	Yes	Yes	Uptake of recommendations from medication review (+)
Galt (1998)[64]	USA	1/1	12	336	Yes	Yes	Yes	Yes	Yes	Reduction in use of unessential medications (+)
Hanlon (1996)[65]	USA	1/1	12	105	No	Yes	No	No	No	MAI (+), HRQoL (0), ADE (0)
Hogg (2009)[66]	Canada	1/1	12-18	121	Yes	Yes	Yes	Yes	Yes	QoC for CDM (+)
Isetts (2006)[67]	USA	6/7	12	285	Yes	Yes	Yes	Yes	Yes	Patients' perceptions of care (0), HRQoL (0)
Isetts (2008)[68]	USA	6/7	12	256	Yes	Yes	Yes	Yes	Yes	Quality-of-care performance measures for hypertension and cholesterol (+)
Krska (2001)[69]	UK	?/?	3	168	No	Yes	No	Yes	No	Resolved PCI (+), HRQoL (0)
Lenander (2014)[70]	Sweden	1/1	12	107	No	Yes	No	Yes	Yes	Resolved MRPs (0), No. of medications (+)
Pindolia (2009)[71]	USA	1/7	24	520	Yes	Yes	No	No	No	Improvement on clinical outcome rules (0)
Roth (2013)[72]	USA	½	6	64	No	Yes	No	No	Yes	Resolved MRPs (+)
Sellors (2003)[73]	Canada	24/12	5	431	No	Yes	No	No	No	No. of daily doses (0)
Tan (2014)[74]	Australia	2/2	6	82	No	Yes	Yes	Yes	No	Resolved MRPs (+)
Zermansky (2001)[75]	UK	4/1	12	581	No	Yes	No	Yes	Yes	No. of changes to repeat prescription changes (+)

(+) = positive effect, (0) = no effect, ADE = Adverse Drug Events, BMI = Body Mass Index, BP = Blood pressure, CDM = Chronic Disease Management, HbA1c = glycosylated haemoglobin, HRQoL = Health Related Quality of Life, LDL-C = low-density lipoprotein cholesterol, MAI = Medication Appropriateness Index, MRP = Medication Related Problem, PCI = Pharmaceutical Care Issues, QoC = Quality of Care

a: see Appendix Table 3for specification

Table 3: Quality assessment of included studies

Author (year)	Selection bias	Study design	Confounders	Data collection	Drop-outs	Global
Adler (2004)[50]	Weak	Strong	Strong	Strong	Strong	Moderate
Avery (2012)[59]	Weak	Strong	Weak	Strong	Strong	Weak
Berdine (2012)[60]	Moderate	Moderate	Weak	Strong	Weak	Weak
Bex (2011)[33]	Moderate	Moderate	Weak	Strong	Moderate	Moderate
Billups (2005)[44]	Moderate	Moderate	Weak	Strong	Strong	Moderate
Bogden (1997)[5]	Moderate	Strong	Strong	Strong	Strong	Strong
Bogden (1998)[34]	Moderate	Strong	Strong	Strong	Strong	Strong
Borenstein (2003)[35]	Weak	Strong	Moderate	Strong	Strong	Moderate
Capoccia (2004)[51]	Moderate	Strong	Strong	Moderate	Strong	Strong
Carter (2001)[61]	Moderate	Strong	Weak	Strong	Weak	Weak
Carter (2008)[36]	Weak	Strong	Strong	Strong	Moderate	Moderate
Choe (2005)[18]	Strong	Strong	Strong	Moderate	Moderate	Strong
Coast-Senior (1998)[19]	Moderate	Weak	Weak	Moderate	Strong	Weak
Davis (2007)[62]	Strong	Moderate	Weak	Strong	Moderate	Moderate
Edelman (2010)[55]	Weak	Strong	Strong	Strong	Strong	Moderate
Evans (2010)[54]	Moderate	Strong	Strong	Strong	Strong	Strong
Finley (2003)[52]	Moderate	Strong	Strong	Strong	Weak	Moderate
Freeman (2013)[63]	Strong	Moderate	Weak	Moderate	Moderate	Moderate
Galt (1998)[64]	Weak	Moderate	Weak	Moderate	Weak	Weak
Hall (2009)[53]	Moderate	Moderate	Weak	Strong	Weak	Weak
Hammad (2011)[48]	Strong	Strong	Strong	Strong	Strong	Strong
Hanlon (1996)[65]	Strong	Strong	Strong	Moderate	Strong	Strong
Heisler (2012)[4]	Moderate	Strong	Strong	Strong	Weak	Moderate
Henry (2013)[20]	Moderate	Moderate	Weak	Weak	Moderate	Weak
Hetro (2015)[57]	Moderate	Moderate	Weak	Strong	Weak	Weak
Hirsch (2014)[37]	Weak	Strong	Strong	Strong	Strong	Moderate
Hogg (2009)[66]	Moderate	Strong	Strong	Moderate	Strong	Strong
Hunt (2008)[38]	Weak	Strong	Strong	Strong	Weak	Weak
Ip (2013)[21]	Moderate	Moderate	Strong	Strong	Moderate	Strong
Irons (2002)[22]	Moderate	Moderate	Strong	Strong	Moderate	Strong
Isetts (2006)[67]	Weak	Moderate	Moderate	Strong	Moderate	Moderate
Isetts (2008)[68]	Moderate	Moderate	Strong	Strong	Weak	Moderate
Jameson (2010)[23]	Weak	Strong	Strong	Strong	Strong	Moderate
Koenigsfeld (2012)[58]	Moderate	Moderate	Weak	Strong	Moderate	Moderate
Krska (2001)[69]	Moderate	Strong	Strong	Moderate	Strong	Strong
Lenander (2014)[70]	Moderate	Strong	Strong	Weak	Moderate	Moderate

Lowrie (2012)[49]	Weak	Strong	Strong	Strong	Strong	Moderate
Magid (2013)[39]	Moderate	Strong	Strong	Strong	Strong	Strong
Margolis (2013)[40]	Moderate	Strong	Weak	Strong	Strong	Moderate
McAdam-Marx (2015)[24]	Moderate	Moderate	Strong	Strong	Moderate	Strong
McCord (2006)[25]	Moderate	Moderate	Weak	Strong	Moderate	Moderate
McFarland (2012)[26]	Moderate	Moderate	Strong	Strong	Weak	Moderate
Mehos (2000)[41]	Moderate	Strong	Strong	Strong	Strong	Strong
Mourão (2012)[27]	Strong	Strong	Strong	Strong	Moderate	Strong
Neto (2011)[56]	Moderate	Strong	Strong	Strong	Strong	Strong
O'Neill (2014)[42]	Moderate	Weak	Strong	Strong	Moderate	Moderate
Pindolia (2009)[71]	Weak	Moderate	Weak	Strong	Moderate	Weak
Roth (2013)[72]	Moderate	Moderate	Strong	Strong	Strong	Strong
Rothman (2005)[28]	Moderate	Strong	Strong	Strong	Strong	Strong
Salvo (2012)[29]	Moderate	Moderate	Weak	Strong	Strong	Moderate
Scott (2006)[30]	Moderate	Strong	Strong	Strong	Strong	Strong
Sellors (2003)[73]	Moderate	Strong	Strong	Strong	Strong	Strong
Shane-McWorther (2005)[31]	Moderate	Moderate	Weak	Strong	Moderate	Moderate
Simpson (2011)[32]	Weak	Strong	Strong	Strong	Strong	Moderate
Smith (2013)[45]	Moderate	Moderate	Strong	Strong	Moderate	Strong
Straka (2005)[46]	Strong	Strong	Strong	Strong	Strong	Strong
Tahaineh (2011)[47]	Strong	Strong	Weak	Strong	Moderate	Moderate
Tan (2014)[74]	Moderate	Moderate	Strong	Moderate	Moderate	Strong
Wong (2013)[43]	Moderate	Strong	Strong	Strong	Strong	Strong
Zermansky (2001)[75]	Weak	Strong	Strong	Moderate	Strong	Moderate
Sum weak	14 (24%)	2 (3%)	19 (32%)	2 (3%)	10 (17%)	10 (17%)
Sum moderate	38 (64%)	23 (39%)	2 (3%)	10 (17%)	20 (34%)	26 (44%)
Sum strong	8 (14%)	35 (59%)	39 (66%)	48 (81%)	30 (51%)	24 (41%)

Table 4: The impact of the degree on integration of NDPs on health outcomes in primary care.

No. of improved outcomes / no. of assessed outcomes (no.of intervention patients)

	All outcomes (n=89)			Disease-specific CPS (no. of assessed outcomes: 61)			Patient-centered CPS (no. of assessed outcomes: 28)		
	No integration	Partial integration	Full Integration	No integration	Partial integration	Full integration	No integration	Partial integration	Full integration
Clinical health outcomes									
Death or hospitalization	0/1 (1090)			0/1 (1090)					
Surrogate clinical health outcomes									
HbA1c	1/1 (50)	2/6 (687)	8/11 (1369)	1/1 (50)	2/6 (687)	8/10 (1169)			0/1 (200)
Lipids	2/2 (120)	2/2 (5909)	4/7 (1225)	2/2 (120)	2/2 (5909)	3/6 (1025)			1/1 (200)
BP	2/3 (159)	4/4 (430)	7/11 (4198)	2/3 (159)	4/4 (430)	7/11 (4198)			
BMI			1/2 (261)			0/1 (61)			1/1 (200)
Metabolic syndrome status	1/1 (112)			1/1 (112)					
Cardiovascular risk reduction		0/1 (176)	2/2 (244)		0/1 (176)	2/2 (244)			
Subtotal	6/8 (75%)	8/13 (62%)	22/33 (68%)	6/8 (75%)	8/13 (62%)	20/30 (67%)			2/3 (67%)
Patient reported health outcomes									
HRQoL	0/2 (273)	0/1 (523)	0/2 (453)			0/1 (168)	0/2 (273)	0/1 (523)	0/1 (285)
Patient satisfaction, perceptions of care	0/1 (105)	0/1 (523)	1/2 (360)			1/1 (75)	0/1 (105)	0/1 (523)	0/1 (285)
Depression severity		0/1 (268)	0/2 (116)		0/1 (268)	0/2 (116)			
Subtotal	0/3 (0%)	0/3 (0%)	1/6 (17%)		0/1 (0%)	1/4 (25%)	0/3 (0%)	0/2 (0%)	0/2 (0%)
Proxies of health outcomes									
Adherence rate		1/1 (268)	1/1 (75)		1/1 (268)	1/1 (75)			
Reduction of (unwanted) medications	0/1 (431)	2/2 (688)	1/1 (336)				0/1 (431)	2/2 (688)	1/1 (336)
Medication errors, pharmaceutical care issues, prescribing appropriateness	6/7 (12.293)	3/4 (290)	3/5 (753)		1/1 (22)	0/2 (120)	6/7 (12.293)	2/3 (268)	3/3 (633)
Uptake of recommendations from MR			1/1 (314)						1/1 (314)
Subtotal	6/8 (67%)	6/7 (86%)	6/8 (75%)		2/2 (100%)	1/3 (33%)	6/8 (75%)	4/5 (80%)	5/5 (100%)
Total	**12/19 (63%)**	**14/23 (61%)**	**29/47 (62%)**	**6/8 (75%)**	**10/16 (63%)**	**22/37 (59%)**	**6/11 (55%)**	**4/7 (57%)**	**7/10 (70%)**

BP = Blood pressure, BMI = Body Mass Index, HbA1c = glycosylated haemoglobin, HRQoL = Health Related Quality of Life, MR = Medication Review

For each health outcome, the number of studies that demonstrated significant improvement is divided by the total number of assessed studies. Since studies can include more than one primary outcome, the total number of assessed outcomes (89) exceeds the total number of included studies (60).

The numbers in parentheses reflect the accumulated number of intervention patients in studies assessing the specific health outcome.

Figure 1. Flowchart of the study selection

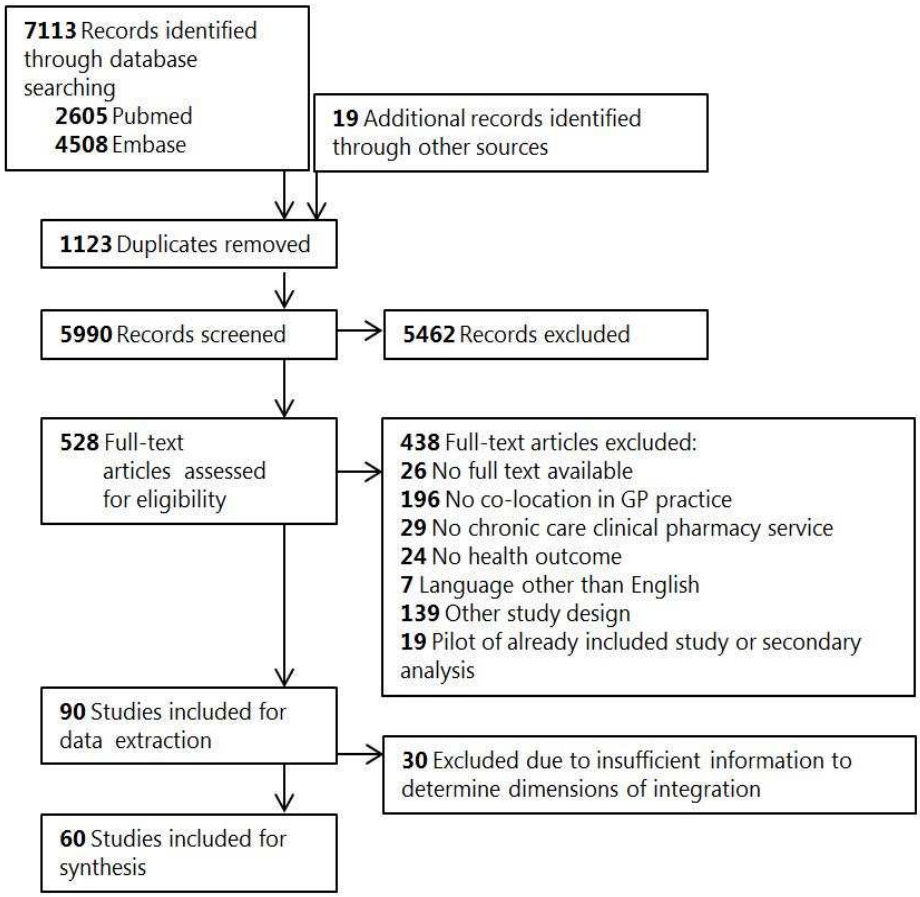
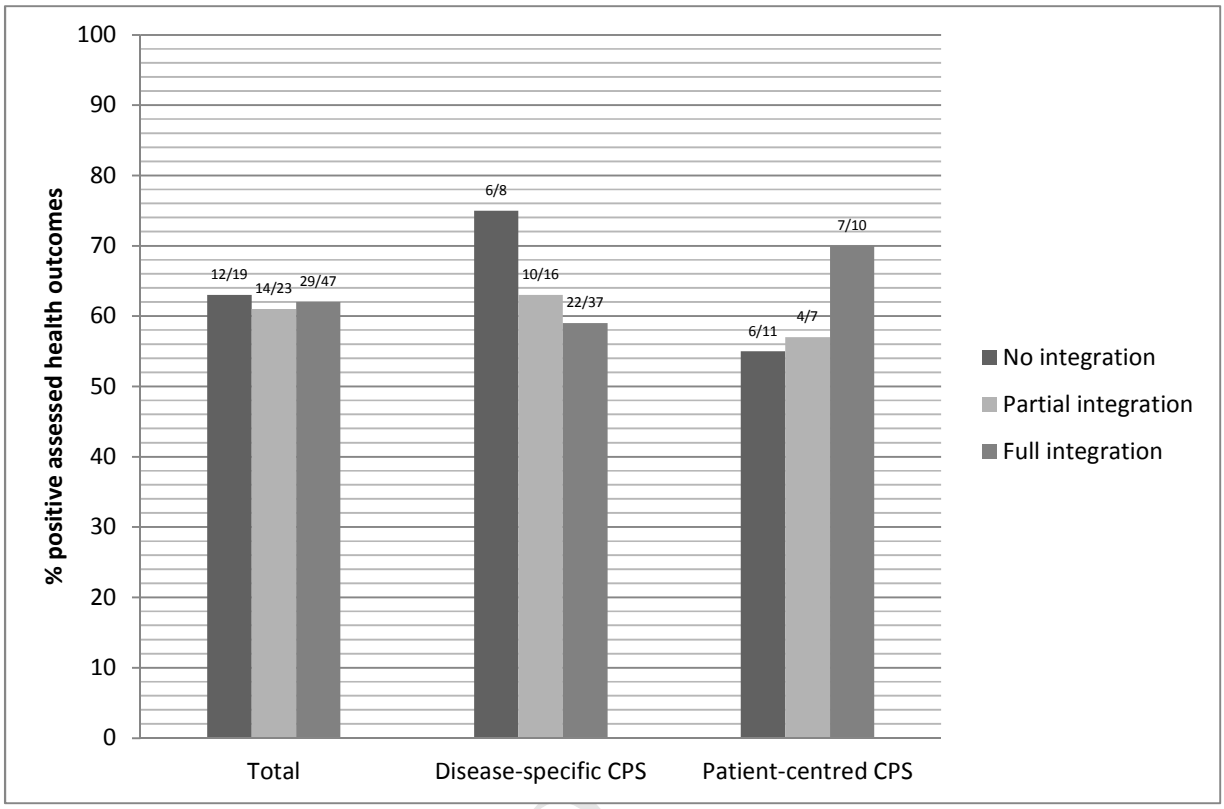


Figure 2: Outcomes by degree of integration of NDPs on health outcomes in primary care.



For each category of integration the total number of significant improved outcomes is divided by the total number of assessed outcomes. The results are also stratified by disease-specific CPS and patient-centered CPS.

Appendix A

Table 1: Search strategies for Pubmed and Embase

Pubmed search June 2016	**Embase search June 2016**
("pharmacist"[Title/Abstract] OR "pharmacists"[Title/Abstract] OR "pharmaceutical service"[Title/Abstract] OR "pharmaceutical services"[Title/Abstract] OR "pharmacy"[Title/Abstract]OR "pharmacists"[MeSH Terms] OR "pharmaceutical services"[MeSH Terms])	pharmacist:ti,ab OR pharmacists:ti,ab OR pharmacy:ti,ab OR 'pharmaceutical service':ti,ab OR 'pharmaceutical services':ti,ab OR 'pharmacist'/exp OR 'pharmacy'/exp
("family practice"[Title/Abstract] OR "general practitioner"[Title/Abstract] OR "primary care"[Title/Abstract] OR "general practitioners"[Title/Abstract] OR "general practice"[Title/Abstract] OR "family physician"[Title/Abstract] OR "physicians, family"[MeSH Terms] OR "family practice"[MeSH Terms] OR "general practitioners"[MeSH Terms] OR "general practice"[MeSH Terms])	'family practice':ti,ab OR 'general practitioner':ti,ab OR 'general practitioners':ti,ab OR 'general practice':ti,ab OR 'community dwelling':ti,ab OR 'family physician':ti,ab OR 'community dwelling':ti,ab OR 'ambulatory patient':ti,ab OR 'ambulatory elderly':ti,ab OR 'ambulatory patients':ti,ab OR 'primary care':ti,ab OR 'general practice'/exp OR 'general practitioner'/exp
("patient care"[Title/Abstract]) OR "interprofessional relation"[Title/Abstract] OR "interprofessional relations"[Title/Abstract] OR "cooperation"[Title/Abstract] OR "collaboration"[Title/Abstract] OR "consultation"[Title/Abstract] OR "referral"[Title/Abstract] OR "refer"[Title/Abstract] OR "home medicines review"[Title/Abstract] OR "medication review"[Title/Abstract] OR "medication reviews"[Title/Abstract] OR "communitydwelling"[Title/Abstract] OR "ambulatory patient"[Title/Abstract] OR "ambulatory elderly"[Title/Abstract] OR "ambulatory patients"[Title/Abstract] OR "pharmaceutical care"[Title/Abstract] OR "drug utilization review"[Title/Abstract] OR patient care[MeSH Terms] OR interprofessional relations[MeSH Terms]OR cooperative behaviour[MeSH Terms]OR counseling[MeSH Terms]OR professional role[MeSH Terms] OR (referral and consultation[MeSH Terms] OR "drug utilization review"[MeSH Terms] OR "review"[Title/Abstract])	'patient care':ti,ab OR 'interprofessional relation':ti,ab OR 'interprofessional relations':ti,ab OR cooperation:ti,ab OR collaboration:ti,ab OR consultation:ti,ab OR referral:ti,ab OR refer:ti,ab OR 'home medicines review':ti,ab OR 'medication review':ti,ab OR 'medication reviews':ti,ab OR review:ti,ab OR 'pharmaceutical care':ti,ab OR 'drug utilization review':ti,ab OR 'patient care'/exp OR 'patient referral'/exp

Table 2a: excluded studies with disease-specific CPS

Author (year)	Dimension of integration				
	Organizational	**Informational**	**Clinical**	**Functional**	**Normative**
Anaya (2008)[84]	No	Yes	Yes	N/A	Yes
Barnes (2014)[85]	Yes	Yes	No	N/A	N/A
Bruhn (2013)[86]	Yes	Yes	Yes	N/A	N/A
Carter (2015)[87]	Yes	Yes	Yes	No	N/A
Chung (2014)[88]	Yes	Yes	N/A	N/A	Yes
Cording (2002)[89]	Yes	Yes	N/A	Yes	Yes
Duran-Parrondo (2011)[90]	No	N/A	Yes	N/A	Yes
Erickson (1997)[91]	Yes	Yes	No	N/A	No
Gums (2014)[92]	Yes	Yes	Yes	No	N/A
Gums (2015)[93]	Yes	Yes	Yes	No	N/A
Jacobs (2012)[94]	No	Yes	No	N/A	No
Jamieson (2010)[95]	No	Yes	N/A	N/A	N/A
Johnson (2010)[96]	No	N/A	N/A	N/A	N/A
Kelly Hester (2000)[97]	No	N/A	N/A	No	No
Monte (2009)[98]	No	N/A	No	Yes	N/A
Shane-McWorther (2015)[99]	N/A	No	N/A	No	Yes
Solomon (1998)[100]	Yes	N/A	No	N/A	N/A
Stading (2009)[101]	Yes	Yes	N/A	N/A	N/A
Thumar (2014)[102]	No	Yes	No	Yes	N/A
Tobari (2010)[103]	Yes	Yes	No	N/A	N/A
Trompeter (2009)[104]	No	Yes	N/A	Yes	N/A
Villa (2009)[105]	N/A	N/A	N/A	N/A	N/A

Table 2b: excluded studies with patient-centered CPS

Author (year)	Dimension of integration				
	Organizational	**Informational**	**Clinical**	**Functional**	**Normative**
Hamley (1997)[106]	Yes	N/A	N/A	N/A	N/A
Harris (2009)[107]	Yes	Yes	No	N/A	N/A
Jameson (1995)[108]	N/A	N/A	No	N/A	N/A
Jameson (2001)[109]	N/A	Yes	No	N/A	N/A
Laucka (1996)[110]	No	Yes	No	N/A	N/A
Lowe (2000)[111]	No	No	No	N/A	N/A
Morrison (2015)[112]	No	Yes	No	N/A	Yes
Taylor (2003)[113]	No	Yes	No	N/A	N/A

Table 3: Clinical integration based upon six measurable elements. The NDP was considered clinical integrated when the result on ≥ four elements was positive ("Yes").

Ref.	Patient counselling by NDP	Follow-up by NDP	Face-to-face communication GP and NDP	Multiprofessional collaboration (≥3 care providers)	Other patient directed activities outside scope of intervention	Prescribing authority	Clinical integration
Adler (2004)[50]	Yes	Yes	Yes	Yes	Yes	No	Yes
Avery (2012)[59]	No	Yes	Yes	No	No	No	No
Berdine (2012)[60]	Yes	Yes	Yes	No	Yes	Yes	Yes
Bex (2011)[33]	Yes	Yes	Yes	Yes	Yes	No	Yes
Billups (2005)[44]	No	Yes	No	No	Yes	No	No
Bogden (1997)[5]	Yes	No	No	No	No	No	No
Bogden (1998)[34]	Yes	No	Yes	No	No	No	No
Borenstein (2003)[35]	Yes	Yes	No	No	No	No	No
Capoccia (2004)[51]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Carter (2001)[61]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Carter (2008)[36]	Yes	Yes	Yes	Yes	Yes	No	Yes
Choe (2005)[18]	Yes	Yes	Yes	Yes	Yes	No	Yes
Coast-Senior (1998)[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Davis (2007)[62]	Yes	Yes	No	No	Yes	No	No
Edelman (2010)[55]	Yes	Yes	Yes	Yes	Yes	No	Yes
Evans (2010)[54]	Yes	Yes	Yes	No	Yes	No	Yes
Finley (2003)[52]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Freeman (2013)[63]	Yes	No	Yes	Yes	Yes	No	Yes
Galt (1998)[64]	Yes	Yes	Yes	Yes	Yes	No	Yes
Hall (2009)[53]	Yes	Yes	No	Yes	No	Yes	Yes
Hammad (2011)[48]	Yes	Yes	Yes	No	No	No	No
Hanlon (1996)[65]	Yes	No	Yes	No	No	No	No
Heisler (2012)[4]	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Henry (2013)[20]	Yes	Yes	Yes	Yes	Yes	No	Yes
Hetro (2015)[57]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hirsch (2014)[37]	Yes	Yes	Yes	No	No	Yes	Yes
Hogg (2009)[66]	Yes	Yes	Yes	Yes	Yes	No	Yes
Hunt (2008)[38]	Yes	Yes	Yes	No	No	Yes	Yes
Ip (2013)[21]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Irons (2002)[22]	Yes	Yes	No	No	Yes	Yes	Yes
Isetts (2006)[67]	Yes	Yes	Yes	Yes	No	No	Yes
Isetts (2008)[68]	Yes	Yes	Yes	Yes	Yes	No	Yes
Jameson (2010)[23]	Yes	Yes	Yes	No	No	No	No
Koenigsfeld (2012)[58]	Yes	Yes	Yes	No	Yes	No	Yes
Krska (2001)[69]	Yes	Yes	No	Yes	No	No	No
Lenander (2014)[70]	Yes	No	Yes	Yes	No	No	Yes
Lowrie (2012)[49]	Yes	Yes	Yes	Yes	No	Yes	Yes
Magid (2013)[39]	Yes	Yes	No	Yes	Yes	Yes	Yes
Margolis (2013)[40]	Yes	Yes	No	Yes	Yes	Yes	Yes
McAdam-Marx (2015)[24]	Yes	Yes	Yes	Yes	No	Yes	Yes
McCord (2006)[25]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
McFarland (2012)[26]	No	Yes	No	Yes	No	Yes	No
Mehos (2000)[41]	Yes	Yes	No	No	No	No	No
Mourão (2012)[27]	Yes	Yes	No	No	No	Yes	No
Neto (2011)[56]	Yes	Yes	Yes	Yes	Yes	No	Yes
O'Neill (2014)[42]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pindolia (2009)[71]	Yes	Yes	Yes	No	No	No	No
Roth (2013)[72]	Yes	Yes	Yes	No	No	No	No
Rothman (2005)[28]	Yes	Yes	Yes	Yes	No	Yes	Yes
Salvo (2012)[29]	Yes	Yes	No	Yes	Yes	Yes	Yes
Scott (2006)[30]	Yes	Yes	No	Yes	No	Yes	Yes

Sellors (2003)[73]	Yes	Yes	Yes	No	No	No	No
Shane-McWorther (2005)[31]	Yes	Yes	No	Yes	Yes	No	Yes
Simpson (2011)[32]	Yes	Yes	Yes	Yes	No	No	Yes
Smith (2013)[45]	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Straka (2005)[46]	Yes	Yes	Yes	No	No	Yes	Yes
Tahaineh (2011)[47]	Yes	Yes	No	No	Yes	No	No
Tan (2014)[74]	Yes	No	Yes	Yes	Yes	No	Yes
Wong (2013)[43]	Yes	No	No	No	No	No	No
Zermansky (2001)[75]	Yes	Yes	Yes	No	No	No	No

Highlights

What is already known about this subject

- Co-location of a non-dispensing pharmacist in primary care practice enables (in)formal communication, probably enhancing integrated patient care;
- The degree of integration of non-dispensing pharmacists into multidisciplinary health care teams varies strongly between settings.

What this study adds

- This study shows the relative value of integration of clinical pharmacy services in primary care;
- Full integration may not improve the outcomes of disease-specific clinical pharmacy services in primary care;
- Full integration may improve outcomesof patient-centred clinical pharmacy services in primary care however requires additional research.