Title: Effectiveness of pharmacist care in the improvement of adherence to antidepressants: a systematic review and meta-analysis

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Abstract

BACKGROUND: Pharmacists can play a decisive role in the management of ambulatory patients with depression who poorly adhere to antidepressant drugs.

OBJECTIVE: To systematically evaluate the effectiveness of pharmacist care on improving adherence to antidepressants in depressed outpatients.

METHODS: A systematic review and meta-analysis of randomized controlled trials (RCTs) was conducted. RCTs were identified through electronic databases (Medline, Central, ISI web of knowledge and CSIC database) from inception to April 2010, reference lists were checked and experts were consulted. RCTs that evaluated the impact of pharmacist interventions on improving adherence to antidepressants in depressed patients in an outpatient setting (community pharmacy or pharmacy service) were included. Methodological quality was assessed and methodological details and outcomes were extracted in duplicate.

RESULTS: Six RCTs were identified. A total of 887 patients with an established diagnosis of depression who were initiating or maintaining pharmacological treatment with antidepressant drugs and who received pharmacist care (459 patients) or usual care (428 patients) were included in the review. The most commonly reported interventions were patient education and monitoring, monitoring and management of toxicity and side effects, compliance promotion, provision of written or visual information and recommendation or implementation of changes or adjustments in medication. Overall, no statistical heterogeneity or publication bias was detected. Pooled odds ratio, using a random effects model, was 1.64 (95% CI 1.24-2.17). Subgroup analysis showed no statistically significant differences in results by type of pharmacist involved, adherence measure, diagnostic tool or analysis strategy.

CONCLUSIONS: These results suggest that pharmacist intervention is effective in the improvement of adherence to antidepressants. However, data are still limited and we would recommend more research in this area, specifically outside the USA.

Background

Depression is a major health concern worldwide due to its high prevalence, patient impairment and cost.[1-3] Since the first antidepressant was introduced in 1957[4,5], pharmacological treatment for depression has undergone a number of changes but it is still the first approach for treatment of moderate and severe depression.[6] In spite of the efforts to improve side-effect profile and tolerability of medication, adherence to antidepressant drugs is still poor.[7,8]

The pharmacist is one of the most accessible healthcare professionals[9] and can play a decisive role in the management of ambulatory patients. Pharmaceutical care is described as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life" and it involves cooperation with patients and other professionals with the aim of producing specific therapeutic outcomes for the patient.[10] In physical conditions such as heart failure, asthma, diabetes, hypertension and dyslipidemia, pharmacist interventions have been shown to improve patient wellbeing in terms of clinical improvement and adherence.[11-15]

Recently, pharmacists' involvement in the management of patients suffering from mental health disorders has been increasing and studies have been carried out to evaluate the impact of pharmacist interventions in this population. In 2003, Finley et al.[16] conducted a systematic review examining the impact of clinical pharmacists on the care and outcomes of patients with mental disorders including, among other diagnoses, schizophrenia, depression and behavioural disturbances. The pharmacist interventions described in the review included drug monitoring, treatment recommendations, patient education, drug management and education to providers on prescribing patterns. The results of this work indicated a positive effect of pharmacist interventions in patients with mental health problems, although there were several sources of

heterogeneity relating to the study design, patient populations, measured outcomes and treatment settings. Furthermore, since this review was published, more research has been conducted on this issue so these results would need to be updated.

More recent systematic reviews have shown that multidisciplinary strategies for the management of patients with mental health problems in primary care have a positive effect on antidepressant use and depressive outcomes.[17-19] These studies concluded that interventions conducted by case managers with a specific mental health background were more effective in improving symptom outcomes than those conducted by case managers without a specific mental health background, such as pharmacists. However, no differences were detected when the outcome assessed was antidepressant use. Furthermore, in these analyses pharmacists were grouped with other health professionals so their specific contribution to the results is difficult to determine. Overall, most of the literature in this field appeared not to show statistically significant differences between intervention and control groups and seemed to be inconclusive. We therefore conducted a meta-analysis to increase the power of the study and to try to improve effect size estimate.

In general, interventions conducted by pharmacists are usually focused on medication and, consequently, adherence to medication is the primary outcome in most of these studies. For this reason we decided to focus our review on adherence improvement. Furthermore, in patients with depression, it has been stated that there is a significant positive association between antidepressant use and improved depression outcomes.[17,18]

The objective of this study is to systematically review randomized controlled trials (RCTs) evaluating the impact of pharmacist interventions on outpatients with regard to improvement of adherence to antidepressants when treating a depressive disorder.

Methods

We followed the PRISMA guidelines for reporting meta-analysis.[20]

Literature search

We performed a systematic review of the published literature for RCTs evaluating the impact of pharmacist interventions on the improvement of adherence to antidepressant pharmacological treatment of outpatients with depressive disorder (major depressive disorder and dysthymic disorder) according to DSM (Diagnostic and Statistical Manual of Mental Disorders) or ICD (International Classification of Diseases) criteria. In order to identify all articles involving interventions intended to improve use of antidepressants, the databases were searched separately by two investigators (AFS and MRV). Literature searches were completed from inception to April 2010, without language restrictions, through Medline, the Cochrane Central Register of Controlled Trials database, the Institute for Scientific Information (ISI), and the Spanish National Research Council (CSIC) databases.

The search strategy used was: [("Pharmaceutical Services"[Mesh] OR pharmac* OR "pharmaceutical intervention" OR "pharmacy counsel*" OR "pharmacy-based coaching") AND ("Depressive Disorder"[Mesh] OR "depression" OR "Antidepressive Agents"[Mesh] OR "antidepressant*") AND ("Patient Compliance"[Mesh] OR "Treatment Refusal"[Mesh] OR "Patient Dropouts"[Mesh] OR adherence OR dropout OR compliance)].

Abstracts of all citations were obtained for study selection. Citation indices and reference lists of retrieved articles were checked for additional studies not identified in the original database search. Expert informants from the pharmaceutical industry and the School of Pharmacy (University of Barcelona) were consulted to retrieve grey literature (such as unpublished reports and conference abstracts).

Study selection

Studies were screened for inclusion by reviewing the title, the published abstract, and the full article where necessary. First selection was made in duplicate (A.F.S. and M.R.V.). The final screening, which reviewed full text articles, was done by two researchers (A.S.B. and M.R.V.). One of the researchers (A.S.B.) was blind for the authors of the articles and the journals in which they were published. In the case of disagreement, a third researcher (A.F.S.) was consulted.

We included RCTs with ambulatory patients diagnosed using a validated psychiatric interview or a clinical diagnosis for a mood disorder, and initiating or maintaining treatment with antidepressants. No restriction by type of antidepressant medication was applied. Nor were restrictions imposed with respect to age, gender or ethnicity. Interventions taken into account included educational messages and counseling, monitoring and medication dosage-adjustment, and management of adverse effects. Our definition of intervention excluded all research in which the pharmacist's role was only focused on the review of medication patterns (i.e., detection of medication related problems, such as drug interactions, without a subsequent intervention delivered to the patient to solve the problems). As the intervention should be applied directly to the patient, articles evaluating the effect of pharmacist intervention in institutions, doctors or families were excluded. Articles were rejected if the study was conducted in an acute inpatient facility or hospital, or if it was a multidisciplinary model in which the role of the pharmacist was not well established. Nevertheless, there was no restriction regarding the setting where the intervention was done, so that community pharmacies or pharmacy services in hospitals or primary care centers were included. Regarding outcome measures, any measure evaluating adherence to medication was accepted: pharmacy records, electronic pill-container and self-reported adherence.

Quality assessment

The quality of the studies was assessed independently by Y.L.H. and M.R.V. using the Jadad scale.[21] The Jadad scale is a three-item scale that considers three features of a study; randomization, double-blinding and flow of patients. Adequate description of allocation concealment was also evaluated so total summed scores range from 0 to 7, with the higher scores indicating higher quality.[22-24] However, blinding of pharmacists and participants was not possible because of the type of intervention assessed in this meta-analysis so finally total scores ranged from 0 to 5. Inter-reviewer reliability for the quality of studies was measured by Kappa statistics (0.958).

Data abstraction and quantitative data synthesis

By using a standardized abstraction form, two reviewers (M.R.V. and Y.L.H.) independently extracted key features of the characteristics, methods and outcomes of articles that met the inclusion criteria. Key features included: study design, period of study, setting, sample size, number of pharmacists, intervention components, the main outcome measures reported by the authors and results and analysis strategy (i.e., per-protocol or intent-to-treat). In the case of disagreement, a third reviewer (J.G.C.) also checked the data and agreement was reached. Inter-reviewer reliability was measured by Kappa statistics (0.910).

Dichotomous and continuous measures of the outcome were extracted. For continuous data the standardized mean difference (SMD) was computed with 95% confidence interval (CI). Random effects model was used to calculate pooled odds ratios and 95% confidence interval. Statistical heterogeneity was assessed employing the Cochran's Q test and I-squared statistic. Publication bias was assessed using the funnel plot and Egger’s test.

In order to assess the possible effects of clinical heterogeneity in the meta-analysis results, subgroup analyses were performed according to setting of pharmacist doing the intervention (community pharmacies or pharmacy services in hospitals or primary care centers), main adherence measure (pharmacy records, electronic pill-container or self-reported adherence), and type of diagnosis used for inclusion (only clinical or with a validated diagnostic instrument). Those subgroup analyses were pre-specified. Moreover, subgroup analyses were performed according to the analysis strategy (intent-to-treat or per-protocol) as a means of assessing its effect in the results of the meta-analysis.

Analyses were performed using Comprehensive Meta-analysis, version 2 (Biostat, Englewook, NJ, USA).

Results

Literature search and study selection

The electronic search strategy identified 438 potentially relevant papers, while 7 additional studies were retrieved via the manual search of citation indices and reference lists. In all, 43 were duplicated titles indexed in multiple databases and were excluded. Of the 395 remaining studies, 367 were excluded by reviewing title and abstract (221 described other interventions, the population in 78 were not depressed patients, 63 were not RCTs and 5 did not evaluate adherence) and 22 were excluded by reviewing full-text articles (7 did not evaluate compliance, 7 were not RCTs, 6 described other interventions and 2 were only descriptive) (Figure 1). Correspondence was conducted with the corresponding author of one article describing study methods which matched the criteria for selection. Results at 6-month follow-up were published but no results were reported from that moment on.[25] Even though we received an answer from the author, data was unavailable in this case.

- Insert Figure 1 -

Characteristics and methodological quality of the included studies

- Insert Table 1 –

We identified 6 studies for inclusion in the analysis[26-31] which assessed pharmacist interventions in patients initiating or maintaining a treatment with antidepressant medication (Table 1). Overall, 1049 subjects were randomized, 527 (50.2%) of whom were randomized to an intervention group and 522 (49.8%) to a control group. However, because of per-protocol analyses in some studies, results are reported for only 887 patients (84.9% of randomized patients), 459 (51.7%) belonging to the intervention group and 428 (48.3%) to the control group. Most of the studies (4 out of 6) were carried out in the USA[26-28,30] while there was one European study[29], performed in the Netherlands, and one study conducted in Australia.[31] The studies were carried out between 1998 and 2005 and the publication years ranged from 2003 to 2006. There were no baseline significant differences in sociodemographic characteristics between the control and intervention groups. However, in three of the studies baseline differences related to antidepressant medication[27,30] and clinical characteristics[28] were reported. In the study by Rickles et al.[30], intervention participants were more likely than control participants to have a history of psychotropic medication use (41.9% vs 15.6%; $P<0.05$). In the study by Adler et al.[27], intervention participants were more likely to have first used antidepressants more than a year before the initial questionnaire (56.1% vs. 45.2%; $P<0.05$). Finally, in the study by Capoccia et al.[28], more patients in the intervention group had been diagnosed with major depression at

baseline than in the control group (21% vs. 9%; P<0.05). However, in the case of the articles by Adler et al.[27] and Capoccia et al.[28], statistical analyses were controlled for prior experience with antidepressants and baseline SCID score respectively to minimize bias.

All patients had an established diagnosis of depression and were initiating [n=658 (74.2 %)] or maintaining [n=229 (25.8%)] pharmacological treatment with antidepressant drugs. In the study by Brook et al.[29], only patients taking nontricyclic antidepressants were considered for inclusion and in the study by Finley et al.[26], 96% and 88% of control and intervention patients respectively were prescribed selective serotonin reuptake inhibitors. A total of 3 different methods of assessing adherence to antidepressants were defined; self-reported adherence (n=5)[26-28,30,31], pharmacy records (n=4)[26,27,29,30] and electronic pill-container (n=1).[29]

In 3 of the 6 studies[27,28,30], depression was diagnosed by means of validated diagnostic instruments based on DSM-IV criteria including the Primary Care Screener for Affective Disorders (PC-SAD), the Primary Care Evaluation of Mental Disorders (PRIME-MD) and the Beck Depression Inventory II (BDI-II). Baseline severity of depression was reported as being moderate to severe based on different measures (Beck Depression Inventory; Hopkins Symptom Checklist, Brief depression inventory and K10).

While the follow-up period ranged from 2 to 12 months, in 4 of the studies it was 6 months.[26,27,29,30] Where possible, data from 6 months was used to perform the analysis (n=5).[26-30]

Community pharmacists applied the intervention in 3 of the studies[29-31], and pharmacists from a pharmacy service of a primary care setting performed it in the other 3 studies.[26-28]

In one case[29], information about the intervention was extracted from a previous publication related to the study.[32] In all 6 studies the intervention included patient education and monitoring. Other common interventions were monitoring and management of toxicity and side effects (n=5)[26-30], adherence promotion (n=4)[26,27,30,31] and provision of written or visual information

(n=3).[26,29,31] In two of the studies[26,28], in which the intervention was conducted by a clinical pharmacist, the pharmacist could recommend or conduct changes or adjustments in medication. Methodological quality ranged from 2 to 5 on the Jadad scale, and 4 of the studies scored 3 or more.[26,27,29,30] The most commonly absent item was an adequate description of concealment of allocation.

Intent-to-treat analyses were conducted in 3 of the 6 studies.[26,28,29] In the study by Adler et al.[27], it is stated that an intent-to-treat analysis was conducted. However, not all randomized patients were included in the analysis, only those with any 6-month data. That is to say, 533 patients were randomized but information was only given for the 384 that completed the 6-month assessment. According to CONSORT guidelines[33], in order to preserve fully the huge benefit of randomization, intent-to-treat analysis should include all randomized participants in the analysis, all retained in the group to which they were allocated. Using this conservative definition of the intent-to-treat approximation analysis, we decided to classify the Adler et al.[27] study in the group of studies that conducted per-protocol analysis.[27,30,31]

In 2 of the studies, some of the included patients were already on antidepressants at the time of enrolment.[27,31] The study by Adler et al.[27] reported results of patients initiating and maintaining treatment with antidepressants at the time of enrolment, while in the study by Crockett et al.[31] this information was presented in aggregated form and it was not possible to discern who was being initiated or maintained on medication. For the present meta-analysis, results from all patients were included, regardless of whether patients were initiating or maintaining pharmacological treatment. In the study by Capoccia et al.[28], compliance information at 6-months of follow-up was used. In the study by Finley et al.[26], two different ways of reporting adherence were employed: the Mean Possession Ratio and the percentages of compliant patients. In the meta-analysis, the information about the percentage of compliant patients at 6 months was used.

Meta-analysis

- Insert Figure 2 -

No significant heterogeneity was found between the included studies (Q=2.677; 5 df; P=0.750; I-squared<0.001; Tau-squared<0.001). Pooled odds ratio demonstrated a significant benefit from pharmacist interventions in the improvement of adherence to antidepressant pharmacological treatment (1.639; 95% confidence interval 1.236 to 2.174; P<0.001) (Figure 2).

When we compared the effectiveness of pharmacist intervention in depressed patients, after grouping by type of pharmacist implementing the intervention (community pharmacy or pharmacy service), type of diagnosis (clinical or validated psychiatric instrument), type of adherence measure (pharmacy records, electronic pill-container or self-reported) and analysis strategy (per-protocol or intent-to-treat), we observed that there are no significant differences as confidence intervals from different subgroups clearly overlapped (Figure 3).

- Insert Figure 3 -

The funnel plot of standard error against the natural logarithm of the odds ratio (Figure 4) and the Egger test for assessing bias (P=0.460) suggested that there was little publication bias in the selection of studies.

- Insert Figure 4 -

The effect of removing one study in turn was assessed and showed that statistically significant results do not depend on any of the individual studies. Cumulative meta-analysis was also performed proving that the pooled estimate is robust over time.

Discussion

The results of the present meta-analysis suggest a positive effect of pharmacist interventions on antidepressant use in terms of adherence. These results are similar to those reported on collaborative care by Bower et al.[17] that found a positive effect of collaborative care on adherence to antidepressants (OR=1.92; 95% CI 1.54-2.39). Subgroup analysis showed no significant differences between groups when grouping by type of pharmacist conducting the intervention, type of diagnostic procedure, type of adherence measure or analysis strategy used.

These results should be interpreted with the following limitations in mind. Firstly, although a significant improvement in adherence to antidepressant medication was identified, it is unclear whether this will result in an improvement in depressive symptoms. However, previous studies have reported a positive association between improved antidepressant use and depressive symptoms suggesting that the effects of collaborative care on symptoms of depression may be mediated through changes in adherence to antidepressants.[17,18]

Secondly, the RCTs included were different in some methodological approaches, such as setting of pharmacist performing the intervention, type of intervention performed and type of diagnostic measures. In this respect, studies considering different outcome measures were used, which could limit internal validity. Although no statistical heterogeneity was detected, Cochran's Q test has low power when the number of studies included in the meta-analysis is small and the I-squared statistic also suffers from large uncertainty in this situation.

In a similar way, the power of the Egger test for assessing bias can also be affected by the low number of studies included.

Thirdly, a 6-month follow-up period is a short time if we are referring to antidepressant treatment, which should be continued for at least 6 months after remission of an episode of depression.[6] However, it is well known that drop-out occurs mostly at the beginning of treatment with antidepressants.[7] Even though a short follow-up period could have influenced the effect sizes of pharmacist intervention versus controls, the 2 month trial by Crockett et al.[30] did not happen to alter the results, as we confirmed in the robustness of analysis.

Fourthly, it should also be noted that most studies were conducted in the USA and the results may not generalize to other contexts. Finally, some baseline differences of the compared groups were identified in 3 of the studies[27,28,30] which could introduce bias. However, in 2 of these studies[27,28] statistical methods to adjust for the baseline differences were used to minimize bias while the third one[30] reached the highest score on the Jadad scale and described an adequate randomization process and allocation concealment.

In spite of these limitations, this study is, to the best of our knowledge, the first published systematic review and meta-analysis of pharmacist intervention in depressed patients. Analysis proved that the pooled estimate was robust and suggested that there was little publication bias.

Conclusion

The present review indicates that pharmacists' interventions in the care of outpatients treated with antidepressants can significantly improve adherence to medication. Patient education and monitoring, along with monitoring and management of side effects and compliance promotion were the most commonly reported interventions in both pharmacy service and community pharmacy. Two of the studies conducted in a pharmacy service also allowed pharmacists to

recommend or conduct changes or adjustments in medication. However, no significant differences were found in terms of improvement of adherence to antidepressants when subgroup analyses were conducted by setting of pharmacist involved in the intervention.

The present review indicates that the data generated from the published RCTs on pharmacist interventions in depressed patients are still limited. Only 6 studies have been identified, implying that the power of some of the statistics used may be limited and it is possible that we have not been able to detect existent heterogeneity between studies or publication bias. As such, we would recommend more research in this area, mainly outside the USA, to provide definite answers to the question we explored.

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Table 1. Characteristics of included studies

	Country	Setting (number of pharmacists)	Key components of pharmacist intervention	Main adherence measure (other adherence measures)	Main diagnostic procedure	Baseline level of depression by group (Measurement tool)	Main analysis strategy	Randomized Patients (N)	Number of women (%)	Mean age	Follow-up (months)	Quality
Finley et al. (2003)[26]	USA	PS (2)	Medication education, depression education, adherence promotion, obtaining patient clinical history, monitoring drug efficacy and toxicity, recommendation for changes in medication to the physician, advising about other available treatment options, providing written information.	Pharmacy records (Self-reported)	Clinical	I=18.7 C=18.3 (BIDS)	ITT	125 (I=75 C=50)	106 (85%)	54	6	4
Adler et al. (2004)[27]	USA	PS (5)	Medication education, depression education, adherence promotion, obtaining patient medication history, monitoring drug efficacy and toxicity, facilitating communication with the physician.	Self-reported (Pharmacy records)	VDI	I=23.2 C=23.2 (mBDI)	PP	384[c,d] (I=202 C=182)	364 (72%)[g]	42[g]	6	5

Capoccia et al. (2004)[28]	USA	PS (2)	Medication education, depression education, adjustment of medication dosage and time of dose, change or discontinuation of antidepressants, monitoring and management of side effects, provision of medication refill authorizations, facilitating the access to patient assistance programs and appointments with mental health service providers.	Self-reported	VDI	I=1.83 C=1.75 (SCL-20)	ITT	74 (I=41 C=33)	42 (57%)	39	12	2
Brook et al. (2005)[29]	Netherlands	CP (19)	Medication education, depression education, adherence promotion, monitoring and management of side effects, providing written and visual information[b].	Electronic pill container (pharmacy records)	Clinical	I=3.1 C=2.8 (SCL-13)[b]	ITT	135 (I=64 C=71)	95 (70%)	43	6	3
Rickles et al. (2005)[30]	USA	CP (14)	Medication education, depression education, adherence promotion, monitoring and management of side effects, contact with prescriber if needed,	Pharmacy records (Self-reported)	VDI	I=28.9 C=27.0 (BDI-II)	PP	63 (I=31 C=32)	53 (84%)	38	6	5

			monitoring patient progress.									
Crockett et al. (2006)[31]	Australia	CP (32[a])	Medication education, monitoring patient progress, providing written and visual information.	Self-reported	Clinical	I=23.0 C=21.7 (K10)	PP	106[e,f] (I=46 C=60)	84 (79%)[e]	46[e]	2	2

Abbreviations: PS=Pharmacy Service; CP=Community Pharmacy; VDI=Validated diagnosis instrument; I=Intervention; C=Control; N=Sample size; BIDS=Brief Inventory for Depressive Symptoms (range 0–42); mBDI=modified Beck Depression Inventory (range 0-63); SCL-20=20-item Hopkins Symptom Checklist (range 0-4); SCL-13=13-item Hopkins Symptom Checklist (range 1-5); BDI-II=Beck Depression Inventory (range 0-63); K10=10-question screening scale of psychological distress (range 10-50); ITT=Intent-to-treat; PP=Per-protocol.

[a] Number of pharmacies, number of pharmacists was not reported. [b] Data extracted from Brook OH et al. (2003)[32]. [c] 234 of the randomized patients were initiating treatment with antidepressants and 150 were already taking antidepressants at the time of inclusion. [d] 533 patients (I=265 C=268) were randomized but information was given only for the 384 that completed the 6-month assessment. [e] 119 (I=51 C=68) patients were randomized but results were reported for the 106 patients that completed the 2-month assessment. [f] 27 patients had been on antidepressant medication for less than one month at the beginning of the study. [g] Information from the 507 patients that completed the initial intervention.

Figure legends

Figure 1. Flow diagram of studies screened, assessed for eligibility and included in the review

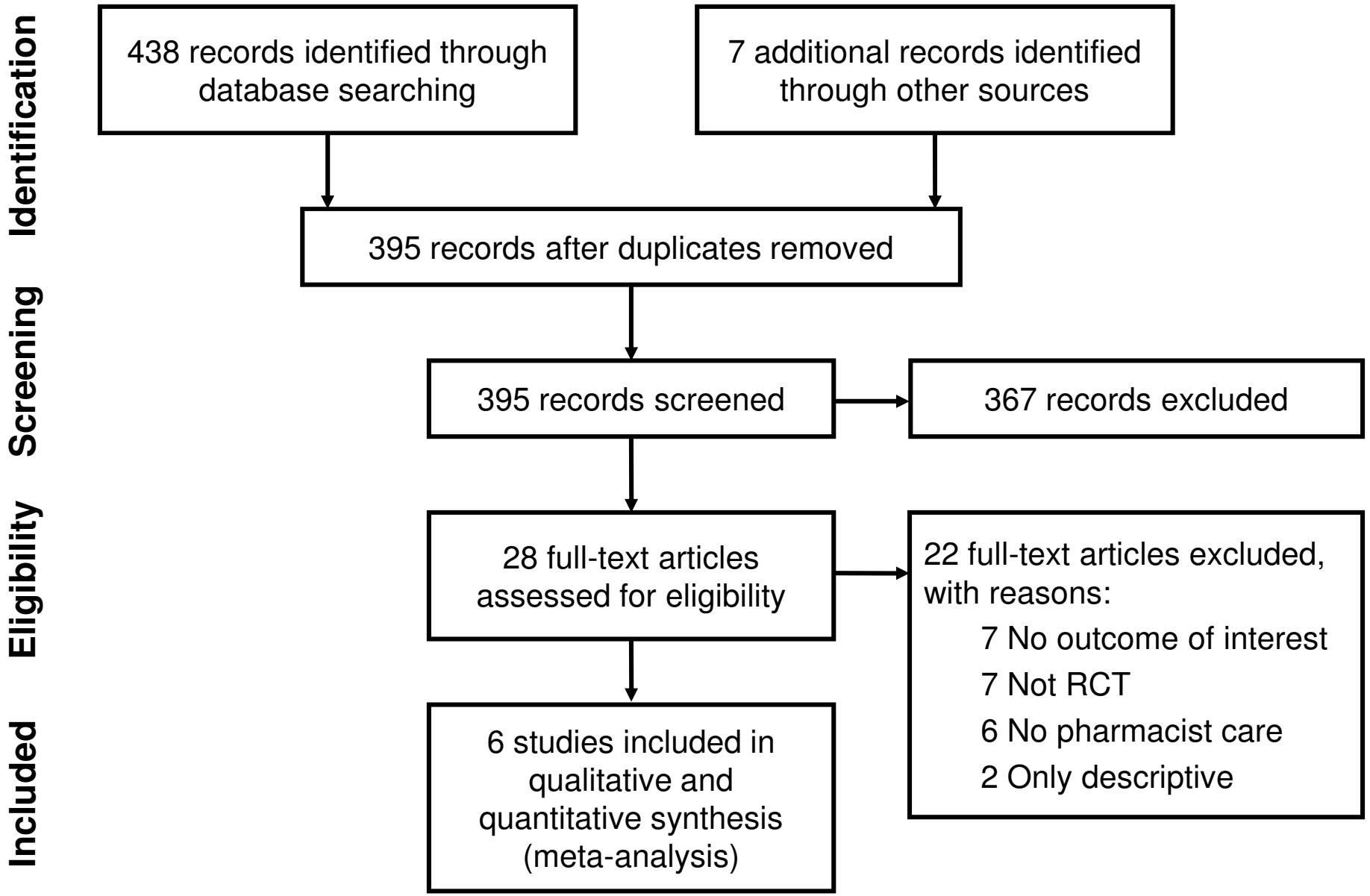
RCT = Randomized Controlled Trial.

Figure 2. Meta-analytic results

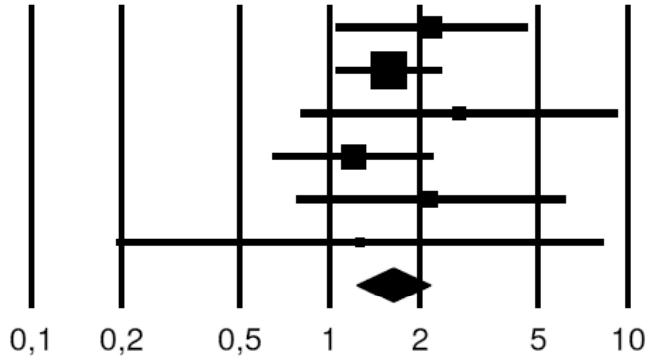
Figure 3. Subgroup analyses by setting of pharmacist implementing the intervention, type of diagnosis, main of adherence measure and strategy of analysis

VPI=Validated psychiatric instrument; EPC=Electronic pill container.

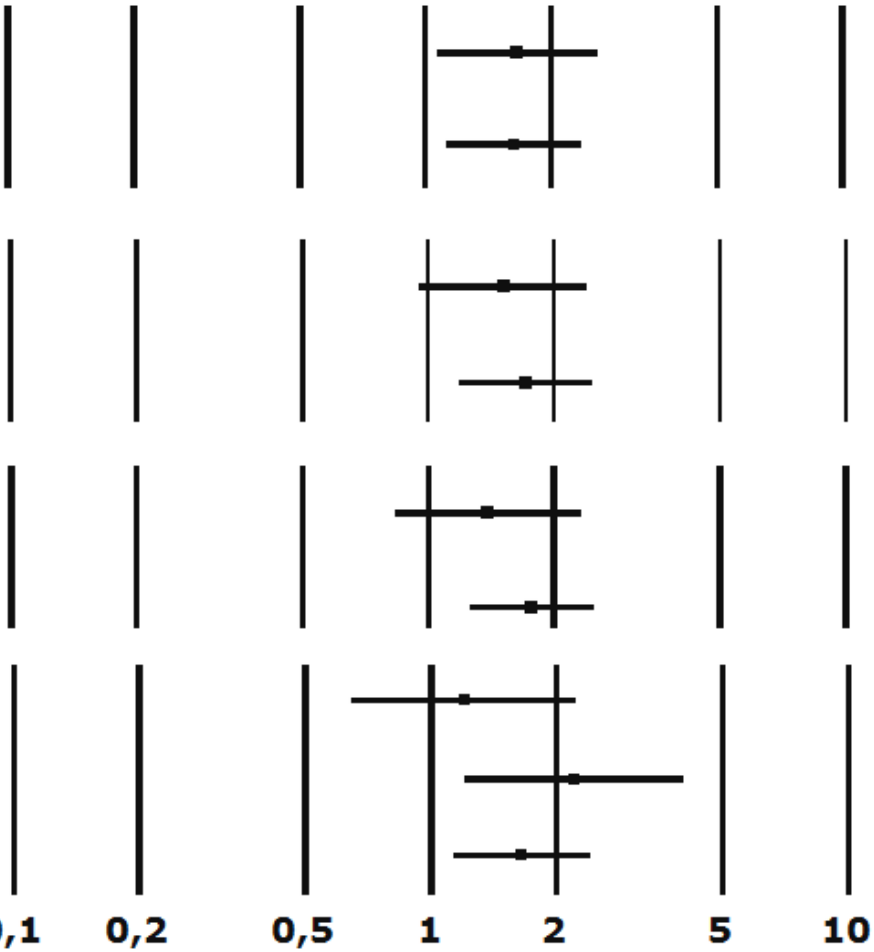
Figure 4. Funnel plot of Standard Error by Log odds ratio

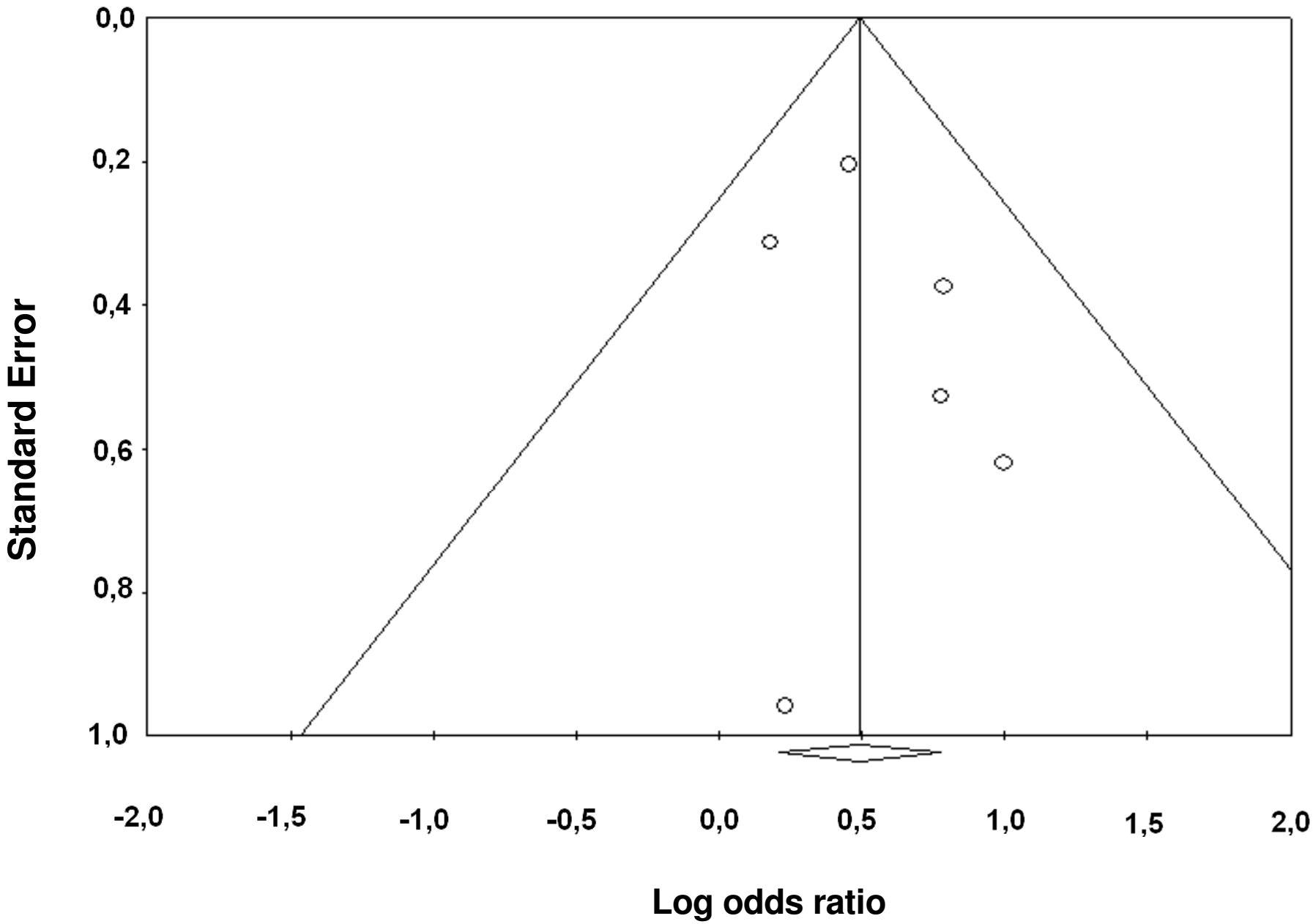

Identification
Screening
Eligibility
Included
438 records identified through database searching
7 additional records identified through other sources
395 records after duplicates removed
395 records screened
367 records excluded
28 full-text articles assessed for eligibility
22 full-text articles excluded, with reasons:
7 No outcome of interest
7 Not RCT
6 No pharmacist care
2 Only descriptive
6 studies included in qualitative and quantitative synthesis (meta-analysis)

Study name	Odds ratio	Lower limit	Upper limit	p-Value	Intervention	Control	Relative weight
Finley PR (2003)	2,199	1,055	4,585	0,035	75	50	14,76
Adler DA (2004)	1,576	1,052	2,358	0,027	202	182	48,94
Capoccia KL (2004)	2,712	0,804	9,147	0,108	41	33	5,39
Brook OH (2005)	1,198	0,649	2,212	0,563	64	71	21,19
Rickles NM (2005)	2,175	0,774	6,111	0,140	31	32	7,46
Crockett J (2006)	1,263	0,193	8,252	0,807	46	60	2,26
Pooled	1,639	1,236	2,174	0,001	459	428	



Group by	Subgroup	Statistics for each study				Odds ratio and 95% CI
		Odds ratio	Lower limit	Upper limit	p-Value	
Analysis strategy	Intent-to-treat	1,656	1,068	2,568	0,024	
	Per protocol	1,628	1,126	2,353	0,010	
Main diagnostic procedure	Clinical	1,520	0,963	2,399	0,072	
	VPI	1,718	1,199	2,459	0,003	
Setting of pharmacist	Community pharmacy	1,389	0,836	2,308	0,204	
	Pharmacy Service	1,765	1,257	2,479	0,001	
Main adherence measure	EPC	1,198	0,649	2,212	0,563	
	Pharmacy records	2,191	1,204	3,987	0,010	
	Self-reported	1,645	1,130	2,393	0,009	

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Standard Error
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1,5
2,0
Log odds ratio