Effectiveness of Interventions to Improve Medication Adherence in Adults With Depressive Disorders: A Meta-Analysis

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Abstract

Background: Non-adherence to medications is a major obstacle in the treatment of depressive disorders. We systematically reviewed the literature to evaluate the effectiveness of interventions aimed at improving adherence to medications among adults with depressive disorders.

Methods: We searched Medline, EMBASE, The Cochrane Central Register of Controlled Trials (CENTRAL), PsycINFO, Social Science Citation Index and Science Citation Index for randomized or non-randomized controlled trials up to September 2019. Risk of bias was assessed using the criteria of the Cochrane Collaboration. Meta-analyses, cumulative and meta-regression analyses for adherence were conducted.

Results: Forty-five trials (n= 24,413) were included. Pooled estimate indicates an increase in the probability of adherence to antidepressants at 6 months with the different types of interventions (OR 1.28; 95% CI: 1.07 to 1.54). The improvement in adherence is obtained from 3 months (OR 1.57, 95% CI: 1.22 to 2.01) but it is attenuated at 12 months (OR 1.25, 95% CI: 0.99 to 1.53). Selected articles show methodological differences, mainly the diversity of both the severity of the depressive disorder and intervention procedures. Patients with depression and anxiety seem to benefit most from intervention (OR 2.77, 95% CI: 1.74 to 4.42) and collaborative care is the most effective intervention to improve adherence (OR 1.67, 95% CI: 1.17 to 2.40).

Conclusions: Our findings indicate that interventions aimed at improving short and medium-term adherence to medications among adults with depressive disorders are effective. However, the evidence on the effectiveness of long-term adherence is insufficient and supports the need for further research efforts.

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1. Introduction

Depression is a common mental disorder typically chronic, disabling and frequently comorbid that affects more than 260 million people every year (1) and causes considerable personal suffering and has great economic costs for Western societies (2).

Although pharmacological treatment of depressive disorders has shown a considerable efficacy, non-adherence to appropriately prescribed medications remains a major challenge in current clinical psychiatric practice that compromises the effectiveness of available treatments and interferes with patient recovery (3). The impact of non-adherence increases the likelihood of relapse and/or recurrence, emergency department visits, and hospitalization rates; increases symptom severity and decreases treatment response and remission rates (4). Non-adherence subsequently translates to an increase in medical and total healthcare utilization (4). Recent literature shows early adherence rates to prescribed medication for depression ranging between 74% and 82% (5, 6), but unfortunately, approximately 50% of patients prematurely discontinue therapy (7, 8).

Socio-demographic variables, such as age, positive attitudes to prescribed medication and previous experiences were found to be factors predicting better adherence. Conversely, experience of side effects, dissatisfaction with treatment and a poor patient–professional relationship were found to be associated with poorer adherence (9, 10).

Several interventions have been designed to improve medication adherence. Some evidence suggests that multifaceted interventions targeting the patient, physician and structural aspects of care are more effective than single-component interventions (11, 12).

The aims of the present study are to identify, critically assess and synthesize the available scientific evidence on the effectiveness of interventions aimed at improving adherence to medications among adults with depressive disorders.

2. Material Y Methods

A systematic review and meta-analysis were performed according to the Cochrane Handbook (13) and reported in accordance to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (14). The protocol of the present review has been registered in Prospero (CRD42017065723).

2.1. Information sources and search strategy

The following electronic databases were searched (September 2019): Medline (OVID interface), EMBASE (Elsevier interface), CENTRAL (The Cochrane Library interface), PsycINFO (EBSCO interface), SCI-EXPANDED (Web of Science interface) and SSCI (Web of Science interface). The search strategy was initially developed in Medline, using a combination of controlled vocabulary and free text terms and was then adapted for each of the other databases. Search terms included the following: depressive disorder, medication and adherence. Searches were limited to the English and Spanish languages and no date restriction was imposed. The full search strategy is available in Supplementary Material (see Supplementary Table 1). The reference lists of all included papers were also examined to identify possible additional studies meeting selection criteria.

2.2. Selection criteria

Studies were eligible for inclusion if they fulfilled the following criteria: 1) randomized controlled trials (RCTs) or non-randomized controlled trials (nRCTs), with allocation of both individuals and clusters; 2) any type of intervention aimed at increasing adherence to anti-depressive medications administered to adults (18–65 years) with a diagnosis of depressive disorder. If a study addressed a heterogeneous group of patients, the study was included as long as the results for patients meeting the inclusion criteria were reported separately or they accounted for more than 80% of the target population; 3) usual care or alternative intervention as comparison group; 4) studies assessing short-term (closest to 3 months), medium-term (closest to 6 months) or long-term (closest to 12 months) adherence to prescribed medication; 5) studies published in English or Spanish. Exclusion criteria included: 1) studies examining patients with bipolar depression or schizoaffective disorder; and 2) studies with fewer than 10 study participants.
2.3. Study selection process
Two reviewers addressed eligibility separately. Firstly, the title and abstract of references identified in the electronic search were screened. Secondly, the full text of the studies that appeared to fulfil the pre-specified selection criteria was read and evaluated for inclusion. Disagreements between reviewers were resolved through discussion with the research team until consensus was reached.

2.4. Data collection process
A data extraction form was prepared by the authors, pilot tested on two studies and refined accordingly. One reviewer extracted the following data from the included studies: identification of the article (author, date of publication, country), study objective and methodology (design, context, duration), details of participants (selection criteria and demographics), interventions (type, modality and number of sessions), comparators and outcomes (definition, measurement method), and finally results. A second reviewer subsequently verified the extracted data. When any required information was missing or unclear in a paper, an effort was made to contact the corresponding author.

2.5. Risk of bias assessment
Two reviewers independently and in duplicate assessed risk of bias of included studies using the Cochrane Risk of Bias tools for RCT (RoB 2.0) (15) with the additional guidance for cluster-RCT (16) and nRCT (ROBINS-I) (17). Discrepancies of judgments between the reviews were discussed by the research team until consensus was reached.

2.6. Assessment of publication bias
According to the recommendations of the Cochrane Collaboration (13), the presence of publication bias was assessed considering the size and sponsorship of the included studies, and by constructing a funnel plot and computing the Egger’s regression test using metafunnel and metabias commands in STATA version 14, respectively.

2.7. Analysis and synthesis of results
Meta-analyses and forest plots were performed for the adherence rate using the metan commands in STATA version 14. Effects of interventions were estimated as odd ratios (OR), with 95% confidence intervals (CI). Heterogeneity was assessed using the I² statistic. When there was heterogeneity (I² ≥ 25%), meta-analyses were performed using a random-effects model using the method of DerSimonian and Laird and taking the estimate of heterogeneity from the Mantel-Haenszel model. When there was neither clinical nor statistical heterogeneity, a fixed-effect model was used (18).

Several sources of heterogeneity relating to the characteristics of the study population and the interventions were anticipated. Predictive variables included age, gender, diagnoses, type of intervention, providers of the intervention (multidisciplinary vs. non-multidisciplinary team), modality of intervention (face-to-face vs. telephone, mails and/or website) and number of sessions. When reported in most studies, the effect of these study-level variables on the effectiveness closest to six months using subgroup analyses (diagnoses, type of intervention, providers of intervention and modality of intervention) and meta-regression techniques (age, gender, and number of sessions) were explored using the metareg command in STATA version 14.

Sensitivity analyses were conducted to assess the stability of the effects of excluding certain types of studies (n-RCT).

The evolution of evidence on the effectiveness of interventions aimed at increasing adherence to anti-depressive medications over time were explored using cumulative meta-analysis. Studies were sequentially added by year of publication to a random-effects model using the metacum user-written command in STATA version 14.

3. Results
Out of a total of 3,698 initially identified references after eliminating duplicates, 38 studies were selected after full-text screening (Fig. 1). The manual search provided seven additional studies, thus, 45 studies (published in 49 papers) were finally eligible for inclusion according to the pre-established selection criteria (19, 20, 29–38, 21, 39–48, 22, 49–58, 23, 59–67, 24–28).

3.1. Characteristics of included studies
The 45 included trials were published in English between 1976 and 2017 (Table 1). Thirty-two are individual-RCT (19, 22, 36–39, 42, 44–46, 48, 50, 23, 51–53, 56–61, 64, 24, 65–67, 25, 28, 32–35), eight are cluster-RCT (20, 26, 30, 40, 43, 53, 54, 63), four are individual-nRCT (31, 41, 47, 49), and one is cluster-nRCT (29). The duration of reported follow-up ranged from 4 to 76 weeks (median 32 weeks).
| Study Country | Design | Follow-up (w) | Sample | Age (years) Mean, (SD) | Gender (female) (%) | Diagnoses | Inclusion Criteria | Type | Modality | Nº of sessions | Duration (m) |
|---------------|--------|---------------|--------|------------------------|---------------------|------------|--------------------|------|-----------|----------------|--------------|
| Adler et al., 2004 | RCT | 16 | 533 | 268 | 265 | 42.3 (13.9) | 71.80 | MDD + PDD | ≥ 18 years | MDD and/or PDD (DSM-IV) | English reading comprehension |
| USA | | | | | | | | | | | |
| Akerblad et al., 2003 | Cluster RCT | 24 | 1,031 | 366 | 339 | 48.4 (14.36) | 28.10 | MDD | ≥ 18 years | MDD (DSM-IV) | SSRI prescription | Education + support (programme RHYTHMS) |
| Sweden | | | | | | | | | | | |
| Aljumah and Hassali, 2015 | RCT | 16 | 239 | 119 | 120 | 39.5 (NR) | 58.16 | MDD | 18–60 years | MDD (DSM-IV) | AD prescription |
| Saudi Arabia | | | | | | | | | | |
| Al-Saffar et al., 2008, 2005 | RCT | 20 | 300 | 100 | 100 | NR | 33.10 | MDD | ≥ 18 years | Unipolar depression (ICD-10) | TCA or SSRI prescription | Education + support |
| Kuwait | | | | | | | | | | |
| Browne et al., 2002 | RCT | 24 | 707 | 212 | 196 | 42.4 (NR) | 68.00 | PDD + MDD | 18–75 years | PDD ± MDD (DSM-IV) | Interpersonal psychotherapy |
| Canada | | | | | | | | | | |
| Capoccia et al., 2004 | RCT | 52 | 74 | 41 | 33 | 38.7 (13.5) | 57.00 | Depressive episode | ≥ 18 years | Depressive episode | New AD prescription | CCM |
| USA | | | | | | | | | | |
| Chang et al., 2014 | Cluster RCT | 24 | 915 | 503 | 411 | 46.03 (21.49) | 66.30 | MDD | ≥ 18 years; MDD; newly prescribed antidepressant; capable of self-management and understand English. | Monitoring and feedback to physicians about the patient’s symptom severity |
| USA | | | | | | | | | | |
| de Jonghe et al., 2001 | RCT | 24 | 167 | 83 | 84 | 34 (19–60) | 62.00 | PDD ± MDD | 18–60 years; DSM-III criteria MDD with or without dysthymia; 17-item HDRS ≥ 14; written informed consent. | Short Psychodynamic Supportive Psychotherapy |
| Netherlands | | | | | | | | | | |

*: Own estimation; **: data sent by email by authors; AD: Antidepressant; AG: Agoraphobia; Base: Baseline; CBT: Cognitive behavioural therapy; CCM: Collaborative care strategy; GAD: Generalized anxiety disorder; GP: General practitioner; IG: Intervention group; m: months; MDD: Major depressive disorder; MMAS: Morisky Medication Adherence Scale; MMSE: Mini-Mental State Examination; PC: Panic disorder; PDD: persistent depressive disorder or Dysthymic Disorder; Reminder APP: Medication reminder app; SDM: Shared decision making.
| Study                | Design | Follow-up (w) | Sample | Intervention                                                                 |
|---------------------|--------|---------------|--------|------------------------------------------------------------------------------|
| Desplenter et al.,  | Cluster | 52           | 99     | Tailoring counselling or counselling intervention                              |
| 2013                | NRCT   |               | 41     | MDD ≥ 18 years; MDD according to DSM-IV-TR criteria; antidepressant medicine; Dutch speaking; could be reached by telephone for follow-up |
| Belgium             |        | 58           | 46.10  | 62.60                                                                        |
| Dietrich et al.,    | Cluster | 24           | 405    | CCM                                                                          |
| 2004                | RCT    |               | 224    | MDD or PDD (DSM-IV)                                                          |
| USA                 |        | 181          | 42.0   | Patients who had a telephone                                                |
|                     |        |              | (20.80)*| Hopkins symptom checklist-20 score ≥ 0.5                                     |
| Gervasoni et al.,   | NRCT   | 2            | 131    | Monitoring and motivational support                                          |
| 2010                |        | 81           | 50     | Moderate or severe depressive episode                                        |
| Switzerland         |        |              | 36.24  | 59.54                                                                       |
|                     |        |              | (19–62)|                                                                              |
| Guo et al., 2015    | RCT    | 24           | 81     | Measurement-based care                                                       |
| China               |        | 44           | 37     | Moderate to severe MDD                                                       |
|                     |        |              | 41.10  | 64.16                                                                       |
|                     |        |              | (12.10)|                                                                              |
| Hammonds et al.,    | RCT    | 4            | 57     | Medication reminder app                                                      |
| 2015                |        | 30           | 27     | AD prescription                                                              |
| USA                 |        |              | 20.6   | English speaking                                                             |
|                     |        |              | (4.3)  | Patients who had an Android or iPhone smartphone                             |
| Interian et al.,    | RCT    | 20           | 50     | Motivational Enhancement Therapy                                             |
| 2013                |        | 26           | 24     | AD prescription                                                              |
| USA                 |        |              | 40.6   | Motivational Enhancement Therapy                                             |
|                     |        |              | (16.90)*| AD prescription                                                              |
| John et al., 2016   | RCT    | 6            | 39     | Educational                                                                   |
| India               |        | 17           | 22     | ICD-10 criteria; diagnosed by psychiatry residents and confirmed by a senior member; MDD ≥ 18 years; Mild depression, moderate depression or PDD. |
|                     |        |              | 34 (21–46) | 61.53                                                                      |

*: Own estimation; **: data sent by email by authors; AD: Antidepressant; AG: Agoraphobia; Base: Baseline; CBT: Cognitive behavioural therapy; CCM: Collaborative Care; GAD: Generalized anxiety disorder; GP: General practitioner; IG: Intervention group; m: months; MDD: Major depressive disorder; MMAS: Morisky Medication Adherence Scale; PC: Panic disorder; PDD: Persistent depressive disorder or Dysthymic Disorder; Reminder APP: Medication reminder app; SDM: Shared decision making.
| Study Country | Design | Follow-up (w) | Sample | Intervention |
|---------------|--------|---------------|--------|--------------|
| Katon et al., 2002 USA | RCT | 112 | 171 | NR | 18–80 years; new AD; ≥11 SCL-20 and > 4 DSM-IV or < 4 DSMIV and ≥ 11.5 SCL-20. |
| Katon et al., 2001 USA | RCT | 52 | 386 | 194 | MDD or PDD |
| Katon et al., 1999 USA | RCT | 24 | 228 | 114 | MDD or PDD |
| Katon et al., 1996 USA | RCT | 12 | 153 | 31 | 18–75 years |
| Keeley et al., 2014 USA | Cluster RCT | NR | 175 | 85 | Depression |
| Klang et al., 2015 Israel | nRCT | 24 | NR | 173 | Depressive episode |

*: Own estimation; **: data sent by email by authors; AD: Antidepressant; AG: Agoraphobia; Base: Baseline; CBT: Cognitive behavioural therapy; CCM: Collaborative Care; CCM: Generalized anxiety disorder; GP: General practitioner; IG: Intervention group; m: months; MDD: Major depressive disorder; MMAS: Morisky Medication Adherence Scale; PC: Panic disorder; PDD: Persistent depressive disorder or Dysthymic Disorder; Reminder APP: Medication reminder app; SDM: Shared decision making.
| Study Country | Design | Follow-up (w) | Sample | Intervention |
|---------------|--------|---------------|--------|--------------|
| Klutcher et al., 2002 Canada | RCT | 29 | 269 | 131 | 138 | NR | NR | MDD | MDD (DSM-IV) Contraceptive method in females of childbearing years. |
| LeBlanc et al., 2015 USA | Cluster RCT | 24 | 297 | 138 | 139 | 43.5 (43.54)* | 66.92 | Moderate to severe depression | ≥ 18 years Moderate/Severe depression PHQ-9 score ≥ 10 |
| Lin et al., 2003 USA | RCT | 52 | 386 | 194 | 192 | 46.0 (17.85)* | 26.40 | High risk for recurrent depression | 18–80 years AD prescription Improvement of depressive episode (≥ 4 DSM-III-R major depressive symptoms or 4 major depressive symptoms + SCL-20 score ≥ 1.5) High risk of relapse (≥ 3 lifetime depressive episodes or a history of dysthymia) |
| Lin et al., 1999 USA | RCT | 19 | 156 | 63 | 53 | 44.10 (13.60) | 81.00 | MDD | SCL-20 score ≥ 0.75; 18–80 years; AD |
| Mantani et al., 2017 Japan | RCT | 17 | 164 | 81 | 83 | 40.90 (NR) | 53.05 | MDD ± anxiety | 25–59 years; MDD without psychotic features (DSM-5 and PRIME-MD); antidepressant-resistant, BDI-II score ≥ 10 for ≥ 4 weeks; AD in monotherapy (not antipsychotics or mood stabilizers); smartphones users; being an outpatient; no plan to transfer within 4 months |
| Meglic et al., 2010 Slovenia | NRCT | 24 | 19 | 10 | 9 | 35.71 (12.11) | 86.00 | Depression or mixed anxiety and depression disorder | ICD10 group F32 or F41.2; first time or after a remission > 6 months; newly AD; internet and mobile phone; BDI-II score ≥ 14 |

*: Own estimation; **: data sent by email by authors; AD: Antidepressant; AG: Agoraphobia; Base: Baseline; CBT: Cognitive behavioural therapy; CCM: Collaborative Care Management; DP: Dysthymia; GP: General practitioner; IG: Intervention group; m: months; MDD: Major depressive disorder; MMAS: Morisky Medication Adherence Scale; PC: Panic disorder; PDD: Persistent Depressive Disorder or Dysthymic Disorder; Reminder APP: Medication reminder app; SDM: Shared Decision Making.
| Study Country                  | Design   | Follow-up (w) | Sample   | Intervention                                                                 |
|-------------------------------|----------|--------------|----------|-----------------------------------------------------------------------------|
| Mundt et al., 2001 USA        | RCT      | 30           | 246 124  | MDD (DSM-IV) Symptom duration of ≥ 1 month                                 |
|                               |          |              |          | AD prescription Hamilton Depression score ≥ 18                              |
| Myers and Calvert, 1984 UK    | RCT      | NR           | 120 40   | Depression, reactive or endogenous Dothiepin prescription                   |
| Myers and Calvert, 1976 UK    | nRCT     | NR           | 89 46    | 21–77 years ≥ Attack of primary depression, reactive or endogenous          |
|                               |          |              |          | Dothiepin prescription                                                     |
| Nwokeji et al., 2012 USA      | RCT      | 52           | 166 101  | MDD (DSM-IV) Hamilton Depression score ≥ 15                                |
| Perahia et al., 2008 11 European countries | RCT | 4           | 962 485  | ≥ 18 years MDD (DSM-IV) Hamilton Depression score ≥ 15                     |
|                               |          |              |          | Access to a telephone                                                       |
| Perlis et al., 2002 USA       | RCT      | 28           | 132 66   | MDD (DSM-III-R)                                                             |
|                               |          |              |          | CBT                                                                         |
| Pradeep et al., 2014 India    | Cluster RCT | 24       | 260 122  | Women ≥ 18 years MDD (DSM-IV-TR)                                            |
|                               |          |              |          | Education + support                                                         |
| Richards et al., 2016 UK      | Cluster RCT | 52       | 581 276  | ≥ 18 years Depressive episode (ICD-10)                                      |
|                               |          |              |          | CCM                                                                          |
| Study                      | Country | Design  | Follow-up (w) | Sample | Intervention                                                                 |
|---------------------------|---------|---------|---------------|--------|-------------------------------------------------------------------------------|
| Rickles et al., 2006, 2005| USA     | RCT     | 24            | 63     | 31                             | 32 | 37.6 (17.15)* | Depressive symptoms ≥ 18 years BDI-II score ≥ 16 Willingness to take AD | Education + monitoring |
| Salkovskis et al., 2006   | UK      | RCT     | 26            | 77     | 39                             | 38 | 40.5 (NR)     | Depressive disorder AD prescription and 17–70 years. | Self-help programme |
| Simon et al., 2011        | USA     | RCT     | 24            | 197    | 104                            | 93 | 45.5 (NR)     | Depressive disorder ≥ 18 years new AD; no AD ≥ 270 days before; online messaging | Support |
| Simon et al., 2006        | USA     | RCT     | 24            | 207    | 103                            | 104 | 43.0 (21.21)* | MDD or PDD New AD prescription | Support |
| Smit et al., 2005         | Netherlands | RCT     | 52            | 267    | 112                            | 72 | 42.8 (19.39)* | MDD 18–70 years MDD (DSM-IV) | Education |
| Vannachavee, 2016         | Thailand| RCT     | 6             | 60     | 30                             | 30 | 45.3 (22.70)* | MDD 18 years MDD (DSM-IV-TR) A new AD prescription Thai speaking | Educational, motivational and cognitive intervention |
| Vergouwen et al., 2009, 2005| Netherlands | Cluster RCT | 26          | 211    | 101                            | 110 | 43.0 (20.29)* | MDD ≥ 18 years MDD (DSM-IV) | Education + support + active participation in treatment process with discussion on AD |
| Wiles et al., 2014, 2013  | UK      | RCT     | 52            | 469    | 234                            | 235 | 49.6 (11.7)   | MDD + PD, social phobia or GAD 18–75 years AD prescription Patients' adherence to the prescribed AD Beck Depression Inventory score ≥ 14 | CBT |
| Wiles et al., 2008        | UK      | RCT     | 16            | 25     | 14                             | 11 | 45.3 (NR)     | Depressive disorder 18–65 years; AD; ≥ 15 BDI-II; positive Morisky-Green-Levine test; ICD-10 criteria. | CBT |

*: Own estimation; **: data sent by email by authors; AD: Antidepressant; AG: Agoraphobia; Base: Baseline; CBT: Cognitive behavioural therapy; CCM: Collabo Generalized anxiety disorder; GP: General practitioner; IG: Intervention group; m: months; MDD: Major depressive disorder; MMAS: Morisky Medication Adherence controlled; PC: Panic disorder; PDD: persistent depressive disorder or Dysthymic Disorder; Reminder APP: Medication reminder app; SDM: Share decision making.
Most of the studies enrolled patients with depression at different levels of severity. However, five studies required a combination of major depressive disorder with panic disorder, social phobia or generalized anxiety disorder, or anxiety (37, 46, 47, 53, 65, 66).

All the studies assessed individual interventions and used usual care as comparator. In general, the number of sessions or contacts of the interventions ranged from 1 to 20. A total of 11 studies assessed the effects of the Collaborative Care Model (CCM) consisting of the following four elements of collaborative care: 1) a multi-professional approach to patient care; 2) a structured management plan, included either or both pharmacological and non-pharmacological interventions; 3) scheduled patient follow-ups to provide specific interventions, facilitate treatment adherence, or monitor symptoms or adverse effects; and 4) enhanced inter-professional communication. Five studies assessed the effects of interventions with only an educational focus while six studies evaluated the effects of education and support, three of them used the RHYTHMS programme, a patient education programme which mails information directly to patients being treated with antidepressant medications in a time-phased manner. Education was also added to Cognitive Behavioural Therapy (CBT), CBT and motivational interview, coaching, monitoring and psychiatric consultation. Psychotherapy was another type of included intervention; in particular, six studies used CBT, one study included short psychodynamic supportive psychotherapy and one study included interpersonal psychotherapy. Other types of interventions were shared decision-making, support, counselling, the use of medication reminder applications for mobile phones, Enhanced Care and Treatment Initiation and Participation, an intervention aimed at modifying factors such as psychological barriers, concerns about treatment, fear of antidepressants and misconceptions of depression treatment.

Intervention modalities included face-to-face meetings alone (18 studies) or in combination with telephone conversations (2 studies), leaflets (1 study), videotapes (2 studies), mails (1 study) or website. Nine studies used telephone-conversations and two studies used the same intervention in combination with mails and one study combined the same intervention with letters. Moreover, leaflets were used in three while consultation of websites was included in two studies. Another intervention modality was the use of a smartphone (2 studies).

The intervention providers varied among studies: multidisciplinary teams (17 studies), primary care professionals - general practitioners, clinicians or internal medicine doctors (8 studies), pharmacists (6 studies); psychiatrists, psychologists or therapists (5 studies), nurses (2 studies), research assistant (1 study), and health worker (1 study). In the remaining studies, the providers were required to deliver intervention (2 studies) or not reported (1 study).

Twenty-three studies provided short-term (ranged from 4 to 16 weeks), 21 studies provided mid-term (ranged from 20 to 36 weeks), and seven studies provided long-term (ranged from 48 to 76 weeks) outcomes. The types of adherence measures included were: self-report (e.g., questionnaires, diaries or interviews); or other non-self-report measures (e.g., electronic measures, pill count or plasma drug concentration).

### 3.2. Risk of bias in the included studies

Out of the 40 RCTs identified, 3 were classified as having low risk of bias in all RoB 2.0 domains (24, 37, 58) see Table 2. In the remaining RCTs, the most common methodological concerns involved bias arising from the randomization generation and allocation concealment process (3 RCTs had a high RoB) and bias in measurement of the outcome (6 had a high RoB).
### Table 2
Risk of bias of included RCTs

| Cluster-RCTs | Study         | Domains                              | Effect of assignment to intervention | Missing outcome data | Measurement of the outcome | Selection of the reported result |
|--------------|---------------|--------------------------------------|--------------------------------------|----------------------|---------------------------|---------------------------------|
|              | Akerblad 2003 | High                                 | Low                                  | Low                  | Low                       | Some concerns                  | Low                             |
|              | Chang 2014    | Low                                  | Low                                  | Low                  | Low                       | Some concerns                  | Low                             |
|              | Dietrich 2004 | Some concerns                        | Low                                  | Low                  | Some concerns             | Low                             | Low                             |
|              | Keeley 2014   | Low                                  | Low                                  | Low                  | Some concerns             | Some concerns                  | Low                             |
|              | LeBlanc 2015  | Unclear                              | Low                                  | Low                  | Some concerns             | Some concerns                  | Low                             |
|              | Pradeep 2014  | Some concerns                        | Low                                  | Low                  | Some concerns             | Low                             | Low                             |
|              | Richards 2016 | Low                                  | Low                                  | Low                  | Low                       | High                           | Low                             |
|              | Vergouwen 2009, 2005 | Low | Low | Low | Some concerns | Some concerns | Low |

| Individually RCTs | Study            | Domains                              | Effect of assignment to intervention | Missing outcome data | Measurement of the outcome | Selection of the reported result |
|------------------|------------------|--------------------------------------|--------------------------------------|----------------------|---------------------------|---------------------------------|
|                  | Adler 2004       | Low                                  | Low                                  | Low                  | High                      | Low                             |
|                  | Aljumah & Hassali, 2015 | Low | Some concerns | High | Low | Low |
|                  | Al-Saffar 2008, 2005 | Low | Low | Some concerns | Some concerns | Low |
|                  | Browne 2002      | Low                                  | Low                                  | Some concerns        | Low                       | Low                             |
|                  | Capoccia 2004    | Some concerns                        | Low                                  | Low                  | Some concerns             | Low                             |
|                  | De Jonghe 2001   | Low                                  | Some concerns                        | Low                  | Some concerns             | Some concerns                  | Some concerns                  |
|                  | Guo 2015         | Some concerns                        | Low                                  | Low                  | Some concerns             | Some concerns                  | Some concerns                  |
|                  | Hammonds 2015    | Some concerns                        | Some concerns                        | Some concerns        | Low                       | High                            |
|                  | Interian 2013    | Some concerns                        | Low                                  | Low                  | Low                       | Low                             |
|                  | John 2016        | Low                                  | Low                                  | Some concerns        | High                      | Some concerns                  | Some concerns                  |
|                  | Katon 2002       | Some concerns                        | Low                                  | Some concerns        | Some concerns             | Some concerns                  | Some concerns                  |
|                  | Katon 2001       | Some concerns                        | Some concerns                        | Low                  | Some concerns             | Low                             |
|                  | Katon 1999       | Low                                  | Low                                  | Low                  | Low                       | Low                             |
|                  | Katon 1996       | Some concerns                        | Some concerns                        | Low                  | Some concerns             | Low                             |
|                  | Katon 1995       | Low                                  | Low                                  | Low                  | Some concerns             | Low                             |
|                  | Klutcher 2002    | Low                                  | Some concerns                        | High                 | Some concerns             | Low                             |
|                  | Lin 2012         | Some concerns                        | Low                                  | Low                  | Some concerns             | Low                             |

High: high risk of bias; Low: low risk of bias; Unclear: unclear risk of bias

RCTs: randomized controlled trials
Risk of bias was generally low-to-moderate across all identified n-RCTs, all presenting risk of bias in at least three domains (Table 3).

Table 3. Risk of bias of included n-RCTs

| Study                          | Bias due to confounding | Bias in selection of participants | Bias in classification of interventions | Bias due to deviations from intended interventions | Bias due to missing data | Bias in measurement of outcomes | Bias in selection of the reported result |
|-------------------------------|-------------------------|-----------------------------------|------------------------------------------|---------------------------------|-------------------------|---------------------------------|-------------------------------------------|
| Desplenter et al., 2013       | Moderate                | Low                               | Low                                      | Low                             | NI                      | Moderate                         | Moderate                                  |
| Gervasoni et al., 2010        | Serious                 | Low                               | Moderate                                 | Low                             | NI                      | Low                             | Low                                       |
| Myers and Calvert, 1976       | NI                      | NI                                | Low                                      | Low                             | Moderate               | Moderate                         | Moderate                                  |
| Klang et al., 2015            | Moderate                | Low                               | Low                                      | Low                             | Moderate               | Moderate                         | Moderate                                  |
| Meglic et al., 2010           | Moderate                | Low                               | Moderate                                 | Low                             | Moderate               | Moderate                         | Moderate                                  |

Serious: serious risk of bias; Moderate: moderate risk of bias; Low: low risk of bias

NI: No information; nRCTs: non-randomized controlled trials

3.3. Publication bias

No evidence of publication bias was found according to the funnel plot of the observed effect (Fig. 2) and the Egger’s regression test (P = 0.51).

3.4. Synthesis of results
Nevertheless, subgroup analyses indicate how other characteristics of the intervention may not help to enhance adherence. The modality of intervention and support for the usefulness of brief interventions or therapies to improve adherence to treatment. Moreover, the number of sessions was negatively related to adherence. Although it is not clear regarding the optimal number of sessions, this result provides healthcare provider and the health care delivery system, are more effective than single-component interventions to improve medication adherence (with previous literature and suggests that multifaceted interventions targeting all dimensions that affect medication adherence problems, i.e., the patient, the symptoms in adults with depressive disorders (effective than primary or mental healthcare teams. This finding supports the idea that collaborative care is not only clinically effective for the management of high risk for recurrent depression (I² = 70.00%) and major depressive disorder with or without dysthymic disorder (OR, 0.68, 95% CI: 0.30 to 1.50; p = 0.29; I² = 70.70%) were not statistically significant.

3.5.1. Diagnosis

Interventions aimed at improving adherence to medications when addressed to adults with depression at different levels of severity were associated with a significantly increased effect size (OR MDD or PDD and anxiety studies 2.77, 95% CI: 1.74 to 4.42; p < 0.01; OR High risk for recurrent depression 1.69, 95% CI: 1.13 to 2.54; p = 0.01; OR Major depressive disorder or dysthymic disorder 1.28, 95% CI: 1.06 to 1.55; p < 0.01; I² = 36.00%). However, pooled effect sizes of studies on patients with depressive symptoms (OR, 2.50, 95% CI: 0.86 to 7.31; p = 0.29; I² = NA%), depressive episode (OR, 0.88, 95% CI: 0.69 to 1.12; p = 0.29; I² = 0%), and major depressive disorder with or without dysthymic disorder (OR, 0.68, 95% CI: 0.30 to 1.50; p = 0.29; I² = 70.70%) were not statistically significant.

3.5.2. Type of intervention

In the case of CCM interventions, the pooled result showed a significant increase in adherence (OR 1.67, 95% CI: 1.16 to 2.21; p < 0.01; I² = 52.30%) compared to the control group. However, statistically significant differences were not found for other specific forms of intervention (see Supplementary Table 3).

3.5.3. Providers of the intervention

A multi-professional approach to patient care involving at least one primary care provider and another health professional (e.g., nurse, psychologist, psychiatrist or pharmacist) was associated with an increased effect size (OR 1.58, 95% CI: 1.11 to 2.25; I² = 60.20%). A non-multidisciplinary approach was not statistically significant (OR 1.15, 95% CI: 0.94 to 1.40; I² = 42.90%).

3.5.4. Modality of intervention delivery

Effect sizes did not significantly differ by the modality of intervention delivery used (see Supplementary Table 3).

3.5.5. Other sources of heterogeneity

The number of intervention sessions was related to adherence (β, -0.08; 95% CI: -0.14 to -0.01). However, none of the other sources of heterogeneity investigated (age and gender of participants) had an effect.

3.6. Cumulative meta-analysis of outcome at 6 months

By plotting the emergence of interventions aimed at improving adherence to medications over time (Fig. 4), it is unclear whether earlier trials meeting the inclusion criteria demonstrated a high degree of heterogeneity or a high percentage of negative results. There is a sufficient body of evidence to demonstrate a reliable, consistent and statistically significant benefit of interventions aimed at improving adherence to medications over usual care. In general, the overall effect size has remained relatively stable within an effect size between OR 1.14 and 1.56.

4. Discussion

Our findings support and confirm the notion that interventions aimed at improving adherence to medications among adults with depressive disorders are effective in improving short and medium-term outcomes in adherence. The evidence, when given using cumulative meta-analysis, shows that further trials are unlikely to overturn this positive result. However, it is possible to appreciate a small decline in effect size over time.

The evidence shows that collaborative care is effective in improving adherence. In this respect, a multi-professional approach to patient care was more effective than primary or mental healthcare teams. This finding supports the idea that collaborative care is not only clinically effective for the management of symptoms in adults with depressive disorders (68, 69), but could also have a major effect on improving adherence to treatment (Ho et al., 2016). This is in line with previous literature and suggests that multifaceted interventions targeting all dimensions that affect medication adherence problems, i.e., the patient, the healthcare provider and the health care delivery system, are more effective than single-component interventions to improve medication adherence (11, 12). Moreover, the number of sessions was negatively related to adherence. Although it is not clear regarding the optimal number of sessions, this result provides support for the usefulness of brief interventions or therapies to improve adherence to treatment.

Nevertheless, subgroup analyses indicate how other characteristics of the intervention may not help to enhance adherence. The modality of intervention and the provider profile were unrelated to effect size. Effectiveness is essentially similar in mail, website and/or telephone, and face-to-face interventions.
Computer support systems, mobile technologies, web-based e-mail or telephone-based assistance can be used for improving adherence to medication (70, 71). In this regard, these interventions may be available across different geographic areas and in different clinical settings (72).

Generally, it might be expected that patients with severe symptoms would have different treatment and support needs, and thus may profit from this type of interventions compared to patients with moderate or mild symptoms. However, the findings here show a weak association between severity of symptoms and adherence outcome. Several interventions are effective in improving adherence outcomes among patients diagnosed with depression and anxiety at the same time. Although effectiveness is also demonstrated in the cases of patients at high risk of recurrent depression and in patients with major depressive disorder or dysthymic disorder, the results do not present such high values. Other patient characteristics such as age or gender were unconnected to adherence outcome.

The main limitation of the present review is the methodological differences between studies, mainly the diversity of both intervention procedures and severity of depressive disorder of participants. Interventions aimed at improving medication adherence among adults with emotional disorders have been designed with varying levels of intensity. Consequently, the review here found significant between-study heterogeneity. Subgroup and meta-regression analyses have been used to explore some of the issues related to the diversity of interventions and patients that affect the magnitude of effectiveness. Finally, the systematic review was limited to studies written in English and Spanish.

Despite all these limitations, the comprehensive systematic review provided an assessment of the effectiveness of different types of interventions aimed at improving medication adherence among adults with emotional disorders, supported by meta-analyses, using cumulative meta-analysis, exploring important sources of heterogeneity and following rigorous and transparent methods.

The systematic review reported here shows that interventions aimed at improving short and medium-term adherence to medications among adults with depressive disorders are effective. Patients with depression and anxiety at the same time seem to benefit most from interventions and collaborative care is the best option to improve adherence. Compared with outcomes over the short and medium-term, the available evidence on the effectiveness of long-term adherence is insufficient and supports the need for further research efforts.

Declarations

Ethics approval and consent to participate: Not applicable

Consent for publication: Not applicable

Availability of data and materials: All data generated or analysed during this study are included in this published article and its supplementary information files.

Competing interests: The authors declare that they have no competing interests.

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Authors’ contributions:

BGrL and TP-S participated in the conceptualization, methodology, writing and the editing. CR-A, DB-Q, MT-M participated in the supervision, drafting and revision. MT-M also participated in the project administration. All authors read and approved the final manuscript.

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Figures

Figure 1

Flow diagram of the selection process of studies
Funnel plot – Potential publication bias
### Figure 3

Forest plots for effect of intervention on adherence rate

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| Ader (2004) | 1.62 (1.13, 2.34) | 2.75 |
| Aitcheson (2006) | 3.90 (1.24, 12.28) | 0.90 |
| Aitcheson (2005) | 2.92 (0.31, 9.41) | 0.88 |
| Aitcheson (2004) | 1.32 (0.36, 4.47) | 0.85 |
| Chang (2013) | 1.81 (1.79, 1.83) | 2.95 |
| de Jongh (2001) | 0.94 (0.37, 2.40) | 1.34 |
| de Jongh (2000) | 0.91 (0.37, 2.40) | 1.34 |
| Hammond (2010) | 1.86 (0.64, 5.45) | 1.09 |
| Interven (2010) | 1.86 (0.64, 5.45) | 1.09 |
| Karon (1999) | 2.72 (1.26, 5.89) | 2.06 |
| Karon (1998) | 4.46 (1.20, 15.60) | 2.49 |
| Karon (1997) | 1.47 (0.53, 4.08) | 1.17 |
| Karon (1998) | 2.43 (1.53, 3.87) | 2.44 |
| Karon (1997) | 1.68 (1.24, 2.29) | 2.58 |
| Marfell (2017) | 3.08 (1.27, 7.16) | 0.85 |
| Myers (1984) | 2.74 (0.46, 16.32) | 0.46 |
| Petruca (2014) | 0.92 (0.38, 2.40) | 0.43 |
| Richards (2016) | 0.50 (0.32, 0.93) | 2.29 |
| Rickels (2006) | 1.08 (0.59, 1.96) | 0.81 |
| Simon (2006) | 3.47 (0.57, 2.14) | 0.15 |
| Simon (2005) | 3.47 (0.57, 2.14) | 0.15 |
| Simon (2005) | 3.47 (0.57, 2.14) | 0.15 |
| Simit (2009) | 1.04 (0.31, 3.49) | 0.93 |
| Simit (2009) | 1.04 (0.31, 3.49) | 0.93 |
| Verghese (2005) | 16.34 (2.39, 192.07) | 0.01 |
| Wallis (2009) | 1.35 (0.52, 3.47) | 0.46 |
| Overall (I² = 64.9%, p = 0.000) | 1.57 (1.22, 2.01) | 39.31 |

### 6 months

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| Ader (2004) | 1.56 (1.08, 2.25) | 2.76 |
| Aitcheson (2006) | 1.97 (1.04, 3.76) | 2.82 |
| Aitcheson (2005) | 3.91 (0.90, 15.94) | 0.73 |
| Aitcheson (2004) | 1.75 (0.86, 3.59) | 0.73 |
| Borese (2002) | 0.98 (0.67, 1.46) | 0.79 |
| Capocci (2004) | 1.33 (0.45, 3.87) | 1.10 |
| Chang (2013) | 1.90 (1.09, 3.32) | 2.76 |
| de Jongh (2001) | 0.94 (0.35, 2.63) | 1.63 |
| de Jongh (2000) | 1.79 (0.91, 3.55) | 2.82 |
| Hammond (2010) | 2.93 (1.74, 4.84) | 0.99 |
| Karon (1999) | 2.60 (1.23, 5.52) | 2.58 |
| Karon (1998) | 1.85 (1.23, 2.86) | 2.68 |
| Karon (1997) | 0.80 (0.57, 1.16) | 2.10 |
| Kuclikiew (2002) | 0.85 (0.44, 1.61) | 1.91 |
| Leffler (2015) | 0.99 (0.80, 1.27) | 2.45 |
| Leffler (2015) | 0.93 (0.80, 1.09) | 2.24 |
| Perini (2002) | 0.94 (0.31, 2.91) | 1.60 |
| Perini (2002) | 0.90 (0.30, 2.79) | 1.48 |
| Simon (2011) | 3.77 (1.48, 9.49) | 1.98 |
| Simon (2009) | 0.51 (0.10, 2.50) | 1.57 |
| Simit (2006) | 0.99 (0.30, 3.25) | 1.30 |
| Simit (2006) | 1.00 (0.34, 3.26) | 0.92 |
| Verghese (2005) | 1.85 (0.95, 3.60) | 1.57 |
| Overall (I² = 67.0%, p = 0.000) | 1.28 (0.71, 2.26) | 43.05 |

### 12 months

| Study ID | OR (95% CI) | % Weight |
|----------|-------------|----------|
| Capocci (2004) | 1.04 (0.41, 2.63) | 1.31 |
| Karon (2001) | 1.72 (1.14, 2.56) | 2.63 |
| Karon (2001) | 1.72 (1.14, 2.56) | 2.63 |
| Keedey (2014) | 1.31 (0.71, 2.45) | 0.92 |
| Lin (1999) | 0.60 (0.36, 1.00) | 1.71 |
| Richards (2016) | 0.91 (0.58, 1.40) | 2.34 |
| Simit (2006) | 1.03 (0.56, 1.94) | 1.10 |
| Simit (2006) | 0.97 (0.49, 1.91) | 1.00 |
| Simit (2006) | 0.98 (0.38, 2.83) | 1.39 |
| Ward (2014) | 0.73 (0.39, 1.37) | 1.53 |
| Subtotal (I² = 13.2%, p = 0.302) | 1.23 (0.90, 1.65) | 17.64 |
| Overall (I² = 59.8%, p = 0.000) | 1.36 (1.19, 1.58) | 100.00 |

**Note:** Analyzed using the random-effects model.

Odd ratio (95% Confidence Interval)
Figure 4
Cumulative meta-analysis of studies ordered by year of publication

Supplementary Files
This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx
- SupplementaryTable2.docx
- SupplementaryTable3.docx
- SupplementaryTable4.docx