

Interventions to Increase Depression Treatment Initiation in Primary Care Patients: a Systematic Review

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INTRODUCTION: Nearly 50% of depressed primary care patients referred to mental health services do not initiate mental health treatment. The most promising interventions for increasing depression treatment initiation in primary care settings remain unclear.

METHODS: We performed a systematic search of publicly available databases from inception through August 2017 to identify interventions designed to increase depression treatment initiation. Two authors independently selected, extracted data, and rated risk of bias from included studies. Eligible studies used a randomized or pre-post design and assessed depression treatment initiation (i.e., ≥ 1 mental health visit or antidepressant fill) among adults, the majority of whom met criteria for depression. Interventions were classified as simple or complex and subclassified into intervention strategies that were graded for strength of evidence.

RESULTS: Of 9516 articles identified, we included 14 unique studies representing 16 (4 simple and 12 complex) interventions and 8 treatment initiation strategies. We found low to moderate strength of evidence for collaborative/integrated care (3 studies), treatment preference matching (2 studies), and case management (2 studies) strategies. However, there was insufficient evidence to determine the benefit of cultural tailoring (2 studies), motivation (alone, with reminders or with cultural tailoring (5 studies)), education (1 study), and shared decision-making strategies (1 study). Overall, we found moderate strength of evidence for complex interventions (8 of 12 complex interventions demonstrated statistically significant effects on treatment initiation).

DISCUSSION: Collaborative/integrated care, preference treatment matching, and case management strategies had the best evidence for improving depression treatment initiation, but none of the strategies had high strength of evidence. While primary care settings can consider using some of these strategies when referring depressed

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Received January 30, 2018 Revised April 26, 2018 Accepted June 25, 2018 Published online August 14, 2018 patients to treatment, our review highlights the need for further rigorous research in this area.

 $K\!E\!Y$ WORDS: depression; patient engagement/participation; primary healthcare.

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INTRODUCTION

Between 5 and 13% of primary care patients carry a diagnosis of depression, ^{1–3} contributing to morbidity and mortality. ^{4–10} Numerous efficacious treatments exist, ^{11–13} but nearly four in five depressed individuals worldwide fail to receive minimally adequate treatment. ¹⁴ Depression is under-recognized in primary care, contributing to low treatment uptake. ^{13,15} Yet, even when recognized, half of referred patients fail to attend psychotherapy visits ¹⁶ or fill their first prescribed antidepressant medication. Even collaborative care programs, a team-based approach to delivering depression treatment in primary care settings, face 50% no show rates for initial visits with depression care managers. ^{17–19}

Lack of depression treatment initiation in primary care, the de facto location of depression care for most adults, ²⁰ is concerning. ⁹ The process of engagement in depression treatment is a continuum of behaviors from intention to initiation to retention. Initiation is associated with treatment completion: as high as 40-60% of those who initiate therapy receive minimaly adequate treatment or complete a course according to some studies. 14,21 Prior reviews assessing mental health engagement interventions have focused on patient activation, attitudes, or communication strategies^{22,23} or included patients with mental illnesses other than depression. 23,24 Few systematic reviews have sought to identify interventions for increasing treatment initiation (≥ 1 mental health visit or antidepressant prescription fill),²⁵ particularly in depressed primary care populations. The purpose of this review is to identify interventions applicable to primary care settings that increase depression treatment initiation.

METHODS

Search Strategy

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA; Fig. 1), and the protocol was published on PROS-PERO (CRD42015026375). We searched Ovid MEDLINE, EMBASE, The Cochrane Library, CINAHL, and PsycINFO (Online Supplemental Table 1) for articles published from database inception to August 2017 to identify interventions seeking to increase depression treatment initiation. Search

syntax was developed in consultation with an information specialist (LF) and comprised all relevant subject headings and free text terms used to define depression, randomized controlled trials (RCTs), clinical trials, and treatment initiation. We identified additional articles by reviewing reference lists of relevant reviews and studies and by utilizing the Similar Articles feature in PubMed and the Cited Reference Search in Scopus. Sources of gray literature (e.g., OpenGrey database) were searched as well as registries of ongoing trials, dissertations, and conference abstracts. Eligible designs included RCTs or pre-post design studies.

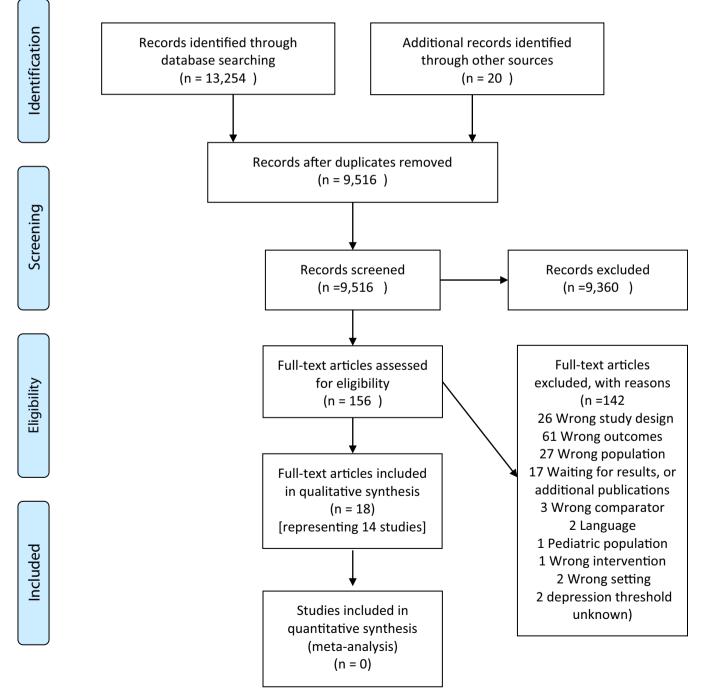


Figure 1 Cohort diagram of identification, screening, eligibility, and included studies.

Study Selection

Study inclusion criteria were (1) participants ≥ 18 years old; (2) relevant to primary care defined as interventions occurring in primary care, mixed primary and mental health, or community settings, including mental health settings with levels of complexity or contexts applicable to primary care and treatment initiation (e.g., a mental health clinic assessed the effect of a culturally tailored mental health booklet on treatment entry among patients scheduled for first time visits); (3) RCTs or pre-post study designs; and (4) depression treatment initiation outcome defined as attending ≥ 1 visit with a mental health specialist (including depression care managers, defined as social workers or nurses tasked with directly providing psychotherapy or managing medications) or filling ≥ 1 antidepressant prescription.²⁵ We excluded studies (1) with participants < 18 years old; (2) not designed to increase treatment initiation; (3) non-English language publication; (4) mental health settings targeting patients already in care; and (5) targeting a population in which < 60% of participants had clinical diagnoses of depression or elevated depressive symptoms on a screening tool. To adhere to a pragmatic approach, we included studies seeking to increase treatment initiation in populations with mixed psychiatric diagnoses so long as a majority of the study population had depression. We contacted authors to clarify the study population when unclear. Our information specialist (LF) conducted the initial database search; then, two authors independently screened titles and abstracts for relevant papers with discrepancies resolved by consensus with a third author (LF, CG, and NM) within Covidence software (Veritas Health Innovation, Melbourne, Australia). Two authors independently reviewed full text copies of the relevant abstracts and titles using pre-defined eligibility criteria, with a third author available to resolve discrepancies (LF, MO, NM).

Data Extraction

We developed a standardized data extraction form to ensure uniformity. Two authors independently extracted information on study characteristics (LF, MO), including study location; study design; eligibility criteria; depression assessment method; intervention components; follow-up time; number of participants enrolled (total, intervention, and control); and demographic characteristics (sex, age, race, ethnicity). We categorized interventions as simple or complex based on the number, difficulty or variability of interacting components, behaviors required by those delivering or receiving the intervention, groups or organizational levels, and outcomes and degree of flexibility or tailoring permitted. 26–28 Simple interventions had simple linear pathways between the intervention and outcome.²⁸ In addition, we categorized interventions as patient, provider, system, or multilevel based on level of randomization and intervention.²⁹ Discrepancies in data extraction were resolved through consensus with another reviewer (IK).

Outcome Measure

The primary outcome of interest was depression treatment initiation (i.e., attendance at ≥ 1 appointment with a mental health specialist or self-reported or objective antidepressant initiation such as pharmacy fill of first prescription (i.e., primary adherence)). The secondary outcome measures, if available, were treatment retention (e.g., number of visits, proportion of days covered by an antidepressant medication as calculated from refill data)³⁰ and mean change in depressive symptoms.

Assessment of Risk of Bias

Two authors independently assessed risk of bias utilizing the Cochrane Risk of Bias Tool for RCTs and the Quality Assessment Tool for Quantitative Studies for observational trials (MO, LF).^{31,32} We reviewed related method papers or contacted study authors when inadequate details were provided. Any discrepancies were resolved by consensus.

Data Analysis and Synthesis

Due to clinical and methodological heterogeneity and low numbers of similar studies, we decided post hoc not to conduct pooled quantitative analyses and synthesized data qualitatively. Two coders (NM, MO) independently grouped interventions into categories that reflected key intervention components (isolated from controls), using a previously developed classification model for engagement strategies that focuses on information, activation, and collaboration at patient and provider levels,³³ and guided by prior systematic reviews on behavioral interventions.³⁴ We enlisted one author to achieve consensus (IK). "Motivation" strategies included motivational interviewing, patient activation, or other behavioral interventions (i.e., goal setting). Finally, we graded the strength of evidence (SOE) for each intervention strategy on treatment initiation, retention, medication adherence, and depressive symptoms per an Agency for Healthcare Research and Quality and Effective Healthcare Program protocol; the grade incorporated four key considerations to determine strength of a stated effect: risk of bias (including study design and aggregate quality), consistency, direction, and precision across studies testing a particular strategy or intervention type (i.e., simple or complex) on a particular outcome (e.g., initiation).³⁵

RESULTS

Initial database search yielded 9516 unique references. Subsequent screen of the titles and abstracts for relevant papers resulted in 156 potentially relevant papers for full text review and 18 papers that met inclusion criteria representing 14 unique studies in this review (Fig. 1, Online Supplemental Table 2).^{25,30,36–51} We excluded two studies because they included mixed psychiatric disorders but no description of whether the majority of participants were depressed.^{52,53}

Study Characteristics

Studies were published between 2000 and 2016, with the majority (n = 12) conducted in the USA. Of the 14 unique studies, 4 recruited patients from community settings (e.g., electoral roll, managed care beneficiaries), 42,44,45,50 2 recruited patients from both primary care and mental health clinics, 38,40,41,46 6 from primary care or outpatient or community health settings, ⁴⁸ and 2 from mental health clinics with interventions highly applicable to the primary care setting. 36,49 Sample sizes ranged from 42 to 2022 participant; mean participant age ranged from 35 to 83 years. Depression diagnosis eligibility was determined using a structured interview (n = 4), 36,37,39,43,47,50 validated depression screening tools (e.g., Center for Epidemiologic Studies Depression Scale [CESD] or Patient Health Questionnaire [PHQ]-9) (n = 7), 30,38,40,41,44,46,48,49,51 a combination of interview and validated screening tool (n = 2), 25,45 and psychological distress tools (n = 1) (Table 1).⁴²

There was 1 pre-post design, 1 pre-post design within an RCT, ^{46,48} and the remainder were RCTs. ^{25,30,36–47,49–51} For studies presenting multiple follow-up periods, we used the minimum follow-up time to isolate intervention effect on treatment initiation. The minimum follow-up time ranged from 4 to 48 weeks; 2 did not clearly report follow-up times (Table 1). ^{48,49}

Outcome Measures

There was some variability in the definition of treatment initiation. Studies reported ≥ 1 therapy visits (mental health, psychiatry, psychology or counseling visits; n=7), 36,38,40,41,49,46,48,50,51 medication use (n=1), 30 a composite of therapy or medication (n=1), 25 or separately reported therapy and medication (n=4). $^{37-42,44}$ One study comparing the effect of treatment preference matching vs. mismatching (n=1) used refusal of randomization after participant notification of study arm as a proxy for treatment non-initiation (a primary outcome). 45 Treatment retention outcomes included percent of visits attended, 45 mean number of visits attended, 34,36,38,40,41,49 proportion of days covered (PDC) by antidepressant, 30,34 and treatment completion (Table 1). 44 Change in depression symptoms was assessed as an outcome by 8 trials (Online Supplemental Table 2).

Risk of Bias

We report risk of bias for all 18 papers representing 14 unique studies (Fig. 2, Online Supplemental Fig. 1). Overall, the prepost trial by Lara (2003) had a weak global rating⁴⁶ according to the Quality Assessment Tool for Quantitative Studies.³¹ Of the remaining RCTs, only one had low risk of bias³⁹ according to the Cochrane tool. Seven did not clearly report a randomization method.^{25,36,38,41,43,47,50} All displayed moderate to high bias related to blinding participants or personnel and 5 clearly reported blinding of outcome assessors (Fig. 2, Online Supplemental Fig. 1).

Effect of Interventions on Outcomes

Overall, 14 studies assessed 16 interventions (i.e., 2 studies assessed 2 interventions)^{42,51} comprising 4 simple and 12 complex interventions. Overall, 2 of 4 (50%) simple interventions and 8 of 12 (67%) complex interventions reported a statistically significant difference in depression treatment initiation between intervention and control. By definition, simple interventions were patient level while complex interventions comprised both patient and multi- (i.e., system or provider and patient) levels; 6 of 11 patient-level interventions (55%) reported statistically significant differences compared to 4 of 5 multilevel (80%) interventions^{30,37–41,43,47,48} (Table 1).

Our qualitative analyses identified 8 distinct treatment initiation strategies: case management, collaborative/integrated care, cultural tailoring, education, motivation, motivation and reminders, motivation and cultural tailoring, and treatment preference matching. Case management sub-strategies included appointment facilitation, motivation, and education with or without preference matching. Collaborative/integrated care sub-strategies included preference matching and onsite access with or without motivation and education. Below, we provide a summary of strategies organized by simple or complex interventions.

Simple Interventions

Patient Level. Cultural Tailoring. There was no difference in treatment entry between Black patients randomized to receiving targeted educational material about mental health and stigma and those receiving general mental health information (Table 1).³⁶

Motivation. Delgadillo's (2015) mailed theory-based orientation leaflet addressing expectations and barriers did not significantly differ from a mailed appointment confirmation in improving low-intensity cognitive behavioral therapy (CBT) initiation (48/81 (54%) vs. 60/91 (66%)) (Table 1).

Treatment Preference Matching. Kwan (2010) and Raue (2009) matched (vs. mismatched) treatment allocation and preference (therapy or antidepressants), demonstrating significantly improved initiation of assigned treatment that matched preference (26/26 (100%) vs. 37/44 (84%)⁴⁵ and 29/29 (100%) vs. 23/31 (74%)).²⁵ Kwan (2010) demonstrated improvement in proportion of therapy visits attended and dropout rates, but neither study found significant improvement in depressive symptoms (Table 1, Online Supplemental Table 2).

Complex Interventions

Patient Level. Case Management. Kim (2011) found that a telephone case management outreach program that facilitated appointments, referrals, provided appointment reminders, education, engagement, and monitoring of progress for

Table 1 Study Characteristics for Systematic Review of Depression Treatment Initiation Interventions

Study	Theme (level)* (main theme and subthemes isolated compared to control)	Study characteristics (mean age; % Black, % Hispanic % female; depression scale)	Setting (follow-up time for outcome)	Intervention vs. Control	Intervention outcome, frequency (%)	Control outcome, frequency (%)	Effect size, OR (95% CI)	Visit attendance (mean number visits (SD) or % visits attended)
Simple interv Alvidrez (2009)	rentions (Boldface i Cultural tailoring	f p<0.05) 44.8 years; 100%B; 69%F; DSMIV	Mental health clinic (12 weeks)	Targeted educational booklet vs. general	Psych visit 17/22 (76%)	Psych visit 14/20 (71%)	NR	4.9 vs. 4.6
Delgadillo (2015)	Motivation	40 years, 58%F, 40.6 (14.9) years; PHQ9	Primary care IAPT, England (6 weeks)	information Orientation leaflet on expectations, normalize concerns vs. mailed confirmation	Psych visit 44/81 (54%)	Psych visit 60/91 (66%)	B = -0.18 (0.85); AOR = 0.85	Complete 58% vs. 71%; <i>N</i> = NR
Kwan (2010)	Treatment preference matching	38.4 years; 4%B; 7%H; 64%F; DSMIV/BDI- II/HRSD	Community (telephone screening) (16 weeks)	Match to preference for meds or therapy vs. mismatch vs. no preference	Any Tx 26/26 (100%) [†]	Any Tx 37/44 (84%) [†] vs. 31/36 (86%) [†]	$X^2 = 4.60,$ p = 0.03 NR	% visits: 89% vs. 70% vs. 85%
Raue (2009)	Treatment preference matching	51.2 years; 20%B; 40% H; 78%F; DSMIV/HRSD	Ambulatory care clinics (12 weeks)	Match to preference for meds or therapy vs. mismatch	Any Tx 29/29 (100%)	Any Tx 23/31 (74%)	OR = 5.3 (4.3–6.3)	Reported as "Null"
Complex inte								
Kim (2011)	Case management (appointment, education, motivation, reminder)	35 years; 12%B; 33% H; 90%F; K6/QIDS-SR	Medicaid managed care beneficiaries (48 weeks)	Phone calls to facilitate appointments, engage, educate vs. mailed mental health provider list	Any Tx 42/ 234 (19%) [‡] Psychiatry 18/234 (12%) Psy- chology 30/234 (15%) Med 53/234 (27%)	Any Tx 31/ 242 (17%) [‡] Psychiatry 10/242 (7%) Psychology 20/242 (12%) Med 42/242 (27% reported)	OR = 1.51 (1.00– 2.28) OR = 1.90 (1.08– 3.35) OR = 1.66 (1.06– 2.61) OR = 1.34 (0.88– 2.11)	3.6 (2.2) vs. 2.1 (2.0)
Sirey (2016)	Case management (appointment, motivation, preference)	Intervention: 82.9 years; 61%F; 21%B control: 81.0 years; 82%F; 31%B SCID DSMIV	Homebound community dwelling (24 weeks)	Refer acc/ preference, cost; assess barriers, goals; MI; educate vs. recommend provider and educate (6 home visits and 2 calls)	Any Tx 60/81 (74%) [‡]	Any Tx 45/80 (56%) [‡]	AOR = 2.4 (1.17–4.93)	NR

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Medicaid-managed care beneficiaries (vs. providing a list of behavioral providers) did not significantly improve receipt of any mental services or antidepressant use or depressive symptoms but did improve psychiatry visits (18/234 (12%) vs. 10/242 (7%); OR = 1.90, 95%CI 1.08–3.35) and mean number of visits (Table 1; Online Supplemental Table 2). 44 Sirey (2016) evaluated a case management program for elderly depressed adults qualifying for a home meal program, which focused on patient preference matching, patient activation, education, and treatment options. Both intervention and attention control arms received 6 in-home visits and 2 follow-up calls (60/81 (74%) vs. 45/80 (56%), OR = 2.40 95%CI 1.17–4.93]). 50

Motivation/Education. An Internet-delivered CBT and activation intervention (vs. Internet-delivered depression literacy; *education*) both accompanied by weekly calls × 5 weeks (vs. attention control phone calls only) improved reported CBT use (35/121 (29%) vs. 15/136 (11%) vs. 12/157 (8%)) but not medication use or counselor or psychologist help seeking (18% vs. 10% [OR = 1.93, 95%CI = 0.94–3.98] vs. 16%) (Table 1). ³⁰ By consensus, we categorized this as "motivation" and as effective, though the site may have improved perception of receiving online CBT (via access and reminders) but not help seeking behavior. Both internet-delivered *motivation* and *education* significantly improved

Table 1. (continued)

Study	Theme (level)* (main theme and subthemes isolated compared to control)	Study characteristics (mean age; % Black, % Hispanic % female; depression scale)	Setting (follow-up time for outcome)	Intervention vs. Control	Intervention outcome, frequency (%)	Control outcome, frequency (%)	Effect size, OR (95% CI)	Visit attendance (mean number visits (SD) or % visits attended)
Arean (2005) [§] Arean (2007)	Collaborative/ integrated care (education, motivation, preference, onsite) (mult- level)	71.2 years; 12%B; 8%H; 65%F; SCID DSMIV	Primary care clinic (IMPACT Trial) (12 weeks)	Collaborative care vs. usual care	Any Tx Not poor 500/627 (80%) Poor 208/279 (75%) Psych visit and Med#	Any Tx Not poor 319/598 (54%) Poor 162/297 (55%) Psych visit and Med [#]	AOR = 4.18 (3.09– 5.65) AOR = 2.99 (2.02– 4.44)	NR
Bartels (2004), Ayalon (2007) [§] , Arean (2008)	Collaborative/ integrated care (onsite, preference) (multilevel)	73.5 years; 25%B; 15%H; 26%F; MINI/CESD	VA primary and mental health (10 PRISM-E Study sites) (24 weeks)	Integrated Care (onsite, expedite appts, trained specialist communicates with PMD ± brief alcohol intervention) vs. enhanced referral (help cost, transport, expedite appts)	Med 709/999 (71%)	Med 499/1023 (49%)	OR = 2.57 (2.14– 3.08)	3.04 (3.7) vs. 1.91 (3.6)
Wells (2000), Jacoux (2003)	Collaborative/ integrated care (education, motivation, onsite, preference) (multilevel)	43.7 years; 7%B; 29%H; 72%F; CIDI	Primary care clinic (24 weeks)	Video; pamphlets; nurses and providers trained in activation, therapy (QI therapy) or med management (QI med) vs. usual care	Any Tx 51% (48%–54%) Psych visit 38% (35%–41%) Med 35% (32%–38%) (N=913; adjusted %, frequencies NR)	Any Tx 40% (36–44%) Psych visit 26% (22–30%) Med 25% (21–29%) (N = 443; adjusted %, frequencies NR)	t = 3.50, p < 0.001 t = 3.99, p < 0.001 t = 3.38, p < 0.001	2.5 vs. 2.9 vs. 2.2
Yeung (2010)	Cultural tailoring (multilevel)	49 years; 0%B; 0%H; 68%F 100% Chinese; Chinese- PHQ9, HAMD17	Community health center (weeks N/A)	Pre-post Chinese PHQ9 and culturally tailored contact and psychiatric evaluation prior to collaborative care RCT	Psych visit 100/233 (43%)	Psych visit 19/296 (7%)	NR	NR
Christensen (2006)	Education	36.8 years; 73%F; Kessler Psychological Distress Scale	Community electoral in Australia (5 weeks)	5-week depression information website vs. attention control (both phoned)	Psych visit 15/136 (11%)* Med 38/136 (28%)	Psych visit 12/157 (8%)* Med 40/157 (26%)	OR = 1.50 (0.68– 3.33) OR = 1.14 (1.89– 0.68)	NR
	Motivation	36.8 years; 73%F; Kessler Psychological Distress Scale	Community electoral in Australia (5 weeks)	training vs. depression information websites (both phoned with prompts)	Psych visit 35/121 (29%)* Med 30/121 (25%)	Psych visit 15/136 (11%) [#] Med 38/136 (26%)	OR = 3.28 (1.69– 6.38) OR = 1.85 (0.49– 1.48)	NR

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CESD measured depressive symptoms compared to control (Mean difference: -4.5 [-7.3 to -1.8] and -3.6 [-6.3 to -1.0], respectively) (Online Supplemental Table 2).

Motivation and Reminder. A second intervention by Delgadillo (2015) found that mailed theory-informed

leaflets with text reminders (56/82 (68%)) were no more effective than appointment confirmation (60/91 (66%)) or leaflets alone (see simple motivation strategy above), with no significant effects on number of attended visits (Table 1; Online Supplemental Table 2).⁵¹ A trial involving a letter confirmation and phone reminder

Table 1. (continued)

Study	Theme (level)* (main theme and subthemes isolated compared to control)	Study characteristics (mean age; % Black, % Hispanic % female; depression scale)	Setting (follow-up time for outcome)	Intervention vs. Control	Intervention outcome, frequency (%)	Control outcome, frequency (%)	Effect size, OR (95% CI)	Visit attendance (mean number visits (SD) or % visits attended)
Lara (2003)	Motivation and cultural tailoring	35.3 years; 100%F; CESD, DSMIII	Primary/ mental health, Mexico (16 weeks)	Pre-post 6 group sessions (education, self-management, culture and gender tailored) vs. 20-min explanation and educational material	Psych visit: $23/107$ (22%) ($N=179$ preintervention; $N=107$ post)	Psych visit: $8/47$ (17%) $(N = 75 \text{ preintervention}; N = 47 \text{ post})$	$X^2 = 0.176,$ p = 0.67	NR
Zanjani (2008)	Motivation and reminder	53 years; 63%B; 3%H; 4%F; PHQ9	VA primary care confirm eligible by behavioral health lab	1–2 brief motivational and reminder call by behavior specialist, letter, and auto reminder vs. letter and auto reminder	Psych visit 40/57 (70%)	Psych visit 18/56 (32%)	$X^2 = 0.16,$ p < 0.001	3 (3) vs. 2 (3)
Delgadillo (2015)	Motivation and reminder	40 years, 58%F, 40.6 (14.9) years; PHQ9	Primary care IAPT, England (6 weeks)	Theory-based orientation leaflet on expectations and normalize concerns and 48-h text reminder vs. mailed confirmation	Psych visit 56/82 (68%)	Psych visit 60/91 (66%)	B = -0.06 (0.72), AOR = 0.95	Complete Tx 74 vs. 71%; $N = NR$
Le Blanc (2016)	Shared or clinical decision-making and education (multilevel)	Intervention 43.2 years; 72%F control 43.9 years; 62%F; PHQ9	Primary care; cluster RCT of clinicians and patients (4 weeks)	Provider- directed decision aid and education vs. education only	Med: 142/ 158 (90%) filled Rx: 94/ 109 (86%) (if pharmacy available)	Med: 110/ 139 (79%) filled Rx: 82/88 (93%) (if pharmacy available)	NR	> 80% of days covered (95 vs. 98%)

^{*}Unless otherwise specified, all levels were at the patient level

Abbreviations: SCID DSMIV, Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders; CIDI, Composite International Diagnostic Interview; HRSD, Hamilton Rating Scale for Depression; CESD, Center for Epidemiologic Studies Depression Scale; QIDS, Quick Inventory of Depressive Symptomatology; GHQ, General Health Questionnaire; PHQ-D or 9, Patient Health Questionnaire; Psych, psychiatry or psychology, specifically entering or attending at least psychiatry- and psychology-related visit (including CBT and psychotherapy); Med, antidepressant medication; MI, motivational interviewing, motivation connotes motivational interviewing, empowerment, behavioral support, patient activation, and other motivational constructs (e.g., barriers assessment, concerns, outcome expectancy, goal setting); MH, mental health; Tx, treatment; N/A, not applicable; NR, not reported

coupled with a brief (<15 min) motivational phone call before appointments and after no shows significantly improved psychiatry attendance (vs. letter and reminder only) (40/57 (70%) vs. 18/56 (32%)) and total number of appointments.⁴⁹

Motivation and Cultural Tailoring. Lara (2003) found no effect of a pre-post intervention of six 2-h group-based, culturally sensitive, educational sessions about depression and treatment options specific to women (vs. brief education session). 46

Treatment initiation was extrapolated from refusal of randomization after participated notified of the match vs. mismatch status

[‡]Includes any mental health provider visit including primary care provider or visit for medication

^SArean (2005) reports same intervention effects but by race: Psych visit: White 45% (41–48%) vs. 18% (15–21%); Black 41% (30–51%) vs. 12% (5–19%); Medication: White 65% (62–68%) vs. 18% (15–21%); Black 55% (40–58%) vs. 49% (40–58%). Ayalon (2007) assesses intervention at one site with similar findings but more effective in Blacks than Whites

^{||}Results for medication only and therapy only are similar and significant

Results for those not on appropriate treatment at baseline are nearly identical but frequencies by intervention arm are not provided

^{**}Asked whether CBT used in last 2 months; also asked sources of help which included family friends, GP, and counselor/psychologist. For seeking help from counselor/psychologist: (CBT website vs. educational website vs control: 18 vs. 10 vs. 16%; OR = 1.93, 95% CI 0.94–3.98; OR = 1.01 95% CI 0.58–1.76)

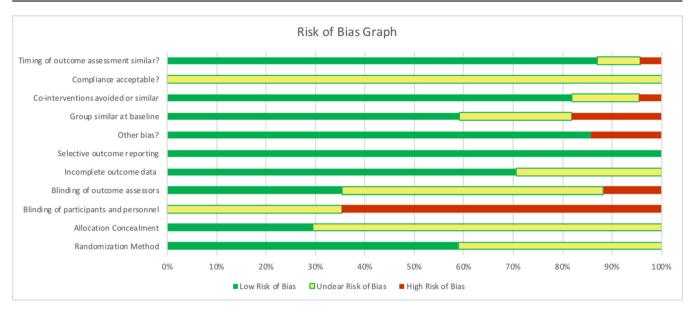


Figure 2 Risk of bias assessments.

Multilevel. Collaborative or Integrated Care. Among patients with substance abuse or depression, Bartels (2004) compared having onsite licensed mental health or substance abuse specialists who communicated with primary care providers and offered brief alcohol treatment options vs. transportation and cost assistance only (both with 2-4-week expedited appointments) and found significant improvement in mental health visit attendance (709/999 (71%) vs. 499/1023 (49%); OR = 2.57, 95% CI 2.143.08)^{38,40,41} but not depressive symptoms³⁸ (Table 1, Online Supplemental 2). Wells (2000) and Jaycox (2003) found that a locally tailored quality improvement (QI) intervention that trained onsite nurses to educate and motivate providers and patients and provide medication management (QI Med) or counseling (QI Therapy) (vs. usual care) significantly improved receipt of any mental health treatment (51% [48–54%] vs. 40% [36–44%]) and depressive symptoms ^{43,47} as well as treatment completion rates. 43 Arean (2005, 2007) found that onsite depression care managers who provided motivation, therapy, medication management, and treatment preference matching improved use of therapy, medications, and depressive symptoms across income and racial groups. 37,39

Cultural Tailoring. Tailoring a community health clinic's collaborative care program to include Chinese-language PHQ-9s and culturally sensitive psychiatric assessments and referrals resulted in pre-post clinic level increase in treatment initiation from 19/296 (7%) to 100/233 (43%).⁴⁸

Shared or Clinical Decision-making and Education. Le Blanc (2016) demonstrated that giving providers an antidepressant decision aid with an instructional session reduced patients' decisional conflict and improved satisfaction with

treatment decisions, but not antidepressant initiation (142/158 (90%) vs. 110.139 (79%)) or depressive symptoms.³⁰

Strength of Evidence

We found moderate strength of evidence (SOE) for improving depression treatment initiation through collaborative/integrated care interventions (complex intervention) (3 of 3 studies reported statistically significant results for "any treatment initiation") (Table 2, Online Supplemental Table 3). Due to small sample sizes and risk of bias, we found low SOE for treatment preference matching (simple intervention) (2 of 2 studies beneficial). There was moderate SOE for the benefit of case management: Kim 2011 showed a trend toward benefit (OR = 1.51, 95%CI 1.00-2.28) and Sirey (2016) (which added a treatment preference matching component) showed benefit (AOR = 2.40, 95%CI 1.17-4.93) but effect sizes and direction were consistent, suggesting overall benefit. For therapy outcomes only, there was insufficient evidence for motivation alone, cultural tailoring, and motivation with reminders (all had 1 beneficial, 1 null trial). There was insufficient (1 trial each) for case management, education, motivation with cultural tailoring, and shared decision-making across outcomes. In exploratory analyses, we found that the majority of interventions employed ≥1 motivational strategy; 6 of 9 showed benefit (all of which were complex and individualized). Excluding four high-risk trials resulted in insufficient evidence for treatment preference matching and insufficient evidence for the effect of collaborative care studies on "any treatment" and medications.

Table 2 Strength of Evidence for Engagement Strategies by Intervention Outcome

Engagement strategy	Outcome*							
	Initiated any depression treatment	Attended ≥ 1 mental health visit	Initiated antidepressant	Persisted with depression treatment	Depressive symptoms			
Case management* (appointment facilitation and education and motivation with or without reminders or treatment preference matching) $(n = 2)$	M (1 benefit, 1 no benefit both with + effects)	I (single RCT benefit)	I (single RCT benefit)	I (single RCT benefit)	I (single RCT no benefit)			
Collaborative care (onsite access, treatment preference matching with or without motivation or education) $(n=3)$	M (+)	M (+)	M (+)	M (+)	M (+)			
(n=3) Cultural tailoring $(n=2)$		I (smaller [n = 42] pre-post intervention showed no benefit; larger, pre-post complex intervention showed benefit)		I (single small pre-post no benefit)	I (single pre-post no benefit)			
Education $(n = 1)$ Motivation $(n = 2)$		I (single RCT no benefit) I (complex website benefit, simple leaflet	I (single RCT no benefit) I (single RCT no benefit)		I (single RCT benefit) I (single complex			
Motivation and cultural tailoring $(n = 1)$ Motivation and reminder $(n = 2)$		no benefit) I (single pre-post no benefit) I (motivational calls benefit; leaflet no benefit; both small trials)		I (motivational calls benefit; leaflet no benefit)	RCT benefit)			
Shared/clinical decision-making and education $(n = 1)$ Treatment preference matching $(n = 2)$	L (+)	,	I (single RCT no benefit)	I (single RCT no benefit) I (1 benefit, 1 no benefit)	I (single RCT no benefit) L (-)			
Complex interventions $(n = 8)$	M (+)	M (+)	I (3 benefit, 3 no benefit)	M (+)	M (+)			
Simple interventions $(n = 6)$	L (+) (preference)	L (-)	no ochent)	L (-)	I (single pre-post trial no benefit)			

Definitions of grades of overall strength of evidence: High, high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect; Moderate, moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate; Low, low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate; Insufficient, evidence either is unavailable or does not permit estimation of an effect. Most of which were due to the fact that only one study was included above; (+), benefit for outcome (p < 0.05); and (-), null for outcome

https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/methods-guidance-grading-evidence methods.pdf

DISCUSSION

We identified 16 (4 simple and 12 complex) interventions representing 8 strategies for increasing depression treatment initiation in primary care. A greater proportion of complex (8 of 12), including multilevel (4 of 5), interventions reported statistically significant effects on treatment initiation than simple patient-level (2 of 4) interventions. Further, we found low to moderate strength of evidence for benefit of complex interventions and for collaborative/ integrated care, case management, and treatment preference matching strategies. We found insufficient evidence for education, motivation (alone, with reminders or with cultural tailoring) and shared decision-making. Although our primary outcome of interest was treatment initiation, we also found moderate strength of evidence for complex, particularly collaborative care, interventions on treatment retention, and depressive symptom outcomes.

Barriers to initiating depression treatment when offered have been attributed to factors such as stigmatization, 55,56 low self-efficacy, 7 and poor access to care. Treatment engagement research has sought to target these barriers, but often focuses on improving intermediate outcomes such as self-reported intention or provider behaviors (e.g., referral rates), 9 and less often on actual depression treatment initiation. Identifying effective engagement strategies is essential to optimizing the effectiveness of depression treatment. 61

Our study confirms that collaborative/integrated care, long shown to be effective in improving depression treatment and depressive symptoms in primary care settings, ^{9,62–65,66,67,68} is an important complex, multilevel strategy for increasing treatment initiation. We also found some evidence that case management, another complex but patient-level strategy, may improve treatment initiation, similar to its effect on other health behaviors. ³⁴ Our review adds to the literature by highlighting

promising active ingredients within these programs. All collaborative/integrative care interventions employed treatment preference matching or onsite access, with the later more effective than simply facilitating appointments, transportation and costs. Treatment preference matching, even alone, appeared to be an effective approach to increasing treatment initiation. Despite the importance of eliciting patient preference, providers often mismatch treatment (e.g., prescribing antidepressants in those preferring psychotherapy). Higher quality studies will be integral to establishing the benefit of patient preference matching alone and the degree to which it is a key ingredient of case management and collaborative care. To

We further highlight several strategies that warrant further study, such as cultural tailoring, motivation, and shared decision-making. Shared decision-making is emphasized in primarv care, 76-78 but we found no evidence that improving the process of decision-making only (including two studies not meeting inclusion criteria) changes behavior. 30,79,80 Many posit shared decision-making improves provider guideline adherence⁸¹ as well as affective-cognitive variables but not health behaviors in patients.⁸² It may be that treatment preference matching, a component of shared decision-making, is sufficient or an active ingredient. Some have suggested pairing decision aids with motivational interventions to alter patient behaviors. 83 While we found insufficient evidence for motivation due to biased, small and inconsistent trials, most interventions employed ≥ 1 motivational component (n = 9) and 6 of these showed benefit (all of which were complex and delivered actively, i.e., via calls or websites). Further highquality research is needed to understand whether motivational strategies are effective alone or need to be delivered within complex interventions. Technologies such as video-based multimedia⁵⁹ and patient portals may be useful for scaling motivational interventions.8

Relatedly, we demonstrate that complex interventions (e.g., more components, contacts, or duration) may be needed to improve treatment retention, depressive symptoms, and anti-depressant treatment initiation. Because many simple interventions were not powered to assess depressive symptoms, further research is needed to elucidate differences between simple and complex interventions. One approach would be to implement simple interventions in integrated settings to improve initiation as well as foster retention and clinical outcomes.

There are several limitations to our review. We excluded non-English language studies, which may have contributed to publication bias. Relatedly, the majority of trials, including those with small samples, reported benefit. There was also wide heterogeneity in outcome measurement precluding meta-analysis, while the small number of trials within each strategy limited our ability pool effects in any single category. However, we applied a rigorous grading approach to determine SOE. Additionally, treatment initiation itself may be a low bar to achieve and insufficient for improving patient outcomes.

Nonetheless, treatment initiation remains a vital first step, and this remains one of the first systematic reviews to identify pragmatic interventions to improve depression treatment engagement behaviors in primary care settings. While we applied rigorous methods to categorize strategies, some there may have been overlap or mis-categorization. Finally, the included studies had moderate to high risk of bias and none were graded as high SOE, though this is common in behavioral interventions.

Overall, our review provides practical strategies for increasing depression treatment initiation in primary care. Patient engagement interventions that advocate feasibility with patients, providers, and organizational workflows will be key. Our review highlights the crucial need for more rigorous, low-risk studies confirming the effectiveness of these strategies, particularly collaborative care, case management, treatment matching, and motivation, which by their very nature make blinding difficult. Furthermore, research is needed understand how best to engage primary care team members in delivering these strategies.³³

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Author Contributions Nathalie Moise, Louise Falzon, and Megan Obi had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Moise and Falzon; acquisition of data: Falzon; analysis and interpretation of data: Moise, Falzon, Obi, Kronish, Bryant, and Gonzalez; drafting of the manuscript: Moise, Falzon, Obi, and Kronish; critical revision of manuscript for important intellectual content: Moise, Falzon, Obi, Bryant, Gonzalez, Patel, and Kronish; statistical analysis: Moise, Falzon, and Obi; obtained funding: Moise and Kronish; and study supervision: Kronish.

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Compliance with Ethical Standards:

Conflict of Interest: The authors declare that they do not have a conflict of interest.

Transparency: Dr. Moise affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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