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STATE OF THE ART REVIEW

Depression in primary care: part 2—management

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Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors

ABSTRACT

Depression is a common and heterogeneous condition with a chronic and recurrent natural course that is frequently seen in the primary care setting. Primary care providers play a central role in managing depression and concurrent physical comorbidities, and they face challenges in diagnosing and treating the condition. In this two part series, we review the evidence available to help to guide primary care providers and practices to recognize and manage depression. The first review outlined an approach to screening and diagnosing depression in primary care. This second review presents an evidence based approach to the treatment of depression in primary care, detailing the recommended lifestyle, drug, and psychological interventions at the individual level. It also highlights strategies that are being adopted at an organizational level to manage depression more effectively in primary care.

Introduction

The vast majority of people with depression are treated in the primary care setting, with estimates ranging from 64% in America to 90% in the UK.[1 2] Primary care providers have a distinct role and skill set that complement but are not substitutes for specialist mental health input.[3] Most primary care providers screen for, diagnose, and treat depression and ensure routine follow-up. Even when specialist mental health input is needed, primary care providers maintain an important role in managing the chronic physical comorbidities, tackling social vulnerabilities, and monitoring psychiatric risk.

Depression is broad and heterogeneous and thus can be taken to mean a multitude of different terms (fig 1). This review focuses on major depressive disorder (MDD) in primary care and does not cover the management of other depressive disorders. MDD is an umbrella term that covers the constellation of signs and symptoms that constitute a depressive episode and that place a limitation on functioning. The disorder may be graded on severity from mild, through moderate, to severe and psychotic and may present as a single episode or be recurrent.

As outlined in the first review of this series,[4] MDD commonly occurs with other emotional, substance use, and physical disorders that should be considered when deciding on interventions. We have not detailed here specific treatment strategies adapted to each potential comorbidity. We have, however, emphasized the need to consider the presence of comorbidities when screening for and diagnosing depression in primary care and included, where appropriate, a discussion on interventions known to be effective for patients with such comorbidities. We also have not included specific interventions for subclinical chronic depression (also called dysthymia or dysthymic disorder) or for subtypes of depression such as bipolar depression, perinatal depression, or seasonal affective disorder.

Natural course of depression in primary care

The PREDICT-NL study, a prospective cohort study from 2012, examined the natural course and outcome of MDD in primary care (from now on called depression).[5] At baseline, 174 (13%) of 1338 consecutive attendees had depression, of which 17% had a chronic course, defined as still having symptoms after 39 months, and 40% had a fluctuating course; 43% remitted. Those patients with chronic depression were noted to have more depressive and somatic symptoms and greater mental dysfunction at baseline, independent of age, sex, level of education, presence of a chronic disease, and lifetime depression, compared with those who remitted from baseline.[6] Other studies have found a similar range of factors to be associated with chronic or recurrent depression. These factors include a previous history of recurrent depression, a history of dysthymia, psychiatric comorbidities, comorbid chronic medical illness, younger age at onset, family history of mood disorders, greater severity of depressive symptoms at baseline, and incomplete recovery following acute treatments. Low level of social integration and/or negative social interactions also seem to appear concurrently with chronic depression.[7-10]

Given this natural course, depression in primary care should be managed as any other chronic disease.[11] Management requires a clear treatment pathway and the use of evidence based strategies for individual primary care providers supported by organizational strategies at the practice level.

Sources and search criteria

To collect and review the evidence available on depression in primary care, we searched the PubMed and

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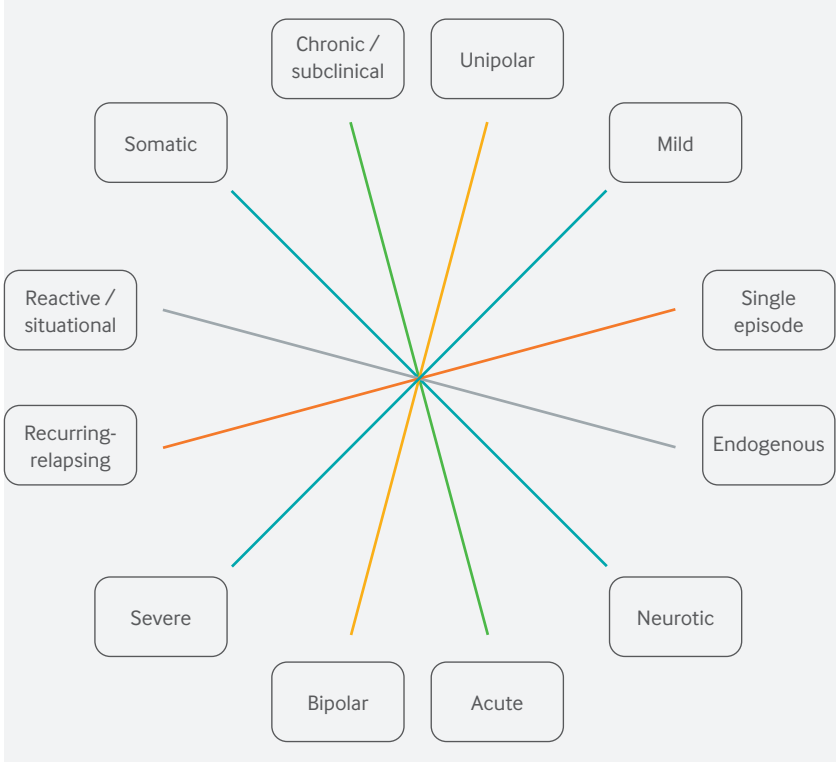

Fig 1 | Depression as a multidimensional construct. Depression as a disorder is defined by the *Diagnostic and Statistical Manual of Mental Disorder*, 5th edition, and the International Statistical Classification of Diseases and Related Health Problems, 11th revision, according to a characteristic constellation of diagnostic features that limit day to day functioning or impair social interactions. However, as an ontological concept, depression constitutes myriad terms. It may, for example, be unipolar (that is, only depressive episodes are experienced) or bipolar (previously called manic depression). It may be classified by severity as mild, moderate, or severe (with or without psychosis). It may be a single episode or present as a relapsing-remitting illness. Depression may be considered reactive to particular social events or circumstances or may arise de novo in the absence of any external factors. It may be experienced with a high degree of anxiety symptoms (neurotic or agitated depression) or manifest with very few emotional symptoms but many physical effects on sleep, energy, pain, and libido ("somatic syndrome"). Depression may also present as a chronic, unrelenting, subthreshold disorder as opposed to an acute or subacute, discrete episode. These terms are not exhaustive and do not include subclasses of depression such as seasonal affective disorder, perinatal depression, or premenstrual dysphoric disorder

Cochrane databases for relevant articles published between 1 January 2007 and 30 September 2017 by using medical subject headings (MeSH) terms including "depressive disorder", "depression", and "major depressive disorder" in combination with "primary care" and "general practice". We did individualized searches for specific interventions thought relevant through the review process. We limited our search to the English language. We reviewed titles and abstracts, excluding publications not relevant to primary care or for which MDD was not the main focus of the study.

We then used a pragmatic prioritizing framework to determine which studies to include in the review. This incorporated the level of evidence, with systematic reviews and meta-analyses given priority and interventional studies prioritized over observational studies; recency, with more recent studies prioritized over older studies; and sample size, with larger studies prioritized over those with smaller sample sizes. Where competing priorities existed—for example, a more recent smaller interventional study with similar objectives to a larger but older randomized controlled trial (RCT), we assigned priority by consensus between the authors on the basis of the methodology, study population, aims of the study, and outcome measures.

In addition, we searched the reference lists of included studies for further relevant studies. If a study had been conducted before our search timeframe of the past 10 years, we considered it for inclusion if we deemed it important by virtue of its size or methodology or the absence of other research conducted in the area. References to older, but noteworthy, validation studies were made as appropriate.

General principles of intervention

Aims of treatment

Depression is treated to achieve three inter-related outcomes: recovery, remission, or response. The key measure is remission from depression, conceptualized as a return to a state of normal functioning and minimal symptoms.[12] Recovery is defined as two months of remission and is closely associated with improvement in functioning and quality of life.[13] Recovery should therefore be considered the ultimate aim of treatment.[14]

However, when recovery is not achieved, the aims of treatment are less clear. Response is operationally defined as a reduction in symptoms of 50% from baseline.[12] However, patients themselves may consider symptom reduction as less important than improvements in features such as optimism and self confidence, and the correlation between symptom reduction and meaningful improvements is not robust.[15 16] Nevertheless, residual symptoms are associated with increased risk of relapse,[17] decreased likelihood of recovery over time, and increased psychosocial and socioeconomic impairment.[18 19] Hence, the reduction of symptoms, either in intensity or in frequency, should be sought when full recovery is not possible.[20 21]

Choosing a treatment

Many psychological, pharmacological, and psychosocial interventions, either alone or in combination, are available to treat a person diagnosed as having depression. Although evidence on the comparative effectiveness of treatments within and between the different classes of interventions is limited,[22] two comparative reviews of psychological and drug treatments concluded that they are of comparable efficacy in primary care.[23 24] Different guidelines recommend different initial management options. For example, the National Institute for Health and Care Excellence (NICE) in England recommends avoiding antidepressant drugs for mild depression and combining drug treatment with psychotherapy for more severe forms of depression.[25] The guidelines of the Royal Australian and New Zealand College of Psychiatrists suggest that psychological management may be sufficient for depression of mild to moderate severity and recommend using antidepressants when this fails or in severe depressive disorder,[26] whereas American guidelines (both of the American College of Physicians and of the Institute for Clinical Systems Improvement, the latter having

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published guidelines specifically for the management of depression in primary care)[27 28] suggest that drug treatment and psychotherapy can be considered equivalently for initial treatment.

Approaches to intervention

One key feature shared among these guidelines is that the management of depression should follow a stepped care approach in which the intervention depends on the severity of presentation. As outlined in our first review, severity is categorized by a subjective assessment of limitation of functioning rather than number of depressive symptoms. Although depression will respond to treatment in most people, at least half will have a further episode of depression after their first episode, and in 10% it will follow a persistent or chronic course.[29] Therefore, the treatment of depression in primary care should often adopt a chronic disease management approach in which symptoms should be tracked at baseline and longitudinally throughout the treatment course, and treatment adherence and side effects should be monitored. Adjustments should be made to a patient's treatment plan over time, on the basis of these systematic assessments.[30]

As the comparative effectiveness of one intervention over another for the treatment of depression is limited, an individual patient's personal preferences and circumstances should be considered alongside the clinical evidence. Treatment choice should, therefore, ideally be informed by a shared decision making (SDM) approach, in which the clinician and the patient, informed about the range of options available, arrive at a healthcare choice together.

A cluster randomized controlled trial in 2015 of 117 patients and 301 primary care clinicians found that the use of a decision aid improved satisfaction with the decision between clinicians and patients, reducing conflict, and improved patients' knowledge about treatment options without affecting the duration of the clinical encounter. The decision aid had no effect on clinical outcomes or adherence to drug treatment.[31] However, the time for the consultation in both intervention and control groups was 40 minutes, so more practicable approaches to SDM in primary care need to be studied.

The SDM approach is consistent with the growing interest in empowering patients to become equal partners in the management of their condition and extends to decisions on when to intervene. NICE, for example, advocates active monitoring for subthreshold forms of depression and in patients who present with mild depression and do not want treatment.[25] It is important to recognize that active monitoring is not a passive process (as suggested by its older term "watchful waiting") but involves consistent, longitudinal, systematic assessment of clinical state and some degree of supportive counseling and problem solving. An RCT in 2013 of 220 patients randomized to receive active monitoring before starting drug treatment in primary care found that a significant minority (16-22%) recalled that a discussion with their general practitioners changed their thinking or their personal relationships or made them feel more able to talk to family and friends.[32]

Interventions in primary care

Psychological interventions

Psychological interventions have long been established as treatments for relieving or reducing depressive symptoms.[33-35] Recent decades have seen increasing diversification in the theory and practice of psychological treatments into a variety of individual, group, short term, and long term options.[36] For the purposes of this review, we concentrate on therapies that can be feasibly delivered in primary care settings, defined as those that are time limited, require fewer resources, and lend themselves to being put into practice (table 1). These include low intensity treatments that are brief and have minimal (or sometimes no) input from a trained professional, such as guided self help, computerized cognitive behavioral therapy (cCBT), and psychological counseling, as well as high intensity treatments that are delivered face to face by a qualified psychotherapist in group or individual settings and include cognitive behavioral therapy (CBT), interpersonal therapy, behavioral activation, and short term psychodynamic psychotherapy (STPP).

Several systematic reviews have found little or no difference in the effectiveness of different modalities of brief, time limited therapies—either low or high intensity—compared with longer term interventions such as long term psychoanalytic or psychodynamic approaches.[56-62] A large meta-analysis of 30 studies covering 5159 participants with a range of depressive conditions from chronic subthreshold depression to MDD in the primary care setting found effect sizes in the small to moderate range for a variety of psychological therapies.[62] Standardized mean differences ranged from −0.24 (95% confidence interval −0.47 to −0.02) for face to face interpersonal therapy and −0.30 (−0.40 to −0.13) for face to face CBT to −0.40 (−0.69 to −0.11) for guided self help (where a negative number favors the intervention).

Of all psychological interventions, CBT is the most studied.[63] Evidence suggests that CBT has efficacy over treatment as usual, particularly for the treatment of depression with comorbid physical conditions, but effectiveness over other psychological, or pharmacological, interventions for depression has not been established.[46-48] We also found good evidence to support the use of problem solving therapy, particularly in situational forms of depression (that is, those reactive to stressful social circumstances)[49] and for interpersonal therapy in treatment of acute depression and in relapse prevention (table 1).[51]

Factors affecting the outcomes of psychological interventions

Several studies and meta-analyses support the finding that the therapeutic relationship between therapist and client may be more predictive of the outcome of therapy than the actual type of therapy provided.[64-66] These relational factors include qualities within the therapist such as the client's perceptions of the therapist's empathy and credibility ("genuineness"), as well as particular behaviors or skills including empathic understanding, defined as the degree to which the therapist successfully communicates personal understanding of the client's experience; positive regard, defined as the extent to

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Table 1 | Most commonly delivered psychological interventions in primary care. All are brief and time limited (at most 16 weeks), except for short term psychodynamic psychotherapy (20-30 weeks)

Modality	Description	Principal studies	Evidence synthesis
Low intensity interventions			
Guided self help*	Self administeredintervention designed to treat depression through use of books or other self help manuals. Clinician facilitates use of this material, but contact is limited usually to between three and six sessions[37]	Meta-analysis of 21 RCTs (810 participants) comparing guided self help with face-to-face interactions (either group or individual) for depression (6 RCTs) and anxiety disorders.[38] In 17 studies, participants were recruited from general population through media announcements. Self help could be delivered by book, computer program, internet, or audio recordings. Face-to-face interactions in studies for depression were largely behavioral in nature (cognitive restructuring, activity scheduling, relaxation, and problem solving). No significant difference was seen in effect size (d=−0.02, 95% CI −0.20 to −0.15) up to 12 months post-intervention. Dropout rates were high but not significantly different between groups	Guided self help has been studied more extensively in treatment of anxiety disorders than depressive disorders. However, it seems to be more effective than unguided self help for treatment of depression and equivalent to other low intensity psychosocial interventions in general population. Effects may not be sustained long term, and guided self help may be less effective in clinical populations
		13 RCTs conducted in adults (454 participants) with depression (4 studies) or anxiety disorders comparing guided with unguided self help.[39] Guided self help was defined as access to CBT self help materials with active guidance from professional or para-professional therapist of no more than 3 hours. Control group patients were either on waiting list or received discussion group support, usual care, relaxation, or internet guided minimal CBT. Mean weighted effect size (d) was 0.69 (P<0.01; 95% CI not given) overall after intervention and 0.31 for participants recruited from clinical populations (most participants were recruited from general population by media announcements). Mean effect size reduced to 0.19 at 1 year follow-up	
Psychological counseling	Reviewed literature suggests two distinct forms of counseling: non-specific, generic form that serves largely supportive function; and model specific form, often based on humanistic or experiential work of psychologist Carl Rogers (termed psychological counseling here).[40] Latter adheres to BACP definition of "a systematic process which gives individuals an opportunity to explore, discover and clarify ways of living more resourcefully, with a greater sense of wellbeing"[41]	RCT of 130 participants with ICD-10 diagnosis of depressive episode randomized to receive CBT in primary care, counseling, or treatment as usual.[42] CBT and counseling were both found to be as effective as each other and superior to GP care at 4 months but not at 12 months (as measured on BDI, Brief Symptom Inventory, and Social Adjustment Scale). Counseling was delivered by following manual based on work of Carl Rogers. BDI scores indicated depression in moderate to severe range at baseline	Counseling has been studied almost exclusively as intervention provided in primary care. Psychological counseling seems to have robust evidence base for treatment of depression, as effective as other manualized forms of therapeutic interventions such as CBT
		Individual patient data analysis of 33 243 participants receiving either counseling for depression or CBT within 103 IAPT services in England found counseling to be as effective as CBT post-intervention.[43] Greater variability existed between sites than between type of treatment. CBT was more effective for participants who received >18 sessions	
Computerized cognitive behavioral therapy (cCBT)*	Form of CBT (see below) that is delivered via either computer program or internet. It can be used with no or minimal therapist involvement (self guided) or augmented by regular contact with therapist (guided cCBT)	Meta-analysis of 14 RCTs (2807 participants) comparing cCBT (both guided and self guided) with control (TAU, WL, attention); pooled SMD=−0.48 (−0.63 to −0.33) post-intervention but −0.05 (−0.19 to −0.09) beyond 6 months.[44] Pooled SMD from 12 comparisons that provided data on function post-treatment was −0.05 (−0.31 to 0.22). There was significant publication bias and increased attrition in the cCBT group	cCBT may offer benefit to some people with mild to moderate depression if they are able to complete course. However, effects are not sustained and attrition is high
		Meta-analysis using individual participant data from 3876 participants from 13 RCTs on self guided cCBT delivered over internet.[45] Self guided cCBT was significantly more effective than controls on severity of depressive symptoms (β=−0.21; Hedges g=0.27) and treatment response (β=0.53; odds ratio 1.95, 1.52 to 2.50; NNT=8). Adherence to treatment was associated with lower depressive symptoms (β=−0.19; P=0.001) and greater response to treatment (β=0.90; P<0.001). Follow-up ranged from 6 to 16 weeks post-randomization. Baseline measures of severity indicated depression in moderate range on average	
High intensity interventions			
Cognitive behavioral therapy (CBT)	Discrete, time limited, structured psychological intervention in which patient works collaboratively with therapist to identify types and effects of thoughts, beliefs, and interpretations on current symptoms; develops skills to identify and monitor problematic thoughts, beliefs, and interpretations; and learns repertoire of strategies to counteract problematic thoughts, beliefs, and interpretations[25]	Meta-analysis of 115 RCTs found CBT to be superior to control (WL, TAU, or placebo) with mean effect size (g) of 0.53 (0.43 to 0.62) after adjustment for publication bias.[46] This corresponds to NNT of 3. CBT was not more effective than other therapies or drugs, but combined treatment was more effective than drugs alone (g=0.49)	CBT seems to have effect in moderate to large range over TAU or WL controls in treatment of depression. It seems to be particularly effective when depression is comorbid with another physical disorder and in treatment of depressive disorder rather than in amelioration of depressive symptoms not meeting threshold for diagnosis of disorder. However, there is no convincing evidence that CBT is more effective than other therapies or drugs in treatment of depression
		Meta-analysis of 29 RCTs evaluating CBT for depression in people with physical disorder. CBT was superior to control conditions, more particularly in studies restricted to participants with depressive disorder (SMD=−0.83, −1.36 to −0.31) than in studies of participants with depressive symptoms (SMD=−0.16, −0.27 to −0.06).[47] CBT was not more effective than other forms of therapy	
		Systematic review including qualitative assessment and meta-analysis comparing benefits and harms of CBT with second generation antidepressants in initial treatment of current major depressive episode in adults.[48] 11 RCTs (1511 participants) were included. No statistically significant difference was seen in risk ratio for response (0.91, 0.77 to 1.07) or remission (0.98, 0.73 to 1.32) or in change in Hamilton Rating Scale for Depression (SMD=−0.38, −2.87 to 2.10). Difference in dropout rates was not statistically significant	
Problem-solving therapy (PST)	Based on theory that depression is associated with difficulties in solving individual's social problems because of direct effects of depression, such as negative ruminations, and lack of knowledge. Therapist works with patient to identify and prioritize key problem areas,break these down into specific, manageable tasks, and develop appropriate coping behaviors	Meta-analysis of 30 RCTs (3530 participants) comparing PST with control conditions or other therapies found large effect size (g=0.79, 0.57 to 1.01) in comparison with controls but with very high heterogeneity among studies (I^2=84, 77 to 88).[49] When only 9 high quality RCTs with low risk of bias were compared with controls, effect size reduced to g=0.34 (0.22 to 0.46). No significant difference was seen between PST and other therapies (reminiscence, CBT, guided self help, stress management). Subgroup analyses indicated significantly lower effects for individual interventions in studies with participants who met criteria for major depression, studies in which intention to treat analyses were conducted instead of completers only analyses, and studies with pill placebo and care as usual control groups	PST is probably an effective treatment for depression with small effect size. It seems to be more effective in people with depressive symptoms related to social problems, as opposed to depressive disorder

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Modality	Description	Principal studies	Evidence synthesis
Interpersonal psychotherapy (IPT)	Based on premise that depressive symptoms are strongly influenced by disruptions in close personal attachments leading to sense of loss and difficulty navigating roles within relationships. Therapy uses techniques such as role play, communication analysis, supportive listening, and use of therapeutic relationship to help patient[50]	Meta-analysis of 90 RCTs (11 434 participants) evaluating IPT in treatment of range of common mental disorders; two thirds of studies were aimed at prevention, treatment, or relapse prevention of depression.[51] IPT had moderate to large effects in treatment of acute depression (g=0.60, 0.45 to 0.75; NNT=3) compared with control. Once monthly maintenance IPT was significantly more effective than placebo at preventing relapse (odds ratio 0.47, 0.25 to 0.87; NNT=6). No differences were found in comparison with other therapies or drugs	IPT has most commonly been studied in treatment of active depressive disorder and in prevention of relapse. It seems to be very effective for both. Effects were maintained at 6 month follow-up after treatment of acute phase depression
Behavioral activation (BA)	BA is a discrete, time limited, structured psychological therapy, in which the therapist and patient work collaboratively to identify the effects of behaviors on current symptoms, feelings, and/or other psychosocial problems and seek to reduce symptoms and problematic behaviors through tasks such as reducing avoidance, graded exposure, activity scheduling, and reinforcing positive behaviors	A meta-analysis of 26 RCTs totaling 1524 participants suggested a reduction in symptoms for people with mild to moderate depression compared with controls (SMD −0.74, −0.91 to −0.56). Study quality was low and follow-up short[52] A meta-analysis of 9 RCTs totaling 2157 participants found internet delivered BA to be superior to wait list control (SMD −0.58, −1.22 to −0.07; low quality evidence) and treatment as usual (SMD −0.68, −0.83 to −0.53; moderate quality evidence) and non-inferior to other behavioral therapies (SMD 0.09, −0.19 to 0.36; very low quality evidence) and mindfulness (SMD −0.27, −0.71 to 0.17; low quality evidence)[53]	BA may be more effective than control for people with mild to moderate depression when given in person, but results should be interpreted with caution as most studies are of very low to low quality and follow-up is limited
Short term psychodynamic psychotherapy (STPP)	In psychodynamic therapy, the therapist and patient explore and gain insight into conflicts and how these are represented in current situations and relationships including the therapeutic relationship. This allows patients to explore feelings originating in the past, with a focus on interpreting and working through conscious and unconscious conflicts. Traditionally open ended, STPP limits therapy to 20 sessions. However, in contrast to other time limited therapies, recipients are not taught specific skills (for example, thought monitoring, re-evaluating, or problem solving)	Meta-analysis of 54 studies (33 RCTs) totaling 3946 participants.[54] STPP was significantly more effective than control at reducing depressive symptoms (d=0.57-1.18) and improving quality of life (d=0.49-0.69). No significant difference was found between STPP and other psychotherapies at post-treatment or follow-up (average of 12 months). Many studies included participants with underlying personality disorder or personality vulnerabilities RCTs of STPP across a range of common mental disorders compared with WL controls, TAU, or sham psychological intervention.[55] 33 RCTs were included (2173 participants), of which 5 considered depressive disorders and 13 considered depressive symptoms (1415 participants). STPP improved depressive symptoms more than control in the short term (<3 months; SMD=−0.50, −0.61 to 0.39) and medium term (3-6 months; SMD=−0.034, −0.60 to −0.09) but not in long term follow-up (>6 months)	STPP may be more effective than control at reducing depressive symptoms comorbid with other psychiatric conditions, particularly personality disorder, anxiety disorder, and somatoform disorders, but its effectiveness in pure depressive disorder is less well established

BACP=British Association for Counselling and Psychotherapy; BDI=Beck Depression Inventory; CBT=cognitive behavioral therapy; IAPT=Increasing Access to Psychological Therapies; ICD-10=International Statistical Classification of Diseases, 10th revision; NNT-number needed to treat; RCT=randomized controlled trial; SMD=standardized mean difference; TAU=treatment as usual; WL-wait list.
*Interventions that could be feasibly delivered by a primary care practitioner with minimal training as opposed to a specialist psychologist or psychotherapist.

which the therapist communicates non-judgmental care and respect; and congruence, or the extent to which the therapist is non-defensive and "real."[66] The possibility of fostering and maintaining this relationship through remote technology, particularly through video messaging and online, has received great interest in primary care. In the meta-analysis of psychological interventions in primary care described above, remotely delivered therapies had equivalent outcomes to those delivered in person, replicating an earlier review in 2011.[67]

Until recently, the potential for CBT to be provided online, without regular guidance from a trained psychologist, had garnered mixed results through RCTs. However, in 2017, a meta-analysis of self guided, internet based CBT using individual participant data of 3876 participants from 13 studies found that self guided internet CBT was significantly more effective than controls for treatment response (odds ratio 1.95, 1.52 to 2.50; number needed to treat 8).[45] Adherence to treatment was associated with greater response (β=0.90; P<0.001). In contrast, unstructured psychological interventions such as self help and generic counseling have been found to be less effective when delivered in the absence of a therapist or with minimal therapeutic contact.

Overall, the evidence suggests that non-specific factors such as the therapeutic relationship and the client's expectations are very important for the outcome of most therapies, particularly in low intensity, unstructured interventions such as generic counseling or self help, and that this therapeutic relationship can be maintained through remote technologies. Moreover, emerging evidence shows that for highly structured interventions such as CBT, the therapy may be delivered in a highly manualized form, without the influence of a therapist, and so may be a useful first step for people with mild to moderate depression in primary care.

Adverse effects

Although there is a dearth of research on the possible harms of psychological interventions,[68 69] these interventions are not without risk. One recent study found that 1 in 20 people reported lasting adverse effects based on a national survey of 14 587 respondents who had received psychological treatments for anxiety or depression in England.[70] The survey did not qualify the types of adverse effects, but the separate development of a recently validated questionnaire to identify the negative effects of psychological treatments (the Negative Effects Questionnaire) found that the most common harms reported were resurfacing of unpleasant memories (38%), increased lasting stress (38%), and increase in anxiety (37%).[71] The impact of these adverse effects is not known, but primary care providers should make patients aware that anxiety may increase on starting therapy before improvement in depressive symptoms is achieved.

Pharmacological interventions

Antidepressants are often considered the cornerstone of treatment. However, several guidelines, including those from NICE in England and the Royal Australian and New Zealand College of Psychiatrists, reserve the use of antidepressants for moderate to severe forms of depression, where severity is defined by impact on everyday functioning.[25 26]

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Box 1 | Classes of antidepressants

Antidepressants can be broadly classified as:

- First generation antidepressants:
  - Tricyclic antidepressants (TCAs)—for example, amitriptyline, clomipramine, nortriptyline
  - Monoamine oxidase inhibitors (MAOIs)—for example, phenelzine, tranylcypromine
- Serotonin reuptake inhibitors (sometimes called second generation antidepressants):
  - Selective serotonin reuptake inhibitors (SSRIs)—for example, citalopram, fluoxetine, paroxetine
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs)—for example, duloxetine, venlafaxine
  - Serotonin antagonist and reuptake inhibitors (SARIs)—for example, trazodone, nefazodone
- Atypical antidepressants (sometimes called third generation antidepressants):
  - Tetracyclics—for example, mirtazapine
  - Norepinephrine and dopamine reuptake inhibitor (NDRI)—bupropion

Prescription of antidepressants worldwide is increasing.[72] A retrospective analysis of antidepressant prescribing trends in UK primary care in 2016 found that whereas the rate of antidepressant prescribing increased from 61.9 per 1000 person years in 1995 to 129.9 per 1000 person years in 2011, the incidence of new prescriptions did not (21.3/1000 person years in 1995; 17.9/1000 person years in 2011).[73] Therefore, upward trends in primary care may be better explained by the longer use of antidepressants rather than an increase in new prescriptions. This may reflect the growing awareness of depression as a chronic or relapsing-remitting disorder, similar to other long term conditions such as hypertension, diabetes, or asthma, and, as for those conditions, drug intervention should be titrated according to routine and regular monitoring.

First line agents

Box 1 shows the classes of antidepressants. Selective serotonin reuptake inhibitors (SSRIs) are recommended as first line agents because of their tolerability and costs,[25-27] and this is reflected in general prescribing practices over the past few years. In 2010, by far the most commonly prescribed class of antidepressants in America was the SSRIs, followed by bupropion, and the serotonin-norepinephrine (noradrenaline) reuptake inhibitors (SNRIs).[74] In UK primary care, SSRIs were also the most commonly prescribed antidepressants followed by tricyclic antidepressants and SNRIs (bupropion is not licensed for the treatment of depression in the UK).[75]

Comparative data

Until recently, several systematic reviews had not been able to establish firm conclusions on the efficacy or tolerability of one antidepressant (any SSRI, duloxetine, mirtazapine, venlafaxine) over another.[76-82] However, in 2018, a large network meta-analysis comparing 21 antidepressants with placebo or another antidepressant in adults with MDD found comparative differences.[83] The review included 522 double blind RCTs (116 477 participants) and, importantly, included a substantial volume of unpublished data. All antidepressants were more effective than placebo for both remission and response, with amitriptyline, mirtazapine, duloxetine, venlafaxine, and paroxetine being the most efficacious (range of odds ratios 1.75-2.13 for response) and clomipramine, trazadone, citalopram, fluoxetine, and bupropion being least effective (1.49-1.58 for response). Agomelatine, fluoxetine, and escitalopram were better tolerated than other antidepressants (range of odds ratios 0.43-0.77), whereas amitriptyline, duloxetine, trazadone, and venlafaxine had the highest dropout rates (1.30-2.32).

This review focused only on the acute treatment of depression (eight weeks), and the vast majority of participants (89%) had moderate to severe depression. This is especially relevant to primary care populations, which have a higher prevalence of mild to moderate depression compared with those in specialist settings, and thus such significant differences may not translate across to populations with less severe and/or more chronic depression.[84 85] The most recent meta-analysis on the effectiveness of antidepressants restricted to primary care analyzed 66 studies (15 161 participants) and found modest effect sizes for SSRIs over placebo (odds ratio 1.69, 1.40 to 2.04).[86] It also concluded that no comparative differences exist between the different classes of antidepressants. Drug selection, therefore, still often depends on the relative side effect profile of the various antidepressants (table 2) and the patient's preference.[87]

Adverse effects

Tricyclic antidepressants have adverse cardiovascular and anticholinergic effects and are particularly toxic in overdose, limiting their use.[96] SSRIs tend to have a more benign side effect profile (except in older adults; see below). The most common side effects are headache and gastrointestinal symptoms.[97] As previously noted, depression is highly comorbid with other conditions, both behavioral and physical, and the risks associated with polypharmacy and antidepressants is an important concern in primary care, particularly in older adults.

In 2012 the American Geriatric Society categorized SSRIs as potentially inappropriate drugs for older adults with a history of falls or fractures.[98] Several studies have found an association between the use of all antidepressants, particularly SSRIs, and falls and fractures in older adults.[99 100] An older longitudinal analysis (1997-2004) of 2948 older people living in the community found an adjusted odds ratio of 1.62 (1.15 to 2.28) for SSRIs and 1.48 (1.12 to 1.96) for antidepressants overall.[101] However, most evidence to date comes from observational studies; and use of antidepressants and falls are both common in this patient population, so causation cannot be inferred.[102]

SSRIs also significantly increase the risk of gastrointestinal, and possibly cerebrovascular, bleeds in older adults,[103] although the odds are modest (odds ratio 1.66, 1.44 to 1.92 for upper gastrointestinal bleeding) except when combined with other high risk drugs (for example, non-steroidal anti-inflammatory drugs: odds ratio 4.25, 2.82 to 6.42).[104] Taken together, these findings suggest

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Table 2 | Relative side effects of antidepressants commonly prescribed in primary care

Drug	Sedation	Insomnia	Paradoxical anxiety*	Headache*	Nausea*	Anticholinergic effects	Cardiac conduction	Hypotension	Falls in older adults	Sexual dysfunction	Weight gain	Gastrointestinal bleed	Lethality in overdose
Selective serotonin reuptake inhibitors													
Citalopram	–	–	–	–	++	–	+	–	+++	+++	–	++	+
Escitalopram	–	–	–	–	++	–	+	–	+++	+++	–	++	+
Fluoxetine	–	–	+	–	++	–	–	–	+++	+++	–	++	–
Paroxetine	+	+	+	+	++	+	–	–	+++	+++	+	+++	–
Sertraline	–	+	+	++	++	–	–	–	+++	+++	–	+++	–
Tricyclic antidepressants													
Amitriptyline	+++	–	–	–	+	+++	+++	+++	++	+++	++	+	+++
Clomipramine	++	+	+	–	++	++	+++	+++	++	+++	+	+++	++
Nortriptyline	+	+	+	–	+	+	++	++	++	+	–	–	+++
Serotonin-norepinephrine reuptake inhibitors													
Duloxetine	–	+	–	–	++	–	–	–	++	++	–	+	++
Venlafaxine	–	+	+	+	+++	–	+	+	++	+++	+	+	++
Other													
Mirtazapine	+++	–	–	–	+	+	–	+	++	–	++	+	+
Trazodone	+++	–	–	–	+	+	+	+	++	+	+	+++	+
Bupropion	–	++	–	–	+	+	–	–	+	–	–	–	++

Tricyclic antidepressants (TCAs), paroxetine (the shortest acting selective serotonin reuptake inhibitor (SSRI)), and dual reuptake inhibitors (mirtazapine and venlafaxine) seem to be associated with greatest incidence of side effects.[87 88] Paradoxical agitation may uncommonly occur on starting treatment, particularly with some TCAs and the SSRIs (except citalopram and escitalopram).[88-90] Longer term adverse effects include sexual dysfunction, which occurs in 50-70% of people (both men and women) treated with SSRIs but is rarely reported.[91 92] These can have a significant negative effect on quality of life and treatment concordance, so distinguishing them from symptoms of depression is important.[78] People treated with mirtazapine have significantly reduced incidence of sexual dysfunction, estimated to be around 25%.[92-94] Anticholinergic effects include, but are not limited to, dry mouth, blurred vision, and dizziness. Cardiac conduction abnormalities include, but are not limited to, QT_c prolongation.

Key: +++ very common; ++ common; + uncommon; – very uncommon.

*Paradoxical anxiety, headache, and nausea are most common on initiation.

Adapted from Taylor DM, Barnes TRE, Young AH, eds. *The Maudsley Prescribing Guidelines in Psychiatry*, 13th ed. Wiley Blackwell, 2018; and *Clinical Practice Guideline on the Management of Depression in Adults*. Ministry of Health, Spanish National Health Service, 2014.[87 95]

that primary care providers should use antidepressants, and particularly the SSRIs, with caution in older adults and possibly at lower doses and with more active monitoring for side effects.

Starting and withdrawing antidepressants

All antidepressants exert maximal effects within the first two weeks of treatment.[105 106] If no response has occurred by three weeks, the drug should be changed or the dose increased. However, as slow responders have also been described, even minimal improvement at three weeks could suggest eventual response.[107] Depression is a relapsing-remitting illness in 50-85% of patients, and about half of all people who stop their antidepressants immediately on remission will have a relapse within three to six months.[108] Evidence supports continuing treatment for at least six months after remission, as this has been shown to reduce the three year odds of relapse by 65%.[109 110]

At least a third of patients have symptoms on stopping antidepressants.[111] Withdrawal effects can occur with all antidepressants, with the possible exception of the recently introduced agomelatine and vortioxetine.[112 113] Symptoms are most likely with drugs that have short half lives (for example, paroxetine and venlafaxine)[114 115] and present as flu-like symptoms, electric shock-like sensations, irritability, insomnia, dizziness, and increased tearfulness. They usually appear within five days of cessation and may be mild and self limiting; however, in some cases they can interfere with functioning.[87 116] The incidence may be reduced by gradually withdrawing antidepressants over four weeks.[117] Fluoxetine, the SSRI with the longest half life, has the lowest association with withdrawal symptoms of all the SSRIs.[118]

Lifestyle interventions

Although drugs and psychological interventions are the principal modes of treatment for depression, interest has been growing around reducing the population risk of depression by modifying social factors or enhancing individual wellbeing through lifestyle modifications.[119] Unfortunately, the evidence base for the effect of practical social or self help on depressive outcomes remains poor, although it is growing.[120]

Most studied have been the effects of physical activity, sleep hygiene, and measures to reduce social isolation on depression. Of these, the effect of physical activity holds most promise. In 2017 a meta-analysis of 49 prospective cohort studies (266 939 participants followed up for 1 837 794 person years) found that high levels of physical activity (as measured by a composite score of self reported frequency, intensity, and volume of exercise) reduced the odds of developing depression compared with low levels of physical activity in adults (adjusted odds ratio 0.78, 0.70 to 0.87).[121] Overall, the quality of the studies was moderate to high; however, the impact of physical activity on acute depression was less robust. A meta-analysis of 35 RCTs (2498 participants) found a modest effect favoring exercise over no treatment or treatment as usual (pooled standardized mean difference of −0.66 (−0.86 to −0.46) in reducing severity of depressive symptoms. However, when only high quality studies were included, the pooled standardized mean difference was not statistically significant for improvement, remission, or quality of life.[121]

A strong bidirectional association has been found between reduction in sleep duration and quality and depression, but few well conducted studies have considered the effect of sleep interventions on depression.[122 123]

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A small RCT in 41 participants with depression and insomnia, in which CBT for insomnia delivered by a therapist for four sessions was compared with an eight week self help program, found a significant reduction in depressive symptoms for CBT for insomnia that was maintained at three month follow-up.[124] All participants were also treated with antidepressants. Studies on social isolation are small, lack external validity, or have found no significant effects on depressive outcomes.[125]

The evidence supports lifestyle interventions as possible adjuncts to established treatments for depression. They may have more positive benefits on intermediate outcomes such as reducing loneliness, improving self esteem, and reducing fatigue than for improving depressive disorder itself and so could be offered to patients who wish not to have psychological or drug treatments and are deemed suitable—for example, those in whom an active monitoring approach is taken.[126]

Physical activity seems to have the strongest evidence base, although further high quality research is needed before it can be recommended as a standalone treatment, even in mild depression. Despite this, primary care providers have an important role in supporting the overall health and wellbeing of patients, many of whom have multiple comorbidities. As such, lifestyle modifications can be an important approach to patient centered care more generally.

Ongoing management

Sequenced approach

The approach to the management of depression when the first intervention fails was established by the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, one of the largest RCTs in mental illness research (n=2876).[127] This set a landmark in proposing the treatment of next choice for people with depression. Over seven years, a series of pragmatic RCTs were conducted to evaluate various drug treatments and CBT as augmentation or switching strategies for patients who did not respond to citalopram (chosen as the index antidepressant) (fig 2). The study design limited the randomization of participants at each level of the process to only his/her range of acceptable treatments in an effort to reflect clinical practice accurately. Participants had to have at least moderate depression as measured on the Hamilton Depression Rating Scale. The primary outcome was remission, with response, defined as an improvement of 50% from baseline, as a secondary outcome.[128] About a third of participants achieved remission with citalopram and a further 10-15% responded but did not reach remission. At the second level, about 25% of participants recovered.

Importantly, no significant differences were seen in the strategies tried. Over the course of all four treatment levels, almost 70% of patients who did not withdraw from the study became symptom free, but the proportion who recovered diminished with each further step. The rate at which participants withdrew from the trial was clinically significant and rose with each level, doubling from 21% dropout after level 1 to 42% dropout after level 3.[127]

The STAR*D trial established that a stepwise approach to the management of depression is effective, and when one intervention has failed another intervention—whether a switch to or augmentation with a drug from the same or a different class or talking therapy—may prove effective. However, efficacy reduces with each intervention tried, and intolerability increases.[128]

Primary care providers may not feel comfortable managing depression by using all the steps trialed in STAR*D—for example, augmentation with lithium or triiodothyronine or the use of tranylcypromine. Most guidelines and professional organizations such as the American Association of Family Physicians have suggested inviting specialist input after two failed interventions in depression (often taken to signify treatment resistance in depression).[129] Given the complexities of managing treatment resistant depression (TRD) in primary care, we support this recommendation. However, individual providers may need to balance these recommendations against ease of access to specialists and other barriers to referral.

Referral to specialist services

Several international studies have shown that only about 20-25% of patients with depression are referred for specialist mental healthcare.[130-132] Primary care providers encounter considerable barriers, both organizational and individual, when referring patients to specialist mental health settings, including availability of and access to the preferred professional, speed of response, and timely provision of information back to the primary care provider.[133 134] Newer models of integrated care can obviate the need for actual referral by using blended in-reach and outreach approaches—for example, through care coordinators supervised by psychiatrists.[135]

The decision to refer patients for specialist input is complex, involving clinician, patient, and practice related factors.[136] Considerable variation exists in individual referral rates, as primary care providers tend to use clinical judgment rather than recommended guidance on when to refer patients.[137] Therapeutic confidence in managing an individual patient's depression and perceived severity of depression seem to play a strong part.[138] When guidelines are strictly followed, the proportion of people referred increases to about 60%,[139] suggesting that family physicians manage a significant burden of disease. English, European, and Australian guidelines recommend referral to specialist services for severe depression, particularly if mood congruent psychotic features are present and if considerable suicidal risk exists.[25 26 95] NICE in England and the Institute for Clinical Systems Improvement in the US suggest that earlier referral should be considered when depression co-occurs with other psychiatric disorders (particularly anxiety disorders and personality disorders)[25 27] or complicates physical illness,[25 27] or if multiple somatic concerns exist.[95] Most guidelines advocate referral for TRD.[25-27 95]

Treatment resistant depression

TRD is usually taken to mean failure to respond to two antidepressant drugs of different classes taken at adequate doses for at least four weeks each.[140 141] The STAR*D trial found that 50% of patients, drawn from a combination of primary care and outpatient psychiatric clinics in

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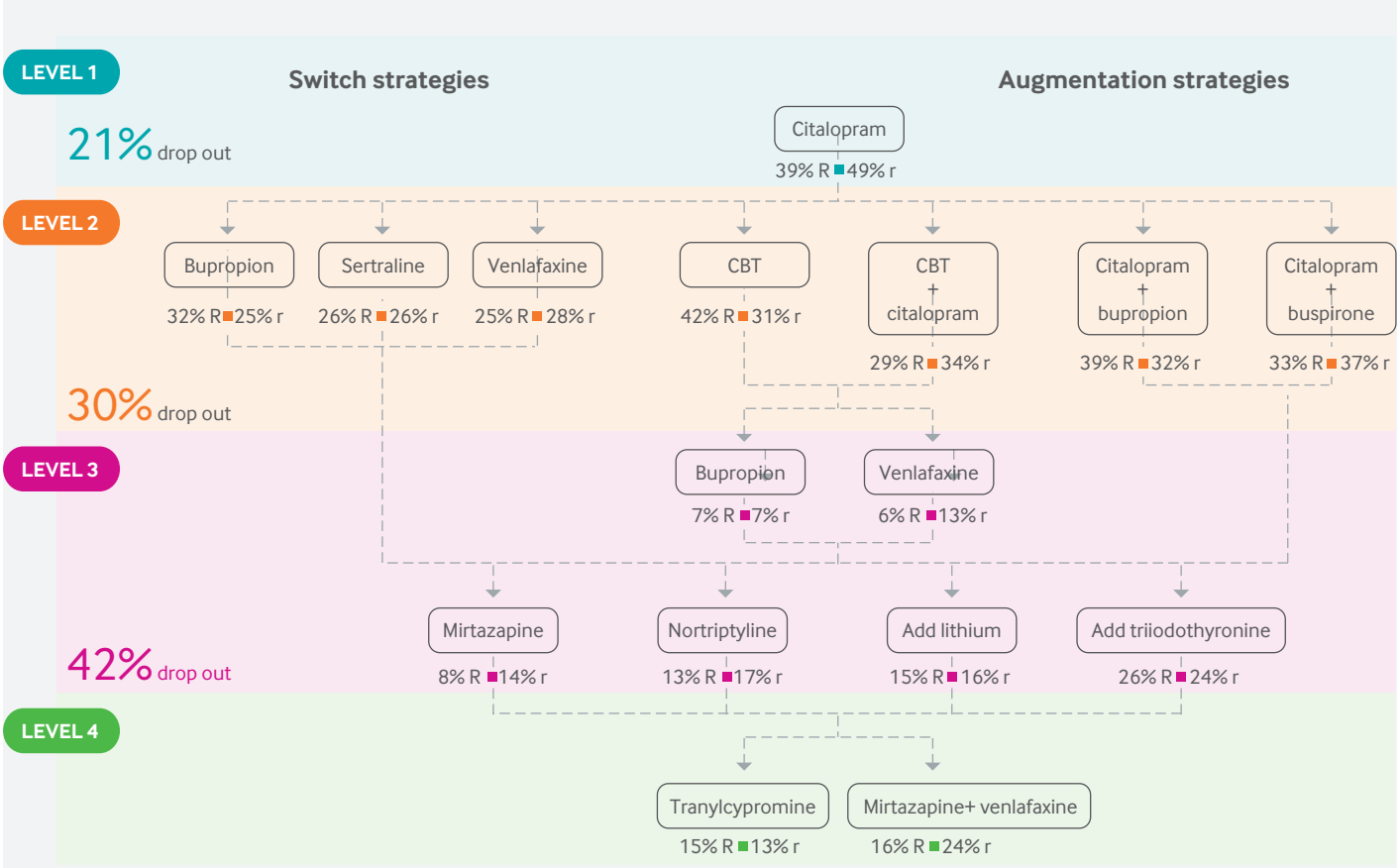

Fig 2| STAR*D algorithm.[127] At level 1, participants were given the selective serotonin reuptake inhibitor (SSRI) citalopram for 12-14 weeks. Those who recovered were followed up for a 12 month period during which citalopram was continued. Those who did not recover or could not tolerate citalopram could move on to the next level. Level 2 was designed to help determine an appropriate next treatment step between switching to a different drug and adding on to the existing citalopram. Those who joined the "switch" arm were randomly assigned to sertraline, bupropion, or venlafaxine. These drugs were chosen for comparison because they represent three different classes of antidepressants: sertraline, like citalopram, is an SSRI; venlafaxine is a "dual action" reuptake inhibitor with both norepinephrine and serotonergic actions, and bupropion is an atypical antidepressant that acts on different neurotransmitters. Participants who chose to augment were given either the atypical antidepressant bupropion or buspirone, which is not an antidepressant but enhances the action of antidepressants. Participants could also switch to, or add on, cognitive psychotherapy. Those who did not become symptom free after 14 weeks, or who experienced intolerable side effects, could continue on to the next level. At level 3, those who chose to switch were randomly assigned to either mirtazapine (a tetracyclic antidepressant) or to nortriptyline (a tricyclic antidepressant). Both have a different mechanism of action from any of the antidepressants that had been tried before. In the level 3 augmentation arm, participants were randomly assigned to either lithium or triiodothyronine, both of which potentiate the effectiveness of antidepressant drugs. At level 4, participants who had not become symptom free at any of the previous levels (and were therefore considered to have highly treatment resistant depression) were taken off all other drugs and randomly switched to one of two treatments—the monoamine oxidase inhibitor (MAOI) tranylcypromine or a combination of venlafaxine and mirtazapine. These treatments were selected to compare a first generation antidepressant, rarely used except when other antidepressants have failed, and a combination strategy that had been suggested to have benefit in treatment resistant depression from earlier research. CBT=cognitive behavioral therapy; R=remission; r=response (taken to mean 50% reduction in depression rating scale)

the US, met this definition.[142] A more recent Canadian estimate of the prevalence of TRD in primary care alone found the figure to be lower at 22%, based on a case report analysis of 1212 patients receiving antidepressants, probably reflecting the milder forms of depression seen in primary care populations.[141]

Many of the strategies used to manage TRD are unsuitable in primary care, either because they require specialist input on initiation such as the strategies advocated in STAR*D or other common practices used now such as augmentation with second generation antipsychotics (olanzapine, risperidone, quetiapine)[143] or because of lack of provision, for example, for psychoanalytic psychotherapy.[144]

However, primary care providers still play an important role in the assessment and management of TRD. Firstly, they can help in distinguishing treatment resistance from inadequate treatment. Multiple studies have found non-adherence to antidepressants to be as high as 40-50% in community samples.[145-147] Some evidence suggests that most patients considered to have TRD in primary care have not had drugs prescribed at the recommended doses or for the recommended length of time or have not taken them as prescribed.[148] Secondly, primary care providers help in monitoring the effect and some of the side effects of commonly used treatment strategies such as augmentation with lithium or antipsychotics.

Finally, given the difficulties in accessing specialist services that some patients encounter, primary care providers may wish to be aware of some emerging strategies for TRD that may be suitable in primary care. For example, the CoBalT study in 2012 recruited 469 participants

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Box 2 | Essential elements for measurement based care in primary care setting[163]

- Assessments that are:
  - Targeted to a specific issue with key outcomes
  - Tailored to the individual
  - Based on psychometrically and conceptually sound clinical measures
  - Brief and inexpensive
- Action plans that are:
  - Tailored to the individual
  - Action oriented and evidence based for stepped care
  - Flexible to allow treatment revision and adaptation
  - Evaluable to track the patient's progress

with TRD from 73 general practices across England and Scotland and compared augmentation of antidepressants with 12-18 sessions of CBT with treatment as usual.[149] It found an odds ratio of 2.89 (2.03 to 4.10) for treatment response at 12 months after augmentation with CBT, giving a number needed to treat of four for response. The study needs to be replicated, but it suggests that drug treatment in combination with psychological input may be more effective than either alone.[150]

Strategies for effective management of depression in primary care

The management of depression in the primary care setting is often suboptimal, and evidence suggests that as few as 20-40% of older adults with depression or dysthymic disorder prescribed treatment for depression in primary care show substantial clinical improvements at 12 months.[151] Time constraints, conflicting demands, and diverging priorities are major barriers to primary care providers effectively treating depression.[152] Thus, to meet the needs of patients and the expectations for implementing evidence based approaches to care, primary care providers will need to be better prepared to diagnose and treat depression and, perhaps more importantly, be supported by a practice infrastructure that adapts the functionality of the chronic care model. Purchasers and policy makers will also need to develop and implement policies that support and incentivize these structures and activities in the primary care setting.

Training primary care providers

Despite their increasing role in the management of depression,primary care providers typically have minimal training in behavioral health. Poor levels of detection, treatment, and monitoring of depression have been extensively documented.[153-155] Providers often feel ill prepared to meet the needs of these patients, and training for depression has been perceived as inadequate by some professionals.[156]The delivery of behavioral health services in the primary care setting thus requires a new approach to the way physicians are trained and monitored to practice across the span of their primary care careers.[157]

Considerable research has been conducted to identify specific strategies to improve the performance of primary care professionals in recognizing and treating depression. Most efforts that have focused on improving screening, education of primary care professionals, development of clear treatment guidelines, and strengthening referral systems have been ineffective in reducing the burden of depression in primary care overall.[158] Educating primary care professionals on the detection and treatment of depression alone has not been found to improve recognition, treatment, or outcomes for depression.[159 160] However, a systematic review in 2012 showed that training plus the additional implementation of guidelines and the use of more complex interventions in primary care resulted in a significant reduction in depressive symptoms.[161]

Management based care

Importantly, the consistent use of a measurement based care (MBC) approachto management of depression in the primary care setting has emerged as a strategic approach that involves patients in the decision making process and assures that they do not "fall through the cracks."[162] MBC, defined as enhanced precision and consistency in disease assessment, tracking, and treatment to achieve optimal outcomes,[163] is an approach that has been used universally in the chronic medical disease management model and offers great potential for the management of depression in primary care. MBC has several key features, which are summarized in box 2.

MBC, however, is not without its limitations, and critics cite concerns about a focus on measurement,potentially at the expense of the doctor-patient relationship.[164] An MBC approach should complement the primary care professional's clinical judgment, and, as with treating any chronic illness, working with patients to improve their adaptive and problem solving skills as well as their capacity for self management and self monitoring should also be a priority.Primary care professionals play an important role in creating a positive experience of careoverall, and they must establish a therapeutic alliance with patients, as well as with families and caregivers.

Importantly, when considering their role, primary care providers must determine the level of intervention that the practice can support to manage depression effectively. If a team based approach is in place in the practice, the primary care professional should assume a central leadership role. If a referral is made, he or she must function as the coordinator of care, ensuring timely and consistent communication with the specialist. The nature and quality of collaboration and continuity often depend on communication and the referral relationship itself, which may affect patients' outcomes and the overall quality of care.[165 166]

These findings support the growing recognition that structural changes within a practice are often needed to appropriately manage depression in primary care.

Practice infrastructure

Developed according to the principles of chronic care, models for the pragmatic delivery of care for people with depression in primary care have emerged with a strong evidence base, particularly the collaborative care model (CCM).[151] A recent systematic review found that this team based approach was associated with significant improvement in depression outcomes compared with usual care.[167]

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Box 3 | Core processes involved in the collaborative care model[135]

Collaboration between different providers
A multidisciplinary group of health professionals (usually a primary care provider, care management staff, and psychiatrist) provides care in a coordinated fashion, being collectively responsible for the health outcomes of a defined population of patients

Stepped care approach
The members of the team are empowered to work at the top of their professional training by delivering specifically proven, evidence based treatments in a such manner that the most effective yet least resource intensive treatment is delivered first, "stepping" up or down according to response

Outcomes driven improvement
The team uses systematic, disease specific, patient reported outcome measures (for example, symptom rating scales) to drive clinical decision making

In many ways the CCM operationalizes the MBC approach through three core processes (box 3).[135] The CCM can improve physical and mental health outcomes in primary care with little to no net health costs.[168] However, it has not been adopted widely outside well resourced or academic centers, as successful implementation requires alignment of financial incentives to support system redesign, adequate funding to sustain change, and adaptation to local contexts and practices.[169 170] New evidence from qualitative systems-wide analysis has shown that a multitude of structural factors (for example, co-location of care, electronic infrastructure), processes (team working, care coordination, quality outcome measurement), external contexts (reimbursement, licensing arrangements), and internal factors (organizational culture) interact with each other to either facilitate or hinder effective delivery of mental healthcare in primary care.[171] Integration of primary care and specialist mental healthcare can therefore be considered a product of transformative change that is dependent on internal and extra-organizational systems and contexts.

In such a complex landscape, primary care providers can feel overwhelmed by healthcare delivery redesign and struggle with how to implement this type of team based care for patients with mental health needs in the primary care setting. To meet the challenge, a framework has been developed that delineates the steps primary care practices can take to build up towards more advanced models of integrated care delivery for people with common mental disorders.[172] With use of a maturity matrix structure, options for implementation include screening and referral processes; multidisciplinary team working; care coordination; systematic quality improvement; measurement based, stepped care; self management; and linking with community/social services, which can be adopted singly or in combination according to local need and the strengths of providers. The framework is being piloted in the state of New York.[173]

Broader community connections

In addition to preparing providers to apply appropriate clinical strategies at the primary care level and building a practice infrastructure, it is important to establish a set of connections with behavioral health specialists and other resources in the community, along with policies that promote and encourage better outcomes for patients. Primary care practices should have a network of trusted and reliable specialist partners that can provide both formal and informal consultation, as well as ongoing care for more complex or treatment resistant patients whose needs extend beyond the practice's capacity. Ideally, these partnerships should be characterized by having formalized agreements that specify respective responsibilities, assure access, provide "greased" referral mechanisms, include information sharing arrangements, and detail any financial expectations. Effective care often involves tackling the key social determinants of health, along with behavioral health conditions. Thus, it is important to foster effective linkages to housing, vocational, and other supportive social services and to community organizations and resources, and for relevant social determinants to be incorporated into care plans.

Payment policies

Current reimbursement and accountability models generally fail to support and incentivize both the establishment and maintenance of the recommended practice infrastructure and provider behaviors. Payment policies, regardless of the system of care in which they are embedded, need to provide flexibility, start-up cost support, integrated team training, data management infrastructure, and incentives for establishing and sustaining the practices described above. One major mechanism to facilitate such transformative change is the accountable care organizations initially developed in America, and now being translated to European and Australian contexts. These facilitate coordination across a range of provider settings and link reimbursement to improvements in outcomes for a defined patient population.[174]

There are clear synergies between accountable care organizations and the processes advanced by the CCM. The key will be adapting newly developed payment policies and accountability mechanisms to instill a sense of shared accountability between behavioral health and general medical providers. Newer payment approaches need flexibility to circumvent limitations in fee-for-service models and support the CCM infrastructure—for example, by incorporation of care coordinators. An essential step will be the development of quality measures at the interface of depression and physical health. At present, ratified measures—and indeed clinical guidelines—tend to focus on single conditions, whereas depression often co-occurs with other conditions,[175] both physical and psychiatric.[176] Work has begun to identify the gaps in the evidence base and prioritize areas of need for the development of quality outcomes, both clinical and personal recovery focused, that could aid primary care professionals in their goal of meeting the physical, psychological, and social needs of their patients with depression.[177 178]

Emerging treatments

New and emerging interventions have been, or are in the process of being, developed in psychotherapy, pharmacotherapy, and physical treatments for the management

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Table 3 | Summary of recommendations

Point of care	Recommendations	Elaboration/caveats
General principles	The aim of treatment should be remission from depression for ≥2 months. Emphasis should be placed on return to functioning over reduction in symptoms. However, where this is not possible, symptom reduction should be sought as it is associated with reduced relapse and increased likelihood of recovery over time [B]	Patients themselves may value improvements in features such as self confidence and optimism above symptom reduction [C]
	Treatment choice should ideally be made using an SDM approach taking into consideration the patient's circumstances and preferences [B]	The use of decision aids to support an SDM approach takes time (one study suggested a median of 40 min), so this may not be practicable in primary care. Facilitating the SDM approach may require changes at the organizational level or expanding the roles of other health professionals such as physician associates or prescribing pharmacists [C]
	Management should follow a stepped care approach, in which treatment is guided by the severity of depression, requiring active monitoring of symptoms and functioning [A]	
Treatment of mild depression	Consider active monitoring for patients who do not want psychological or pharmacological interventions [C]	
	A program to increase physical activity, either in group or individual settings, may be more effective than no treatment or treatment as usual in reducing severity of symptoms [D]	Evidence supports physical activity as a strategy for primary prevention of depression at a population level, although "moderate to vigorous exercise" may be needed to produce results [B]
	Low intensity psychological interventions are more effective than control: (1) psychological counseling that adheres to a psychological modality [B]; (2) self help guided by a psychologically trained professional [B]; (3) computerized CBT [A]. Many of these therapies may be offered remotely through digital technology and have efficacy over treatment as usual or wait list control [B]	Non-specific interpersonal factors, especially the therapeutic relationship between therapist and client, client expectation, and suitability for psychological intervention as judged by a clinician, may be more important than the type of therapy offered [B]
Treatment of moderate to severe depression	Specific high intensity psychological interventions and pharmacological interventions have comparative effectiveness above control [A]	
	High intensity psychological interventions with effectiveness above control include CBT [A], PST [B], and (IPT) [B]	
	If considering drug treatment, recommendations should be made on the basis of the patient's preference and circumstances, especially considering the relative side effect profile of the different antidepressants [B]	SSRIs should be prescribed with great caution in older adults because of increased risk of falls [B], fractures [B], hyponatremia [B], upper gastrointestinal bleeding [B], and cerebrovascular bleeding [C]
Management of non-response to initial treatment	Change to other drug—either within class or from a different class—may prove effective if the first intervention has failed [A]	According to the STAR*D trial, the effectiveness of interventions decreases and attrition increases with each failed intervention [A]
	Change from psychological therapy to pharmacological intervention may prove effective if the first intervention has failed [A]	
	Combination of pharmacological and psychological treatments may be more effective than either alone [A]	
Prevention of relapse	Antidepressants continued for ≥6 months after remission reduce risk of relapse [A]	
	Certain psychological treatments, provided as maintenance interventions during remission, are effective at preventing relapse above control. These are CBT [B], IPT [B], and MBCT [C]	
Referral to specialist services	There is low level evidence to guide decisions to refer patients for specialist services. Of these, high risk of suicide, treatment resistance, and severity of depression are the most commonly cited reasons [C]; patient preference and co-occurring mental or physical disorders are also commonly cited [D]	Most primary care physicians use clinical judgment to refer patients to specialist services, based on their perceived competencies and confidence in managing the patient [C]
		When guidelines advocating a stepped care approach are followed, referral rates increase [C]
	In addition, several guidelines recommend referral to specialist services when two interventions, which the patient has adhered to for an adequate length of time, have failed (this is often taken to mean treatment resistance) [C]	
Organizational changes	Simple educational strategies aimed at helping primary care professionals to better detect and treat depression may not be effective at improving diagnosis of depression or reducing severity of depression, unless combined with organizational strategies such as revision of professional roles (eg, introduction of nurse led case management) or formal integration of services [C]	
	MBC—a practice that bases clinical care on routine and systematically collected outcome data throughout treatment—may be more effective than usual care at achieving response and remission and reducing time to both [B]	MBC should be used to complement clinical judgment, in a patient centered manner, in collaboration with patients, their families, or caregivers [D]
	The CCM is more effective than usual care at reducing severity of depression, achieving remission, and improving satisfaction and quality of life for older adults with depression and in those with co-occurring long term physical conditions treated in primary care [A]	The CCM is a complex intervention that requires changes to multiple processes at multiple levels of a system and should be considered a transformative change in primary care [C]
	The CCM is probably cost effective (at a health system level) at treating depression in primary care when targeted to specific subgroups (eg, older adults and those with co-occurring chronic physical conditions) [B]	

CBT=cognitive behavioral therapy; CCM=Collaborative Care Model; IPT=interpersonal therapy; MBC=measurement based care; MBCT=mindfulness based cognitive therapy; PST=problem solving therapy; SDM=shared decision making.
Evidence for each recommendation was graded using the Oxford Centre for Evidence-Based Medicine (CEBM)'s levels of evidence.[196] A=consistent level 1 studies; B=consistent level 2 or 3 studies or extrapolations from level 1 studies; C=level 4 studies or extrapolations from level 2 or 3 studies; D=level 5 evidence or troublingly inconsistent or inconclusive studies of any level. Level 1=systematic reviews (with homogeneity) of randomized controlled trials (RCTs) or individual RCTs (with narrow confidence interval); level 2=systematic reviews (with homogeneity) of cohort studies, individual cohort study (or low quality RCT—eg, <80% follow-up), "outcomes" research, or ecological studies; level 3=systematic review (with homogeneity) of case-control studies or individual case-control study; level 4=case series (and poor quality cohort and case-control studies); level 5=expert opinion without explicit critical appraisal or based on physiology, bench research, or "first principles."

of depression. Most of these are still used principally in experimental or specialist settings, but they may become more widespread in the future.

Third wave psychotherapies

The so-called third wave psychotherapies seem to have the most applicability to primary care. These are a heterogeneous group of therapies that both expand and deviate from traditional cognitive and/or behavioral approaches and include acceptance and commitment therapy (ACT) and mindfulness based cognitive therapy (MBCT). Whereas previous modalities have aimed to eliminate or reduce problematic cognitions or dysfunctional behaviors, third wave therapies focus on empowering the patient by increasing skills and behavioral repertoires so as to be able to respond to various stressful and non-stressful events.[179] They have been of particular interest in the treatment of depression co-occurring with complex physical illnesses such as cancer or physical pain.[180]

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QUESTIONS FOR FUTURE RESEARCH

1. How can we further develop the science of "precision medicine" for depression treatment to inform such questions as:
   - For relatively mild forms of depression, how can patients and their primary care providers differentiate who should receive "watchful waiting" (that is truly watchful, consistent with measurement based care) and who should receive active intervention?
   - How can primary care professionals determine to which drugs a patient is most likely to respond? To which psychological therapy? To which combination of the two?
   - How can primary care professionals differentiate patients who may develop manic symptoms in response to antidepressant treatment?
   - What are the most effective strategies in treating treatment resistant depression?
2. Given the bidirectional impact of depression and social, employment, educational, and economic outcomes, how can primary care professionals best integrate interventions across healthcare and social service settings?
3. What are the best ways to train, support, and incentivize healthcare professionals to recognize, understand, and effectively treat depression?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

We sought feedback from several different sources in compiling and modifying our reviews. Members of the Wellbeing Network Hounslow Community who live with depression in west London gave us feedback on the written manuscripts. They placed a particular emphasis on being actively listened to by their general practitioners (GPs) when presenting with depression and for GPs to take a holistic view of their condition. Patients wanted to feel included in treatment decisions and to be able to build trusting relationships with their GP. Self management strategies, supportive therapy, and, when needed, targeted psychotherapy were held in high regard. Many people commented on the lack of time GPs had and the need for specific training on assessing and managing mental health needs, especially when co-occurring with other illnesses such as anxiety disorders or physical conditions.

Members of the Ealing Primary Care Mental Health Services Service Users Forum also shared insights from their care being transferred from specialist to primary care services in England. Common themes included adjusting to the reduced frequency of contact in primary care (compared with specialist services); how to access care, particularly in crisis; and the level of mental health training available to primary care professionals. Care coordination functions and a single point of contact were frequently proposed solutions to some of these difficulties.

Finally, we sought individual and personal insight from a retired GP who has lived with paraplegia from a spinal cord injury for many years as well as with major depressive disorder, which is treatment resistant. The depression preceded the spinal cord injury and is unrelated to it. He told one of the authors (PR) that at times the depression has been more disabling for him than his paraplegia. He spoke about his experiences of living with both mental and physical disability, which exemplified many of the themes identified through the focus groups: "I was taking antidepressants at the time of my accident (although I was not depressed). Early on in my rehabilitation I did become depressed and had suicidal thoughts, perhaps because my antidepressants were stopped and on discharge I became very fed up. The difference between being in a wheelchair-friendly hospital environment and the outside world was stark. This was 30 years ago when things were worse than they are now. After a year or so I did improve on antidepressants and went back to work. For the next 25 years I was fine—not bothered by my disability. Although I continued to have recurrent depression, it was treated successfully with medication. I had an active life filled with holidays, academic interests, and spinal cord injury charities. But over the past two years things have got worse. The antidepressants no longer controlled my depression and the symptoms resulted in me spending most of my life in bed asleep or in a chair. As a result, I became less fit, less strong, and more disabled. The depression and increased disability resulted in less social contact. I resent my disability now."*

*Written permission to use this quote has been granted by the subject.

Two meta-analyses of ACT in a variety of mental and physical problems found it to have small to moderate effects sizes over control in reducing depression.[181 182] However, both analyses suggested serious biases in the published literature. A systematic review found "very low quality evidence" that ACT was as effective as traditional CBT in the treatment of depression. MBCT has weak evidence of efficacy in treating acute depression.[183] However an individual data level meta-analysis of 1248 participants that found fewer patients who received MBCT had a depressive relapse over a 60 month follow-up compared with non-MBCT interventions (including drugs) or control (hazard ratio 0.69, 0.58 to 0.82), suggesting that it may be more efficacious in the prevention of depressive relapse than in the treatment of the acute disorder.[184]

Drug treatments

New drug treatments for depression have also become available but are not yet routinely used in primary care.[185 186] Some are unsuitable for use in primary care. Ketamine, a glutamatergic antagonist, for example, has received much attention and may produce dramatic effects in symptom reduction; however, it is administered by intravenous infusion and is associated with significant adverse effects including potential for abuse.[187 188] Attempts to deliver it intranasally have proved disappointing.[189] However, since the acceptance of this review for publication the US Food and Drug Administration has approved the use of an intranasally delivered form of ketamine (esketamine) for treatment resistant depression. The promise of ketamine has raised the possibility of developing compounds to target neurotransmitters beyond the traditional serotonergic and noradrenergic systems.[190] These include cannabinoid derivatives and anti-inflammatories.[191] Early studies with celecoxib (a non-steroidal anti-inflammatory drug) in combination with SSRIs have provided mixed results on efficacy and tolerability.[192 193] More success has been seen with agomelatine, a melatonin receptor agonist. A large network meta-analysis published in 2018 found that agomelatine was more effective than other antidepressants in head-to-head comparisons and was better tolerated, although both these results may have been skewed by the novelty effect.[83]

Physical procedures

Primary care providers should generally be aware of the growing interest in the use of non-invasive physical procedures such as repetitive transcranial magnetic stimulation (rTMS) to manage depression. A powerful electromagnet is placed on the scalp and produces electrical currents in specific cortical and subcortical structures of the brain. Most of the literature has assessed its efficacy in TRD, in which good evidence shows that it performs better than sham treatment. A meta-analysis of 81 RCTs (4233 participants) found that rTMS was significantly more effective than sham treatment for response, acceptability, and remission (odds ratios varied from 2.48 and 4.95 depending on the location of the nodes and intensity of the rTMS being delivered).[180] However, rTMS did not outperform any active comparators, replicating previous findings that it is not superior to other treatments for TRD such as electroconvulsive therapy.[194 195] Primary care professionals should, therefore, advise patients that it may benefit some patients with TRD, but not all, and there is not enough evidence to support its use as monotherapy.

Conclusions

Effective management of depression in primary care requires strategies at the individual and organizational level. Table 3 shows our recommendations. At the individual level,

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choosing the most suitable intervention depends on clinical and person specific factors, including relative benefits and harms, interactions with other conditions or interventions, previous response, and the patient's preference. Treatment choice should be considered a collaborative venture in which the most preferable intervention is chosen according to the patient's circumstances and preferences. Collaboration is also needed within the wider system. Adequately training primary care providers in the recognition and treatment of depression and mechanisms to facilitate efficient working practices between specialist and primary care services (such as routine measurement based care) can support primary care professionals to better help their patients with depression.

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