Chapter 6

Other treatments

Edward S Friedman

Psychotherapy for depression

Several depression-focused psychotherapies [1] have been developed to be time-limited treatments. They have an explicit goal of helping the individual achieve rapid relief of depressive symptoms, inasmuch as they are treatments comparable to pharmacotherapy in time course and efficacy. Furthermore, by emphasizing short-term goals, these therapies capitalize on the acute nature of many episodes of depression. Shared features of the depression-focused psychotherapies include their specific linkage of a theoretical model of phenomenology with strategies for symptom reduction, with specification of methods to facilitate training and enhance fidelity, and with acceptance of the need to identify observable and measurable goals and outcomes. The major types of time-limited depression-focused therapies that have reliably established comparability to antidepressant medications in randomized controlled trials (RCTs) include cognitive therapy (CT) [2] and IPT [3]. The particular theoretical orientation of each model of treatment also yields predictions about specific outcomes, such as the effects of CT on measures of dysfunctional attitudes or interpersonal pyschotherapy (IPT) on measures of social adjustment. Finally, these therapies share several pragmatic features, including their compatibility for use in combination with pharmacotherapy and their suitability for use by therapists with a range of backgrounds and training.

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IPT aims to relieve depression through the recognition that depression occurs within an interpersonal context regardless of its severity, phenomenology, or presumed etiology. IPT therapists help patients to understand and modify interpersonal problems associated with depression. Additional long-term benefits include improved social function and prophylaxis against relapse. IPT developed from the recognition that high rates of life stressors are associated with the onset of unipolar depression. Consequently, IPT often focuses on the relationship between attachment bonds and vulnerability to depression. Helping the patient strengthen his or her intimate relationships may enhance the apparent protective or "neutralizing" role of social support. Another important aspect of the depressed person's social milieu is his or her performance in the workplace, with friends and peer groups, and in the neighborhood or community. Attention to social role performance thus includes the individual's current and long-term patterns of functioning in diverse situations, as well as more recent or still-evolving role transitions. IPT is a psychoeducational intervention because, in addition to the strong social emphasis, therapists teach patients about depression and its treatment. This includes providing practical advice or recommendations to help patients better tolerate the symptoms of depression and manage impairments associated with the depressive state. These efforts also serve to help lessen the demoralization and hopelessness experienced by most depressed people. The therapy may be quite active in this regard, including providing assistance to patients through the use of problem-solving strategies. IPT therapists are encouraged to identify one or more of four common interpersonal conflict situations to serve as the focus for therapeutic change: unresolved grief, role disputes, role transitions, and interpersonal deficits.

The cognitive model of depression and CT derive from the work of Aaron Beck [2]. Beck recognized that depressed patients view themselves, the world, and their future in a negative manner (*the cognitive triad*). These negative cognitions (*automatic negative thoughts*) provide the gateway for the cognitive therapist to understand the depressed patient's phenomenological world. The patient is taught to identify and challenge dysfunctional thoughts, understand their guiding beliefs, and revise their dysfunctional attitudes. Therapists help patients discover their

unconscious attitudes through the use of Socratic questioning and guided discovery exercises. According to the CT model, depression results from unconscious dysfunctional beliefs being activated by current environmental stimuli, eliciting thoughts of helplessness, hopelessness, and worthlessness. It is believed that adverse early experiences are responsible for the individual learning inadequate coping strategies. This stress-diathesis model may explain why only some individuals become depressed after a stressor such as divorce or unemployment. The therapeutic relationship in CT is described as being one of *collaborative empiricism*, where the therapist assumes the role of a coach or teacher in addition to providing the more traditional nonspecific elements of empathy, understanding, and support. Through this model of interaction the therapist and patient develop step-wise goals to reduce symptoms, improve management of pressing day-to-day problems, and increase morale. Collaboration is explicitly fostered via the use of summarization and feedback to ensure that the patient thoroughly understands the material being covered. CT also draws heavily on the principles and methods of behavior therapy, including activity scheduling, graded task assignments, guided practice, and individualized homework assignments. Explicit, step-wise strategies are used to improve recognition of problem areas and effect changes in thoughts, behaviors, and feelings. As with other types of psychotherapy, the establishment of a strong therapeutic relationship based upon warmth, empathy, and genuineness is crucial to obtaining positive outcomes. A strong therapeutic alliance enhances learning and the mastery of targeted therapeutic tasks. Compared with the process of more traditional dynamic therapies, CT requires greater therapist activity.

Furthermore, CT differs from dynamic or experiential therapies in that affect is specifically used to identify a cognitive process by which depressed patients learn to solve problems and gain greater control over dysphoric and anhedonic moods. Like IPT, typical CT treatment of acute depression involves 12–14 therapy sessions over a 3- to 4-month period. Longer-term CT therapy can be useful for prevention of relapse of acute depressive episodes, and to revise core beliefs and dysfunctional behavioral patterns in individuals with longstanding personality or characterologic disorders.

Combination psychotherapy and psychopharmacotherapy

The goal of both psychotherapy and pharmacological treatment is to eliminate all manifestations of disorder, but individuals frequently do not achieve adequate clinical response, and relapse and recurrence are common [4]. Often referred to as "combined" or "combination" treatment, psychiatric treatment utilizing both psychotherapy and pharmacology is frequently used in practice to treat depression [1,5,6]. There are several different definitions of "combined" treatment; for example, the combination of treatment can be offered simultaneously or additively. Additive treatment can be in one of two sequential orders: psychotherapy (either individual or group) first augmented by medication or pharmacological treatment supplemented by therapy. Combined treatment can be "split" and provided by multiple providers, or integrated, with the psychiatrist providing both treatments.

Lacking a strong empirical basis, much of the existing literature discussing the pros and cons of combined treatment is based on clinical opinion and theoretical speculation. The prevailing arguments for and against combining therapy and medication are highlighted in Figure 6.1 [6]. There are a growing number of clinical trials showing combined treatment to be superior to either type of intervention used alone for depression [5,7]. Nevertheless, expert consensus panels have recommended combination treatment for the treatment of depression, especially when the illness presentation or course is complicated [8,9]. Some circumstances in which combination treatment may be helpful include the following:

- when either treatment alone, optimally given, is only partially effective
- if the clinical circumstances suggest two discrete targets of therapy (eg, symptom reduction addressed by medication and social/occupational problems addressed by psychotherapy)
- if the prior course of illness is chronic; for relapse prevention in patients achieving only a partial response to pharmacotherapy in the acute phase
- to aid in improving medication adherence and treatment compliance.

Pros and cons of combined psychotherapy and pharmacology

Adding psychotherapy	
Pros	**Cons**
Helps with medication management and improves compliance	May lead therapist to ignore biological factors and place too much responsibility on the patient
May increase positive expectancy of medication (placebo effect)	Therapy could place undue stress on patients with biologically driven illness states
Decreases risk of relapse of psychiatric disorder)	
Improves social and occupational functioning	
Lessens impact of psychosocial stressors and allows patient to gain self-understanding of more adaptive coping strategies	
Adding pharmacology	
Pros	**Cons**
Provides symptom relief and helps patient engage better in therapy (eg, improve concentration, hyperarousal, or decrease fatigue)	Prematurely decreases target symptoms and decreases motivation for therapy or to learn new ways to cope without medication
Stabilizes ego functions to enable better psychotherapy participation	May imply to patients that they cannot handle their disease
May increase positive expectancy of therapy (placebo effect)	Elicits negative transference reactions or undercuts psychological defenses
Decreases distorted or irrational thinking that interferes with therapy progress	Medications can interfere with learning and memory or cause "state-dependent" learning in therapy
	Increases risk of relapse if discontinued, which may negatively impact on prevention efforts of therapy

Figure 6.1 Pros and cons of combined psychotherapy and pharmacology. Adapted from Szigethy et al [6].

The intriguing findings of Mayberg and colleagues demonstrating the brain regions associated with antidepressant and cognitive-behavioral therapy (CBT) activity provides an explanatory model for combined treatment. Mayberg identified the prefrontal cortex as being a target of pharmacotherapy, with the highest concentration of serotonin in the brain [10]. Goldapple and co-workers, analyzed patients treated with an selective serotonin reuptake inhibitor (SSRI; paroxetine) and CBT, and demonstrated that CBT is associated with characteristic metabolic changes in the frontal cortex, cingulate, and hippocampus rather than

the characteristic changes in the prefrontal cortex, hippocampus, and cingulate regions that result from treatment with SSRIs [11]. Mayberg and colleagues interpret these findings as indicating that CBT and medications have different primary anatomical targets of action, with cortical "top-down" effects characterizing psychotherapy effect and subcortical "bottom-up" effects accounting for the effect of medication [10]. These imaging data lend support to a theoretical position suggesting that combination treatment of depression may be synergistic in its benefits because the different modalities affect different brain regions.

There are clinician and patient factors that influence the use of combination treatments. Clinicians have theoretical biases that can influence the therapeutic process during combination treatment, some oriented by preference and training to practice a specific form of psychotherapy, such as psychoanalysis, CBT, or IPT (Figure 6.2) [12]. These clinicians may view psychotherapy as the primary treatment modality with pharmacological agents being used adjunctively. For psychoanalysts, obstacles to combination treatment may include the following:

- maintaining their theoretical orientation while assessing the benefit from adjunctive medication;
- a relative inexperience with medication treatments; and
- a lack of role models for combined treatment.

Psychological treatment for mild, moderate, or severe depression

Improving symptoms

Likely to be beneficial:

- ITP (mild-to-moderate depression)
- CT (mild-to-moderate depression)
- Combining antidepressants and psychological treatment (mild-to-moderate and severe depression)

Unknown effectiveness:

- Befriending (mild-to-moderate depression)
- Nondirective counseling (mild-to-moderate depression)
- Problem-solving therapy (mild-to-moderate depression)

Reducing relapse rate

Unknown effectiveness:

- CT (weak evidence for reduced relapse rates 1–2 years after mild-to-moderate depression)
- Relapse prevention program (no significant difference in response rates)

Figure 6.2 Psychological treatment for mild, moderate, or severe depression. CT, cognitive therapy; IPT, interpersonal psychotherapy. Adapted from Butler et al [12].

From a CBT perspective, the focus of combined treatment is the synergistic use of each modality to maximize the effect of the other modality. For a psychopharmacologically oriented psychiatrist, psychotherapy may be seen as a modality to primarily augment the use of medication. Although there may be disagreement about which approach is the most clinically efficacious, most psychiatrists agree that, optimally, combining modalities should be complementary and improve overall patient care. Another critical factor to consider in evaluating if combination treatment should be used is patient expectation and acceptance of two treatments. It is important to explore patients' understanding of treatment options, their objections to different components, and depression treatments available to them. Providing psychoeducation about combination treatment may also minimize medication noncompliance and improve treatment adherence. Thus, the examination of interpersonal, emotional, and cognitive obstacles to treatment may promote more positive pharmacological outcomes. Fostering the patient's readiness to change and strengthening the doctor–patient alliance are important factors mediating the efficacy of medication treatment. In conclusion, the delivery of combined treatment is often complicated by multiple providers, and the expectancies of patients and the providers, each bringing their own life experiences, expectations, fears, fund of knowledge, and theoretical biases to the treatment setting.

Physical treatments

In addition to pharmacological and psychological treatments of depression, there are a number of physical treatments (eg, electroconvulsive therapy [ECT], phototherapy, and acupuncture) with evidence for their use. There are also several experimental stimulation treatments for depression that are currently under study, including vagus nerve stimulation (VNS), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS).

Electroconvulsive therapy

ECT has been proven to be a safe and effective treatment for depression, and has been used successfully for more than 70 years [13]. Several recent, large-scale, multisite, collaborative studies have confirmed the efficacy of ECT for depression. In the Consortium for Research in ECT

(CORE) study, 217 individuals with major depression received a course of ECT; the investigators reported a remission rate of 75% at completion and 65% at 4 weeks [14]. Similarly, another multisite collaborative study of 290 depressed individuals receiving ECT reported a remission rate of 55%. In another study, the CORE investigators examined whether receiving an additional 10 treatments of ECT or continuation pharmacotherapy improved rates of relapse over 6 months of follow-up. They found no difference between the treatments, with one-third relapsing and less than half remaining well, and concluded that both treatments had limited efficacy [15].

The UK ECT Review Group (2003) performed a systematic review and meta-analysis of short-term efficacy from randomized controlled ECT trials. They report that real ECT was significantly more effective than simulated (sham) ECT (6 trials, 256 patients, standardized effect size [SES] −0.91, 95% confidence interval [CI] −1.27 to −0.54), treatment with ECT was significantly more effective than pharmacotherapy (18 trials, 1144 participants, SES −0.80, 95% CI −1.29 to −0.29), and bilateral electrode placement was more effective than unipolar (22 trials, 1408 participants, SES −0.32, 95% CI −0.46 to −0.19) [16]. Another meta-analytic review of randomized controlled ECT trials compared ECT with simulated ECT, placebo, or antidepressants. They found a significant superiority of ECT in all comparisons: ECT versus simulated ECT, ECT versus placebo, ECT versus antidepressants in general, ECT versus tricyclic antiepressants (TCAs), and ECT versus monoamine oxidase inhibitors (MAOIs). In addition, they compared nonrandomized controlled ECT trials and found a significant statistical difference in favor of ECT versus antidepressants. They suggest that ECT is a valid therapeutic tool for treatment of depression, including severe and resistant forms [17].

The American Psychiatric Association (APA) Task Force on ECT [18] provides a good review of current clinical standards for the treatment, training, and privileging of ECT treatment [19]. The primary indications for treatment are a lack of response or intolerance to antidepressants, a previous good response to ECT, the need for a rapid treatment response

because of psychosis or risk of suicide, or the presence of extremely severe or chronic depression. Clinicians must review with the patient and/or family members appropriate alternative treatments, and evaluate the risks and benefits of ECT treatment for the individual. Factors associated with reduced ECT efficacy include prolonged duration of the current depressive episode, lack of response to medication, and the presence of a comorbid personality disorder [13]. There are no absolute contraindications, although those with unstable cardiac disease (eg, ischemia or arrhythmia), cerebrovascular disease (eg, recent cerebral hemorrhage or stroke), or increased intracranial pressure are at increased risk for complications [20].

Phototherapy

Phototherapy – the use of light treatment – was developed to treat, and has become the first-line treatment for, individuals with seasonal affective disorder (SAD) [21]. Meta-analysis has suggested the efficacy of light therapy in the treatment of seasonal and nonseasonal depression with effect sizes equivalent to that of most antidepressant pharmaceutical trials [22], although caution is warranted as the quality of studies included is poor and in the UK, the 2009 NICE guideline review that included better quality studies concluded that SAD should be managed in the same way as nonseasonal depression [23]. However, the guidelines acknowledge that phototherapy has been associated with an improvement in depression fatigue, sleepiness, and health-related quality of life [24]. In addition, it has shown efficacy for the treatment of premenstrual [25] and antepartum depression [26]. Three out of four SAD sufferers are women and the usual age of onset is between 18 and 30 years [27]. As is characteristic for the disorder, winter seasonal depression spontaneously remits in the spring and summer (less frequently, some individuals have a depressive pattern characterized by summer depression and spontaneous winter remission). The most common form of phototherapy is white light treatment of 2500–10,000 lux (equaling the light exposure of a bright sunny day). Phototherapy has been recommended as a first-line treatment for

SAD by some authorities [9], but not others [23]. There is also evidence that phototherapy may accelerate remission in nonseasonal depression together with medication [25].

In 1980, Lewy and colleagues were the first to recognize that melatonin could be suppressed with bright light. Melatonin is believed to regulate circadian rhythmicity and bright light appears to be responsible for melatonin suppression, the key regulatory mechanism for maintaining normal biological rhythms. Thus, phototherapy appears to aid maintenance of normal biological rhythmicity by compensating for circadian phase advances in the sleep cycle (through late afternoon exposure) and for phase delays (through early morning exposure) [28].

In addition, some investigators propose that phototherapy also affects neurotransmitter function and that this may also contribute to its antidepressant activity in vulnerable individuals [29].

Other physical treatments

Similar to ECT, these treatments use devices to introduce an electrical current that theoretically alters neuronal circuits. Positive outcomes with surgical legion procedures since the 1940s to interrupt brain circuits (such as anterior cingulotomy and subcaudate tractotomy) suggest a role for stimulation treatments that are less invasive for severe and treatment-resistant major depressive disorders (MDDs). The stimulation treatments utilize focused excitation of brain regions to, theoretically, produce a desired behavioral alteration. Models of limbic-cortical dysfunction in MDD have been proposed that characterize the depression phenotype at the neural systems level [30] and provide a theoretical basis for neuromodulation treatments. Studies are now in progress on a number of different therapeutic neuromodulation treatments.

Vagus nerve stimulation

In 2005, VNS was approved by the FDA for individuals with treatment-resistant depression [31]. It had previously been approved for use as an adjunctive therapy for epilepsy. VNS requires a surgically implanted, battery-powered pulse generator and electrical lead wound around the left vagus nerve. This provides intermittent stimulation, typically 30

seconds on and 5 minutes off. The most common adverse effects are voice alteration during stimulation and hoarseness, dyspnea, and cough. Hypomania may be a treatment-induced adverse effect and there is a risk of surgical infection. The device is programmed using an external programming system to alter the generator output. VNS stimulation did not demonstrate acute phase efficacy in one small open-label study (18 of 59 responded positively) [32], but has shown promising results to suggest benefit to patients with low-to-moderate degrees of treatment resistance and over longer-term treatment [33]. A 12-month, nonrandomized study of similar type treatment-resistant patients compared VNS treatment plus treatment-as-usual to treatment-as-usual alone and found significantly greater symptomatic benefit in the VNS group [34]. Nahas et al reported that, after 2 years of VNS treatment, the response rate was 42% and remission rate 22%, and that 81% were still actively using the device (implying that those who did not reach response criteria still perceived a subjective benefit from the device) [35]. Currently, a large multisite study is under way to assess VNS efficacy at several different generator settings.

Transcranial magnetic stimulation

Transcranial magnetic stimulation (TMS) has been used to treat patients who have not benefited sufficiently from pharmacotherapy and psychotherapy. TMS is applied without sedation, externally delivering the stimulation to the brain through the cranium. Several small (usually single site), sham-controlled trials of TMS and meta-analysis of their results support its efficacy for the treatment of MDD [36]. Recently, a double-blind, multisite study trial of over 300 medication-free patients with major depression were randomized to active or sham TMS. Sessions were conducted five times a week for 4–6 weeks. Active TMS was significantly superior to sham TMS, with remission rates approximately two-fold higher for active TMS, and active TMS was well tolerated with a low dropout rate for adverse events (generally mild and limited to transient scalp discomfort or pain). The investigators report a small effect size with a number needed to treat (NNT) of 11 – roughly comparable to NNT values reported for antidepressant medications [37]. To date,

the existing literature suggests a potential role for TMS for depressed individuals with treatment-resistant depression, but the optimum treatment parameters remain to be established. A commercial TMS device was FDA approved for treatment of depression in the USA in October 2008, becoming the second stimulation treatment thusfar approved for depression treatment in the USA.

Deep brain stimulation

Deep brain stimulation (DBS) also has FDA approval for the treatment of epilepsy and is being studied for the treatment of depression [38]. In DBS, electrodes are surgically implanted in the subgenual cingulate area, also known as Brodmann area 25. This area of the anterior cingulate cortex has been shown to be metabolically overactive in patients with depression or in healthy individuals who are induced to feel sad. This area is thought to be involved in cortisol regulation, stress response, sleep modulation, emotional regulation of the limbic system, motivation, and drive. Mayberg and colleagues found that chronic stimulation of white matter tracts adjacent to the subgenual cingulate gyrus was associated with a striking and sustained remission of depression in four of six patients participating in an open-label trial [39]. Antidepressant effects were associated with a marked reduction in local cerebral blood flow as well as changes in downstream limbic and cortical sites, measured using positron emission tomography. The authors suggest that disruption of focal pathological activity in limbic-cortical circuits, using electrical stimulation of the subgenual cingulate white matter, can effectively reverse symptoms in otherwise treatment-resistant depression. Such preliminary findings are promising and further, confirmatory, studies are currently under way. Adverse effects of DBS include surgical risks, such as infection, hemorrhage, and seizure, and a risk of infection from the subcutaneously planted battery and wires. Mood-related risks include induction of hypomania. Stimulation-associated adverse effects include sensorimotor changes, insomnia, autonomic changes (eg, transient increases in heart rate and blood pressure), and memory flashbacks.

Lifestyle and complementary therapies

Many individuals with mild-to-moderately severe depressive episodes seek lifestyle and complementary therapies, such as exercise, hypericum extracts (St John's wort), and omega-3-fatty acids (O-3-FA).

Exercise

There have been a few RCTs addressing the use of exercise to treat depression. Dunn and colleagues performed a randomized, placebo-controlled, 12-week study in adults (age 20–45 years) with MDDs to determine if higher total energy expenditure and frequency of exercise improved depressive symptoms and, if so, whether there is an exercise dose-response relationship [40]. They reported that increasing energy expenditure (by >17.5 kcal/kg per week) significantly reduced depressive symptoms, but there was no main effect of exercise frequency. They concluded that aerobic exercise at a dose consistent with public health recommendations is an effective treatment for MDDs of mild-to-moderate severity [38]. Blumenthal and colleagues performed a prospective RCT involving 202 adults with major depression who were treated with group-supervised exercise, home-based exercise, antidepressant (sertraline 50–200 mg daily), or placebo. After 4 months, patients who received active treatments tended (P=0.057) to have higher remission rates than those on placebo. These authors conclude that the efficacy of exercise seems to be generally comparable to antidepressant treatment [41]. In an earlier report, Babyak et al followed individuals who completed the above study and found that fewer in the exercise group relapsed over the next 6 months [42].

Exercise has also been examined as an augmentation treatment for depression. Trivedi and colleagues examined the use of exercise to augment SSRI treatment in 17 MDD patients with incomplete remission of depressive symptoms [43]. Patients underwent a 12-week individualized exercise program while continuing their antidepressant (unchanged in type or dose). Intent-to-treat analyses yielded significant decreases in depressive symptoms. This study provides preliminary evidence for exercise as an effective augmentation treatment for antidepressants. These

investigators suggest that exercise is a lower-cost augmentation strategy with numerous health benefits, and it may further reduce depressive symptoms in those who partially respond to antidepressants [43].

Lawlor and Hopter performed a systematic review and meta-regression analysis of RCTs of exercise as an intervention in the management of depression [44]. Hampered by poor-quality evidence they, nevertheless, found that the difference in effect sizes between exercise and CT (four studies) was not significant. Similarly, in the study comparing exercise and antidepressant, or both, there was no significant difference in outcomes between treatments. As with the case for acupuncture treatment for depression, the preliminary evidence argues for additional studies to validate these preliminary findings [44].

St John's wort

St John's wort (*Hypericum perforatum*) is the herbal therapy most commonly available worldwide for the treatment of depression. Its main active principle has not yet been identified and preparations of this compound are often unstandardized. It can interact with antidepressants acting on the 5HT system, such as SSRIs. Adverse effects are generally mild.

A number of clinical trials suggest that St John's wort may enhance 5HT function and be effective in the treatment of mild-to-moderate depression. Linde and colleagues performed a systematic review and meta-analysis to investigate if extracts of H. perforatum are more effective and more tolerable than placebo and antidepressants in the treatment of depression [45]. They reviewed 23 randomized trials (total of 1757 outpatients) in patients with mild or moderately severe depressive disorders. They report that Hypericum extracts were significantly superior to placebo and as effective as standard antidepressants, and concluded that there is evidence for Hypericum extracts being more effective than placebo for treatment of mild-to-moderately severe depression [45]. A more recent, double-blind RCT of Hypericum extract compared with fluoxetine and placebo in 135 patients with major depression found that Hypericum was significantly more effective than fluoxetine and tended toward superiority over placebo. However, this study was compromised

by the limitation of the dosage of fluoxetine to 20 mg/day, the low end of its recommended prescribing range (20–60 mg/day) [46].

A review of other recent trials continues to provide inconclusive evidence about Hypericum's efficacy for depression. Shelton et al studied 200 outpatients with major depression and reported Hypericum not to be effective compared with placebo [47]. This group examined the 95 patients who did not respond and found them not to be highly treatment resistant, further arguing against its efficacy versus antidepressants [48]. The Hypericum Depression Study Group trial [49] performed a multisite study with 340 depressed individuals comparing Hypericum with placebo and sertraline; they report that this study failed to support its use. On the other hand, reports by Kasper et al [50] and Lecrubier et al [51] found it to be safe and more effective than placebo.

Omega-3-fatty acids

The family of O-3-FAs includes eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Greater dietary intakes of O-3-FAs may be beneficial for depressed mood and has generated interest in their use as an antidepressant treatment. However, at present, it is unclear whether they have a potential role [52]; for example, one randomized, double-blind, clinical trial of DHA in 36 individuals with major depression failed to find a significant effect of DHA monotherapy [52]. Another randomized trial examined the efficacy of EPA in treating depression in those with bipolar depression. In a 12-week, double-blind study, participants were randomly assigned to adjunctive treatment with placebo or two doses of EPA. They reported significant improvement with EPA compared with placebo and both doses were well tolerated [4].

Sontrop and Campbell evaluated the evidence for the efficacy of O-3-FAs in patients with unipolar and postpartum depression [53]. They note that studies in this area are confounded by a lack of power or incomplete control. In four of seven double-blind RCTs reviewed by these authors, depression was significantly improved with O-3-FA. However, although clinical significance was demonstrated, preservation of blinding may have been a major limitation, making it unclear whether O-3-FA

supplementation is effective independently of antidepressant treatment for depressed patients in general, or only for those with abnormally low concentrations of these O-3-FAs [53].

Lin and colleagues performed a systematic review and meta-analysis of clinical trials in the English literature of O-3-FA efficacy [54]. A total of 10 double-blind, placebo-controlled studies in patients with mood disorders receiving O-3-FAs for 4 weeks or longer were included. They found a significant antidepressant effect for O-3-FAs in unipolar and bipolar depression. However, significant heterogeneity among these studies and publication bias were noted, with the conclusion that it is still premature to validate this finding [54]. Similarly, Appleton et al reviewed 18 RCTs and included 12 in a meta-analysis. They concluded that the evidence examining the effects of O-3-FAs on depressed mood is limited, and difficult to summarize and evaluate because of considerable heterogeneity [55]. Furthermore, the available evidence provides little support for the use of O-3-FAs to improve depressed mood, and suggest that larger trials with adequate power to detect clinically important benefits are required to help clarify this issue.

Acupuncture

Despite its being practiced for thousands of years, there is little evidence supporting the use of acupuncture in the English-speaking medical literature, and only uncontrolled trials for acupuncture for treatments of illnesses that prominently include depression in Chinese and Russian reports [56]. Allen and colleagues examined the effectiveness of acupuncture for depression versus acupuncture treatment of nonspecific symptoms and a waiting-list condition in a small sample of 38 women with major depression. After 8 weeks of treatment, there was a statistically significant difference ($P<0.05$) between the specific versus nonspecific acupuncture treatment, but only a marginal difference ($P>0.12$) between the specific treatment and the waiting-list control [57]. However, effect size calculations show that the specific treatment had a large effect size ($d=1.16$, where d is Cohen's d) compared with nonspecific treatment, which, in turn, had a moderate-to-large effect size compared with waiting

list (d=0.61) suggesting an effect comparable to standard treatments such as psychotherapy and pharmacotherapy [57].

Smith and Hay performed a Cochrane Database Systematic Review of acupuncture studies for depression, including all published and unpublished RCTs comparing acupuncture with sham acupuncture, no treatment, pharmacological treatment, other structured psychotherapies (CBT, psychotherapy, or counseling), or standard care [58]. The participants included men and women with depression (defined by clinical state description, or diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th edition or International Classification of Mental and Behavioral Disorders, 10th revision criteria). The primary outcomes were reduction in depression severity measured by self- or clinician-rating scales and rates of remission versus nonremission. Meta-analysis was performed using seven trials comprising 517 participants. Five trials (409 participants) included a comparison between acupuncture and medication. Two other trials compared acupuncture with a waiting-list control or sham acupuncture. Participants generally had mild-to-moderate depression. There was no evidence that medication was better than acupuncture in reducing the severity of depression (weighted mean difference 0.53, 95% CI −1.42 to +2.47), or in improving depression, defined as remission versus no remission (RR 1.2, 95% CI, 0.94–1.51). The authors conclude that there is insufficient evidence to determine the efficacy of acupuncture compared with medication, waiting-list control, or sham acupuncture [58].

In summary, the limitations of the current acupuncture studies (diagnostic imprecision, variation in the treatment provision, and small sample size) compromise our ability to determine its true effectiveness compared with other depression treatments, and further study is needed.

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