HHS Public Access

Author manuscript

Curr Treat Options Psychiatry. Author manuscript; available in PMC 2020 December 11.

Published in final edited form as:

Curr Treat Options Psychiatry. 2019 December ; 6(4): 380–400. doi:10.1007/s40501-019-00194-8.

New Somatic Treatments for Child and Adolescent Depression

Kathryn R. Cullen, M.D.,
Department of Psychiatry, University of Minnesota, F282/2A West Building 2450, Riverside Avenue South, Minneapolis, MN 55454, USA;

Laura E. Padilla, B.A.,
Department of Neuroscience, University of Minnesota;

Victoria N. Papke,
Department of Psychology, University of Minnesota

Bonnie Klimes-Dougan, Ph.D.
Department of Psychology; University of Minnesota

Abstract

Purpose of Review: Depression is a common clinical problem in youth, with prevalence increasing significantly during the adolescent period. Although several evidence-based treatments are currently available for treating depression in adults, only a subset of these have been investigated in a pediatric sample. Unfortunately, even well-established, first-line interventions do not lead to sufficient treatment response for many children and adolescents suffering from depression. However, recent research has been conducted in the area of somatic treatments for youth with depression. This review focuses on current (past three years, including published results and ongoing studies) research on somatic treatments for adolescent depression in the following categories: psychopharmacology, nutraceuticals, interventions implicating motor and sensory systems, and neuromodulation.

Findings: Results from recent randomized, controlled trials testing psychopharmacological options suggest that while antidepressants that have been recently approved for adult patients are safe and tolerable in children and adolescents, none have yet outperformed performed placebo in efficacy. Nutraceuticals, motor-sensory interventions, and neuromodulation techniques, present safe and promising results, but few have been tested against controls to support effectiveness over current treatment options.

Summary: This review of research on pediatric depression treatment from the past 3 years highlights some disappointments (negative results following some of the well-designed clinical

Corresponding Author: rega0026@umn.edu.

Conflict of Interest
The authors declare no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

trials) and gaps (preliminary studies in need of follow up with robust methodology) but also some promising directions in research of the efficacyof these treatments in a pediatric sample. We offer suggestions for future research including consideration of treatment timing, sequencing, the role of symptom severity in directing treatment selection, the potential value of combined treatments, consideration of how to best account for high placebo response rates, and the incorporation of neurobiological assessments to examine mechanisms and biomarker predictors of treatment response.

Keywords

depression; treatment; adolescent; psychopharmacology; nutraceuticals; neuromodulation

Introduction

Depression is a common clinical problem in youth. While about 1–2% of children suffer from depression with equal prevalence in boys and girls [1], the prevalence increases significantly during the adolescent period, with rates in adolescent girls 2–3 times that of boys after puberty [1], and up to 20% of adolescents experiencing depression at some point before they reach adulthood [2]. Several evidence-based treatments are currently available to address depression in youth. Well-established, first-line interventions include cognitive behavioral therapy (see recent review [3]), interpersonal psychotherapy [4], and selective serotonin reuptake inhibitor medications, especially fluoxetine [5,6] and escitalopram [7], which are the only medications approved by the Federal Drug Administration (FDA) for the treatment of depression in youths under 18. Unfortunately, not all adolescents respond to these interventions. Thirty to fifty percent of adolescents will not respond to their first treatment intervention [8], and about 10% of adolescents with depression do not improve despite multiple trials of standard treatments [9]. Therefore, novel treatment strategies are urgently needed. This paper will review the most recent research on somatic treatments for youth presenting with depression. Somatic interventions are defined more broadly as interventions that affect emotional changes through the body. So, while there have been important recent advances in psychotherapy (e.g., [3,10–14] to list a few), this review will focus on four categories of somatic treatments, including (1) psychopharmacology, (2) nutraceuticals, (3) interventions implicating motor and sensory systems, and (4) neuromodulation. We are favoring the most recent research advances (past one to three years) and accordingly highlight recently published randomized control trials but will also include publications from preliminary studies (e.g. open-label designs, case reports) and studies that are currently underway (with protocols published on ClinicalTrials.Gov) as summarized in Table 1.

Psychopharmacology

Several newer western style medications that are antidepressant agents that have already been established as effective in adults with depression have recently been investigated in pediatric samples. These include selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, multimodal antidepressants, and glutamate-modulating

agents. Here we review the available data from the results emerging in the past three years for adolescents.

New Selective Serotonin Reuptake Inhibitors (SSRIs).

Vilazodone is a selective serotonin reuptake inhibitor and a partial 5HT1A receptor agonist that received FDA approval for the treatment of depression in adults in 2011. A randomized, double-blind, placebo controlled trial 529 adolescents ages 12–17 years with major depressive disorder (MDD) reported that vilazodone was safe and well-tolerated, but that the active treatment group did not separate from placebo with respect to clinical outcome measures [15].

New Selective Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs).

Desvenlafaxine is an SNRI that is similar in chemical make-up to venlafaxine (a medication that is FDA-approved for depression in adults but does not yet have this approval for those under 18). A recent randomized, placebo-controlled trial compared 8 weeks of treatment two different doses of desvenlafaxine (doses were based on weight but low-dose group was in the 20–35mg/day range and high-dose group was in the 25–50mg/day range) or placebo in 363 children and adolescents (ages 7–17 years) with MDD [16]. The results indicated that neither of the desvenlafaxine groups separated from placebo [16]. A second randomized, placebo-controlled trial of 339 children and adolescents (ages 7 to 17 years) compared 8 weeks of treatment with desvenlafaxine (25–50mg/day) versus placebo or fluoxetine (20mg/day) [17]. Neither of the active drug groups showed significant superiority over placebo; therefore, since fluoxetine was the reference group, this study was deemed a failed trial. A second recent SNRI, *levomilnacipran*, received FDA approval for treating major depression in adults in 2013. Two studies are currently investigating the safety and efficacy of levomilnacipran for treating depression in pediatric samples (ClinicalTrials.gov, NCT03569475, NCT02431806.) However, no results are yet available from these studies.

Multimodal Antidepressants.

Vortioxetine is a new antidepressant that acts on multiple receptors. Specifically, it is an antagonist for receptors 5-HT3, 5-HT7, and 5-HT1D; a partial agonist for 5-HT1B; an agonist for 5-HT1A; and an inhibitor of the 5-HT transporter [18–20]. Vortioxetine received FDA approval for treating major depression in adults in 2013. In a recent open-label study, 48 children and adolescents with depression and/or anxiety underwent two weeks of treatment with vortioxetine [21]. Pharmacokinetic analysis revealed that vortioxetine's maximum serum concentration and area under the curve (AUC) for concentration over 24 hours were 30–40% lower in adolescents than in children. Whereas, its median oral clearance was lower in children than in adolescents [21]. The treatment was associated with mild side effects in most (75–79%) of the participants, including headache (25%) (one case was classified as severe), nausea (23%), and sedation (23%). A 6-month open-label extension study concluded that vortioxetine dosed at 5–20 mg/day for children and adolescents with depressive disorder or anxiety disorder was safe and well-tolerated [22]. Although no results are yet available from randomized, controlled trials, there are two current studies investigating vortioxetine versus fluoxetine in children (clinicaltrials.gov, NCT02709655) and adolescents (clinicaltrials.gov, NCT02709746).

Glutamate system-modulating agents.

Ketamine is an N-methyl-d-aspartate (NMDA) receptor antagonist and anti-inflammatory agent. It has been shown to have short-term effectiveness with a rapid reduction of depression symptoms in adult patients in several studies [23]. Although there has been significant enthusiasm about ketamine as an intervention for treatment-resistant depression (TRD), ketamine is not yet FDA-approved for treating depression in adults or in youth. Our group recently conducted a small pilot study exploring the safety and efficacy of open-label study with intravenous ketamine in adolescents [24]. We found that ketamine was well tolerated. We also found that ketamine was associated with a full clinical response in only 5 out of 13 adolescents with TRD, with a significant overall pre-post reduction in depression scores in this sample. At the time this review is written, there are two ongoing randomized controlled trials evaluating the tolerability and efficacy of ketamine in adolescents, although no results are yet available (clinicaltrials.gov, NCT03889756, NCT02579928).

Esketamine, the enantiomer of ketamine and also an NMDA antagonist, has also been shown to produce fast-acting antidepressant effects in adults with TRD [25]. Since esketamine can be delivered intranasally, it is potentially more feasible for broad application than intravenous ketamine. Two randomized controlled trials have been conducted testing the efficacy, safety, and tolerability of esketamine in adults with TRD [26,27] leading to its approval in 2019 by the FDA for treating depression in adults. In one recent randomized controlled trial, 346 adults with TRD were randomly assigned to receive twice-weekly nasal spray treatment (esketamine [56 or 84 mg] or placebo) plus an open-label oral antidepressant taken daily for 4 weeks [28]. While there was no significant difference in either esketamine groups compared to placebo group, treatment effect for esketamine groups were greater than what is considered clinically meaningful for approved antidepressants versus placebo, and safety and efficacy was supported [28]. While no results have been published studying the use of esketamine in TRD with an adolescent sample, there is one ongoing randomized controlled trial evaluating the efficacy and rapid effects of intranasal esketamine (28 mg, 56 mg, and 84 mg) versus oral midazolam in 145 adolescents (ages 12–17) with MDD and suicidal ideation (clinicaltrials.gov, NCT03185819).

Nutraceuticals

Increasing attention has been paid to the role of diet in mental health; an accumulating body of evidence has linked depression in adolescents with nutritional [29] and metabolic deficiencies [30]. Here we review recent advances directly testing the use of nutraceuticals in the treatment of adolescent depression.

Creatine monohydrate is an organic compound that is often used for ergogenic purposes in order to increase physical performance, but also plays an important role in energy homeostasis, brain function and development [31]. Creatine has recently been shown to have fast-acting antidepressant properties, operating through cellular signaling mechanisms similar to ketamine [32], suggesting its potential as a viable treatment option for depression. Previous research has indicated that adding creatine to an SSRI in the treatment of female adults diagnosed with MDD can lead to a faster and greater treatment response [33]. One recent, randomized controlled trial was conducted to see if creatine is effective in treating

female adolescents (N=28, ages 13–20 years old) with TRD [34]. Participants were assigned placebo or dosage of 2, 4, or 10 g of creatine daily, and were scanned before and after 8 weeks of treatment using phosphorus-31 magnetic resonance spectroscopy (^{31}P-MRS) to measure phosphocreatine (PCr) in the frontal lobe [34]. There was no difference in adverse events, weight gain or serum creatinine in groups [34]. In this study, mean frontal lobe PCr increased in the 2, 4, and 10 g groups, whereas PCr fell slightly in the placebo group. As hypothesized, frontal PCr values were inversely correlated with depression scores. While pre-post changes in depression scores were not significantly different between groups, participants assigned to the group receiving 2 g of creatine showed the strongest clinical response [34]. Importantly, this research provides a possible evidence for a mechanism of change, but the findings with regard to group differences remain tentative and merit replication. Other studies are needed to evaluate creatine use as an antidepressant treatment in youth and to determine if these results extend to males.

Saffron, the dried stigmas of the plant *Crocus sativus*, is a commonly used spice that has also been recently shown to have antidepressant properties [35]. Several clinical trials have compared saffron to common antidepressants (fluoxetine, imipramine, and citalopram) have reported that saffron possesses similar antidepressant effects and fewer side effects, suggesting that it may be an efficacious and safe new treatment for depression [36]. In the only study to date examining saffron for depression in adolescents, 68 adolescents 12–16 years old with mild-to-moderate depressive or anxiety symptoms were randomized to receive either saffron extract (affron®, 14 mg b.i.d) or placebo tablets for 8 weeks [37]. The group receiving affron® reported a greater decrease in total internalizing scores, as well as greater improvements in overall internalizing symptoms, separation anxiety, social phobia, and depression symptoms, compared to the placebo group [37]. In addition, affron® was well tolerated [37].

N-acetylcysteine (NAC) is a nutritional supplement related to the amino acid L-cysteine. NAC has properties that are of broad interest to psychiatry, as it serves as both a glutamate modulator and an antioxidant by boosting the body and brain's primary antioxidant glutathione [38]. NAC has been examined as an intervention for depression in adults; while some of these studies have provided support for NAC's efficacy in adult depression [39–41], a Cochrane analysis concluded that the evidence was not yet sufficient to support this intervention for adult depression [42]. Our group recently completed an open-label study testing NAC as an intervention for 35 female adolescents with self-injury (25 of whom also met criteria for a depressive disorder) [43]. We observed that depression symptoms decreased significantly after the intervention, independently of the significant decrease in self-injury [43]. Since NAC is a well-tolerated and widely available supplement, this intervention may merit further research to identify the biological mechanisms and to investigate whether a reduction in depression symptoms could be demonstrated when compared to placebo, which is something we are addressing in our upcoming study (clinicaltrials.gov, NCT04005053).

Vitamin D.

The potential role of vitamin D in mental health generally and especially in depression is widely accepted, such that vitamin D levels are frequently included in basic lab panels in medical assessments for patients with depression. A 2017 systematic review of Vitamin D studies in pediatric mental health concluded that substantial evidence is available linking vitamin D deficiency with poor mental health outcomes in youth, and cited evidence from open-label trials suggesting promise of vitamin D supplementation for treating depression. However, it was noted that randomized controlled studies in adults have yielded mixed findings regarding the efficacy of supplementation, and noted the lack of such studies in youth with depression [44]. In a recent open-label study, 940 girls (306 of whom had depression) received injections of high-dose vitamin D3 (50,000 units / week) for 9 weeks [45]. Depression symptoms (but not aggression scores) decreased significantly after the intervention. A randomized, placebo-controlled trial is currently being conducted in European adolescents with depression and low vitamin D levels in which 200 adolescents will receive 2640 units of vitamin D3 or placebo daily for 28 days [46] (German Clinical Trial Register, DRKS00009758).

Interventions implicating motor and sensory systems

Several interventions implicating motor and sensory systems have been shown to be effective in the treatment of MDD. In this section, we will review motor and sensory system interventions recently studied in adolescents, including yoga and meditation, exercise, and light therapy.

Yoga and Meditation.

Hatha yoga, the commonly practiced school of yoga in western countries, emphasizes physical body poses, techniques for breathing, and especially awareness of the body and breath [47]. A recent, randomized controlled trial testing 90-minute Hatha yoga practice groups versus 90-minute attention control education groups twice weekly for 8 weeks in adults with depression found that participants assigned to the yoga practice group showed statistically and clinically significant reductions in depression severity compared to the control group [48]. In adolescents, there is currently one randomized controlled trial evaluating hatha yoga versus group CBT (control) as treatment for adolescents with depression, although no results are available yet (clinicaltrials.gov, NCT03831360). In addition, there is an ongoing open-label study using a mind-body skills group program to help treat depression in adolescents. The mind-body skills group incorporates meditation, guided imagery, breathing techniques, autogenic training, biofeedback, genograms, and self-expression through words, drawings, and movement. However, no results are currently available (clinicaltrials.gov, NCT03363750).

Exercise.

While there are no recent trials examining exercise as a treatment option for adolescent depression, it has been shown that, in general, physical activity may decrease depressive symptoms, as low physical activity has been associated with the development of psychological disorders [49]. A recent meta-analysis of 23 randomized controlled trials

examined exercise as a treatment for depression, which included 977 participants, although participants did not extend to the adolescent population [50]. The meta-analysis included aerobic (such as running) and anaerobic exercise (such as weightlifting) and evaluated exercise as both an independent intervention and adjunct intervention to an antidepressant [50]. The results suggest that exercise may be a viable treatment intervention as well as an adjunct treatment for adults but this line of research is yet to extend to adolescents. Furthermore, the mechanisms by which exercise relieves depression remains an active area of study. In adult depression research, considerable research has investigated whether consistent aerobic exercise increases neuroplasticity-promoting molecules such as brain derived neurotrophic factor (BDNF); meta-analyses have revealed inconclusive results but have suggested that further research is needed investigating this potential mechanism [51,52]. Importantly, adolescent preclinical research is beginning to examine possible mechanisms by which exercise might alter critical brain structures like the hippocampus [53] in adolescent animals, providing a useful example of methods by which this work might be advanced.

Bright Light Therapy has been established as efficacious in treating not just seasonal depression but MDD as well, according to recent studies [54]. Light therapy was commonly executed using light therapy boxes, but light glasses are quickly becoming favored as a more feasible option, as they allow users to go about their daily activities [55]. A recent open-label clinical trial evaluated the feasibility and efficacy of bright light therapy (in addition to treatment-as-usual) in depressed adolescents [55]. Participants received bright light therapy with light glasses for 4 weeks and showed significant improvement in depressive symptoms, sleep problems, and global clinical impression [55]. Additionally, a randomized controlled trial is currently examining the use of bright light therapy via light glasses as treatment for depressed adolescents compared to placebo light therapy, although no results following the protocol are available [56] (German Clinical Trials Register, DRKS00013188).

Neuromodulation

The use of neuromodulation for neuropsychiatric treatment has a long history filled with stigma, restricted use, and ethical concerns [57]. As evidence about the safety, tolerability and efficacy of these approaches are documented [58–61]], there is an increased interest and promise for understanding and utilizing these more brain-based, neuro-enhancing technologies as therapeutic tools to treat adolescent depression. In this section, we will review some current advancements in both non-invasive and invasive neuromodulation techniques that are increasingly being studied as treatment options for adolescents.

Electroconvulsive therapy (ECT), which involves electrical stimulation of the brain while a patient is under general anesthesia, is a well-established and highly effective therapy for treatment-resistant mood disorders, with a reported 60–80% response rate in adults [58]. Due to the stigma associated with ECT and lack of knowledge about potential effects on the developing brain, its use in adolescents has been limited to a last resort in treatment-resistant cases or life-threatening situations [57]. The American Academy of Child and Adolescent Psychiatry (AACAP) has not updated its practice parameters regarding ECT use in adolescents since 2004. However, in the past three years, a handful of studies have

investigated the safety and efficacy of ECT for adolescents, including two retrospective chart reviews and a case report. The general consensus from these studies is that ECT is a safe and effective treatment for adolescent depression, with patients showing a decrease in their depressive symptoms after treatment [62–64]. In a retrospective chart review, Rootes-Murdy and colleagues reported a 58.33% response rate and 37.50% remission rate to ECT in 48 young patients (ages 14–25) being treated for unipolar and bipolar depression [64]. There is some preliminary evidence for predictors of treatment response for ECT as in this study with youth; ECT had lower response and remission rates in those who engage in non-suicidal self-injury (NSSI), especially in adult female patients [64]. The authors also noted a lower response rate for adolescents compared to that reported for adults, underscoring the need for research examining developmental differences in disease and treatment response mechanisms. Recent investigations have found that ECT treatment in adults with TRD decreases subgenual cingulate cortical activity to levels almost comparable to healthy controls [65], although this critical line of research that provides a method for identifying neural mechanisms of ECT treatment has not yet been undertaken in adolescents. Considering both the promising results in adult patients, along with the FDA changing ECT's status from the most restrictive Class III regulatory category for medical devices to Class II (special controls) for treating depression, bipolar disorder, and catatonia in patients 13 years or older [66], there is promise for future studies using ECT for child and adolescent TRD.

Transcranial magnetic stimulation (TMS) is an intervention that modulates regional cortical excitability by stimulating neurons using magnetic pulses in various frequencies, pulse patterns and motor thresholds to enhance neuroplasticity [60,67]. Current studies use high-frequency (10 Hz) repetitive TMS (rTMS) to treat depression by eliciting prolonged cortical excitability changes, with all studies reporting that rTMS treatment is safe, tolerable, and feasible in adolescents [68–71]. In an open-label, MRI-guided high-frequency rTMS study, 6 out of 10 adolescents with TRD responded to a 6–8 week rTMS treatment course, with limited, mild, and transient adverse effects (i.e., scalp discomfort, headaches, dizziness), and sustained clinical improvement over 6-month follow up [68]. In another open-label, exploratory investigation testing rTMS for 6 weeks in 19 adolescents with depression, 47% of adolescents showed overall clinical response, and predicted suicidal ideation significantly decreased over the 6 weeks of treatment [70]. In a shorter, 3-week, open-label trial of rTMS in 32 adolescents and young adults (13–21 years), depression symptoms were significantly reduced, with 14 subjects achieving remission and 16 subjects achieving partial remission [69]. Finally, a naturalistic study investigating add-on rTMS in adolescent patients (N=42, ages 10–18), compared to adults (N=75, ages 18–80, split into two groups: 18–60, 60+), found that depressive symptoms decreased in all age groups, but response and remission rates were greater in adolescents compared to adults [71]. Taken together, current literature suggests the potential promise for rTMS for treating depression in adolescents. However, given the known high placebo response rates in adolescents, confirmatory results from sham-controlled studies are still needed. There are three ongoing clinical trials assessing various novel strategies for rTMS application in adolescents with depression. First, an open-label study is using the "deep" TMS device (BrainSway™, which is thought to penetrate deeper into brain tissues than standard devices) with modifications from the FDA-approved

adult protocol including 10 Hz pulse frequency with a gradual increase in stimulation intensity throughout the study while monitoring safety following an observed seizure in an initial study patient using the adult protocol [72]. Second, a double-blind, randomized control trial is comparing 1 Hz to 10 Hz stimulation (NCT03363919). Third, an open-label study is investigating theta burst stimulation, a novel approach which has gained considerable excitement in the adult depression research based on its ability to achieve similar efficacy with shorter duration of rTMS sessions, for adolescents with depression (NCT03845504). At the time this review is written, no results have been posted on these studies.

Transcranial direct or alternating current stimulation (tDCS or tACS) involves delivering low direct or alternating current stimulation via electrodes on the scalp to modulate regional cortical excitability and promote neuroplasticity. tDCS has been shown to be safe in adults, children and adolescents [67,73] and to have therapeutic effects in adults with MDD [74]. A recent meta-analysis reviewed 9 randomized controlled trials (N=623) evaluating the efficacy of tDCS versus sham tDCS and found that tDCS was significantly more effective than sham for reducing depression symptoms in most of the studies analyzed [74]. Additionally, pairing tDCS with cognitive training has emerged as a strategy to leverage Hebbian plasticity and boost the effects of each intervention [75–77]. Although no studies investigating the use of tDCS in adolescent depression have yet been published, several studies are now evaluating the use of tDCS alone and through combined interventions in treating depression in youth. First, there is an ongoing open-label study investigating the tolerability and efficacy of tDCS in children and adolescents with epilepsy and comorbid depression (clinicaltrials.gov, NCT03368469; no results have been posted). Second, an ongoing, randomized, sham tDCS-controlled study from our group is evaluating whether tDCS can enhance the therapeutic effects of mindful-breathing training (MBT) in adolescent depression and examine the mechanisms of this combined treatment through electroencephalogram (EEG) and magnetic resonance imaging (MRI) (clinicaltrials.gov, NCT03897699; no results posted at this time). Lastly, an ongoing, randomized, sham tDCS-controlled study is investigating whether combined tDCS and CBT is more effective in reducing depression symptoms in adult patients compared CBT+sham tDCS and CBT alone (clinicaltrials.gov, NCT02633449; no results have been posted).

Vagus Nerve Stimulation (VNS) is an invasive neuromodulatory technique that uses an implanted electrical stimulator to stimulate the vagus nerve [78]. Despite potential promise and interest [61] and the FDA approval for its use in treating severe, recurrent unipolar and bipolar depression in adult patients in 2005, no studies have yet tested this intervention for adolescents with depression, due to its invasive nature. However, current literature shows promise in VNS's noninvasive counterpart, transcutaneous auricular vagus nerve stimulation (taVNS), which consists of a small device placed on the patients' ear leading to afferent vagus nerve stimulation [79]. Overall, current studies have evaluated the efficacy, safety and tolerability in adults with MDD and have found promising results, though study designs vary in whether participants continue psychotropic/antidepressant medication, showing significant decrease in depressive symptoms [80–82]. Currently, only one, nonrandomized control study has investigated the efficacy of self-administered taVNS alone in treating MDD in adults with mild or moderate MDD compared to sham taVNS (stVNS) (N=161,

ages 18–70) [80]. Results showed that the active treatment cohort showed significantly greater clinical improvement than the sham cohort at 4 weeks, with clinical improvement sustained over 12 weeks, and good tolerability (the only adverse effect of taVNS reported by patients was tinnitus, which improved after stopping taVNS) [80]. From a subset of these participants that completed functional MRI (fMRI) scans at baseline and 4 weeks post-treatment, differences in resting-state functional connectivity and fMRI activity in multiple regions were reported in patients that received taVNS and stVNS [83–87]. Though no reports are yet available from tVNS studies in adolescent depression, an ongoing, randomized and sham-controlled trial is assessing clinical and brain activation changes to taVNS versus sham in depressed patients (ages 15–70 years) and healthy controls (clinicaltrials.gov, NCT03592446).

Conclusions

Depression continues to be a common, impairing and potentially fatal problem for adolescents. Therefore, it is vitally important that research continues to push the envelope to increase the number of treatment options that are effective, tolerable, and feasible for achieving remission of symptoms. Although there are well-established first-line somatic and psychotherapeutic interventions, a large portion of adolescents do not respond to them [8]. In this paper, we have focused on very recently completed (from the past three years) and ongoing studies on somatic interventions for adolescent depression. Although the results of large, well-designed, placebo-controlled studies testing recent psychopharmacology agents that have proven efficacy in adults have been disappointing, progress in other areas (e.g., nutraceuticals, interventions implicating motor and sensory systems and neuromodulation) are cautiously promising. The review of recent work reveals important considerations that must be accounted for as we move forward including: treatment timing, symptom severity, a combination of therapies, and neurobiological assessments to examine mechanisms and biomarker predictors of treatment response.

Some of the most rigorous methodologies using randomized controlled trials have shown that downward extensions of treatments that have been validated in adults are generally less promising with adolescents, with very few resulting in reduction of depression symptoms that are greater than placebo, and most leading to undesirable adverse effects. However, it should be noted that several of the clinical trials described here that are studying psychopharmacology interventions for adolescent depression are still ongoing; therefore we await results from those studies' evidence to determine if they are promising. For example, there is some optimism for the use of ketamine and esketamine to treat adolescents with TRD, as well as patients with imminent suicidality, due to the rapidness of es/ketamine's antidepressant effects. Likewise, advancements in non-pharmacological therapeutic approaches such as nutraceuticals, sensory-motor interventions and neuromodulation suggest potential promise for providing options that are effective, safe, tolerable, and feasible for incorporating into an adolescent's lifestyle. Though current studies have demonstrated the effectiveness of these treatment options in a few cases, it is important to reiterate that the greater portion of these protocols used open-label designs and have not been subjected to rigorous validation. Using randomized placebo-controlled trials in future study designs can help us better understand how and to what extent these non-

pharmacological somatic treatments are impacting depression symptoms. Additionally, in many of the studies, patients continued psychopharmacological treatments while undergoing testing of the new treatment options, leaving the question of whether the intervention might be best on its own or in combination with other treatments unanswered. Future research designs could address this question directly by comparing single-treatment versus combined treatment arms. For example, certain combinations of therapies may serve to reduce symptoms in a synergistic manner by potentially enhancing brain plasticity, like ongoing studies combining tDCS and MBT, tDCS and CBT, or creatine monohydrate and SSRIs. Similarly, the sequence of multiple treatments may be a critical factor for consideration in efficacy studies.

Evaluation of ongoing adolescent depression intervention research should take into consideration the many factors that go into treatment selection, which (among others) include depression severity, risk of the intervention, risk of undertreated depression, and feasibility. For mild or moderate depression, there may be less urgency and allow the flexibility for a trial of lower-risk, accessible options such as the use of nutraceuticals, yoga, exercise, bright light, taVNS, and/or tDCS. While the evidence for these interventions at present is not completely robust, there are hints that they may be sufficient to lead to positive outcomes while also avoiding high risk of harmful or unpleasant adverse effects. It is possible that less-established (or possibly less potent) methods (e.g., yoga, bright light therapy, or tDCS) might be considered as part of the recommended therapeutic regimen (e.g. as augmenting agents) or to maintain long-term treatment response. On the other hand, for more severe cases, when symptoms are entrenched, these treatment options may be less likely to benefit patients, at least as used as a monotherapy. ECT still has the strongest body of evidence for effectiveness in adolescents with TRD, seconded by TMS and ketamine, although the field still lacks any publications reporting efficacy versus placebo or sham for any of these interventions in adolescents with TRD. Since ECT requires anesthesia and close supervision after each treatment, its use is limited to a narrow subset of treatment-resistant patients; without these and the cognitive side effects, ECT might be a more widely-used treatment given its high rate of response. In contrast, noninvasive neuromodulation (TMS, taVNS and tDCS) require no anesthesia, incur fewer risks, and can be implemented in outpatient settings (potentially even in the home). Similarly, intranasal administration of esketamine, compared to intravenous administration of ketamine, makes it more feasible for broad application. That being said, based on the risks of severe depression in adolescents, extrapolation of findings from adults makes more sense, especially in the setting of significant suicide risk and need for rapid response.

The advancement of somatic approaches will require more concerted efforts to identify possible mechanisms of treatment and enhance personalization. Research considering mechanisms is needed in order to improve upon our current options and develop novel treatments. For example, our group has found that changes in brain activation and functional connectivity in depressed adolescents before and after being treated with an SSRI is associated with improvement [88]. Additionally, when considering treatment options for adolescent depression, we must also consider not only what works, but what works for whom. Therefore, it is necessary to evaluate predictors and moderators of treatment response to facilitate personalization. Recently, our lab conducted a preliminary study that found that

favorable SSRI treatment response was predicted by baseline functional connectivity, task activation and cortisol levels in the context of a stressor [89]. Incorporation of neuroscience techniques into clinical trials for adolescent depression treatment will be important in the next era of research.

In conclusion, progress on adolescent depression treatment research in recent years is cautiously promising. Continued efforts to explore new avenues and to apply rigorous approaches (avoiding false trails) are needed. Attention to developmental context, treatment timing, symptom severity, and combination therapies must be considered. Finally, efforts are needed to identify biological mechanisms, predictors, and moderators of treatment response in adolescent depression to be able to tailor treatment plans to benefit each patient as much as possible.

References and Recommended Reading

Recently published papers of particular interest have been highlighted as:

• Of importance

[1]. Fleming JE, Offord DR. Epidemiology of childhood depressive disorders: a critical review. J Am Acad Child Adolesc Psychiatry. 1990;29:571–80. [PubMed: 2201675]

[2]. Lewinsohn PM, Rohde P, Seeley JR. Major depressive disorder in older adolescents: prevalence, risk factors, and clinical implications. Clin Psychol Rev. 1998;18:765–94. [PubMed: 9827321]

[3]. Oud M, de Winter L, Vermeulen-Smit E, Bodden D, Nauta M, Stone L, et al. Effectiveness of CBT for children and adolescents with depression: A systematic review and meta-regression analysis. Eur Psychiatry. 2019;57:33–45. [PubMed: 30658278]

[4]. Gunlicks-Stoessel ML, Mufson L. Interpersonal Psychotherapy for Depressed Adolescents. Dulcan's Textbook of Child and Adolescent Psychiatry. p. 887–95.

[5]. Emslie GJ, Heiligenstein JH, Wagner KD, Hoog SL, Ernest DE, Brown E, et al. Fluoxetine for acute treatment of depression in children and adolescents: a placebo-controlled, randomized clinical trial. J Am Acad Child Adolesc Psychiatry. 2002;41:1205–15. [PubMed: 12364842]

[6]. Emslie GJ, Kennard BD, Mayes TL, Nightingale-Teresi J, Carmody T, Hughes CW, et al. Fluoxetine versus placebo in preventing relapse of major depression in children and adolescents. Am J Psychiatry. 2008;165:459–67. [PubMed: 18281410]

[7]. Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. J Am Acad Child Adolesc Psychiatry. 2009;48:721–9. [PubMed: 19465881]

[8]. March J, Silva S, Vitiello B, TADS Team. The Treatment for Adolescents with Depression Study (TADS): methods and message at 12 weeks. J Am Acad Child Adolesc Psychiatry. 2006;45:1393–403. [PubMed: 17135984]

[9]. Maalouf FT, Atwi M, Brent DA. Treatment-resistant depression in adolescents: review and updates on clinical management. Depress Anxiety. 2011;28:946–54. [PubMed: 21898710]

[10]. Raj S, Sachdeva SA, Jha R, Sharad S, Singh T, Arya YK, et al. Effectiveness of mindfulness based cognitive behavior therapy on life satisfaction, and life orientation of adolescents with depression and suicidal ideation. Asian J Psychiatr. 2019;39:58–62. [PubMed: 30579108]

[11]. Weisz JR, Kuppens S, Ng MY, Vaughn-Coaxum RA, Ugueto AM, Eckshtain D, et al. Are Psychotherapies for Young People Growing Stronger? Tracking Trends Over Time for Youth Anxiety, Depression, Attention-Deficit/Hyperactivity Disorder, and Conduct Problems. Perspect Psychol Sci. 2019;14:216–37. [PubMed: 30571478]

[12]. Nejati V, Fathi E, Shahidi S, Salehinejad MA. Cognitive training for modifying interpretation and attention bias in depression: Relevance to mood improvement and implications for cognitive intervention in depression. Asian J Psychiatr. 2019;39:23–8. [PubMed: 30496949]

[13]. Weersing VR, Jeffreys M, Do M-CT, Schwartz KTG, Bolano C. Evidence Base Update of Psychosocial Treatments for Child and Adolescent Depression. J Clin Child Adolesc Psychol. 2017;46:11–43. [PubMed: 27870579]

[14]. Rith-Najarian LR, Mesri B, Park AL, Sun M, Chavira DA, Chorpita BF. Durability of Cognitive Behavioral Therapy Effects for Youth and Adolescents With Anxiety, Depression, or Traumatic Stress:A Meta-Analysis on Long-Term Follow-Ups. Behav Ther. 2019;50:225–40. [PubMed: 30661562]

[15]. Durgam S, Chen C, Migliore R, Prakash C, Edwards J, Findling RL. A Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of Vilazodone in Adolescents with Major Depressive Disorder. Paediatr Drugs. 2018;20:353–63. [PubMed: 29633166]

[16]. Atkinson S, Lubaczewski S, Ramaker S, England RD, Wajsbrot DB, Abbas R, et al. Desvenlafaxine Versus Placebo in the Treatment of Children and Adolescents with Major Depressive Disorder. J Child Adolesc Psychopharmacol. 2018;28:55–65. [PubMed: 29185786]

[17]. Weihs KL, Murphy W, Abbas R, Chiles D, England RD, Ramaker S, et al. Desvenlafaxine Versus Placebo in a Fluoxetine-Referenced Study of Children and Adolescents with Major Depressive Disorder. J Child Adolesc Psychopharmacol. 2018;28:36–46. [PubMed: 29189044]

[18]. Bang-Andersen B, Ruhland T, Jørgensen M, Smith G, Frederiksen K, Jensen KG, et al. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. J Med Chem. 2011;54:3206–21. [PubMed: 21486038]

[19]. Mørk A, Pehrson A, Brennum LT, Nielsen SM, Zhong H, Lassen AB, et al. Pharmacological effects of Lu AA21004: a novel multimodal compound for the treatment of major depressive disorder. J Pharmacol Exp Ther. 2012;340:666–75. [PubMed: 22171087]

[20]. Sanchez C, Asin KE, Artigas F. Vortioxetine, a novel antidepressant with multimodal activity: review of preclinical and clinical data. Pharmacol Ther. 2015;145:43–57. [PubMed: 25016186]

[21]. Findling RL, Robb AS, DelBello M, Huss M, McNamara N, Sarkis E, et al. Pharmacokinetics and Safety of Vortioxetine in Pediatric Patients. J Child Adolesc Psychopharmacol. 2017;27:526–34. [PubMed: 28333546]

[22]. Findling RL, Robb AS, DelBello MP, Huss M, McNamara NK, Sarkis EH, et al. A 6-MonthOpen-Label Extension Study of Vortioxetine in Pediatric Patients with Depressive or Anxiety Disorders. J Child Adolesc Psychopharmacol. 2018;28:47–54. [PubMed: 29035574]

[23]. Han Y, Chen J, Zou D, Zheng P, Li Q, Wang H, et al. Efficacy of ketamine in the rapid treatment of major depressive disorder: a meta-analysis of randomized, double-blind, placebo-controlled studies. Neuropsychiatr Dis Treat. 2016;12:2859–67. [PubMed: 27843321]

[24] ●. Cullen KR, Amatya P, Roback MG, Albott CS, Westlund Schreiner M, Ren Y, et al. Intravenous Ketamine for Adolescents with Treatment-Resistant Depression: An Open-Label Study. J Child Adolesc Psychopharmacol. 2018;28:437–44 [PubMed: 30004254] This preliminary study provides the first publication on the use of ketamine in adolescents for treatment of depression.

[25] ●. Molero P, Ramos-Quiroga JA, Martin-Santos R, Calvo-Sánchez E, Gutiérrez-Rojas L, Meana JJ. Antidepressant Efficacy and Tolerability of Ketamine and Esketamine: A Critical Review. CNS Drugs. 2018;32:411–20. [PubMed: 29736744] This is a critical review of the potential of ketamine and esketamine as treatment options for depression in adults.

[26]. Popova V, Daly EJ, Trivedi M, Cooper K, Lane R, Lim P, et al. Efficacy and Safety of Flexibly Dosed Esketamine Nasal Spray Combined With a Newly Initiated Oral Antidepressant in Treatment-Resistant Depression: A Randomized Double-Blind Active-Controlled Study. Am J Psychiatry. 2019;176:428–38. [PubMed: 31109201]

[27]. Daly EJ, Trivedi MH, Janik A, Li H, Zhang Y, Li X, et al. Efficacy of Esketamine Nasal Spray Plus Oral Antidepressant Treatment for Relapse Prevention in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Psychiatry [Internet]. 2019; Available from: 10.1001/jamapsychiatry.2019.1189

[28]. Fedgchin M, Trivedi M, Daly EJ, Melkote R, Lane R, Lim P, et al. Efficacy and Safety of Fixed-Dose Esketamine Nasal Spray Combined With a New Oral Antidepressant in Treatment-Resistant Depression: Results of a Randomized, Double-Blind, Active-Controlled Study

(TRANSFORM-1). Int J Neuropsychopharmacol [Internet]. 2019; Available from: 10.1093/ijnp/pyz039

[29]. Khanna P, Chattu VK, Aeri BT. Nutritional Aspects of Depression in Adolescents - A Systematic Review. Int J Prev Med. 2019;10:42. [PubMed: 31057727]

[30]. Pan LA, Martin P, Zimmer T, Segreti AM, Kassiff S, McKain BW, et al. Neurometabolic Disorders: Potentially Treatable Abnormalities in Patients With Treatment-Refractory Depression and Suicidal Behavior. Am J Psychiatry. 2017;174:42–50. [PubMed: 27523499]

[31]. Allen PJ. Creatine metabolism and psychiatric disorders: Does creatine supplementation have therapeutic value? Neurosci Biobehav Rev. 2012;36:1442–62. [PubMed: 22465051]

[32]. Pazini FL, Cunha MP, Rosa JM, Colla ARS, Lieberknecht V, Oliveira Á, et al. Creatine, Similar to Ketamine, Counteracts Depressive-Like Behavior Induced by Corticosterone via PI3K/Akt/mTOR Pathway. Mol Neurobiol. 2016;53:6818–34. [PubMed: 26660117]

[33]. Lyoo IK, Yoon S, Kim T-S, Hwang J, Kim JE, Won W, et al. A randomized, double-blind placebo-controlled trial of oral creatine monohydrate augmentation for enhanced response to a selective serotonin reuptake inhibitor in women with major depressive disorder. Am J Psychiatry. 2012;169:937–45. [PubMed: 22864465]

[34] ●. Kondo DG, Forrest LN, Shi X, Sung Y-H, Hellem TL, Huber RS, et al. Creatine target engagement with brain bioenergetics: a dose-ranging phosphorus-31 magnetic resonance spectroscopy study of adolescent females with SSRI-resistant depression. Amino Acids. 2016;48:1941–54. [PubMed: 26907087] This study is exemplary of the experimental therapeutics approach, targeting creatine with a dietary supplement and examining dose-related effects in the brain.

[35]. Lopresti AL, Drummond PD. Efficacy of curcumin, and a saffron/curcumin combination for the treatment of major depression: A randomised, double-blind, placebo-controlled study. J Affect Disord. 2017;207:188–96. [PubMed: 27723543]

[36]. Shafiee M, Arekhi S, Omranzadeh A, Sahebkar A. Saffron in the treatment of depression, anxiety and other mental disorders: Current evidence and potential mechanisms of action. J Affect Disord. 2018;227:330–7. [PubMed: 29136602]

[37]. Lopresti AL, Drummond PD, Inarejos-García AM, Prodanov M. affron®, a standardised extract from saffron (Crocus sativus L.) for the treatment of youth anxiety and depressive symptoms: A randomised, double-blind, placebo-controlled study. J Affect Disord. 2018;232:349–57. [PubMed: 29510352]

[38]. Berk M, Malhi GS, Gray LJ, Dean OM. The promise of N-acetylcysteine in neuropsychiatry. Trends Pharmacol Sci. 2013;34:167–77. [PubMed: 23369637]

[39]. Carvalho AF, Macêdo DS, Goulia P, Hyphantis TN. N-acetylcysteine augmentation to tranylcypromine in treatment-resistant major depression. J Clin Psychopharmacol. 2013;33:719–20. [PubMed: 23899640]

[40]. Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial. Biol Psychiatry. 2008;64:468–75. [PubMed: 18534556]

[41]. Berk M, Dean OM, Cotton SM, Jeavons S, Tanious M, Kohlmann K, et al. The efficacy of adjunctive N-acetylcysteine in major depressive disorder: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry. 2014;75:628–36. [PubMed: 25004186]

[42]. Caddy C, Amit BH, McCloud TL, Rendell JM, Furukawa TA, McShane R, et al. Ketamine and other glutamate receptor modulators for depression in adults. Cochrane Database Syst Rev. 2015;CD011612.

[43]. Cullen KR, Klimes-Dougan B, Westlund Schreiner M, Carstedt P, Marka N, Nelson K, et al. N-Acetylcysteine for Nonsuicidal Self-Injurious Behavior in Adolescents: An Open-Label Pilot Study. J Child Adolesc Psychopharmacol. 2018;28:136–44. [PubMed: 29053023]

[44]. Föcker M, Antel J, Ring S, Hahn D, Kanal Ö, Öztürk D, et al. Vitamin D and mental health in children and adolescents. Eur Child Adolesc Psychiatry. 2017;26:1043–66. [PubMed: 28176022]

[45]. Bahrami A, Mazloum SR, Maghsoudi S, Soleimani D, Khayyatzadeh SS, Arekhi S, et al. High Dose Vitamin D Supplementation Is Associated With a Reduction in Depression Score Among

Adolescent Girls: A Nine-Week Follow-Up Study. J Diet Suppl. 2018;15:173–82. [PubMed: 28759290]

[46]. Föcker M, Antel J, Grasemann C, Führer D, Timmesfeld N, Öztürk D, et al. Effect of an vitamin D deficiency on depressive symptoms in child and adolescent psychiatric patients - a randomized controlled trial: study protocol. BMC Psychiatry. 2018;18:57. [PubMed: 29490621]

[47]. Coulter D Anatomy of Hatha Yoga: A Manual for Students, Teachers, and Practitioners. Motilal Banarsidass Publ.; 2004.

[48]. Prathikanti S, Rivera R, Cochran A, Tungol JG, Fayazmanesh N, Weinmann E. Treating major depression with yoga: A prospective, randomized, controlled pilot trial. PLoS One. 2017;12:e0173869. [PubMed: 28301561]

[49]. Carek PJ, Laibstain SE, Carek SM. Exercise for the treatment of depression and anxiety. Int J Psychiatry Med. 2011;41:15–28. [PubMed: 21495519]

[50]. Kvam S, Kleppe CL, Nordhus IH, Hovland A. Exercise as a treatment for depression: A meta-analysis. J Affect Disord. 2016;202:67–86. [PubMed: 27253219]

[51]. Kurebayashi Y, Otaki J. Does Physical Exercise Increase Brain-Derived Neurotrophic Factor in Major Depressive Disorder? A Meta-Analysis. Psychiatr Danub. 2018;30:129–35. [PubMed: 29930221]

[52]. Dinoff A, Herrmann N, Swardfager W, Gallagher D, Lanctôt KL. The effect of exercise on resting concentrations of peripheral brain-derived neurotrophic factor (BDNF) in major depressive disorder: A meta-analysis. J Psychiatr Res. 2018;105:123–31. [PubMed: 30219561]

[53]. Dahlin E, Andersson M, Thorén A, Hanse E, Seth H. Effects of physical exercise and stress on hippocampal CA1 and dentate gyrus synaptic transmission and long-term potentiation in adolescent and adult Wistar rats. Neuroscience. 2019;408:22–30. [PubMed: 30926550]

[54]. Al-Karawi D, Jubair L. Bright light therapy for nonseasonal depression: Meta-analysis of clinical trials. J Affect Disord. 2016;198:64–71. [PubMed: 27011361]

[55] ●. Kirschbaum-Lesch I, Gest S, Legenbauer T, Holtmann M. Feasibility and Efficacy of Bright Light Therapy in Depressed Adolescent Inpatients. Z Kinder Jugendpsychiatr Psychother. 2018;46:423–9. [PubMed: 30015544] Preliminary study suggesting promise of bright light therapy for adolescents with depression.

[56]. Holtmann M, Mokros L, Kirschbaum-Lesch I, Kölch M, Plener PL, Ruckes C, et al. Adolescent depression: Study protocol for a randomized, controlled, double-blind multicenter parallel group trial of Bright Light Therapy in a naturalistic inpatient setting (DeLight). Trials. 2018;19:568. [PubMed: 30340625]

[57]. Ghaziuddin N, Kutcher SP, Knapp P, Bernet W, Arnold V, Beitchman J, et al. Practice parameter for use of electroconvulsive therapy with adolescents. J Am Acad Child Adolesc Psychiatry. 2004;43:1521–39. [PubMed: 15564821]

[58]. Weiner RD, Reti IM. Key updates in the clinical application of electroconvulsive therapy. Int Rev Psychiatry. 2017;29:54–62. [PubMed: 28406327]

[59]. Doruk Camsari D, Kirkovski M, Croarkin PE. Therapeutic Applications of Noninvasive Neuromodulation in Children and Adolescents. Psychiatr Clin North Am. 2018;41:465–77. [PubMed: 30098658]

[60]. Croarkin PE, MacMaster FP. Transcranial Magnetic Stimulation for Adolescent Depression. Child Adolesc Psychiatr Clin N Am. 2019;28:33–43. [PubMed: 30389074]

[61]. Yu ZJ, Weller RA, Sandidge K, Weller EB. Vagus nerve stimulation: can it be used in adolescents or children with treatment-resistant depression? Curr Psychiatry Rep. 2008;10:116–22. [PubMed: 18474201]

[62]. Karayağmurlu A, Coşkun M, Elboğa G, Ghaziuddin N, Karayağmurlu E, Gökçen C, et al. Efficacy and Safety of Electroconvulsive Therapy in Adolescents: A Retrospective Chart Review Study From Turkey. J ECT [Internet]. 2019; Available from: 10.1097/YCT.0000000000000602;

[63]. Reinhardt M, Wunsch K, Weirich S, Häßler F, Buchmann J. [Electroconvulsive Therapy (ECT) of a 15-year-old female patient suffering from a severe delusional depression: a case report]. Z Kinder Jugendpsychiatr Psychother. 2018;46:536–41. [PubMed: 30084713]

[64] ●. Rootes-Murdy K, Carlucci M, Tibbs M, Wachtel LE, Sherman MF, Zandi PP, et al. Non-suicidal self-injury and electroconvulsive therapy: Outcomes in adolescent and young adult

populations. J Affect Disord. 2019;250:94–8. [PubMed: 30844603] An retrospective chart review of effectiveness of ECT in adolescents with depression, and exploration of a possible response predictor.

[65]. Argyelan M, Lencz T, Kaliora S, Sarpal DK, Weissman N, Kingsley PB, et al. Subgenual cingulate cortical activity predicts the efficacy of electroconvulsive therapy. Transl Psychiatry. 2016;6:e789. [PubMed: 27115120]

[66]. Food and Drug Administration, HHS. Neurological Devices; Reclassification of Electroconvulsive Therapy Devices; Effective Date of Requirement for Premarket Approval for Electroconvulsive Therapy Devices for Certain Specified Intended Uses. Final order. Fed Regist. 2018;83:66103–24. [PubMed: 30596410]

[67]. Krishnan C, Santos L, Peterson MD, Ehinger M. Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul. 2015;8:76–87. [PubMed: 25499471]

[68]. Wall CA, Croarkin PE, Maroney-Smith MJ, Haugen LM, Baruth JM, Frye MA, et al. Magnetic Resonance Imaging-Guided, Open-Label, High-Frequency Repetitive Transcranial Magnetic Stimulation for Adolescents with Major Depressive Disorder. J Child Adolesc Psychopharmacol. 2016;26:582–9. [PubMed: 26849202]

[69]. MacMaster FP, Croarkin PE, Wilkes TC, McLellan Q, Langevin LM, Jaworska N, et al. Repetitive Transcranial Magnetic Stimulation in Youth With Treatment Resistant Major Depression. Front Psychiatry. 2019;10:170. [PubMed: 30984044]

[70]. Croarkin PE, Nakonezny PA, Deng Z-D, Romanowicz M, Voort JLV, Camsari DD, et al. High-frequency repetitive TMS for suicidal ideation in adolescents with depression. J Affect Disord. 2018;239:282–90. [PubMed: 30031247]

[71]. Zhang T, Zhu J, Xu L, Tang X, Cui H, Wei Y, et al. Add-on rTMS for the acute treatment of depressive symptoms is probably more effective in adolescents than in adults: Evidence from real-world clinical practice. Brain Stimul. 2019;12:103–9. [PubMed: 30237010]

[72]. Cullen KR, Jasberg S, Nelson B, Klimes-Dougan B, Lim KO, Croarkin PE. Seizure Induced by Deep Transcranial Magnetic Stimulation in an Adolescent with Depression. J Child Adolesc Psychopharmacol. 2016;26:637–41. [PubMed: 27447245]

[73]. Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, et al. Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. Brain Stimul. 2016;9:641–61. [PubMed: 27372845]

[74] ●. Wang Y Transcranial direct current stimulation for the treatment of major depressive disorder: A meta-analysis of randomized controlled trials. Psychiatry Res. 2019;276:186–90. [PubMed: 31100509] A meta-analysis of efficacy studies of tDCS as a treatment option for MDD.

[75]. Brunoni AR, Boggio PS, De Raedt R, Benseñor IM, Lotufo PA, Namur V, et al. Cognitive control therapy and transcranial direct current stimulation for depression: a randomized, double-blinded, controlled trial. J Affect Disord. 2014;162:43–9. [PubMed: 24767004]

[76]. Gilmore CS, Dickmann PJ, Nelson BG, Lamberty GJ, Lim KO. Transcranial Direct Current Stimulation (tDCS) paired with a decision-making task reduces risk-taking in a clinically impulsive sample. Brain Stimul. 2018;11:302–9. [PubMed: 29174303]

[77]. Martin DM, Teng JZ, Lo TY, Alonzo A, Goh T, Iacoviello BM, et al. Clinical pilot study of transcranial direct current stimulation combined with Cognitive Emotional Training for medication resistant depression. J Affect Disord. 2018;232:89–95. [PubMed: 29477590]

[78]. Doruk Camsari D, Kirkovski M, Croarkin PE. Therapeutic Applications of Invasive Neuromodulation in Children and Adolescents. Psychiatr Clin North Am. 2018;41:479–83. [PubMed: 30098659]

[79]. Kong J, Fang J, Park J, Li S, Rong P. Treating Depression with Transcutaneous Auricular Vagus Nerve Stimulation: State of the Art and Future Perspectives. Front Psychiatry. 2018;9:20. [PubMed: 29459836]

[80]. Rong P, Liu J, Wang L, Liu R, Fang J, Zhao J, et al. Effect of transcutaneous auricular vagus nerve stimulation on major depressive disorder: A nonrandomized controlled pilot study. J Affect Disord. 2016;195:172–9. [PubMed: 26896810]

[81]. Li X-J, Wang L, Wang H-X, Zhang L, Zhang G-L, Rong P-J, et al. The effect of transcutaneous auricular vagus nerve stimulation on treatment-resistant depression monitored by resting-state fMRI and MRS: The first case report. Brain Stimul. 2019;12:377–9. [PubMed: 30528347]

[82]. Trevizol AP, Shiozawa P, Taiar I, Soares A, Gomes JS, Barros MD, et al. Transcutaneous Vagus Nerve Stimulation (taVNS) for Major Depressive Disorder: An Open Label Proof-of-Concept Trial. Brain Stimul. 2016;9:453–4. [PubMed: 26944188]

[83]. Fang J, Rong P, Hong Y, Fan Y, Liu J, Wang H, et al. Transcutaneous Vagus Nerve Stimulation Modulates Default Mode Network in Major Depressive Disorder. Biol Psychiatry. 2016;79:266–73. [PubMed: 25963932]

[84]. Tu Y, Fang J, Cao J, Wang Z, Park J, Jorgenson K, et al. A distinct biomarker of continuous transcutaneous vagus nerve stimulation treatment in major depressive disorder. Brain Stimul. 2018;11:501–8. [PubMed: 29398576]

[85]. Liu J, Fang J, Wang Z, Rong P, Hong Y, Fan Y, et al. Transcutaneous vagus nerve stimulation modulates amygdala functional connectivity in patients with depression. J Affect Disord. 2016;205:319–26. [PubMed: 27559632]

[86]. Wang Z, Fang J, Liu J, Rong P, Jorgenson K, Park J, et al. Frequency-dependent functional connectivity of the nucleus accumbens during continuous transcutaneous vagus nerve stimulation in major depressive disorder. J Psychiatr Res. 2018;102:123–31. [PubMed: 29674268]

[87]. Fang J, Egorova N, Rong P, Liu J, Hong Y, Fan Y, et al. Early cortical biomarkers of longitudinal transcutaneous vagus nerve stimulation treatment success in depression. Neuroimage Clin. 2017;14:105–11. [PubMed: 28180068]

[88] ●. Cullen KR, Klimes-Dougan B, Vu DP, Westlund Schreiner M, Mueller BA, Eberly LE, et al. Neural Correlates of Antidepressant Treatment Response in Adolescents with Major Depressive Disorder. J Child Adolesc Psychopharmacol. 2016;26:705–12. [PubMed: 27159204] Used fMRI to examine change in neural circuits associated with clinical improvement in adolescents with depression before and after a course of antidepressant treatment.

[89]. Klimes-Dougan B, Westlund Schreiner M, Thai M, Gunlicks-Stoessel M, Reigstad K, Cullen KR. Neural and neuroendocrine predictors of pharmacological treatment response in adolescents with depression: A preliminary study. Prog Neuropsychopharmacol Biol Psychiatry. 2018;81:194–202. [PubMed: 29100972]

Table 1:

Recent RCTs and Open-Label Studies in Child/Adolescent Depression

Treatment	Reference	Study Design	Demographics	Measure	Results
Psychopharmacology					
Vilazodone	Durgam et al. 2018	RCT	N=529 (adolescents [12–17] with MDD) Interval: 10 weeks	Children's Depression Rating Scale-Revised (CDRS-R)	No significant difference between vilazodone and placebo in change from baseline in CDRS, no significant difference in reductions in depression symptoms
Desvenlafaxine	Atkinson et al. 2018	RCT	N=363 (outpatient children [7–11 years] and adolescents [12–17 years] with MDD) Interval: 8 weeks	Children's Depression Rating Scale-Revised (CDRS-R)	Neither dosage groups had significant greater clinical improvement. Did not demonstrate efficacy.
Desvenlafaxine	Weihs et al. 2018	RCT	N=339 (outpatient children [7–11 years] and adolescents [12–17 years] with MDD) Interval: 8 weeks	Children's Depression Rating Scale-Revised (CDRS-R)	Neither desvenlafaxine nor the reference medication, fluoxetine, were statistically significantly different from placebo on the primary endpoint.
Levomilnacipran	Allergan (sponsor) NCT03569475	RCT	N=480 (outpatient children and adolescents [7–17] with MDD) Interval: 8 weeks	Children's Depression Rating Scale-Revised (CDRS-R)	Ongoing trial, no results published.
Levomilnacipran	Forest laboratories (sponsor) NCT02431806	RCT	N=660 (outpatient adolescents [12–17] with MDD) Interval: 10 weeks	Children's Depression Rating Scale-Revised (CDRS-R)	Ongoing trial, no results published.
Vortioxetine	Findling et al. 2017	Open-label	N=48 (adolescents and children [7–17] with depressive or anxiety disorder) Interval: 14–20 days	Maximum serum concentration (Cmax) of Vortioxetine, Area Under Curve (AUC) (0–24h) of Vortioxetine	Cmax and AUC (0–24hr) of vortioxetine were 30–40% lower in adolescents than in children, and the median oral clearance (CL/F) of vortioxetine was lower in children than in adolescents.
Vortioxetine	Findling et al. 2018	Open-label	N=41 (adolescents and children [7–17] with depressive or anxiety disorder) Interval: 14 days	Spontaneously reported adverse events (AEs), Columbia Suicide Severity Rating Scale (C-SSRS), Pediatric Adverse Events Rating Scale (PAERS), Clinical Global Impressions	Dosages of 5–20 mg/day were concluded to be safe and well tolerated.
Vortioxetine	H. Lundbeck A/S (sponsor) NCT02709655	RCT	N=600 (children [7–11] with MDD) Interval: 12 weeks	Children's Depression Rating Scale-Revised (CDRS-R)	Ongoing rial, no results published.
Vortioxetine	H. Lundbeck A/S (sponsor) NCT02709746	RCT	N=750 (children [7–11 years] and adolescents [12–17 years] with MDD) Interval: 12 weeks	Children's Depression Rating Scale-Revised (CDRS-R)	Ongoing trial, no results published.
Ketamine	Cullen et al. 2018	Open-label	N=13 (adolescents [12–18] with TRD) Interval: 2 weeks	Children's Depression Rating Scale-Revised (CDRS-R), Clinician-Administered Dissociative States Scale (CADSS)	Significant decrease in depression scores, dose-response relationship suggested. Generally well tolerated.

Treatment	Reference	Study Design	Demographics	Measure	Results
Ketamine	Yale University (sponsor) NCT03889756	RCT	N=24 (adolescents [13–17] with MDD) Interval: 3 weeks	Children's Depression Rating Scale, Revised (CDRS), drop-out rates	Ongoing trial, no results published.
Ketamine	Yale University (sponsor) NCT02579928	RCT	N=20 (adolescents [13–17] with MDD) Interval: 2 weeks	Montgomery-Asberg Depression Rating Scale, revised (MADRS), Multimodal Anxiety Scale for Children (MASC)	Ongoing trial, no results published.
Esketamine	Janssen Research & Development, LLC (sponsor) NCT03185819	RCT	N=145 (adolescents [12–17] with MDD and suicidal ideation) Interval: 25 days	Children's Depression Rating Scale, Revised (CDRS-R)	Ongoing trial, no results published.
Nutraceuticals					
Creatine	Kondo et al. 2016	RCT	N=28 (females [13–20] with MDD) Interval: 8 weeks	The linear mixed model (LMM), ^{31}P-MRS scans for frontal lobe PCr, Children's Depression Rating Scale-Revised (CDRS-R)	Mean frontal lobe PCr increased in creatinine-receiving groups, while depression scores decreased (inverse correlation)
Saffron	Lopresti et al. 2018	RCT/	N=68 (youth aged 12–16 years, with mild-to-moderate anxiety or depressive symptoms) Interval: 8 weeks	Youth and parent versions of the Revised Child Anxiety and Depression Scale (RCADS)	Reduced anxiety and depressive symptoms, well tolerated with no adverse effects.
N-acetylcysteine	Cullen et. al. 2018	Open-label	N=35 (female adolescents and young adults [16–24] with NSSI, many with depression as weIII) Interval: 28 days	Beck Depression Inventory-II (BDI-II), Barratt Impulsivity Scale, and Symptoms Checklist-90 (SCL-90)	Depression symptoms decreased significantly, independently of the significant decrease in self-injury
N-acetylcysteine	University of Minnesota -Clinical and Translational Science Institute (sponsor) NCT04005053	RCT	N=36 (adolescents and young adults [16–24] with NSSI) Interval: 4 weeks	Change in glutathione concentrations in ACC	Ongoing trial, no results published.
Vitamin D	Bahrami et al. 2018	Open-label	N=940 (adolescent girls, 306 of whom had depression) Interval: 9 weeks	Beck Depression Inventory-II (BDI-II), Buss-Perry Aggression Questionnaire	Depression symptoms (but not aggression scores) decreased significantly after the intervention
Vitamin D	[46] et al. 2018 German Clinical Trial Register, DRKS00009758	RCT	N=200 (children and adolescents with vitamin D deficiency and depressive symptoms) Interval: 28 days	Beck Depressions Inventory (BDI-II)	No results following protocol have been published.
Interventions Implicating the Motor and Sensory Systems					
Hatha yoga	Brown University (sponsor) NCT03831360	RCT	N=54 (adolescents [13–18] with MDD) Interval: 12 weeks	Qualitative interview, Credibility Expectancy Questionnaire (CEQ) – Credibility Subscale, Credibility Expectancy Questionnaire (CEQ) – Expectancy Subscale, Client Satisfaction Questionnaire (CSQ-8), Home practice questionnaire, Systematic assessment of treatment-emergent events-general inquiry (SAFTEE)	Ongoing trial, no results published.

Treatment	Reference	Study Design	Demographics	Measure	Results
Mind-body skills (meditation, guided imagery, breathing techniques, etc.)	Indiana University (sponsor) NCT03363750	Open-label	N=75 (adolescents [13–17] with MDD) Interval: 10 weeks	Children's Depression Inventory-2 (CDI-2)	Ongoing trial, no results published.
Light therapy	Kirschbaum-Lesch et al. 2018	Open-label	N=39 (inpatient youth [12–18] with moderate to severe depression) Interval: 2 vs 4 weeks	Beck Depression Inventory-II (BDI-II)	Significant improvement in depressive symptoms, clinical global impression and sleep issues.
Light therapy	Holtmann et al. 2018 German Clinical Trials Register, DRKS00013188	RCT	N=224 (inpatient youth [12–18] with MDD) Interval: 4 weeks	Beck Depression Inventory-II (BDI-II)	No results following protocol have been published.
Neuromodulation					
Transcranial magnetic stimulation (TMS)	Wall et al. 2016	Open-label	N=10 (adolescents [13–18] with MDD) Interval: 6–8 weeks	Children's Depression Rating Scale-Revised (CDRS-R)	6 out of 10 patients responded to a 6–8 week rTMS treatment course, with limited, mild, and transient adverse effects, and sustained clinical improvement over 6-month follow up
Transcranial magnetic stimulation (TMS)	Croarkin et al. 2018	Open-label	N=19 (adolescents with TRD) Interval: 6 weeks	Columbia Suicide Severity Rating Scale (C-SSRS) "Intensity of Ideation" subscale, Item 13 "Suicidality" on the Children's Depression Rating Scale, Revised (CDRS-R)	47% of adolescents showed overall clinical response, and predicted odds of suicidal ideation significantly decreased over the 6 weeks of treatment
Transcranial magnetic stimulation (TMS)	MacMaster et al. 2019	Open-label	N=32 (adolescents and young adults [13–21] with TRD) Interval: 3 weeks	Hamilton Depression Rating Scale (Ham-D)	Depression symptoms were significantly reduced, with 14 subjects achieving remission and 16 subjects achieving partial remission
Transcranial magnetic stimulation (TMS)	University of Minnesota - Clinical and Translational Science Institute (sponsor) NCT02611206	Open-label	N=30 (adolescents [12–18] with MDD) Interval: 6 weeks	Child Depression Rating Scale – Revised (CDRS-R)	Ongoing trial, no results published.
Transcranial magnetic stimulation (TMS)	Mayo Clinic (sponsor) NCT03363919	RCT	N=120 (adolescents [12–18] with MDD) Interval: 6 weeks	Child Depression Rating Scale - Revised (CDRS-R)	Ongoing trial, no results published.
Transcranial direct current stimulation (TDCS)	Mayo Clinic (sponsor) NCT03368469	Open-label	N=20 (children and adolescents [10–21] with depressive disorder and generalized epilepsy) Interval: 2 weeks	Children's Depression Rating Scale - Revised (CDRS-R)	Ongoing trial, no results published.
Transcranial direct current stimulation (TDCS) plus Mindful Breathing	University of Minnesota-Clinical and Translational Science Institute (sponsor) NCT03897699	RCT	N=60 (adolescents and young adults [16–24] with MDD) Interval: 9 weeks	Change in dorsolateral prefrontal cortex (DLPFC) connectivity	Ongoing trial, no results published.

KEY: RCT = randomized controlled trial, MDD= Major Depressive Disorder, NSSI= Non-Suicidal Self-Injury, TRD= Treatment Resistant Depression