

A Detailed Review of the Safety and Efficacy of Selective Serotonin Reuptake Inhibitor Treatment for Adolescents with Major Depressive Disorder

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Author Bio

Diksha Sriram is currently a senior at the Massachusetts Academy of Math and Science who plans to study neuroscience in the future. She has always been passionate about mental health and would like to work specifically in optimizing personalized medicine and treatment for various mental illnesses based on factors such as age, gender, etc. Her interest was initially sparked by her middle and high school experience, where she decided that she wanted each person to be aware of their options when struggling with mental health and feel safe and comfortable reaching out for help. In her free time, she enjoys singing and songwriting as well as public speaking through the National Speech and Debate Association.

Abstract

Major depressive disorder (MDD) is a serious mental illness consisting of at least one discrete depressive episode in which patients may feel sad, irritable, or empty, lose interest and pleasure in activities, have poor concentration, and/or feel excessive guilt, or low self-worth. According to the National Institute of Mental Health (NIMH), 12.8% of the US adolescent population (12-17 years old) was diagnosed with at least one depressive episode in 2016, with suicide being the 2nd leading cause of death for adolescents. Currently, it is advised to prescribe Selective Serotonin Reuptake Inhibitor (SSRI) medication to moderate to severe cases of adolescent depression after psychological methods have been applied. However, people concern about the safety and efficacy of SSRIs, leading to a drop in antidepressant prescriptions and sales for adolescents. This literature review discusses the functionality of SSRI medication and assesses its benefits and adverse effects. SSRIs increase serotonin levels at synapses, hence easing depressive symptoms caused by the deficiency of serotonin. On the other hand, SSRIs can negatively affect learning, memory, and cognitive function. The review also investigates the effectiveness of the combination of SSRI treatment with other forms of treatment.

Keywords: Major depressive disorder, depression, Selective Serotonin Reuptake Inhibitors, SSRI, adolescent mental health, effects of SSRIs, adolescent psychiatry, cognitive behavioral therapy

Section 1: An overview of Major Depressive Disorder

1.1: Symptoms, effects, and the external triggers of major depressive disorder

Major depressive disorder (MDD) is a pleomorphic and serious mental illness that consists of at least one discrete depressive episode that lasts two or more weeks (Otte et al., 2017). During a depressive episode, patients may feel sad, irritable, or empty, lose interest and pleasure in activities, have poor concentration, and/or feel excessive guilt, or low self-worth. They may also experience disrupted sleep, or excessive tiredness or low energy, and thoughts about dying or suicide. In fact, according to the World Health Organization, an estimated 50% of the approximate 800,000 worldwide suicides per year happen during a depressive episode (*Depression, n.d.*). Furthermore, patients with MDD are 20-fold more likely to die from suicide than a healthy patient (*Depression, n.d.*). The World Mental Health survey indicated that major depressive disorder affects 1 in every 6 adults. MDD leads to many other symptoms as well: changes in appetite and weight, cardiac arrhythmias and dyspnea, changes in body temperature, and more. There is an increased risk of diabetes mellitus, heart disease, stroke, hypertension, obesity, cancer, cognitive impairment, and Alzheimer disease associated with MDD. Thus, it is the second leading contributor to the global chronic disease burden (Otte et al., 2017). The average duration of a depressive episode is between 13-30 weeks and 70-90% of patients recover within one year with therapy and/or pharmaceutical treatment. However, residual symptoms and functional impairment often remain after MDD remission (Otte et al., 2017).

There are many external factors that contribute to MDD such as sexual, physical, or emotional abuse during childhood (Otte et al., 2017). Cognitive changes and emotional dysregulation in the brain's response to fear and stress after experiencing childhood trauma may lead to depression (*Depression | NAMI: National Alliance on Mental Illness, n.d.*). A history of childhood trauma leads to a two-fold increase of developing MDD with higher symptom severity, poorer course, and less response to treatment than patients without childhood trauma. It is important

to note that there is a positive correlation between the number and severity of traumatic life events and the severity and chronicity of MDD (Otte et al., 2017). Other contributors can include life circumstances (marital status, relationship changes, financial status), co-morbidities (sleep disturbances, medical illness, chronic pain, anxiety, attention-deficit hyperactivity disorder), or drug and alcohol misuse (*Depression | NAMI: National Alliance on Mental Illness, n.d.*).

1.2: Proposed mechanisms of major depressive disorder

There is no single mechanism that can explain every aspect of MDD. fMRI imaging studies have shown that synaptic density decreases as a result of depression (Holmes et al., 2019). Figure 1 displays the radioligand [11C]UCB-JVT as a readout for synaptic density (Holmes et al., 2019). A radioligand is a radioactive biochemical compound that aids in diagnosis and research on receptor systems in the body (*Radioligand - an Overview | ScienceDirect Topics, n.d.*). The graph in Figure 1 provides evidence that that the level of synaptic density for healthy volunteers and patients with low severity of depression are about the same. However, there is a major deficit in patients with high severity depression (Holmes et al., 2019). In general, it is associated with smaller hippocampal volume, as visible by smaller synaptic density shown in Figure 1 (Holmes et al., 2019), and changes in activation or connectivity of neural networks. These networks include the cognitive control network, which influences executive functions like selective attention, working memory, stimulus-response mapping, and performance monitoring, and the affective salience network, which is a collection of regions in the brain that consider which stimuli are deserving of attention (Otte et al., 2017). Depression is further associated with changes in how the pituitary gland and hypothalamus respond to hormone simulation (*Depression | NAMI: National Alliance on Mental Illness, n.d.*).

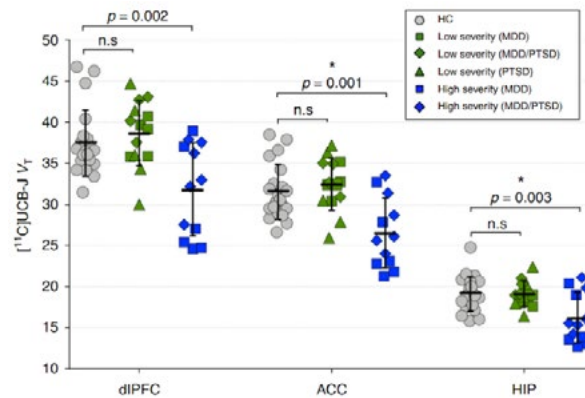


Figure 1: [11C]UCB-JVT readings in the Prefrontal Cortex (PFC), Anterior Cingulate Cortex (ACC), and Hippocampus (HIP), indicating synaptic density (Holmes et al., 2019).

One of the most researched biological systems in MDD is the hypothalamic-pituitary-adrenal (HPA) axis. It serves as a neurobiological model that explains the long-lasting consequences of early trauma. Early-life stress produces an increase in the activity of neural circuits containing corticotropin-releasing hormone (CRH). CRH is then released in the paraventricular nucleus and affects the response to stress and addiction. This effect is caused through the creation and release of the adrenocorticotrophic hormone from the pituitary gland (*Corticotropin-Releasing Hormone (CRH)*, 2019). In addition, CRH is the primary regulator of the HPA axis. Individuals who were sexually or physically abused in childhood demonstrated the hyperactivity of the HPA axis when they are exposed to social stressors again in adulthood (Otte et al., 2017).

The dysfunction of monoamine neurotransmitters, their metabolites, as well as the maladaptive alterations of their receptors in the Central Nervous System (CNS) are involved in the pathogenesis of depression as well. Monoamine neurotransmitters include noradrenaline, dopamine, and serotonin. Selective serotonin reuptake inhibitors (SSRIs) are targeted toward serotonin stabilization (Otte et al., 2017).

1.3: Major depressive disorder in adolescents

Adolescence is defined as the developmental period starting with physical and observable signs

of puberty and ending with the addition of adult responsibilities and social roles to one's life (Rice et al., 2019). According to the National Institute of Mental Health (NIMH), 12.8% of the US adolescent population (12-17 years old) was diagnosed with at least one depressive episode in 2016. In fact, suicide is the second leading cause of death for adolescents. The Center for Disease Control and Prevention records that after puberty, females are more frequently diagnosed with depression. Adolescents with depression usually display increased irritability and impulsivity; decreased grades and school performance; disturbed sleep and appetite; and suicidality (Mullen, 2018). Somatic symptoms are also more common in adolescents with depression (Rice et al., 2019).

A study conducted by Rice et al. (2019) investigated 335 adults with MDD and assessed them and their offspring with clinical interviews on three separate occasions. Depressive symptoms in adolescents were assessed using the Child and Adolescent Psychiatric Assessment (CAPA). The interviews were used to determine which symptoms may or may not be more common in adolescents. For example, loss of interest/anhedonia was more observed in adults. Table 1 displays a full list of symptoms as well as the percentage of MDD cases in adults and adolescents with those symptoms. In general, symptoms such as loss of energy (97.2% of participants), depressed mood (94.6% of participants), insomnia (at least 2 less hours of sleep every night; 86.5% of participants), and worthlessness/guilt (81.1% of participants) were observed to be the most common in adolescents. It is important to note however that irritability rather than depressed mood is more commonly used as a diagnostic factor of depression (Rice et al., 2019).

		Percentage of MDD cases with symptoms	
		Adults	Adolescents
Core symptoms	Depressed mood	98.2	94.6
	Loss of interest/anhedonia	88.1	70.3
	Irritability	46.8	29.7
Vegetative	Change in appetite	56.0	78.4
	Weight gain	3.7	40.5
	Weight loss	7.4	31.4
	Hypersomnia	22.9	22.9
	Insomnia	63.3	86.5
	Psychomotor retardation	30.3	35.1
Cognitive symptoms	Loss of energy	70.6	97.2
	Worthlessness/guilt	85.2	81.1
	Loss of concentration	74.3	38.9
	Suicidality	65.4	50.0

Table 1: The percentage of adults and adolescents with MDD that display certain symptoms (Rice et al., 2019)

Early intervention of MDD is vital, making it crucial to find the right treatment for adolescents in order to avoid impairment to educational, occupational, and social functioning (Mullen, 2018). Evidence for the effectiveness of antidepressants in the treatment of adolescent MDD is less than adult MDD. SSRIs, in particular, are shown to have smaller effects in treatment for depression in adolescents (Rice et al., 2019). An FDA warning on the SSRI paroxetine was issued in June 2003, warning against suicide, worsening depression, agitation, and mania (Hamrin & Scahill, 2005). Therefore, people concern about the safety and efficacy of SSRIs, leading to a drop in antidepressant prescriptions and sales for adolescents (Cousins & Goodyer, 2015). The following review will investigate the functionality as well as the efficacy of SSRI usage for adolescents with MDD.

Section 2: The use of SSRIs to treat major depressive disorder

2.1: Functionality in the adolescent brain

Currently, it is advised to only prescribe SSRI medication to moderate to severe cases of depression in adolescents, after psychological methods have been applied (Cousins & Goodyer, 2015). As mentioned earlier, serotonin is a neurotransmitter in the central nervous system that deals with physiological and behavioral functions including control of sleep and wakefulness, motor function, emotional responses, and more (Hamrin & Scahill, 2005). Serotonin is also involved in synaptic development (Cousins & Goodyer, 2015). Since MDD is associated with reduced serotonin levels in limbic regions of the brain, SSRIs, as the name suggests, block the reuptake of serotonin at the presynaptic transporter site, which results in the increase of serotonin at the synapse. The increase of serotonin at the synapse eventually results in a net increase of serotonin in the brain (Hamrin & Scahill, 2005).

SSRIs have also been shown to increase neurogenesis in the hippocampus, as MDD is associated with lower hippocampal volumes (Cousins & Goodyer, 2015). Boldrini et al. (2013) looked at the right hippocampus of 17 healthy volunteers, 15 patients with untreated MDD, and 10 patients

who were being treated for MDD (5 with tricyclics and 5 with SSRIs). The SSRI-treated group had an amount of granule neurons (GN) in the dentate gyrus (DG) closer to control subjects rather than untreated subjects, as observable in Figure 2. The DG is a part of the hippocampal formation. The observation was only statistically significant in mid DG ($p < 0.028$). Furthermore, mid DG was bigger in treated patients compared to untreated patients and controls ($p = 0.002$). The direct correlation between the number of GN and DG volume indicates that patients on SSRI treatment have larger mid hippocampal volume than unmedicated patients and controls (Boldrini et al., 2013).

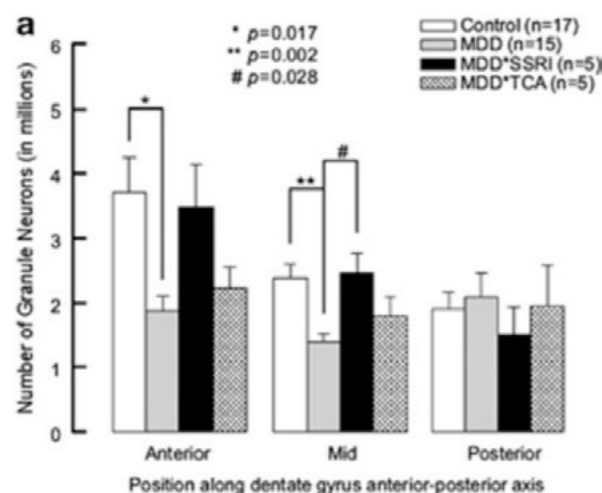


Figure 2: The number of granule neurons in the anterior-posterior axis of the dentate gyrus for healthy volunteers, patients with untreated MDD, and patients with MDD being treated with SSRIs or tricyclic medication.

Certain SSRIs induce the hippocampal neurogenesis by blocking the acid sphingomyelinase (ASM)-ceramide system. Ceramide is involved in oxidative stress. ASM is expressed everywhere to release ceramide from sphingomyelin (Cousins & Goodyer, 2015). A study conducted on mice by Gulbins et al. (2013) showed that when ASM is over-expressed, there is less hippocampal neurogenesis, while antidepressants like the SSRI fluoxetine induced hippocampal neurogenesis. The increase of ceramide independent of ASM also led to the reduction of neurogenesis and the increase of depressive symptoms, which could be corrected by antidepressants (Gulbins et al., 2013).

2.2: Benefits of SSRI usage to treat MDD

Tao et al. (2012) conducted a study using fMRI to determine the effects of antidepressant treatment with fluoxetine in adolescents. The study used a voxel-wise whole brain analysis to look at differences in fMRI activation to emotional faces before and after treatment, hypothesizing that there is an association between treatment and normalization of activation in the amygdala. Participants included 23 depressed adolescents and 22 healthy adolescents. Black and white fearful and neutral facial expressions were selected from the Picture of Facial Affect collection. Participants were randomly presented 10 faces at the baseline, and then again 8 weeks later. Adolescents with depression received 8 weeks of fluoxetine treatment after the initial scan. 60% of the depressed adolescents reported to have responded to the treatment after the 8th week (Tao et al., 2012).

After the initial scan, adolescents with MDD had greater activations than the healthy controls for fear>neutral contrast in the left and right frontal lobe, temporal lobe, putamen, insula, and cingulate gyrus in the right amygdala, right hippocampus, and right occipital cortex. The baseline also showed that adolescents with MDD responded almost the same to fearful or neutral faces. However, by week 8, adolescents with MDD and the control group responded almost the same as each other to neutral and fearful faces. Figure 2 displays activations at baseline and week 8 in the amygdala, orbitofrontal cortex, and subgenual cingulate cortex in adolescents with MDD and healthy control subjects. The post hoc revealed that there was more activation for depressed adolescents in the left and right amygdala at the baseline, which was then normalized by the treatment by week 8. The same phenomenon was observed with the right orbitofrontal cortex and subgenual anterior cingulate cortex. However, only the left amygdala, right orbitofrontal cortex, and right subgenual anterior cingulate cortex reached statistical significance (Tao et al., 2012).

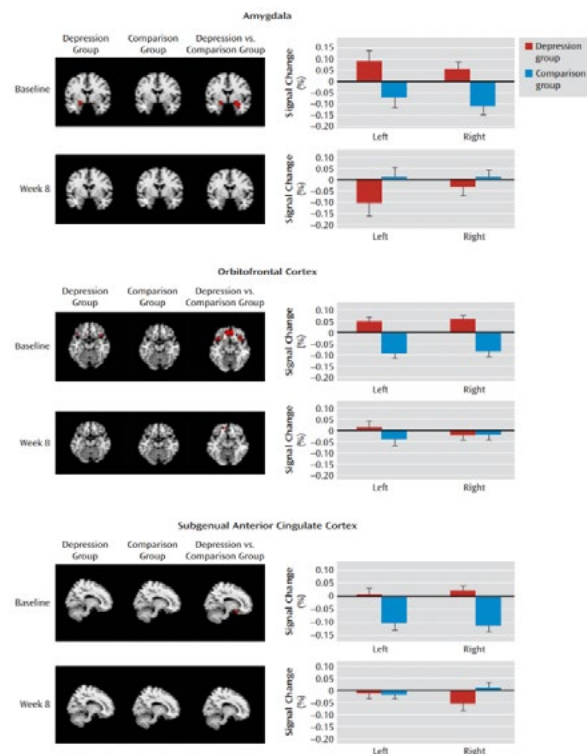


Figure 3: Activations at baseline and week 8 in the amygdala, orbitofrontal cortex, and subgenual cingulate cortex in adolescents with MDD and healthy control subjects.

The study conducted by Tao et al. (2012) concluded that brain activity in adolescents with depression became normalized to levels observed in healthy control patients, which can relieve any concerns about SSRI usage in the pediatric population (Tao et al., 2012). Ambrosini et al. (1999) also studied the effect of the SSRI sertraline in a ten-week open-label trial. The outcome was measured using the Hamilton Depression Rating Scale and the Clinical Global Inventory. The study described a 55% improvement on the scale by week 6 of the experiment and a 76% improvement at the conclusion of week 10. 55% of the 47 adolescents in the study reduced their depression scores by at least 50% from the beginning to the end of the 10 weeks (Ambrosini et al., 1999).

2.3: Adverse effects of SSRI usage to treat MDD

Although SSRIs are efficacious to treat MDD in adolescents, there are some potential adverse effects. Sass & Wörtwein (2012) studied the effects of fluoxetine treatment on learning and

memory in adolescent rats. 24 male Wistar rats were administered fluoxetine and assessed through open field, object recognition (OR), behavioral, and spatial memory tests. The open field test consisted of two trials of 15 minutes given to each rat over the period of two consecutive days. The trial started when the experimenter released the rat facing the arena, and the total distance moved (cm) as well as the percentage of total distance moved was determined and recorded. During both sessions, fluoxetine-treated rats entered the center of the field less and moved shorter distances in the center, indicating higher levels of anxiety ($p < 0.05$ and $p < 0.01$, respectively). OR tests consisted of one 15-minute exploration trial where two identical objects were placed in two square areas. Then, there was a 3-minute discrimination trial in which two new objects were placed in the same square areas, one being identical to the original two objects. The amount of time that the rats' center of gravity entered each square area during each trial was measured and recorded. Fluoxetine-treated rats explored the objects more during the discrimination period and displayed less discrimination between the new and familiar object, indicating their inability to recognize objects from memory. The spatial memory test gave rats 5 swims for 5 consecutive days through a water maze. A computer was used to mark the rats' position in the arena from the start to the end of the maze. The trial was terminated after 60s of swimming. The rats were tasked with remembering the position of the platform during the original trial. Analysis of the tests showed that rats treated with fluoxetine swam significantly shorter distances when trying to locate the position of the original platform ($p < 0.01$), suggesting that rats treated with fluoxetine were less able to recall the location of the platform. The study concluded that there are subtle acute and long-term effects dealing with learning and memory (Sass & Wörtwein, 2012). Similar to the open field test, a study by Oh et al. (2009) showed that treatment with fluoxetine in two different strains of adolescent mice resulted in an anxiogenic response, which again disappeared when the medication was discontinued (Oh et al., 2009). It must be taken into account that these studies have been conducted on animal models, thus making it hard to conclude how these effects of antidepressants translate to the human brain (Tao et al., 2012).

Shehab et al. (2016) conducted a 12-week study on the neurocognitive changes from fluoxetine treatment in 24 adolescents with MDD and 25 healthy

controls. Adolescents with MDD started on 20 mg of fluoxetine, with the option of increasing to 50 mg at the 5th week and 60mg at the 8th week if the score on the Clinical Global Impressions Improvement Scale was 3 or greater. Participants were first given a delayed matching to sample test where they were shown a complex visual pattern and were told to choose the one identical to it from 4 other patterns that were presented simultaneously or with a delay of 0, 4, or 12 seconds. Patients with MDD performed more poorly than healthy controls with less percent correct across assessment times. Participants were also given a rapid visual processing test where they were presented the digits 2 to 9 randomly at 100 digits/minute. They were then told to press the touchpad when they detected a pattern such as 2-4-6 or 3-5-7. Post hoc t-tests revealed a significant difference in total hits between healthy controls and patients with MDD during the 12th week ($p = 0.008$), while there was no significant difference at the baseline. Finally, participants were shown two sets of stacked colored balls, one displayed higher than the other. They were instructed to use a specific number of moves to move the balls one at a time in the lower display to match the balls in the upper display. The average amount of moves for the healthy controls decreased overtime, but it remained high for patients with MDD. Shehab et al. also observed that visual memory in SSRI treated adolescents with MDD is less than healthy controls for up to 12 weeks after the end of treatment. In conclusion, healthy controls were better at finding patterns and sequences while adolescents with MDD were more impulsive and struggled with attention deficits (Shehab et al., 2016).

2.4: Combination treatments with SSRIs

While SSRIs have been a mainstay treatment for adolescents with MDD, there are other options available. Cognitive behavioral therapy (CBT) is a treatment that aims to seek out and change discordant beliefs, attitudes, and behaviors that can contribute to emotional distress (Reinecke et al., 1998). It is a talking therapy that aims to help deal with overwhelming problems by breaking them down to view them in a more positive light (*Overview - Cognitive Behavioural Therapy (CBT)*, 2021). March et al. (2004) conducted a randomized multisite controlled trial of 439 adolescents in which participants were randomly assigned to fluoxetine, CBT, a combination of both, or combination of BT and

the matching placebo of fluoxetine. The combination was the most successful with a 71% response rate whereas placebo only had a 35% response rate. Furthermore, fluoxetine alone only had a 61% response rate and only CBT had a 43% response rate. Figure 3 shows the effects of the various treatments through their scale scores on the Children's Depression Rating Scale-Revised (CDRS-R), Reynolds Adolescent Depression Scale, and the Suicidal Ideation Questionnaire-Junior High School Version. The figure displays the combination of fluoxetine and CBT as the most effective in decreasing the mean scale scores on each scale (March et al., 2004). This study provides evidence that SSRIs are most effective when used in combination with CBT.

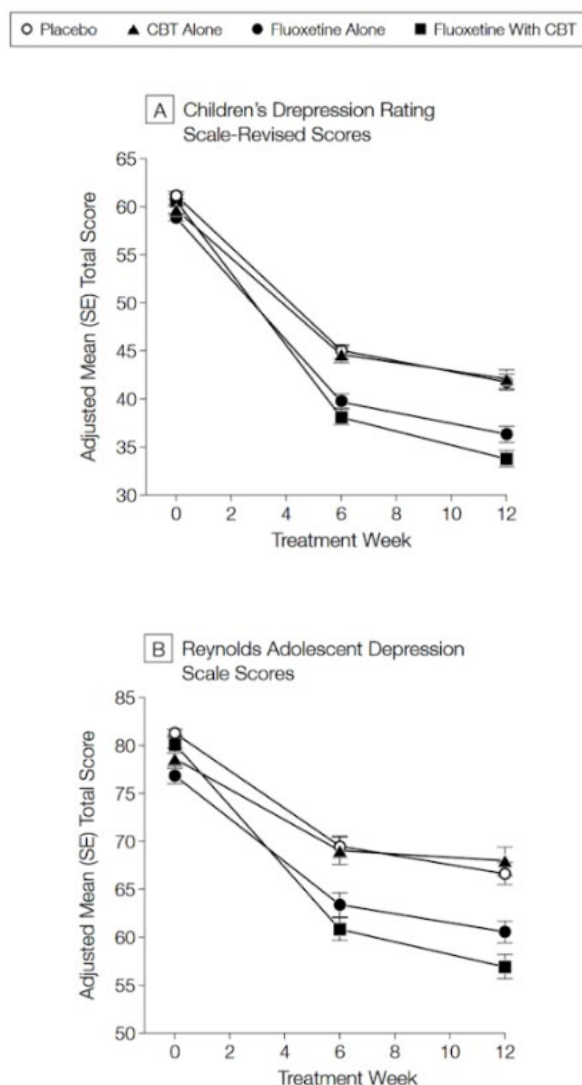


Figure 4: Mean scale scores for participants in the depressed adolescent treatment study (March et al., 2004)

Brent et al. (2008) conducted a similar experiment dealing with the treatment of SSRI-resistant depression in adolescents (TORDIA). Participants were adolescents who were currently only on SSRI treatment for at least 8 weeks and who were not currently receiving CBT. Participants in the experiment were then randomized into 1 of 4 treatments: a different SSRI, venlafaxine, a different SSRI and CBT combo, venlafaxine and CBT combo. Participants were first assessed with the CSRS-R and Clinical Global Impressions-Severity subscale and tested again after 2 weeks of being on an SSRI regimen. Participants whose score decreased less than 30% were enrolled in the study. In this study, a greater number of participants showed an adequate clinical response to CBT (54.8%). Switching to a combination of CBT and another antidepressant was the most effective for patients who were nonresponsive to their current SSRI treatment (Brent et al., 2008). Taken together, CBT is a beneficial add-on therapy for MDD.

Conclusion

MDD is a serious mental illness and must be treated appropriately, particularly in adolescents. SSRIs are a mainstay treatment for adolescents with MDD. While they can greatly aid in stabilizing serotonin levels in the brain and lowering the overall activation levels in critical brain regions, as shown by Tao et al. (2012), as well as reducing depressive symptoms (Ambrosini et al., 1999), they can also have adverse

effects on learning, memory, and cognitive function (Sass & Wörtwein, 2012; Shehab et al., 2016). Results of studies that have used a combination of CBT and SSRIs have proven that method to be the most effective, suggesting that CBT could be a beneficial add-on therapy with no drug-related adverse effects (Mullen, 2018). Identifying the safety and efficacy of treatment options is a step closer in informing patients of their options and finding the most effective treatment for each individual patient.

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