J. Indian Assoc. Child Adolesc. Ment. Health 2021;17(3):154-166

Review Article

Safety and Efficacy of Transcranial Magnetic Stimulation (TMS) in Pediatric Depression

Vishal Gupta, Shivangini Singh, Pawan Kumar Gupta, Sujita Kumar Kar

Address for correspondence: Dr. Sujita Kumar Kar, Department of psychiatry, King George's Medical University, Lucknow, Uttar Pradesh, India. Email: drsujita@gmail.com

---

Abstract

Transcranial Magnetic Stimulation (TMS), a form of Non-Invasive Brain Stimulation (NIBS), has gained popularity in the last couple of decades. It is approved for treating depression in adults and is under investigation in pediatric depression. This paper aims to evaluate Transcranial Magnetic Stimulation (TMS) studies in pediatric depression and provide a narrative overview by reviewing the research databases (PubMed, Science Direct, and Cochrane Library). Recent evidence suggests that in pediatric patients of treatment-resistant depression, repetitive Transcranial Magnetic Stimulation (rTMS) of the frequency of 10 Hz when applied to the left dorsolateral prefrontal cortex (DLPFC), can lead to remission, improvement in depressive symptoms, or decrease in recurrence of episodes. Existing literature also suggests that TMS's adverse effects in the pediatric population are minimal and comparable to those in the adult population. However, the limitations of existing studies, including lack of double-blind sham-controlled randomized trials or RCTs (only one RCT exists to date), small sample sizes, absence of long term follow-ups, and lack of homogenous age distribution, render the evidence insufficient for approval of TMS use in pediatric depression. This review suggests that although there is a scope of TMS use in pediatric depression, more proof is required to establish and quantify its efficacy and standardize its dosing regimens.

Keywords: Pediatric depression, Transcranial magnetic stimulation, efficacy, safety

Introduction

Depression is a common psychiatric disorder seen in populations of all age groups, including the pediatric age group, with a lifetime prevalence in adolescents similar to that seen in adults [1]. Data from the 2016 National Survey of Children's Health (NSCH) showed that more than 3% of children (3-17 years of age) had current depression, of which only 80% received treatment the previous year. It is significant because mental disorders in childhood can negatively affect a child's development by interfering with their ability to achieve social, emotional, cognitive, and academic milestones and function in daily settings [2]. The earlier age of onset of depression can pose an increased risk of suicidality [3]. Like the adult population, not all children or adolescents achieve full remission on receiving antidepressant and psychosocial treatment, and some may even experience recurrence [4]. Depression, with inadequate response to antidepressants and psychotherapy, can be seen in treatment-resistant depression, commonly defined as a minimum of two prior treatment failures with confirmation of previous adequate dose and duration [5]. So, alternate treatment methods need to be explored to add to the current treatment options of pharmacological and behavioral therapies.

The use of various methods of Non-Invasive Brain Stimulation (NIBS), also known as Non Invasive neuromodulation, is increasing rapidly for many psychiatric disorders. These methods include Transcranial Electric Stimulation (TES), Transcranial Magnetic Stimulation (TMS), Transcranial Focused Ultrasound (TFUS), and Transcranial Photobiomodulation (TPBM). TES, which first started in the form of Electroconvulsive Therapy (ECT), has a long history of psychiatry application, especially in depression. The interest of researchers and clinicians working in the field of NIBS has recently grown in TMS. It is widely used to treat unipolar Major Depressive Disorder (MDD) in adults since its approval by the US Food and Drug Administration (FDA). Recently, the FDA also approved its use in Obsessive-Compulsive Disorder (OCD).

Transcranial Magnetic Stimulation (TMS) operates on Faraday's law of electromagnetic induction, which states that an electric current passing through a closed-circuit coil produces a magnetic field and a changing magnetic field is capable of inducing an electric current. So, with the TMS coil placed over the subject's scalp, it is possible to alter the magnetic field rate, and the resultant electric current can modulate the cortical activity at the targeted site [6,7]. Barker et al., developed the first TMS device [8]. They demonstrated cortical modulation and how magnetic stimulation was better than electrical stimulation to reduce patient discomfort and administration ease. Since then, various forms and techniques have been developed and studied for the application of TMS. TMS is known to exert its effect by modulating activity in discrete cortical regions [9,10]. Pascual-Leone et al. (1991) showed lateralization of speech arrest induced by TMS on the left cerebral hemisphere's targeted areas. The effects of TMS persisted beyond the period of stimulation [9]. Roth et al., (2002) attempted targeting deeper brain regions, which can cause pain and other adverse effects [10]. The most common area targeted for childhood depression in trials is the left dorsolateral prefrontal cortex (DLPFC) (Table 1). TFUS and TPBM are other modalities that showed promising results in early studies and are still under research [6].

NIBS has emerged as a safe tool to boost the outcomes of currently available interventions in improving several neuropsychiatric symptoms [11]. Because of its targeted action [7], TMS is considered a well-tolerated and potentially effective treatment approach for depression. Its role in treating depression in the pediatric population is not well established and is still under investigation. Since TMS has the potential to be accepted as a relatively safe and effective treatment modality for pediatric depression, we went through its existing literature to form a narrative review on the efficacy and safety of TMS in pediatric depression.

Methods and Results

We initially conducted a broad search in online research databases (PubMed, Science Direct, and Cochrane Library) using the keywords TMS; repetitive Transcranial Magnetic Stimulation; rTMS; Children; Adolescents; Pediatric population; Depression; Depressive episode; Depressive disorder. It helped in setting a background for the review. Then, the studies mainly consisting of children and adolescents with depression were included. We incorporated the original studies published in English, such as open-label trials, case series, sham-controlled clinical trials, and follow-ups of clinical trials, in the formation of this narrative review, and excluded the studies primarily focusing on NIBS methods other than TMS.

Key findings of the review are as follows:

- Many open-label trials and case studies have demonstrated antidepressant effects of the TMS in pediatric depression when applied at 10 Hz frequency targeting the left dorsolateral prefrontal cortex (DLPFC).
- Limitations of the existing studies, such as small sample size, a limited number of RCTs, no long-term follow-ups, restrict us from making a definite conclusion.
- The past studies have shown that TMS has mild adverse effects, comparable to those in the adult population.

Discussion

TMS's most common therapeutic target for treating depression is the left dorsolateral prefrontal cortex (DLPFC). For the adult population, many sham-controlled, double-blind, randomized control trials (RCTs) have demonstrated that rTMS application to DLPFC has antidepressant efficacy [12–15].

Existing therapeutic TMS studies in the pediatric population for depression mostly consist of small open-label trials and case series with limited follow-ups. Table 1 lists the original studies on TMS use in children and adolescents with treatment-resistant major depressive disorder

(MDD) or depressive symptoms. The majority of them studied the outcomes of 10 Hz rTMS setting, targeting left DLPFC, except Kwon at el. 2011 and Le et al. 2013, who studied 1 Hz rTMS targeting Supplementary Motor Area (SMA), and Lewis CP et al. 2018, who studied single-pulse/paired-pulse TMS (sp/ppTMS). Subjects of minimum age between 6-8 years to a maximum of 17-21 years are included in these studies. They had varying sample sizes, with smaller studies having sample sizes of about 4, to larger having up to 32 [16–26]. The largest existing RCT has a sample size of 103 (n = 103) [27].

Table-1: Original studies on TMS use in children and adolescents with treatment-resistant major depressive disorder (MDD) or depressive symptoms

Study	Year	Study Type	Sample Size	Sample Type	TMS Type	Length	Results
Croarkin et al.	2020	Double-Blind, sham-controlled RCT	103	Adolescents with Treatment-Resistant MDD (12-21 years)	rTMS, 10 Hz, Left DLPFC	Six weeks	No significant difference in remission rates of active group vs. sham group, no serious SEs
Sonmez et al.	2019	Open-Label Study	17	Adolescents with Treatment-Resistant MDD	rTMS, 10 Hz, Left DLPFC	Six months	Effect on hypersomnia apart from antidepressant effects
MacMaster et al.	2019	Open-Label Study	32	Adolescents with Treatment-Resistant MDD (13-21 years)	rTMS, 10 Hz, Left DLPFC	Three weeks	Antidepressant effect, no serious SEs
Lewis CP et al.	2018	Longitudinal Study	10	Adolescents undergoing pharmacological treatment for depression (13-17 years)	sp/pp TMS	Eight weeks	Change in depression severity and suicidal ideation
Wall et al.	2016	Open-Label Study	10	Adolescents with Treatment-Resistant MDD (13-18 years)	rTMS, 10 Hz, Left DLPFC	6-8 weeks	Antidepressant effect, no serious SEs
Yang et al.	2014	Case series	6	Adolescents with TR- MDD (15-21 years)	rTMS, 10 Hz, Left DLPFC	Three weeks	Antidepressant effect, no serious SEs

Mayer et al.	2012	Three year F/U of Open-Label rTMS Study	8	Adolescents with Treatment-Resistant MDD (19-22 years)	rTMS, 10 Hz, Left DLPFC	Three years	No deterioration of depressive symptoms after three years, no serious SEs
Wall et al.	2011	Prospective Open Pilot Study	8	Adolescents with Treatment-Resistant MDD	rTMS, 10 Hz, Left DLPFC	6-8 weeks	Antidepressant effect, no serious SEs
Bloch et al.	2008	Open-Label Study	9	Adolescents with Treatment-Resistant MDD (16-18 years)	rTMS, 10 Hz, Left DLPFC	One month	Antidepressant effect, no effect on suicidality, no serious SEs
Croarkin et al.	2018	An exploratory study in participants of previous Open-Label Trial	19	Adolescents with Treatment-Resistant MDD	rTMS, 10 Hz, Left DLPFC	Six weeks	Antidepressant effect, unclear effect on suicidality, no serious SEs
Kwon et al.	2011	Open-Label Study	10	Children with Tourette's syndrome (mean age 11.2 years)	rTMS, 1 Hz, SMA	12 weeks	No worsening of depressive symptoms, no serious SEs
Le et al.	2013	Open-Label Study	25	Children with Tourette's syndrome (less than 16 years)	rTMS, 1 Hz, SMA	Six months	Improvement in depressive symptoms, no serious SEs
Zhang at el.	2019	Comparative Study (TMS in Adolescents vs. Adults)	117	Adolescents and adults with Mood and Anxiety Disorders	rTMS, 10 Hz, Left DLPFC	Four weeks	Adolescents remission > Adults Remission (depression), no serious SEs

List of abbreviations: RCT: Randomized Control Trial; rTMS: Repetitive Transcranial Magnetic Stimulation; DLPFC: Dorsolateral prefrontal cortex; SEs:Side effects; SMA: Supplementary Motor Area; sp/ppTMS: Single-pulse/paired-pulse TMS; MDD: Major Depressive Disorder; Hz: Hertz

High-Frequency (10Hz) TMS: These studies noted complete remissions or improvements in symptoms [16–23,26] of some of their participants. The available double-blind, randomized, sham-controlled trial, with a large sample of 103 subjects, examined the feasibility, safety, and efficacy of 10 Hz TMS for adolescents with treatment-resistant depression after six weeks of treatment. This study did not find any significant difference in remission in the two groups

(29.2% in the active group versus 29% in the sham group) [27]. To date, this study lacks long-term follow-up findings, and they have addressed that better sham controls (sham devices resembling closely to active devices) in future studies can improve the outcomes. Currently, a few larger RCTs with sham-control arms are ongoing. One study showed better TMS results in adolescents than in adults [28], opening up more exploration in TMS in adolescent depression.

Effect on Suicidality: Mixed results exist about the effect on suicidality [18,23,24]. Lewis CP et al. 2018 demonstrated changes in suicidal ideation using sp/ppTMS [18]. Bloch et al. 2008 and Croarkin et al. 2018 noted no effect and unclear effects, respectively [23,24].

Low-Frequency (1Hz) TMS: Kwon et al. 2011, conducted a pilot open-label 12 weeks cohort study on ten male children (mean age 11.2 years) with Tourette's Syndrome. They administered low-frequency rTMS (1 Hz) over the Supplementary Motor Area (SMA) of the cortex. They noted that there were no side effects or worsening of anxiety or depressive symptoms [24]. Le et al. 2013, also used 1 Hz TMS over SMA in 25 children (under 16 years of age) with Tourette's Syndrome and observed an improvement in depressive symptoms [25]. However, the subjects of both these studies did not have MDD at baseline. These studies are unique because 1 Hz TMS has not been adequately studied in the pediatric population with psychiatric illnesses, including pediatric depression.

Safety: The common outcome of most of the studies listed in Table 1 is that TMS's side-effect profile is mild and transient in most of the subjects. The above mentioned RCT also concluded that there were no new tolerability or safety signals in adolescents [27]. A comparative study by Zhang et al. 2019, which compared the efficacy and clinical outcomes of rTMS in a large sample of adolescents to those of adults (42 adolescents versus 75 adults), noted that there were no identified safety and tolerability concerns in the adolescent group, and this finding matched

the adult group [28]. Krishnan et al. 2015, examined the side effects of TMS in more than 300 children and adolescents (2.5 - 17.8 years of age). Their study indicated that the side effects of TMS were, in general, mild and transient. The most common noted side effects were headache (11.5%), scalp discomfort (2.5%), twitching (1.2%), mood changes (1.2%), fatigue (0.9%), and tinnitus (0.6%). However, they also noted major side effects in four of their subjects. Two had seizures (0.62%), and two experienced syncopes (0.62%). They also addressed the need for more studies with longer treatment and follow-up periods to understand [29]. A recent research article evaluated the safety and tolerability of single and paired-pulse TMS as well as conventional rTMS in the pediatric population. It was found that headache is the most common side effect of rTMS, though it is mostly mild and self-limiting. It has been noticed that as the therapy sessions progress, the side effects gradually disappear or decrease in severity [30].

The most concerning, though very rare, risk among these is seizure induction, and it can occur even in patients without any known risk factors and is similar to the risk in adults [31]. Rarely, there is excessive heating of the TMS coil, imposing a risk of discomfort and, theoretically, scalp burn. It is preventable by using devices with built-in thermal sensors. The use of ear protection can prevent ear-related side effects like tinnitus and hearing loss [32]. Also, since TMS is a magnetic device, it is contraindicated in patients with foreign metal bodies and implant devices, such as cochlear implants [33]. Evidence from the use of TMS in various pediatric neurological disorders suggests that it is a safe modality of treatment, which is well-tolerated, and at the same time, also effective in improving the symptoms of the underlying condition. Therefore, it should be used with appropriate caution in managing psychiatric disorders in children and adolescents, including pediatric depression [34].

Limitations of Existing Studies

Although most of the studies noted some evidence of TMS efficacy in pediatric depression with a favorable side effect profile, their considerable limitations restrict us from making a

significant conclusion to establish its effectiveness, dosing regimens and protocols, and long term safety.

The most noteworthy is limited large double-blind sham-controlled RCTs with long-term follow-ups, and the largest existing one did not find a significant difference in sham versus active arms [27].

Secondly, the majority of the studies did not include subjects of younger age groups. Mayer et al. 2012 recruited participants of mean age 20.4 years at the beginning of the study, yet it is labeled as a study in adolescents [21]. The primary concern of using TMS in children and adolescents is related to its safety [35]. Due to the same reason, most of the research on TMS excludes the pediatric population from the study [36].

Moreover, these studies lack long-term follow-up findings limiting our ability to apply efficacy and safety results in the long term. There is only one 3 years follow-up study by Mayer et al. 2012 [21], but it has a small sample size (n=8).

Other limitations include small sample sizes and lack of homogeneous age distribution. Therefore, there is a need for a more detailed evaluation of its efficient application in the pediatric population [37].

To conclude, previous studies have successfully established TMS as efficacious and safe in the adult population, and recent studies explore its role in adolescent psychiatric illness. Currently, the evidence suggests that TMS can be an alternative treatment option for pediatric depression with favorable outcomes and minimal side effects. Still, the limitations of existing studies restrict us from significantly establishing its efficacy and standard protocols.

Currently, there is limited or no knowledge regarding TMS's efficacy and safety in population of the age group less than 12 years, dosage criteria, and long-term efficacy and safety. To counter these lacunae, we need large RCTs with better sham-control arms, standardized outcome measures, and long-term follow-ups. Also, we need more data on safety and efficacy

of 1 Hz rTMS so that it can be studied in the pediatric population. Expansion of knowledge regarding TMS is needed to make the evidence strong enough to support the approval of TMS use in pediatric depression.

References

1. DeFilippis M, Wagner KD. Management of Treatment-Resistant Depression in Children and Adolescents. Pediatr Drugs. 2014, 16:353–61.
2. Ghandour RM, Sherman LJ, Vladutiu CJ, Ali MM, Lynch SE, Bitsko RH, et al. Prevalence and Treatment of Depression, Anxiety, and Conduct Problems in US Children. J Pediatr. 2019, 206:256-267.e3.
3. Williams JMG, Barnhofer T, Crane C, Duggan DS, Shah D, Brennan K, et al. Pre-adult onset and patterns of suicidality in patients with a history of recurrent depression. J Affect Disord. 2012, 138:173–9.
4. Melvin GA, Dudley AL, Gordon MS, Ford S, Taffe J, Tonge BJ. What happens to depressed adolescents? A follow-up study into early adulthood. J Affect Disord. 2013, 151:298–305.
5. Gaynes BN, Lux L, Gartlehner G, Asher G, Forman- Hoffman V, Green J, et al. Defining treatment-resistant depression. Depress Anxiety. 2020, 37:134–45.
6. Albizu A, Indahlastari A, Woods AJ. Non-invasive Brain Stimulation. In: Gu D, Dupre ME, editors. Encyclopedia of Gerontology and Population Aging [Internet]. Cham: Springer International Publishing, 2019 [cited 2020 Dec 14]. p. 1–8. Available from: https://doi.org/10.1007/978-3-319-69892-2_682-1
7. Gomes-Osman J, Indahlastari A, Fried PJ, Cabral DL, Rice J, Nissim NR, et al. Non-invasive brain stimulation: probing intracortical circuits and improving cognition in the aging brain. Front Aging Neurosc. 2018, 10:177.
8. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. The Lancet. 1985, 325:1106–7.
9. Pascual- Leone A, Gates JR, Dhuna A. Induction of speech arrest and counting errors with rapid- rate transcranial magnetic stimulation. Neurology. 1991, 41:697.
10. Roth Y, Zangen A, Hallett M. A Coil Design for Transcranial Magnetic Stimulation of Deep Brain Regions. J Clin Neurophysiol. 2002, 19:361–370.
11. Chalah MA, Ayache SS. Noninvasive Brain Stimulation and Psychotherapy in Anxiety and Depressive Disorders: A Viewpoint. Brain Sci. 2019, 9:82.

12. Eshel N, Keller CJ, Wu W, Jiang J, Mills-Finnerty C, Huemer J, et al. Global connectivity and local excitability changes underlie antidepressant effects of repetitive transcranial magnetic stimulation. Neuropsychopharmacol. 2020, 45:1018–25.
13. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. Arch Gen Psychiatry. 2010, 67:507–16.
14. Fitzgerald PB, Hoy KE, Anderson RJ, Daskalakis ZJ. A study of the pattern of response to rTMS treatment in depression. Depress Anxiety. 2016, 33:746–53.
15. Berlim MT, Van den Eynde F, Tovar-Perdomo S, Daskalakis ZJ. Response, remission and drop-out rates following high-frequency repetitive transcranial magnetic stimulation (rTMS) for treating major depression: a systematic review and meta-analysis of randomized, double-blind and sham-controlled trials. Psychol Med. 2014, 44:225.
16. Sonmez AI, Kucuker MU, Lewis CP, Kolla BP, Doruk Camsari D, Vande Voort JL, et al. improvement in hypersomnia with high frequency repetitive transcranial magnetic stimulation in depressed adolescents: Preliminary evidence from an open-label study. Prog Neuropsychopharmacol Biol Psychiatry. 2020, 97:109763.
17. Lewis CP, Camsari DD, Sonmez AI, Nandakumar AL, Gresbrink MA, Daskalakis ZJ, et al. Preliminary evidence of an association between increased cortical inhibition and reduced suicidal ideation in adolescents treated for major depression. J Affect Disord. 2019, 244:21–4.
18. 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.
19. Yang X-R, Kirton A, Wilkes TC, Pradhan S, Liu I, Jaworska N, et al. Glutamate alterations associated with transcranial magnetic stimulation in youth depression: A Case Series. J ECT. 2014, 30:242–247.
20. Mayer G, Aviram S, Walter G, Levkovitz Y, Bloch Y. Long-term follow-up of adolescents with resistant depression treated with repetitive transcranial magnetic stimulation. J ECT. 2012, 28:84–6.
21. Wall CA, Croarkin PE, Sim LA, Husain MM, Janicak PG, Kozel FA, et al. Adjunctive use of repetitive transcranial magnetic stimulation in depressed adolescents: a prospective, open pilot study. J Clin Psychiatry. 2011, 72:1263–9.

22. Bloch Y, Grisaru N, Harel EV, Beitler G, Faivel N, Ratzoni G, et al. Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: an open-label study. J ECT. 2008, 24:156–9.
23. 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.
24. Kwon HJ, Lim WS, Lim MH, Lee SJ, Hyun JK, Chae J-H, et al. 1-Hz low frequency repetitive transcranial magnetic stimulation in children with Tourette's syndrome. Neurosci Lett. 2011, 492:1–4.
25. Le K, Liu L, Sun M, Hu L, Xiao N. Transcranial magnetic stimulation at 1 Hertz improves clinical symptoms in children with Tourette syndrome for at least 6 months. J Clin Neurosci. 2013, 20:257–62.
26. 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.
27. Croarkin PE, Elmaadawi AZ, Aaronson ST, Schrodt GR, Holbert RC, Verdoliva S, et al. Left prefrontal transcranial magnetic stimulation for treatment-resistant depression in adolescents: a double-blind, randomized, sham-controlled trial. Neuropsychopharmacol. 2020, 1–8.
28. 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.
29. Krishnan C, Santos L, Peterson MD, Ehinger M. Safety of non-invasive brain stimulation in children and adolescents. Brain Stimul. 2015, 8:76–87.
30. Zewdie E, Ciechanski P, Kuo HC, Giuffre A, Kahl C, King R, et al. Safety and tolerability of transcranial magnetic and direct current stimulation in children: Prospective single center evidence from 3.5 million stimulations. Brain Stimul. 2020, 13:565–75.
31. Allen CH, Kluger BM, Buard I. Safety of Transcranial Magnetic Stimulation in Children: A Systematic Review of the Literature. Pediatr Neurol. 2017, 68:3–17.
32. McClintock SM, Reti IM, Carpenter LL, McDonald WM, Dubin M, Taylor SF, et al. Consensus recommendations for the clinical application of repetitive transcranial magnetic stimulation (rTMS) in the Treatment of Depression. J Clin Psychiatry. 2018, 79(1).

33. Downar J, Blumberger DM, Daskalakis ZJ. Repetitive transcranial magnetic stimulation: an emerging treatment for medication-resistant depression. CMAJ. 2016, 188:1175–7.
34. Malone LA, Sun LR. Transcranial Magnetic Stimulation for the Treatment of Pediatric Neurological Disorders. Curr Treat Options Neurol. 2019, 21:58.
35. Somani A, Kar SK. Efficacy of repetitive transcranial magnetic stimulation in treatment-resistant depression: the evidence thus far. Gen Psych. 2019, 32:e100074.
36. Kar SK. Predictors of Response to Repetitive Transcranial Magnetic Stimulation in Depression: A Review of Recent Updates. Clin Psychopharmacol Neurosci. 2019, 17:25–33.
37. Smajkic A. Depression in adolescents: Current treatments, suicidality and evaluation of novel treatment strategies. Bosn J Basic Med Sci. 2009, 9(Suppl 1):S83–8.

Dr. Vishal Gupta, Ex-Medical Officer, District Early Intervention Center (DEIC); Dr. Shivangini Singh, Junior Resident; Dr. Pawan Kumar Gupta, Associate Professor; Dr. Sujita Kumar Kar, Associate Professor, Department of psychiatry, King George's Medical University, Lucknow, Uttar Pradesh, India.