Transcutaneous Auricular Vagus Nerve Stimulation in Adolescent Treatment Resistant Depression—A Case Report

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Adolescence is a critical time period for the onset of depression, and many patients do not respond to treatment. Transcutaneous auricular vagus nerve stimulation may be a promising alternative. Here, we present the case of an adolescent girl with treatment-resistant depression who received transcutaneous auricular vagus nerve stimulation over the course of 7.5 months. *(J Pediatr 2024;271:114078).*

Depression is of the most prevalent psychiatric disorders, with typical onset in adolescence.[1] However, effective treatment options in adolescents with depression are limited,[2] and only a minority of patients show sufficient treatment response.[3] One existing treatment alternative in adults is implanted vagus nerve stimulation, which has been shown to be effective either as standalone or adjunctive treatment in adults.[4] Because of its invasive nature, potential complications, and side effects, vagus nerve stimulation is not considered safe and ethically acceptable for the use in underage patients with depression. Recent technological advances allow for the noninvasive transcutaneous stimulation of the vagus nerve via the ear. Transcutaneous auricular vagus nerve stimulation (taVNS) already has been explored as treatment option in adults with depression.[5] taVNS also may offer a safe[6] treatment alternative in pediatric patients.[7] Here, we report the case of an adolescent patient with treatment-resistant depression who received active taVNS over the course of 7.5 months.

Case Report

The family presented their 17-year-old daughter (A.) to our specialized outpatient department for an initial diagnostic appointment. A. reported severe symptoms of depression over several years, verified by clinical records since age 11 years. A first psychotherapeutic treatment (cognitive behavioral therapy) combined with self-medication of daily 900 mg of St John's wort was initiated at age 13 years for 1 year. Combined psychotherapy and pharmacologic treatment were reinitiated at age 16 years during a severe depressive episode. Psychotherapy with fluoxetine (up to 30 mg daily) or escitalopram (15 mg daily) did not result in significant improvement, leading the patient to discontinue psychotherapy. Another severe depressive episode was reported at age 17 years before presentation to our clinic. A. expressed the intention to die by suicide after her graduation from high school at age 18 years. Alongside recommendations concerning diet and physical activity, we agreed on a treatment regime with daily taVNS adjuvant to stable medication with escitalopram (15 mg daily) in a home-based setting with weekly personal contact (biweekly on phone) to professional staff. The family provided informed consent for the close monitoring of the case for scientific purposes before treatment initiation. Finally, A. (at age 18 years) provided written informed consent for the publication of this case report in accordance with procedures laid out by our local ethics committee.

The taVNS device used (tVNS-L; tVNS Technologies GmbH) is CE cleared for the use in underage patients with depression. Following existing reporting guidelines,[8] device-locked minimum current was set at 100 μA and maximum 5000 μA (impulse width 250 μs, frequency 25 Hz, 32 seconds [off] 28 seconds [on] cycle), enabling A. to choose an individual stimulation intensity by day. We aimed for a treatment duration of up to 240 minutes per day, applying stimulation to the cymba conchae of the left ear. Treatment was initiated and terminated after 224 days. In total, 270 treatment sessions were logged across 161 days on which the stimulator was in active use. A mean of 1.59 (SD 1.03) treatment sessions were recorded per day of usage. The average duration of a single treatment session (**Figure**, B) was 188.57 minutes (80.06 minutes). The average current (**Figure**, C) was set by the patient at 957.78 μA (203.67 μA), resulting in an average voltage of 23.38 V (18.12 V) and an actual current (eg, current at the cutaneous level between the 2 electrodes) of 420.60 μA (457.57 μA) delivered at the stimulation site. Device log-data showed a linear increase in treatment duration, set current, current, and voltage delivered over treatment. Across 164 days of completed evening (7 PM) prompts of ecological momentary assessment (movisensXS; Movisens GmbH), no single adverse event was reported. Visual

taVNS	Transcutaneous auricular vagus nerve stimulation

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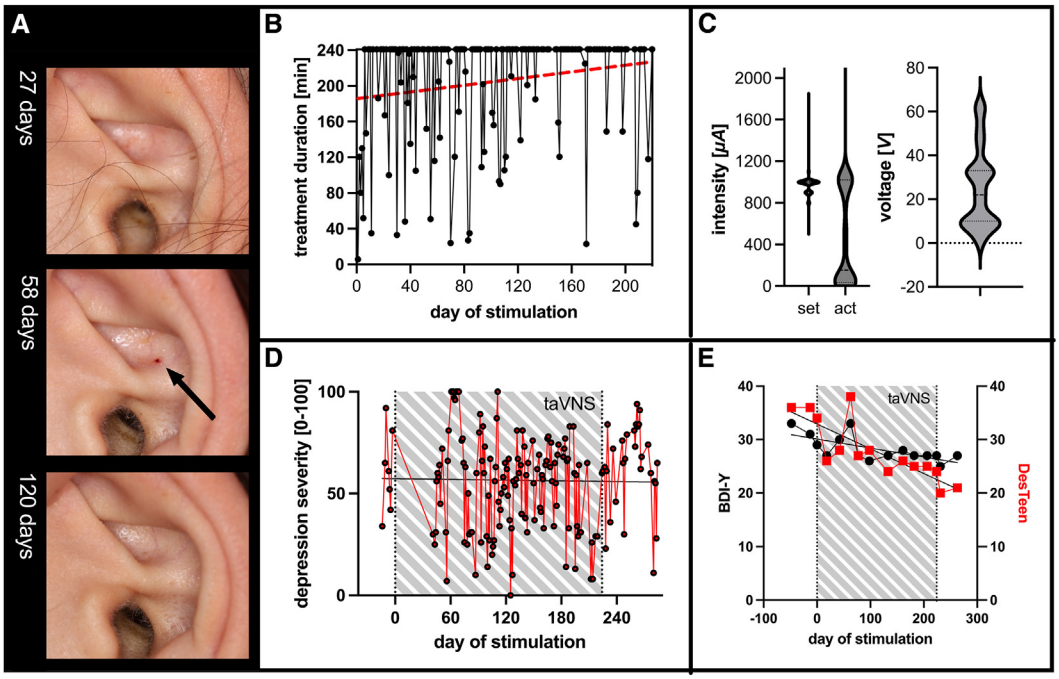

Figure. Stimulation characteristics, clinical effects, and side effects over the course of treatment. **A,** visual inspection of the stimulation site over the course of treatment; **B,** treatment duration (in minutes) by day of stimulation; **C,** patient-selected (set) and actual delivered (act) stimulation intensity in μA; delivered voltage; **D,** daily self-reported depression severity using smartphone-based ecological momentary assessment; **E,** Change in self-reported depression severity assessed using the Beck Depression Inventory for Youth (BDI-Y) and the Depression Screener for Teenagers (DesTeen).

inspection of the stimulation site over the course of treatment (Figure, A) showed some local irritation 2 months into treatment that later vanished. Local skin irritation from electrode placement has been reported as the most common side effect of taVNS.[6]

Self-reported (Beck Depression Inventory for Youth and Depression Screener for Teenagers; Figure, E) and clinician-assessed depression severity (Children's Depression Rating Scale–Revised and Hamilton Depression Rating Scale) improved over treatment (eg, Children's Depression Rating Scale–Revised: pre-: 55, intermediate: 46; post-: 53; follow-up: 47), other outcome measures (Perceived Stress Scale and Difficulties in Emotion Regulation Scale) remained largely unchanged. Parents independently reported improvement from pretreatment to the end of intervention (Child Behavior Checklist/4-18 global: mother/father 72/73 to 59/60). The clinician assessed general level of functioning (0-100) showed initial improvement after baseline (40) at mid-assessment (65) but later deterioration at the end of intervention (41) with later improvement at 1-month follow-up (50). Ecological momentary assessment data (Figure, E) showed only subtle trends toward symptom improvement (eg, depression severity, fatigue). A long-term electrocardiogram was recorded repeatedly to rule out cardiac side effects that were not present (data not shown). Blood draws did not show any aberrations under treatment.

A. successfully graduated from high school and started a part-time job during treatment. After treatment completion, she enrolled at a local university to start her studies. Treatment was terminated in accordance with A. before enrollment at the university, allowing for a stimulation-free follow-up period.

Discussion

The present case illustrates that taVNS over a longer treatment period is feasible in adolescents. A. showed excellent compliance. If reported effects are causally linked to taVNS, they are of smaller size then reported in randomized controlled trials in adults.[5] The protocol of a randomized controlled trial in adolescent depression has been published but the nonregistered study has an unclear status.[9] Importantly, existing taVNS treatment protocols and stimulation settings are not yet designed and adjusted for pediatric patients.[7] Studies addressing neurodevelopment aspects (eg, circadian rhythmicity or electrical characteristics of the vagus in development) are warranted, to empirically derive recommendations for future clinical protocols.[5] Further, research into the potential mechanisms of action (eg, modulation of neural circuitry, anti-inflammatory action) is needed. In contrast to other noninvasive neuromodulation treatments for psychiatric conditions in adolescents (eg, transcranial magnetic stimulation), taVNS may offer a home-based treatment approach with greater scalability, given lower costs and

ease in application. We hope the present case report encourages wider clinical application and further research into taVNS as adjuvant treatment. High resolution monitoring of symptom progression and stimulation parameters offer an opportunity for individual treatment planning and post-hoc analysis into temporal trajectories of taVNS action. ■

CRediT authorship contribution statement

Julian Koenig: Writing – original draft, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Jasper Vöckel:** Writing – review & editing, Supervision, Investigation.

Declaration of Competing Interest

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