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Trigeminal Nerve Stimulator Approved for ADHD

The FDA has approved the first nonpharmacological option for the treatment of ADHD in children, aged 7–12 years, who are not receiving medication. The Monarch external trigeminal nerve stimulation (eTNS) system is a cell-phone sized device that connects to a small patch placed on a patient's forehead and delivers a low-level electrical pulse to the branches of the trigeminal nerve. Neuroimaging studies have shown that eTNS increases activity in brain regions known to be associated with attention, emotion, and behavior regulation. The device is intended to be used in the home while patients are asleep.

Clinical trial results in patients with moderate-to-severe ADHD suggest that eTNS produces significant improvement in symptoms, but response may take up to 4 weeks. Common adverse effects of eTNS include drowsiness, increased appetite, difficulty sleeping, teeth clenching, headache, and fatigue. No serious adverse events were reported in the clinical trials. The Monarch eTNS System should not be used by patients with an active implantable pacemaker, active implantable neurostimulators, or body-worn devices such as insulin pumps. The eTNS System also should not be used in the presence of cell phones, because the phone's low levels of electromagnetic energy may interrupt the therapy.

FDA News Release: FDA permits marketing of first medical device for treatment of ADHD. Available at www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm636379.htm.

Smart Glasses for Emotion Recognition in Autism

According to the results of a randomized trial, a wearable artificial intelligence-based computer vision system running on Google Glass may improve emotion recognition in children with autism spectrum disorder.

Background: The randomized study was preceded by design studies to determine if children can comfortably wear the smart glasses at home and process the information supplied with audio and in their field of vision. The system tracks faces, classifies the emotions of the person the child is interacting with based on facial expression, and provides color- or voice-based cues to the child. The system recognizes 8 emotions: happy, sad, angry, scared, surprise, disgust,

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"meh," and neutral. The child's caregiver manages the system using a smartphone app. There are 3 engagement activity modes: the child tries to elicit a happy emotion; the child guesses the emotion acted out by the caregiver; and free play.

Methods: Participants in the study were children, aged 6–12 years, with autism spectrum disorder who were receiving ongoing applied behavioral analysis (ABA) therapy. Children were randomly assigned to use the Superpower Glass for 6 weeks or to continue with treatment as usual. Families in the intervention group were instructed to perform each of the 3 engagement activities at least once and to use the device at home for 20 minutes 3 times/week and 1 additional time with the ABA therapist. The study had multiple primary outcome measures: the socialization subscale of the Vineland Adaptive Behavioral Scales-II (VABS-II); the Developmental Neuropsychological Assessment-II (NEPSY-II) Affect Recognition domain, and the Emotion Guessing Game (EGG).

Results: A total of 71 children were randomized—40 to Superpower Glass and 31 to the control group. Families in the active treatment group used the glasses a mean of about 12 times with the caregiver and 4 times with the ABA therapist, approximately half of the recommended dose. A total of 8 families in the intervention group withdrew from the study because they found using the device too challenging, and 1 because the device was "too warm."

Relative to the control group, scores on the VABS-II socialization subscale improved to a larger extent in the intervention group (p=0.005). Performance on NEPSY-II Affect Recognition domain and the EGG also showed larger improvement in the treatment participants, although these differences did not reach statistical significance. At 6-week follow-up, some of the treatment effect on the VABS-II was lost, but EGG scores continued to improve.

Discussion: The Superpower Glass intervention has multiple potential mechanisms of action. It reinforces the idea that faces have variation in emotion and also trains the child on how to differentiate emotions. It is also possible that the device generally encourages social interaction in the family.

Study Rating*—17 (100%): This study met all criteria for a randomized controlled trial.

Voss C, Schwartz J, Daniels J, Kline A, et al: Effect of wearable digital intervention for improving socialization in children with autism spectrum disorder: a randomized clinical trial. *JAMA Pediatrics* 2019; doi 10.1001/jamapediatrics.2019.0285. From Stanford University, CA. **Funded by the NIH; and other sources. Six of 13 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

***See Reference Guide.**

Dasotraline in ADHD

The investigational dopamine and norepinephrine transporter inhibitor dasotraline reduced ADHD symptoms and was well tolerated in a manufacturer-sponsored, controlled trial.

Methods: Participants were aged 6–12 years and had a DSM-5 diagnosis of ADHD, with a minimum ADHD Rating Scale–IV (ADHD-RS-IV) score of 28 and a Clinical Global Impression–Severity (CGI-S) score indicating at least moderate severity. Patients were randomly assigned to double-blind fixed doses of dasotraline (2 or 4 mg/day) or placebo, administered in the morning for 6 weeks. Current cognitive behavioral therapy was permitted if it had been started before screening for the study. The primary study outcome was change from baseline in ADHD-RS-IV total score.

Results: The efficacy analysis was based on 336 children with a mean age of 9 years who had a mean ADHD-RS-IV total score of 42 at baseline. The 2-mg dasotraline dose group did not differ from placebo on any primary or secondary outcome measure. The 4-mg group had a significantly larger mean improvement from baseline in the ADHD-RS-IV total score than the

placebo group: 17.5 versus 11.4 points (p<0.001; effect size,* 0.48). Differences from placebo on the ADHD-RS-IV were statistically significant beginning in the first study week and lasting throughout treatment. The 4-mg group also had significantly larger improvements on most secondary outcomes including the CGI-S, ADHD-RS inattentiveness and hyperactivity subscales, and Conners Parent Rating Scale-Revised total and subscales scores (effect sizes ranged from 0.25 to 0.46). The proportion of responders (≥30% improvement in the ADHD-RS-IV total score) was 57.5% for the 4-mg dose, compared with 36.5% for placebo (odds ratio,* 2.4; p=0.002; number needed to treat,* 5). No significant difference from placebo was observed for the study's measure of functional outcome.

Subgroup analyses found no significant effects of age or gender with 4 mg/day dasotraline. However, the effect size was somewhat larger in younger patients (aged 6–9 years) than in older patients (aged 10–12 years), which may be due to weight-related differences in dasotraline exposure. Effect sizes were also larger with 2 mg/day dasotraline in children with a baseline weight of <66 lbs, compared with heavier children, suggesting that lower weight children could benefit from the lower dasotraline dosage.

The most frequently reported adverse effects of dasotraline were insomnia (18.5%), decreased appetite (17%), weight loss (7%), and irritability (5%). The rate of discontinuation due to adverse events was higher in the 4-mg dasotraline group (12%) than in the 2-mg or placebo groups (6%). A total of 7 patients who received dasotraline reported psychosis-like events (e.g., hallucinations, illusions). These were generally mild to moderate and transient and primarily affected younger children with lower body weights.

Discussion: Unlike stimulants, dasotraline does not produce marked peak and trough effects or stimulate dopamine release. It is absorbed slowly, with a 10–12-hour time to peak concentrations and an elimination half-life of ≥2 days. The study authors recommend limiting the 4-mg dose to children weighing 66 lbs in order to minimize the risk of psychosis-like effects.

Findling R, Adler L, Spencer T, Goldman R, et al: Dasotraline in children with attention-deficit/hyperactivity disorder: a six-week, placebo-controlled, fixed-dose trial. *Journal of Child and Adolescent Psychopharmacology* 2019;29 (March 7):80–89. doi 10.1089/cap.2018.0083. From the Kennedy Krieger Institute/Johns Hopkins University, Baltimore, MD; and other institutions. **Funded by Sunovion Pharmaceuticals, Inc. All 9 study authors disclosed potentially relevant financial relationships with commercial sources, including Sunovion.**

***See Reference Guide.**

Assessing Risk for Suicide Attempts

A large longitudinal study found that established risk factors for suicidal thoughts or nonsuicidal self-harm are not the same factors that predict the transition to making a suicide attempt. According to the findings, cannabis or other illicit substance use, nonsuicidal self-harm, and insufficient sleep may be particularly useful in identifying adolescents who are more likely to attempt suicide.

Methods: The analysis was based on data from the U.K.'s ongoing Avon Longitudinal Study of Parents and Children (ALSPAC), a cohort of nearly 14,000 individuals born in 1991 or 1992 and followed regularly since birth. A subsample of participants completed a detailed evaluation of suicidal thoughts and self-harm at ages 16 and 21 years. A multitude of potential psychosocial and mental health risk factors were assessed throughout childhood and adolescence. The final sample consisted of adolescents with no history of suicide attempt, including 310 who reported suicidal thoughts and 380 who reported nonsuicidal self-injury at age 16 years; 107 adolescents reported both suicidal thoughts and self-harm.

Results: By age 21 years, 12% of each of the risk groups had made a suicide attempt. The rate was higher (21%) among those with both suicidal thoughts and self-harm at age 16 years.

In contrast, in a comparison group of adolescents with no history of suicidal thoughts or self-harm, 1% reported a suicide attempt. After adjustment for multiple confounders, several statistically significant risk factors for suicide attempts were identified. (See table.)

Risk factors for transition to first suicide attempt by age 21 years		
	Odds Ratio*	**Significance**
Adolescents with suicidal thoughts at age 16 years		
Cannabis use	2.61	p=0.029
Other illicit drug use	2.47	p=0.045
Nonsuicidal self-harm	2.78	p=0.006
Intellect/openness†	1.62	p=0.025
Adolescents with nonsuicidal self-harm at age 16 years		
Cannabis use	2.14	p=0.038
Other illicit drug use	2.17	p=0.025
Insufficient sleep	1.97	p=0.043
†Measured using the International Personality Item Pool, an inventory of the Big Five personality dimensions		

Discussion: According to the ideation-to-action framework, the factors involved in the development of suicidal thoughts—e.g., depression, impulsivity, and hopelessness—are distinct from the factors that influence the transition to suicide attempts. Most previous studies of the issue have been cross-sectional and did not directly address the ideation-to-action model. Use of cannabis and other illicit drugs were associated with suicide attempts in both risk groups, which suggests they may be particularly robust predictors. Alternatively, substance use may be a proxy for maladaptive coping with stress. The study did not find associations with well-established suicide risk factors such as depression, suicide plans, or impulsivity. Possibly these factors are not directly involved with the transition or, alternatively, they would have been predictive if measured immediately before the suicide attempt.

Mars B, Heron J, Klonsky E, Moran P, et al: Predictors of future suicide attempt among adolescents with suicidal thoughts or non-suicidal self-harm: a population-based birth cohort study. *Lancet Psychiatry* 2019;6 (April):327–337. doi 10.1016/S2215-0366(19)30030-6. From the University of Bristol Medical School, U.K.; and other institutions. **Funded by the American Foundation for Suicide Prevention; and other sources. The authors declared no competing interests.**

***See Reference Guide.**

Second-Generation Antipsychotics and Diabetes Risk

Use of second-generation antipsychotics (SGAs) in adolescence and young adulthood was associated with a dose-related increase in the incidence of type 2 diabetes in a population-based study from Taiwan. This study confirms previous reports and presents some new findings regarding diagnosis-specific risks.

Methods: The study cohort consisted of all young people enrolled in Taiwan's national health insurance program, which covers virtually 100% of the population. Patients at risk were adolescents (aged 12–17 years) and young adults (aged 18–29 years) who received a prescription for any SGA between 2000 and 2011 and were free of diabetes at the time of the prescription. The cohort was divided into 4 groups according to total SGA exposure in cumulative defined daily doses: <30 days; 30 days–6 months; 6 months–1 year; and ≥1 year. The group with the shortest exposure was the reference group for comparing diabetes incidence, which was evaluated from cohort entry through December 31, 2011.

Results: The cohort consisted of >91,000 individuals—18% adolescents and 82% young adults. The SGA was prescribed for schizophrenia in 50% of patients, a major affective disorder in 34%,

and autism spectrum disorder in 5%. A total of 2654 patients (2.9%) had onset of type 2 diabetes during follow-up, occurring at a mean age of 29 years.

SGAs were associated with a dose-related increase in risk for type 2 diabetes, which was statistically significant for the 2 longest exposure categories. Diabetes risk was increased in males and females and throughout the dosage range in young adults. In adolescents, only the longest of the 4 exposure durations was significantly associated with diabetes risk. (See table.) The increase in type 2 diabetes risk was largest in patients with major affective disorders and also significant in those with schizophrenia. Risk was not elevated in patients with autism spectrum disorders. When each of the 8 available SGAs was examined separately, all but paliperidone were associated with increased diabetes incidence (hazard ratios* ranged from 1.10 for olanzapine to 1.40 for ziprasidone).

Adjusted Hazard Ratios for Diabetes Onset by Cumulative SGA Exposure

Duration of SGA Exposure	Total Cohort	Adolescents Only	Patients with Schizophrenia	Patients with Major Affective Disorders
30 days–6 months	1.15	0.65	1.13	1.09
6 months–1 year	1.54	1.08	1.31	1.85
≥1 year	1.91	1.77	1.71	2.35

Discussion: This study differs from others in its choice of a comparison group. The investigators judged that young people with low exposure to SGAs would be a more appropriate comparison group than patients with no medication exposure or those exposed to other psychotropic agents. In this study, young adults had the highest risk of type 2 diabetes, possibly because younger patients may have a superior pancreatic beta-cell reserve and less insulin resistance. The higher incidence of diabetes in young people with major affective disorders may reflect their exposure to other drugs with adverse metabolic effects, as well as neurovegetative symptoms and subclinical thyroid or cortisol dysfunction.

Tu T-H, Huang K-L, Bai Y-M, Hsu J-W, et al: Exposure to second-generation antipsychotics and risk of type 2 diabetes mellitus in adolescents and young adults: a nationwide study in Taiwan. *Journal of Clinical Psychiatry* 2019; doi 10.4088/JCP.18m12284. From Taipei Veterans General Hospital, Taiwan; and other institutions. **Funded by the hospital; and the Ministry of Science and Technology, Taiwan. The authors declared no competing interests.**

Common Drug Trade Names*: olanzapine—*Zyprexa*; paliperidone—*Invega*; ziprasidone—*Geodon

***See Reference Guide.**

MMR Vaccine and Autism

A large, population-based cohort study confirms previous findings that the measles, mumps, rubella (MMR) vaccination does not increase risk of autism in children. The study also did not support other concerns of vaccination critics: that MMR vaccines trigger autism in susceptible subgroups or that it leads to clusters of cases with onset shortly after vaccination.

Methods: The nationwide cohort study included all children born in Denmark between 1999 and 2010. In Denmark, MMR vaccination is voluntary and provided free of charge; it is offered initially at age 15 months. The analysis was adjusted for many autism risk factors, and an autism risk score based on various pre- and perinatal factors was used to stratify cohort members into 10 risk deciles.

Results: The cohort included >657,000 children. After excluding those who died, emigrated, or were later diagnosed with a genetic abnormality related to autism, the remaining 651,000 were followed until the end of the study. More than 95% of children received a first MMR

vaccine, at a median age of 1.3 years. A total of 6517 children received a diagnosis of autism (mean age at diagnosis, 7.2 years), for a calculated rate of 130 per 100,000 person-years.

MMR vaccination was not associated with elevated risk of autism in the entire cohort or in any patient subgroup. Moreover, in 2 subgroups—girls and children born between 1999 and 2001—vaccination was associated with significantly reduced risk of autism. (See table.) Hazard ratios were not elevated in boys, other birth subcohorts, children who received other early childhood vaccinations, those at high risk, or children with siblings with autism.

Risk of autism in MMR-vaccinated vs unvaccinated children

Group	Adjusted hazard ratio*
Total cohort	0.93
Girls	0.79
1999–2001 birth cohort	0.84

Discussion: Since the now-retracted article linking MMR vaccination with autism, no study or meta-analysis has confirmed an association. The present study, by far the largest to date, confirms the lack of association and extends the findings to various subgroups.

Hviid A, Hansen J, Frisch M, Melbye M: Measles, mumps, rubella vaccine and autism: a nation wide cohort study. *Annals of Internal Medicine* 2019; doi 10.7326/M18-2101. From Statens Serum Institut, Copenhagen, Denmark; and other institutions. **Funded by the Novo Nordisk Foundation; and the Danish Ministry of Health. Two of 4 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

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Effect Size: The effect size represents the amount of change in outcome that can be attributed to treatment, where 0.2 indicates a small effect, 0.5 a medium effect, and 0.8 a large effect. It is relatively independent of clinical significance, and large effect sizes do not ensure treatment efficacy.

Hazard Ratio: A measure of the risk of an event relative to exposure, or the probability of an event occurring in an exposed group versus a non-exposed group. A hazard ratio of 0.5 indicates that 1 group has half the risk of the other group.

Number Needed to Treat: Indicates how many patients need to be treated for 1 to benefit. The ideal number needed to treat (NNT) is 1, where everyone improves with treatment. The higher the NNT value, the less effective the treatment.

Odds Ratio: A comparison of the probability of an event. An odds ratio of 1 implies that the event is equally likely in both groups. An odds ratio >1 indicates that the event is more likely to occur in that group than in the comparison group.

Study Rating: A measure of how well a study conforms to quality standards. The study rating uses a checklist system based on the comprehensive Strength of Evidence Report from the Evidence-based Practice Center Program of the Agency for Healthcare Research and Quality (AHRQ). The rating checklists are posted at www.alertpubs.com.