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## Gender Differences in Suicide Trends

According to a study based on data from the Centers for Disease Control and Prevention (CDC), the increase in adolescent suicide rates in the U.S. over the past 40 years has disproportionately affected girls, narrowing the historic gap between male and female youth suicide rates.[1] An editorial suggests that increased use of social media might be driving the overall increase,[2] although it is not clear why this would differentially affect girls.

***Methods:*** The investigators analyzed reports from the CDC's Wide-ranging Online Data for Epidemiologic Research (WONDER) database spanning 1975 to 2016. The analysis included all records in which suicide was identified as the underlying cause of death in an individual aged 10–19 years.

***Results:*** More than 85,000 suicides occurred during the study period, with an overall male predominance of 80%. Overall, suicide rates increased from 1975 to 1992–1993, followed by a general decrease until 2007 when another steady increase began. Between 2007 and 2016 annual rates have increased by 8.9% in girls and by 3.8% in boys. The increase was particularly large in girls aged 10–14 years, who experienced a >12% annual increase in suicides after 2007.

In children aged 10–14 years, the incidence rate ratio* (IRR) of male to female suicides decreased from 3.14 in 1975–1991 to 1.8 in 2007–2014 ($p<0.001$). IRRs in older adolescents (aged 15–19 years) decreased from 4.15 to 3.31 ($p<0.001$) for the same time periods. The male-to-female ratio decreased in all U.S. regions. In the younger group, the change was largest among nonhispanic white youths; IRR decreases were not significant in hispanic and nonhispanic black adolescents. In the older age group, all decreases were statistically significant, but the IRR decrease was largest in American Indian/Alaskan Natives and Asian/Pacific Islanders. Use of guns to commit suicide increased more steeply in males aged 15–19 years than in other groups, while use of hanging or suffocation continued to increase in female adolescents relative to males.

***Discussion:*** The present results—increasing rates of suicide and a narrowing of the gender gap—are consistent with those of previous studies. Racial and ethnic disparities persist, with lower rates in black and Hispanic youths, but the gap between the genders has been narrowing for all groups. It may be particularly concerning that females are more frequently choosing to

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attempt suicide by hanging or suffocation, which are relatively violent and lethal methods, given that females have a higher rate of suicide attempts than males. The pronounced narrowing of the gender gap in 10- to 14-year-olds indicates a need for developmentally sensitive early prevention efforts.

**Editorial.** The study was not designed to identify the causes of these trends, but the growth of youth involvement in social media is a clear and powerful social change that occurred over the same period and warrants more research. Girls may be particularly vulnerable to interpersonal stress caused by social media; they use it more frequently than males and are more likely to experience bullying and negative responses from peers.

[1]Ruch D, Sheftall A, Schlagbaum P, Rausch J, et al: Trends in suicide among youth aged 10 to 19 years in the United States, 1975 to 2016. *JAMA Network Open* 2019; doi 10.1001/jamanetworkopen.2019.3886. From Nationwide Children's Hospital, Columbus, OH; and other institutions. **Funded by the NIMH. One of 6 study authors disclosed a potentially relevant financial relationship; the remaining authors declared no competing interests.**

[2]Luby J, Kertz S: Increasing suicide rates in early adolescent girls in the United States and the equalization of sex disparity in suicide: the need to investigate the role of social media [editorial]. *JAMA Network Open* 2019; doi 10.1001/jamanetworkopen.2019.3916. From Washington University School of Medicine, St. Louis, MO; and Southern Illinois University, Carbondale. **One author disclosed a potentially relevant financial relationship; the remaining author declared no competing interests.**

***See Reference Guide.**

## Treating Combined Depression, Substance Use Disorder

In adolescents with co-occurring depression and substance use disorder, treatment of the 2 conditions should be integrated. Treating depression alone does not reduce substance use, and substance use treatment does not bring about remission of depression. Despite a clinical consensus supporting integrated treatment, few patients receive this kind of care, due in part to inadequate reimbursement, a lack of clinicians with dual training, and a lack of research on integrated treatment.

The Substance Abuse and Mental Health Services Administration and the American Academy of Pediatrics recommend universal substance use screening, brief intervention, and referral to treatment (SBIRT) as part of routine adolescent health care, starting at age 12 years. Screening tools should be brief and highly sensitive and specific. Validated screens include the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Youth Screen; the Brief Screener for Tobacco, Alcohol, and Other Drugs; and the Screening to Brief Intervention (S2BI). The S2BI is structured to discriminate between levels of substance use: none (used once or twice), mild or moderate (monthly), and severe (weekly or more often). Brief intervention, based on the principles of motivational interviewing, is a 5- to 15-minute conversation providing individualized feedback based on the adolescent's level of substance use. Non-users receive positive reinforcement. Mild to moderate substance use requires an interventional approach, including offering a menu of treatment options. For adolescents who also screen positive for depression, the connection between substance use and depression should be explored and concurrent treatment for both disorders recommended. There are numerous online resources for motivational interviewing and SBIRT available from the National Institute on Drug Abuse, SAMHSA, and other organizations.

Adolescents who use substances at least once per week are likely to meet criteria for severe substance use disorders and should be referred for specialized treatment. Using brief intervention and motivational interviewing techniques, the adolescent can be guided to recognize problems related to substance use and accept referral for specialist treatment, which should include psychosocial interventions with adjunctive pharmacotherapy. The availability of treatment programs varies geographically and may depend on insurance and the local availability of child and adolescent providers. Information about local programs can be found on the SAMHSA website at findtreatment.samhsa.gov.

Only fluoxetine (*Prozac*) has been evaluated in clinical trials in adolescents with co-occurring depression and substance use disorder. In 1 trial, depression symptoms were reduced in patients receiving motivational enhancement therapy/cognitive-behavioral therapy (MET/CBT); the addition of fluoxetine resulted in some additional improvement, relative to placebo. In 2 other studies, fluoxetine was not superior to placebo in reducing symptoms of depression or substance use in adolescents with alcohol or cannabis use disorder.

MET/CBT may be the most effective treatment for co-occurring depression and substance use disorders. If depression does not begin to improve within 1 month, the addition of fluoxetine should be considered. If there is no improvement in substance use, options include increased family involvement and referral to more intensive substance use treatment.

Hinckley J, Riggs P: Integrated treatment of adolescents with co-occurring depression and substance use disorder. *Child and Adolescent Psychiatric Clinics of North America* 2019;28:461–472. doi 10.1016/j.chc.2019.02.006. From the University of Colorado School of Medicine, Aurora. **Source of funding not stated. The authors declared no financial relationships with commercial sources.**

## Personalizing ADHD Treatment

In recent years, many new stimulant formulations have become available to treat ADHD. Most innovations involve the 2 existing drugs most commonly used to treat ADHD: methylphenidate and amphetamine. The new formulations offer clinicians unprecedented ability to personalize treatment of ADHD.

Since the last major review of new stimulant formulations in 2004, the emphasis in drug development has been on long-acting formulations and novel delivery systems but several new immediate-release (IR) formulations have also been developed. All of these IR formulations were designed for or can be modified for use by children who have difficulty swallowing. Some are available as solutions or chewable tablets; others are water soluble or can be crushed and mixed with food. As with older IR formulations, twice- or thrice-daily dosing is still required.

Some of the newer long-acting formulations have also been designed for ease in swallowing, as orally dissolving tablets (ODT), suspensions, solutions, or chewable tablets. Some provide a mixture of immediate- and delayed-release particles, allowing once-daily dosing. Efficacy, tolerability, and safety of these formulations are similar to earlier extended-release formulations. Lisdexamfetamine, a d-amphetamine prodrug, has also been developed as capsules and chewable tablets.

A methylphenidate transdermal patch has been introduced that delivers drug for the duration of wear time (no more than 9 hours is recommended), with absorption continuing but declining for several hours afterward. Because the onset of action takes 2 hours, IR methylphenidate may be co-prescribed to reduce the lag. Transdermal methylphenidate has comparable safety and efficacy to other formulations, but there are some unique risks: local contact dermatitis, discomfort when removing the patch, and the risk of accidental poisoning. Previously used patches still contain a large amount of the drug and could pose a hazard to children.

Several new long-acting methylphenidate formulations make use of a novel "beaded" technology, containing varying proportions of microbeads that release methylphenidate in IR and extended release forms, with a duration of action of 12–16 hours. A delayed release/extended release methylphenidate formulation, based on a proprietary delivery system contains microbeads with 2 layers of coating, 1 that delays drug release and a second that regulates release in an extended pattern. This formulation is meant to be taken in the evening, delays release for 8–10 hours, and then provides clinical action up to 22–24 hours post-dose. In addition, a new triple-bead amphetamine formulation provides up to 16 hours of pharmacologic action; these capsules can be opened and sprinkled on food without altering absorption.

| New Stimulant Formulations | | |
|---|---|---|
| **Methylphenidate** | **Amphetamine** | **Lisdexamfetamine (amphetamine pro-drug)** |
| **Immediate Release** | | |
| Generics formulations of *Methylin* oral solution and chewable tablets | *Evekeo* tablets<br>*Evekeo* ODT<br>*Zenzedi* tablet<br>*Procentra* oral solution | — |
| **Long-Acting Formulations** | | |
| *Contempla XR* ODT<br>*Quillivant XR* oral solution<br>*Quillichew ER* chewable tablet<br>*Daytrana* transdermal patch<br>*Aptensio XR* multilayer bead capsule<br>*Adhansia XR* multilayer bead capsule | *Adzenys XR*-ODT<br>*Adzenys ER* oral suspension<br>*Dyanavel XR* suspension<br>*Mydayis* triple bead capsule | *Vyvanse* capsule<br>*Vyvanse* chewable tablet |
| **Delayed, Extended-Release** | | |
| *Jornay PM* microbead capsule | — | — |

Steingard R, Taskiran S, Connor D, Markowitz J, et al: New formulations of stimulants: an update for clinicians. *Journal of Child and Adolescent Psychopharmacology* 2019;29 (5):1–16. doi 10.1089/cap.2019.0043. From the Child Mind Institute, New York; and other institutions. **Source of funding not stated. Three of 5 study authors disclosed potentially relevant financial relationships; the remaining authors declared no competing interests.**

## Viloxazine for ADHD

The investigational extended-release nonstimulant medication viloxazine (SPN-812) was effective and well tolerated in a phase 2 clinical trial in children with ADHD.[1]

***Background:*** Viloxazine is a novel norepinephrine reuptake inhibitor with selective serotonergic activity. An immediate-release preparation has been shown to be effective and well tolerated in adults with ADHD.[2]

***Methods:*** Subjects in this 8-week study were 222 children, aged 6–12 years, with a primary diagnosis of ADHD. After a washout of other ADHD medication, they were randomly assigned to double-blind once-daily viloxazine (100, 200, 300, or 400 mg) or placebo. Viloxazine dosage was titrated over the first 4 study weeks and remained stable thereafter. The primary efficacy outcome was change from baseline to week 8 in the ADHD Rating Scale IV (ADHD-RS-IV) total score.

***Results:*** The efficacy analysis included 206 children who had a baseline assessment and ≥1 post-randomization ADHD-RS-IV assessment. Mean ADHD-RS scores ranged from 41 to 44 at baseline and decreased in all groups. The change was significantly greater with the 3 highest viloxazine dosage groups than with placebo. (See table, next page.) Rates of response (≥25% decrease in ADHD-RS-IV total score) were 46% in the placebo group and ranged from 60% to 68% in the viloxazine groups. Remission (scores ≤18) occurred in 17% of the placebo group and 38–48% of the viloxazine groups. The ADHD-RS-IV hyperactivity/impulsivity subscale showed significant improvement in the 3 highest dosage groups, relative to placebo; differences in the inattention subscale were not significant. Clinical Global Impression (CGI) Improvement and Severity analyses generally showed similar results.

| Change to end of study in ADHD-RS-IV total score | | | | | |
|---|---|---|---|---|---|
| | | Viloxazine | | | |
| | Placebo | 100 mg | 200 mg | 300 mg | 400 mg |
| **Mean baseline score** | 42.4 | 42.4 | 43.9 | 41.3 | 40.8 |
| **Change in total score** | -10.5 | -16.7 | -18.4 | -18.6 | -19.0 |
| **Effect size* vs placebo** | — | 0.453 | 0.547 | 0.596 | 0.623 |
| **Significance vs placebo** | — | p=ns | p=0.03 | p=0.027 | p=0.021 |

The most frequent adverse events with viloxazine were somnolence and headache, both dose-related, and decreased appetite, which also affected the placebo group. A total of 13 patients (7%) discontinued treatment with viloxazine because of headache, irritability, or other adverse events. One patient, in the lowest dosage group, discontinued treatment after experiencing suicidal ideation. ECG changes were generally related to tachycardia, but 7 patients experienced increased QRS duration and 1 an increased PR interval.

***Discussion:*** These preliminary results suggest that extended-release viloxazine is both safe and effective in the treatment of ADHD in young patients. Effect sizes appear similar to other nonstimulants used in ADHD, as do adverse effects. Phase 3 trials in children and adolescents with ADHD are in progress.

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

[1]Johnson J, Liranso T, Saylor K, Tulloch G, et al: A Phase II double-blind, placebo-controlled, efficacy and safety study of SPN-812 (extended-release viloxazine) in children with ADHD. *Journal of Attention Disorders* 2019; doi 10.1177/1087054719836159. From Supernus Pharmaceuticals, Inc., Rockville, MD; and other institutions. **Funded by Supernus. All 9 study authors disclosed relevant financial relationships with commercial sources, including Supernus.**

[2]Johnson J, et al: Double-blind, randomized, placebo controlled study of immediate-release viloxazine (SPN-812 IR) as a novel non-stimulant therapy in adults with attention-deficit/hyperactivity disorder (ADHD). Poster presented at American Academy of Child and Adolescent Psychiatry, San Antonio, TX.

***See Reference Guide.**

## Contraceptives and Bone Loss in Anorexia Nervosa

Oral contraceptive (OC) treatment of osteopenia in young women with anorexia nervosa is fairly widespread but remains a matter of considerable debate. In a case-control study of patients treated in routine clinical practice, OC use was associated with increased areal bone mineral density (aBMD) that improved with an early start and longer duration of use. Effects were most pronounced in women with more severe forms of anorexia.

***Methods:*** Study subjects were 305 adolescents and young women (aged 14.5–35 years) with a diagnosis of anorexia nervosa who were consecutively treated at a university hospital between 2009 and 2016 and a control group of 121 healthy, normal-weight adolescents and young women with normal menstrual cycles. All participants completed a medical questionnaire, assays for hormones and bone metabolism markers, and DXA scans of areal bone mineral density of the whole body and the lumbar spine, femoral neck, hip, and radius. To determine the effects of OC use, 99 patients with anorexia taking OCs were compared with 206 nonusers with anorexia.

***Results:*** As expected, patients with anorexia had lower anthropometric characteristics (body mass index, body fat mass, fat-free soft tissue, and aBMD) than controls, as well as increased levels of CTX, a marker of bone resorption, and lower values of 2 markers of bone formation, osteocalcin and PINP.

OC users had significantly higher aBMD values for whole body and the 4 individual sites than nonusers. Most of these differences remained statistically significant after adjusting for age, weight, fat-free soft tissue, and age of anorexia onset. However, compared with the healthy control group, all aBMD measures were lower in women with anorexia who were taking OCs.

Of multiple makers of bone metabolism, the bone resorption marker CTX and the formation marker osteocalcin were significantly lower in patients taking OCs than patients not taking OCs. The type of OC, estrogen-progestin versus progestin-only, generally did not affect aBMD or bone metabolism markers. After adjustments for other factors, aBMD (whole-body and at all sites) increased with longer duration of OC use; and shorter times between anorexia onset and the start of OC use favorably affected most aBMD measurements.

***Discussion:*** Earlier studies have not resolved the controversy about the effects on bone of OC use in anorexia because of inconsistent results, generally attributable to small sample size and short periods of observation. In the present study, the largest gain in aBMD was observed in women with >3 years of OC use and in women with the lowest BMIs. However, the favorable effects of OCs do not appear to completely offset the effects of anorexia nervosa on bone tissue. It is likely that the onset of anorexia preceded the start of OC use, leaving a period when bone tissue was not protected. Although OCs may limit bone loss in this population, they should not be used as the sole method to protect bone.

Maimoun L, Renard E, Lefebvre P, Bertet H, et al: Oral contraceptives partially protect from bone loss in young women with anorexia nervosa. *Fertility and Sterility* 2019;111 (May):1020–1029. doi 10.1016/j.fertnstert.2019.01.008. From the University of Montpellier, France; and other institutions. **Funded by the Centre Hospitalier Régional Universitaire of Montpellier. The authors declared no competing interests.**

## Reference Guide

**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.

**Incidence Rate Ratio:** The number of new cases of a condition in a defined (specified) group or population expressed as a ratio. For example, if there are 1000 people and a condition develops in 14 of them, the incidence rate is 14 per 1000 or 1.4%.

**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.