Associations of Medical and Nonmedical Prescription Medication Use with Premature All-Cause Mortality Among US Adolescents

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Summary This multi-cohort national longitudinal study evaluated premature all-cause mortality risks in adulthood associated with adolescent medical and nonmedical use of prescription benzodiazepines, opioids, and stimulants using data from 14,718 individuals across 43 independent cohorts (1976–2018) from the Monitoring the Future study, followed up to 44 years into adulthood up to 2021. Results showed that 34.0% (95% confidence interval [CI], 33.3% - 34.8%) of adolescents reported lifetime medical or nonmedical use of prescription medications by age 18. Compared to the medical-use-only group, premature all-cause mortality risk was significantly higher among adolescents reporting both medical and nonmedical use (adjusted hazard ratio [aHR], 2.49 [95% CI, 1.48 - 4.17]), nonmedical-use-only (aHR, 2.44 [95% CI, 1.46 - 4.09]), and no history of prescription medication use (aHR, 1.92 [95% CI, 1.20 - 3.07]). These findings indicate that nonmedical use, rather than medically supervised pharmacotherapy, drives elevated mortality risks. Furthermore, the higher premature mortality risk in the no-use group compared to the medical-use-only group suggests that untreated underlying conditions may carry distinct safety risks, reinforcing the protective value of appropriate clinical pharmacotherapy. For clinical practice, these divergent risk profiles highlight that prescribing controlled substances is safe when supervised, but clinicians must routinely screen and monitor for nonmedical use of prescription medications to identify at-risk youth and intervene promptly. For research and policy, these findings provide critical, nationally representative data to inform adolescent drug screening guideline recommendations, addressing long-standing evidence gaps regarding the potential benefits and harms of early screening and preventive interventions.

The questions following the above will ask you to breakdown your summary.

Background Over one-fifth of US adolescents engage in the medical or nonmedical use of prescription-controlled substances, including benzodiazepines, opioids, and stimulants. While specific co-prescribing patterns have been linked to mortality, separate evidence suggests appropriate medication for conditions like ADHD may actually reduce mortality risks compared to leaving the condition untreated. To date, clinical practice and research has been hampered by a lack of long-term, nationally representative data evaluating how adolescent medical versus nonmedical use of these three major medication classes affects premature all-cause mortality in adulthood. This creates a critical gap in clinical performance and knowledge regarding the true long-term safety of supervised adolescent pharmacotherapy versus the dangers of nonmedical use. This information enhances clinical practice by reassuring providers that medically supervised controlled substance prescribing is safe and potentially protective against untreated disease risks. Concurrently, it alerts clinicians to the severe premature mortality risks associated with nonmedical use of prescription medications that goes undetected and unaddressed, indicating that patient safety could be increased by enhanced psychoeducation, comprehensive screening and monitoring during adolescence.

Educational Learning Objectives

Learning Objective 1 Estimate lifetime medical or nonmedical use of prescription benzodiazepines, opioids, and stimulants among US adolescents.

Learning Objective 2 Determine premature mortality risks of medical and nonmedical use of prescription benzodiazepines, opioids, and stimulants among US adolescents.

Learning Objective 3 Compare premature all-cause mortality risks in adulthood between US adolescents who reported (a) medical-use-only, (b) both medical and nonmedical use, (c) nonmedical-use-only, (d) and no history of prescription medication use.

Methods This longitudinal study utilized nationally representative data from 43 independent baseline cohorts (1976–2018) of 12th-grade adolescents from the Monitoring the Future study. Medical and nonmedical lifetime exposures to prescription benzodiazepines, opioids, and stimulants were assessed via self-reported questionnaires. Exposure was categorized into four mutually exclusive groups by age 18: no use, medical-use-only, nonmedical-use-only, and both medical and nonmedical use. Mortality data were obtained through National Death Index links up to 2021, tracking premature all-cause mortality across a follow-up period of up to 44 years. Adjusted Cox proportional hazard models calculated adjusted hazard ratios for premature all-cause mortality, accounting for sociodemographic factors, academic performance, and other substance use, using person-time from age 18 to death or right-censoring.

Results The sample included 14,718 individuals followed into adulthood. By age 18, 34.0% (95% confidence interval [CI], 33.3%–34.8%) of US adolescents reported lifetime medical or nonmedical use of prescription benzodiazepines, opioids, or stimulants. Using the medical-use-only group as the reference baseline, premature all-cause mortality risk was significantly higher among US adolescents who reported both medical and nonmedical use (adjusted hazard ratio [aHR], 2.49 [95% CI, 1.48–4.17]), nonmedical-use-only (aHR, 2.44 [95% CI, 1.46–4.09]), and no history of

prescription medication use (aHR, 1.92 [95% CI, 1.20–3.07]).

Conclusion Nonmedical use of prescription controlled substances—rather than medically supervised exposure—is associated with elevated premature all-cause mortality risks among US adolescents. The lower premature all-cause mortality risk observed in the medical-use-only group compared to the no-use group suggests that untreated underlying clinical conditions may carry substantial independent risks, underscoring the safety and therapeutic value of properly supervised adolescent pharmacotherapy. Similarly, these findings highlight the severe long-term morbidity and mortality associated with nonmedical use of prescription medications. These divergent profiles show that clinical and policy interventions must explicitly distinguish between medication adherence and nonmedical medication use.

Scientific Significance This study provides the first multi-cohort longitudinal evidence evaluating long-term premature mortality risks associated with both medical and nonmedical adolescent prescription medication exposures in the same nationally representative sample over a 44-year period. By demonstrating that nonmedical use drives mortality while supervised medical use displays a protective hazard profile relative to non-use, this study offers foundational data and evidence to address the debate on the safety of adolescent controlled substance prescribing. It directly informs clinical guidelines regarding adolescent drug screening benefits.

Will your paper cite external research? Yes

Please cite all references here in AMA format.
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