Published in final edited form as:

JAMA. 2024 March 12; 331(10): 831–833. doi:10.1001/jama.2024.1755.

Treating Attention-Deficit/Hyperactivity Disorder Matters

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In this issue of JAMA, Li and colleagues[1] used an observational target trial emulation analysis to investigate whether attention-deficit/hyperactivity disorder (ADHD) medication, continuously prescribed over the 2 years following initial diagnosis, was associated with reduced mortality rates compared with those who were not treated with ADHD medication during the same period. This Swedish register study boasts numerous strengths, including a large, well-powered sample (N = 148 578) across a broad age range (6–64 years), who received an ADHD diagnosis between 2007 and 2018 following a thorough neuropsychiatric evaluation. This study used electronic health records (EHRs) data in a way that approximates a randomized clinical trial (RCT) to assess mortality rates by ADHD medication status over time. Individuals consistently treated with ADHD medication were compared with those who did not receive ADHD medication on 3 outcomes over a 2-year follow-up period: all-cause mortality, natural-cause mortality (eg, medical conditions), and unnatural-cause mortality (eg, accidental injuries, accidental poisoning, and suicide). Overall, those who initiated ADHD medication had a reduced risk for all-cause mortality and unnatural-cause mortality (but not natural-cause mortality) over the 2-year period, except for females, in whom only a reduction in natural-cause mortality was observed.

The findings of this work should be contextualized with the existing literature. While the focus of this new study from Li and colleagues is on how prescribing affects mortality, which is notably higher among those with ADHD,[2] mortality is not the only outcome of interest among adults with ADHD. Adult ADHD is also associated with more common adverse behavioral and neuropsychiatric outcomes,[3] and some of these nonfatal problems (eg, injuries, accidents, substance use) also appear to be mitigated by treatment with ADHD medication.[3,4] Despite the evidence showing that ADHD medication improves morbidity and mortality in ADHD, this condition still goes undiagnosed and under-treated at high rates, particularly in adults with co-occurring substance use disorders, and in marginalized groups, including immigrants.[5–7]

Although the results from Li et al[1] highlight the potential public health importance of treating ADHD, numerous questions remain. Does the type of stimulant matter? Li et al

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found that more than 90% of participants in their study received a prescription stimulant but do not report what percentage received an amphetamine vs a methylphenidate formulation. A recent review suggests that amphetamine formulations have greater effect sizes than methylphenidate in adult populations, perhaps resulting in better outcomes.[8]

Additionally, the present study does not address medication adherence or dosing. For some patients, medication may not have been prescribed at adequate doses or taken with sufficient regularity to reduce the risk of mortality. Future work might examine the effect of these important variables on observed mortality rates. Another question not addressed in this study is whether severity of baseline ADHD symptoms moderates the observed reduction in mortality in those who initiated ADHD medications. Future research should investigate the potential relationship between ADHD symptom severity and mortality outcomes for those receiving medication treatment.

Furthermore, there remains the overarching question of how treating individuals for their ADHD symptoms reduces the risk of unnatural death. Is ADHD treatment directly reducing impulsive behaviors that increase the risk of premature death? Or is the treatment of ADHD symptoms indirectly reducing accidental poisonings by reducing substance use (through better implementation of protective strategies) or reducing suicides by improving depressive symptoms associated with ADHD? Finally, the study was not designed to address whether the benefit of prescribed ADHD medication is maintained over time. This emulation trial analyzed individual outcomes over a 2- and 5-year follow-up. Given that mortality is a relatively uncommon outcome (less than 1% died during the 2-year assessment), future studies evaluating individuals for a longer period is warranted, including a larger sample of older adults.

Perhaps one of the most interesting findings was that in females with ADHD, treatment was associated with reduced risk of natural-cause deaths but not unnatural-cause deaths during the 2-year follow-up. The reasons for this are unknown. It may be that females are engaged in less risky substance use behaviors, thus reducing chances of accidental overdose deaths or poisoning. Also, since females are generally diagnosed with ADHD later in life compared to males, the impact of ADHD medication treatment might be more likely to affect medical conditions rather than mitigate unnatural deaths. While this does not entirely explain how treating ADHD might reduce medical comorbidities, one hypothesis is that reduction in ADHD symptoms allows for better self-care such as healthful eating and exercise.

A key question is how these noteworthy findings translate into clinical practice. Unlike Sweden, where there is universal, government-supported, decentralized health care, in countries like the US significant barriers exist in accessing medical and psychiatric services, particularly among underresourced populations. Even among those who receive stimulant and nonstimulant ADHD medication, most discontinue taking their medication within a few months,[9] diminishing the potential benefit associated with continuous ADHD medication prescribing. Also, there is the valid concern that prescribed stimulant medication might be misused or diverted, particularly among young adults who are using other psychoactive substances. Moreover, an overarching societal concern is that with greater availability of stimulant medication, there might be an epidemic of stimulant misuse and prescription

stimulant use disorder, similar to what has occurred with prescription opioids. While such a scale of misuse has not yet been documented, it is notable that the number of individuals 12 years or older in the US with a prescription stimulant use disorder is estimated at 1.8 million,[10] greater than those with a cocaine or heroin use disorder. It behooves clinicians to conduct a careful assessment for substance use and possible diversion among those being prescribed a stimulant medication.

Perhaps the group that clinicians are most apprehensive in prescribing stimulants to are those with an active substance use disorder. Approximately 8% of the sample in this study had an alcohol use disorder and 9% had a nonalcohol substance use disorder, although it is unclear if there was differential prescribing based on these comorbidities. A recent retrospective longitudinal study using US health insurance claims found that adults with ADHD and substance use disorder were less likely to be prescribed stimulant medication.[11] While the presence of a substance use disorder was considered as a covariate in the models for the purposes of the study, it remains a question for the field whether medication treatment for ADHD should be initiated or deferred when active substance use is present. Individuals with co-occurring substance use disorder and ADHD are a group to target early given their increased risk of accidental injuries, accidental poisonings, or death, but there are also potential risks of providing stimulant treatment to these individuals. A growing literature suggests that patients with active substance use can be effectively treated for their ADHD, and management of possible misuse can be effectively handled if the patient is actively engaged in substance use disorder treatment.[5,12]

Another reason that clinicians may not initiate treatment is the concern about adverse effects and discomfort in managing them. This concern may intensify considering recent data that long-term use of stimulant medications may increase rates of hypertension or atherosclerosis,[13] a risk that stabilizes over time. However, as demonstrated by this study, such risk should be weighed against the risk of premature mortality that appears to be mitigated with ADHD treatment. When necessary, even when hypertension is present, prescription stimulants may be provided if the hypertension is closely monitored and adequately treated.

Even though there are many individuals whose ADHD goes undiagnosed and untreated, the past 5 years have seen a dramatic increase in the percentage of adults being treated for ADHD, particularly in women.[14] Some of this may be due to increased availability of prescribers afforded by telemedicine in the era of COVID-19, opening the additional possibility that some of this increase may be in individuals incorrectly diagnosed with ADHD and inappropriately treated.[15] Overdiagnosis may occur when assessments are brief and clinicians do not attend to possible alternative medical or psychiatric conditions that may mimic the symptoms of ADHD. However, increased treatment rates may also be occurring as more individuals are seeking treatment for their ADHD symptoms and clinicians are more attuned to identifying ADHD in their patients.

In sum, this study by Li and colleagues lends support to extant literature demonstrating that the elevated mortality risk associated with ADHD is substantially reduced among those appropriately prescribed an ADHD medication. Under-treating ADHD is not without

consequences. The health care workforce requires training in screening, diagnosing, and treating ADHD, just as has been done for other psychiatric disorders. Our patients, their families, and society will all benefit as a result.

Conflict of Interest Disclosures:

Dr Levin reported grants from the National Institutes of Health, the Substance Abuse and Mental Health Services Administration, the National Center for Advancing Translational Sciences, and US World Meds; nonfinancial support from Indivior Medication and research support from Aelis Pharmaceutical; royalties from the American Psychological Association; and consulting fees from MLB outside the submitted work. Dr Hernandez reported grants from National Institute on Drug Abuse. Dr Mariani reported receiving grants from the National Institutes of Health and the Substance Abuse and Mental Health Services Administration, and personal fees from Indivior outside the submitted work.

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