

Pharmacotherapies for Attention-Deficit/Hyperactivity Disorder and Risk of Suicidal Behavior: A Within-Individual Study of Stimulants, Atomoxetine, and Alpha-2 Agonists

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ABSTRACT

BACKGROUND: Individuals with attention-deficit/hyperactivity disorder (ADHD) are at increased risk for suicidal behavior. Stimulant and nonstimulant pharmacotherapies are widely prescribed for ADHD, but their effects on suicidal behavior remain unclear.

METHODS: In a U.S. commercial health care insurance claims database, we identified 830,352 individuals diagnosed with ADHD, ages 9 to 64 years, who used at least 1 stimulant, atomoxetine, or alpha-2 agonist medication between 2016 and 2021. We examined the proportions of patients with suicidal behavior (i.e., emergency department visits or hospitalizations for suicide attempts or intentional self-harm) in the months preceding and following treatment initiation. Then, we used a within-individual design to evaluate associations between each medication and risk of suicidal behavior, while accounting for time-varying covariates. Finally, we examined associations for stimulants among subgroups defined by sex, age, and race-ethnicity.

RESULTS: Compared with other off-treatment periods, rates of suicidal behavior were elevated during the 2 months before starting ADHD pharmacotherapy, particularly for atomoxetine (odds ratio [OR] = 2.63 [95% CI, 2.28–3.04]) and alpha-2 agonists (OR = 2.99 [2.64–3.40]). Compared with off-treatment periods (excluding pretreatment), the odds of suicidal behavior were slightly elevated during treatment (OR_{stimulants} = 1.11 [95% CI, 1.04–1.18], OR_{atomoxetine} = 1.17 [1.00–1.38]; OR_{alpha agonists} = 1.31 [1.15–1.49]). Findings were similar across most patient subgroups.

CONCLUSIONS: Within-individual comparisons suggested that risk of suicidal behavior was higher just before and, to a lesser extent, during ADHD medication treatment compared with off-treatment. Further research is needed to determine whether elevations in risk during treatment are attributable to medication effects or to unmeasured time-varying confounding factors, such as a continuation (although attenuated) of the increased risk observed before pharmacotherapy.

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Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental condition that is diagnosed in approximately 1 in 9 youths in the United States (1) and commonly persists into adulthood (2). ADHD is associated with a more than 2-fold increase in the odds of suicide attempt and a 6-fold increase in the odds of death by suicide (3). Among people with ADHD, pharmacotherapies are widely used (4–6) and effective at reducing core ADHD symptoms (7–9), although benefits to functioning and quality of life have been less consistently documented (10–13). In particular, the influence of different types of ADHD pharmacotherapy on suicidal behavior remains unclear.

Stimulant medications, including amphetamines and methylphenidate, are considered first-line treatments for school-age children, adolescents, and adults with ADHD

due to a large body of evidence from randomized controlled trials (RCTs) documenting their safety and efficacy (7–9). The Food and Drug Administration (FDA) has also approved nonstimulant medications for ADHD treatment, including the selective norepinephrine reuptake inhibitor (SNRI) atomoxetine in both youth and adults and the alpha-2 agonists clonidine and guanfacine in youth (7,8). Some comparative studies suggest that nonstimulants are less efficacious than stimulants on average (7,9), and they are often considered as alternative or adjunctive treatment options among patients experiencing an inadequate treatment response or adverse effects from stimulants (14,15), patients deemed at risk for stimulant misuse or diversion (15,16), and patients with medical and psychiatric comorbidities (15,17).

It is plausible that ADHD medications could prevent suicidal behavior by improving ADHD symptoms and overall functioning (7–10), and some observational studies provide evidence of a protective effect of stimulant medications (18–20). However, there are also concerns that certain medications could increase risk for such behaviors. In particular, a meta-analysis of atomoxetine RCTs found that treatment-emergent suicidal ideation, while uncommon overall (<1% of patients), was reported more frequently among pediatric patients receiving atomoxetine than those receiving placebo (21). This prompted the FDA to release a boxed warning in 2005 indicating that clinical need for atomoxetine treatment must be balanced with risk for suicidal ideation (21). However, the effects of atomoxetine on risk for suicidal behavior remain unclear (22). Moreover, evidence on the risks and benefits of alpha-2 agonists remains limited (23,24) even as the use of alpha-2 agonists in the United States has increased substantially (25).

It is not feasible for RCTs to examine the effects of ADHD medications on suicidal behavior due to their limited sample sizes, short follow-up periods, and restrictive eligibility criteria (22,26,27). Observational studies of administrative health care data can address many of these limitations and answer calls for evidence on real-world outcomes of ADHD medication treatments beyond symptom control (28,29). However, such studies are subject to confounding bias because patients cannot be randomized to treatment conditions, and relevant factors such as baseline ADHD symptom severity are frequently unmeasured (30,31). Within-individual comparison designs help address these concerns by comparing risk of suicidal behavior during ADHD treatment periods with risk during off-treatment periods, controlling for all unmeasured factors that are stable over time (18–20,32).

Existing within-individual studies of ADHD pharmacotherapies and suicidal behavior have yielded mixed findings (18–20,32). Three studies found that risk for suicide was lower during stimulant treatment compared with off-treatment (18–20). However, these studies assumed that risk did not vary across off-treatment periods. Another study highlighted that suicidal behavior was elevated during the 90 days before the start of stimulant treatment and found that, compared with earlier off-treatment time, stimulant treatment was initially associated with a modestly greater risk of suicidal behavior, although the risk decreased to baseline levels after 90 days of treatment (32). In addition, the two within-individual studies of nonstimulant medications documented mixed results: One found no detectable association with suicidal behavior (20), while the other found an increased risk (19). However, these studies did not examine potential increases in risk of suicidal behavior before the start of nonstimulant treatment, and only one examined alpha-2 agonist medications (19), with limited statistical precision due to the sparsity of their use.

Furthermore, most existing within-individual studies of ADHD medications and suicidal behavior were conducted in countries outside of the United States (18,19,32). Given marked international differences in prescribing patterns, including greater use of amphetamine and alpha-2 agonist medications in the United States (6), it is unclear whether findings from other countries generalize to the United States. The one existing U.S. study only examined data through 2014

(20), but rates of alpha-2 agonist and stimulant treatment in the United States have increased over the past decade (5,6,25), as has suicidal behavior (33–35). Moreover, no study has examined the effects of ADHD medication treatments on suicidal behavior among subgroups of racially and ethnically minoritized patients in the United States, despite well-documented racial-ethnic differences in patterns of both ADHD diagnosis and treatment (36–40) and suicidal behavior (33–35).

The current study used data from U.S. commercial health care insurance claims to pursue 3 aims in a cohort of individuals diagnosed with ADHD. First, we examined trends in the proportion of patients who had a suicidal behavior event in the months preceding and following the start of stimulant, atomoxetine, and alpha-2 agonist treatments. Second, we evaluated within-individual associations between each of these pharmacotherapies and concurrent risk of suicidal behavior, while also accounting for the time-varying use of other treatments. Finally, we tested associations for the most commonly received treatment, stimulant medication, among subgroups of patients defined by sex, age, and race-ethnicity.

METHODS AND MATERIALS

Study Population

The Indiana University Institutional Review Board determined that this study was not human subjects research. We accessed Optum's deidentified Clinformatics[®] Data Mart (CDM), a database derived from administrative health claims for commercial and Medicare Advantage health plans in the United States. We included patients with commercial insurance who were 9 to 64 years of age, had at least 1 medical claim with an ADHD diagnosis (ICD-10-CM: F90), and filled at least 1 ADHD medication prescription between 2016 and 2021. Patients with unknown sex ($n = 129$) were excluded. To capture complete prescription information at the beginning of each patient's follow-up, we required at least 90 days of enrollment in Optum[®] CDM prior to entry into the study. Thus, follow-up began on January 1, 2016, at age 9, or on the patient's 91st day of enrollment in Optum[®] CDM, whichever occurred last. Patients were followed until December 31, 2021, age 65, their first disenrollment from Optum[®] CDM, or death, whichever occurred first. Follow-up time was structured by patient day. Primary analyses included all prevalent medication users and did not require a period of nonuse prior to the individual's first ADHD medication prescription fill.

Measures

We identified filled prescription claims for ADHD medications using National Drug Codes (NDCs) from the National Library of Medicine's RxNorm system (41,42), including 3 separate categories of medications: stimulants (dexamethylphenidate, methylphenidate, amphetamine, methamphetamine, dextroamphetamine, and lisdexamfetamine), atomoxetine, and alpha-2 agonists (guanfacine and extended-release clonidine). Immediate-release clonidine was excluded because it is commonly prescribed for co-occurring sleep problems rather than ADHD (43). The SNRI viloxazine was excluded because it was only recently approved in 2021 (44). For each medication,

we used prescription fill dates and days' supply to identify continuous treatment periods, defined to start the day immediately following the first prescription fill and terminate at a gap in medication coverage of 30 or more days. Individuals were permitted to have multiple episodes of treatment and to use multiple types of ADHD pharmacotherapy, concurrently or in succession.

We also included time-varying covariates to account for confounding from other treatments. We created daily dichotomous indicators of the receipt of antidepressant medications, antipsychotic medications, and psychosocial treatments. Covariate medication treatments were identified using NDCs from the RxNorm system (41,42). Psychosocial treatments were identified using procedural and revenue codes, as in previous studies (36,40) (codes in Table S1). Because psychosocial treatment effects extend beyond the day of treatment, we assumed that each psychosocial treatment was in effect for a 2-week period following the service date.

Consistent with previous studies (18,20), we identified serious, acute outcome events with time specificity using medical claims for emergency department visits or inpatient hospitalizations with diagnoses for suicide attempt and intentional self-harm (referred to as suicidal behavior for simplicity) (45) (ICD-10-CM codes in Table S1). Individuals were permitted to have multiple suicidal behavior events during the study period. However, we excluded the 6 days immediately following each event under the assumption that repeated claims in the same week represented a single episode of care rather than multiple distinct events. Deaths by suicide that did not result in an emergency department or hospital claim were not captured in this outcome definition.

Statistical Analyses

Analyses were conducted using SAS/STAT version 9.4. First, to examine risk for suicidal behavior before and after the start of ADHD treatment, we plotted the proportion of patients who had a suicidal behavior event in each of the 6 (30-day) months before and after the start of different ADHD pharmacotherapies. These plots were constructed using each patient's first observed episode of stimulant, atomoxetine, or alpha-2 agonist treatment and censoring at treatment discontinuation.

Next, we used a within-individual design to compare risk for suicidal behavior during ADHD treatment with risk during off-treatment baseline periods. We estimated odds ratios (ORs) using conditional logistic regression, treating each individual as a separate stratum (46). Within-individual designs account for all unmeasured confounding factors that are stable over time (11,47). Because the analyses require within-individual variability in exposure and outcome status (48), only patients who started or stopped at least one of the predictor treatments and had at least 1 suicidal behavior event were informative. Given that individuals with ADHD sometimes switch between or concomitantly use multiple ADHD medications (25,49), our analyses simultaneously incorporated separate indicators of each of the 3 medication types, estimating the effect of each medication while accounting for the others. Thus, we accounted for medication switching by simultaneously modeling time-varying indicators for each treatment

at a daily level. Adjusted analyses also incorporated time-varying covariates for the use of other treatments.

Event-dependent exposure, wherein outcome events influence the likelihood of subsequent treatment, can bias within-individual designs if unaccounted for (47). Prior research has shown that suicidal behavior is elevated just before the start of ADHD treatment (32,47). To address this, we classified the 60-day period preceding the start of each treatment episode into its own exposure category (pretreatment), separate from other off-treatment baseline periods, as recommended (47). Otherwise, we classified days on which the individual received ADHD medication as on-treatment and days on which the patient did not receive medication as off-treatment. Because some individuals repeatedly start and stop medication treatment, patient-days near the end of a given treatment episode may have qualified as both on-treatment and pretreatment. We classified such days as pretreatment in primary analyses.

To determine whether findings from the overall study population would generalize across key subgroups of patients, we also conducted within-individual analyses stratified by the patient's age at index, sex, and race-ethnicity. Subgroup analyses focused on stimulant treatment only, given that it accounts for the overwhelming majority of ADHD medication use (6). Age was categorized as 9 to 17, 18 to 29, 30 to 45, and 46 to 64. Consistent with other studies using Optum[®] CDM (36,50), the available race-ethnicity data were derived from an algorithm relying on zip code and name and coded as Asian, Black, Hispanic, White, or unknown. Interaction tests evaluated the statistical significance of differences in medication effects across subgroups.

Sensitivity Analyses

We conducted several sensitivity analyses, including pre-planned analyses and analyses responding to reviewer comments, to evaluate whether changes to the study design would alter our findings. The detailed rationale and methods are provided in the Supplement (Table S2). The first 4 analyses replicated the within-individual analyses in alternate cohorts: incident medication users, individuals who did not spend 30 or more consecutive days in inpatient treatment, individuals who filled no psychotropic medications besides ADHD medications, and individuals who filled more than 1 prescription for ADHD medication. The fifth analysis excluded follow-up time after February 2020 (i.e., during the COVID-19 pandemic). The next 7 analyses tested alterations to exposure classification: classifying treatment status dichotomously, giving on-treatment precedence over pretreatment, testing a longer pretreatment window length, including a 3-day induction lag at the start of treatment, testing alternate lengths of the gap required to terminate a continuous treatment period (i.e., 15 or 60 days), estimating associations for earlier and later on-treatment periods separately, and including a 30-day post-treatment category. The 13th analysis tested altered definitions of psychosocial treatment length. For the 14th analysis, the definition of suicidal behavior was broadened to include events with undetermined intent. The final analysis examined a negative control outcome (appendicitis) to detect possible bias from unmeasured time-varying confounding.

RESULTS

Study Population

A total of 830,352 ADHD medication users were included, with a median follow-up time of 1.9 years (Table 1). The population was majority male (54%) and White (73%), and the median age at start of follow-up was 26 years; 96% of patients received stimulant medications, 6% received atomoxetine, and 7% received alpha-2 agonists. A total of 7940 (1%) ADHD medication users experienced suicidal behavior at least once and were thus informative for within-individual analyses.

Suicidal Behavior Before and After the Start of Treatment

Figure 1 displays the proportions of patients who experienced suicidal behavior in each of the 6 months preceding and following the start of ADHD medication treatment, among the full study population in Figure 1A and among the subpopulation informative to within-individual analyses (i.e., those with at least 1 suicide attempt) in Figure 1B. For ease of viewing, a plot for stimulants is also displayed in Figure S2, along with the point estimates of plots in Tables S4 and S5. Rates of suicidal behavior events were higher among individuals initiating nonstimulants than among those initiating stimulants. Among individuals informative to within-individual analyses, suicidal behavior event rates were elevated in the 2 months prior to treatment initiation and then declined.

Within-Individual Analyses

Adjusted odds of suicidal behavior were elevated during the 60-day pretreatment period ($OR_{prestimulant} = 1.50$ [95% CI, 1.40–1.61]; $OR_{preatomoxetine} = 2.63$ [2.28–3.04];

$OR_{prealpha-2\ agonist} = 2.99$ [2.64–3.40]) compared with other off-treatment periods (Table 2). The odds of suicidal behavior were also slightly higher during on-treatment periods compared with off-treatment periods (i.e., compared with off-treatment periods that excluded the 60-day pretreatment period; $OR_{stimulant} = 1.11$ [1.04–1.18]; $OR_{atomoxetine} = 1.17$ [1.00–1.38]; $OR_{alpha-2\ agonist} = 1.31$ [1.15–1.49]). Covariate parameter estimates are in the Supplement (Table S3). To facilitate interpretation, we also conducted a post hoc analysis that compared on-treatment periods with the 60-day pretreatment periods. On-treatment periods were associated with lower odds of suicidal behavior ($OR_{stimulant} = 0.74$ [95% CI, 0.69–0.79]; $OR_{atomoxetine} = 0.45$ [0.37–0.54]; $OR_{alpha-2\ agonist} = 0.44$ [0.38–0.51]).

Within-individual associations across patient subgroups are displayed in the Supplement (Table S6). The difference in associations between males and females was neither large nor statistically significant, nor were the differences across racial-ethnic subgroups. In analyses stratified by age, stimulant treatment was associated with lower odds of suicidal behavior among those ages 46 to 64 years, which differed significantly from the association among those ages 9 to 17. Findings for other age categories were not statistically different from those for the 9 to 17 category.

Results from the sensitivity analyses are displayed in the Supplement (Table S7). In the incident user analysis, associations between ADHD medication treatments and suicidal behavior were attenuated ($OR_{stimulant} = 1.07$ [0.94–1.23]; $OR_{atomoxetine} = 0.99$ [0.75–1.32]; $OR_{alpha-2\ agonist} = 1.03$ [0.80–1.33]). Associations were also reduced when the pretreatment period was combined with off-treatment periods ($OR_{stimulant} = 0.96$ [0.91–1.02]; $OR_{atomoxetine} = 0.92$ [0.78–1.09]; $OR_{alpha-2\ agonist} = 0.97$ [0.85–1.10]). In the analysis in which on-treatment periods were categorized into earlier and later treatment periods, estimates were difficult to interpret due to low statistical power. In the analysis including a 30-day posttreatment period, the posttreatment period was associated with higher odds of suicidal behavior than other off-treatment periods; however, the estimates for on-treatment were similar. In the negative control outcome analysis, the adjusted odds of appendicitis were elevated during the 60 days prior to stimulant treatment, but no significant associations were observed during treatment. Each of the other sensitivity analyses yielded estimates similar to those of the main analyses, although some were not statistically significant due to reduced sample sizes.

DISCUSSION

In this study of more than 830,000 ADHD medication users in a national U.S. health claims database, we found that the risk of suicidal behavior was most elevated during the period prior to the start of ADHD pharmacotherapy, particularly for patients initiating atomoxetine and alpha-2 agonists. In within-individual analyses that helped account for this pretreatment period as well as measured and unmeasured confounding factors, the odds of suicidal behavior were 11%, 17%, and 31% higher during periods of stimulant, atomoxetine, and alpha-2 agonist treatment, respectively, compared with off-treatment baseline periods. Furthermore, findings for stimulants were similar across most patient subgroups defined by

Table 1. Demographic Characteristics of the ADHD Medication User Cohort (N = 830,352)

	n (%) or Median (IQR)
Sex	
Female	386,144 (46.5%)
Male	444,208 (53.5%)
Race/Ethnicity	
Asian	17,498 (2.1%)
Black	51,941 (6.3%)
Hispanic	62,471 (7.5%)
White	608,662 (73.3%)
Unknown	89,780 (10.8%)
Received ADHD Medication	
Stimulant	795,737 (95.8%)
Atomoxetine	52,114 (6.3%)
Alpha-2 agonist	56,408 (6.8%)
Received Psychosocial Treatment	299,345 (36.1%)
Received Antidepressant Treatment	356,262 (42.9%)
Received Antipsychotic Treatment	79,570 (9.6%)
Had Suicidal Behavior Event	7940 (1.0%)
Age at Follow-Up Start, Years	26 (15–36)
Length of Follow-Up, Years	1.9 (0.9–3.7)

ADHD, attention-deficit/hyperactivity disorder.

ADHD Pharmacotherapies and Risk of Suicidal Behavior

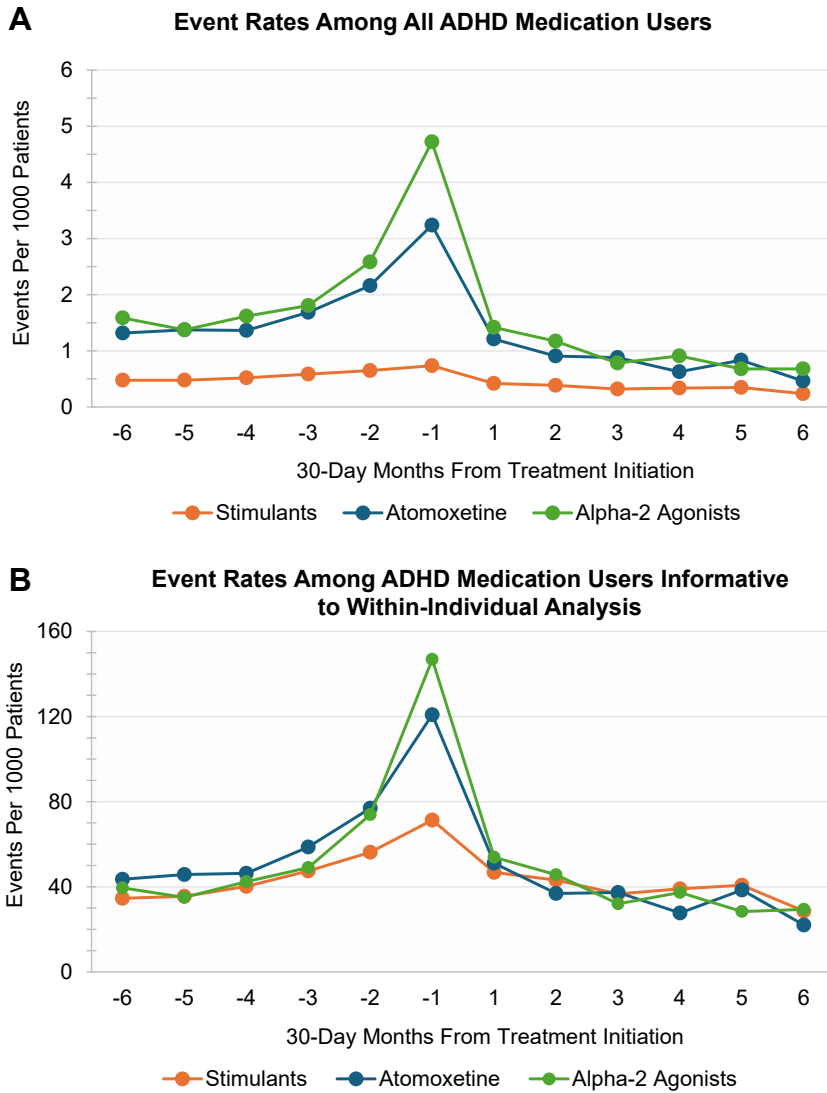


Figure 1. Suicidal behavior event rate in the months preceding and following pharmacotherapy initiation. Note: Panel (A) was generated among all attention-deficit/hyperactivity disorder (ADHD) medication users, while panel (B) was generated among the subset of users informative to within-individual analysis (i.e., those who had at least 1 suicidal behavior event). In each plot, individuals were followed until 180 days after treatment initiation or treatment discontinuation, whichever occurred first. Along the x-axis, -1 represents the last 30-day month before the first treatment day, while 1 represents the first 30-day month of treatment.

Table 2. Within-Individual Associations Between ADHD Pharmacotherapies and Suicidal Behavior

	Received Medication, <i>n</i>	Varied on Medication Status, <i>n</i>	Varied on Medication and SB Event, <i>n</i>	Odds Ratio (95% CI)			
				Adjusted for Other ADHD Medications Only, <i>n</i> = 7625 Informative ^a		Adjusted for Other ADHD Medications and Covariates, <i>n</i> = 7914 Informative ^b	
				Pretreatment	On-Treatment	Pretreatment	On-Treatment
Stimulants	795,737	679,689	6801	1.56 (1.46–1.67)	1.21 (1.14–1.28)	1.50 (1.40–1.61)	1.11 (1.04–1.18)
Atomoxetine	52,114	50,057	1223	2.79 (2.41–3.22)	1.34 (1.14–1.58)	2.63 (2.28–3.04)	1.17 (1.00–1.38)
Alpha-2 Agonists	56,408	50,748	1463	3.16 (2.78–3.59)	1.50 (1.32–1.71)	2.99 (2.64–3.40)	1.31 (1.15–1.49)

Reference for odds ratios is off-treatment periods.

ADHD, attention-deficit/hyperactivity disorder; SB, suicidal behavior.

^aInformative patients had within-individual variability in both SB and at least one of stimulant, atomoxetine, or alpha-2 agonist treatment.

^bInformative patients had within-individual variability in both SB and at least one of stimulant, atomoxetine, alpha-2 agonist, or covariate (i.e., antidepressant, antipsychotic, or psychosocial) treatment.

sex, age, and race-ethnicity. However, it should also be noted that the post hoc analysis comparing on-treatment periods with the 60-day pretreatment periods indicated that on-treatment periods were associated with lower odds of suicidal behavior for all 3 ADHD medication classes.

Our findings differ from those of a previous within-individual study in the United States, which found that pharmacotherapy was associated with reduced odds of suicidal behavior (20). Multiple factors might have contributed to this difference. First, the prior study examined data from 2005 to 2014, predating the transition from ICD-9-CM to ICD-10-CM and resulting changes in the classification—and estimated prevalence—of suicidal behavior in the United States (51). Second, estimates of the real-world effects of ADHD medication treatments could be influenced by changing ADHD medication prescribing practices, including the increasing use of stimulant and alpha-2 agonist medications (5,6,25). Researchers have highlighted that as ADHD diagnosis and treatment become more common, the average severity of symptoms experienced by those initiating treatment decreases, which in turn could reduce the magnitude of average treatment effects (52). Finally, this study excluded the higher-risk period 2 months before treatment from our off-treatment reference category, whereas the prior study compared all on-treatment time with all off-treatment time (20). In a sensitivity analysis adopting the prior study's design, the observed ORs attenuated to insignificance and fell below 1. Notably, our findings are comparable with those from a within-individual study conducted in Hong Kong, which found that the incidence of suicide attempts was elevated just before the start of methylphenidate treatment and declined thereafter (32). More research is needed to determine whether elevations in suicidal behavior during ADHD medication treatment periods are attributable to medication effects or, alternately, to time-varying confounding factors. For example, unmeasured increases in psychiatric symptoms and other stressors could have precipitated both the decision to start ADHD medication treatment and ongoing elevations in risk for suicidal behavior. In our sensitivity analysis examining appendicitis as a negative control outcome, the odds of appendicitis were also elevated during the period just before stimulant initiation. Thus, it is possible that even general emergency contacts with the health care system could precipitate the initiation of ADHD medication treatment.

Our findings further highlight that pretreatment increases in suicidal behavior appear particularly pronounced among individuals who initiate nonstimulant treatments. Given that nonstimulant medications are often used as adjunct and second-line treatments, there are likely unique processes precipitating their use (53), which in turn could be associated with suicidal behavior. For example, alpha-2 agonists are more commonly prescribed to youth with comorbid conditions (17), and atomoxetine may be preferentially prescribed over stimulants to individuals with substance use concerns (15,54,55). Additionally, our sensitivity analysis suggested that risk of suicidal behavior was elevated in the month just after the discontinuation of ADHD medication treatment. Existing research suggests that medication switching in ADHD treatment is common (25,49,56). Thus, one possible explanation for this pattern of findings involves patients experiencing

persistent distress while on stimulant medication treatment, discontinuing the stimulant treatment, and initiating a second-line nonstimulant medication. However, additional research is needed to test these hypotheses directly. Our findings emphasize that future research must consider the unique, time-varying risk processes surrounding both the initiation and discontinuation of different types of ADHD medications.

To evaluate the generalizability of our findings across key understudied patient groups, we also conducted stimulant medication analyses stratified by patient characteristics. Findings were consistent across most groups. However, we observed an interaction by age, wherein stimulant on-treatment periods were associated with a 28% reduction in the odds of suicidal behavior among adults ages 46 to 64, compared with the 8% to 19% increase observed among the younger age groups. There were substantially fewer ADHD medication users in the 46 to 64 age category, consistent with treatment patterns in the United States (37,56). Most individuals with ADHD first initiate medications as children or young adults, and persistence on ADHD medications across multiple years in adulthood is uncommon (56). Consequently, it is possible that older ADHD medication users have unique attributes and experiences differentiating them from younger users. Thus, more research is needed to explore these possibilities and to guide the treatment of adults with ADHD (57,58).

Our findings should be interpreted while considering several limitations. First, our sample only included individuals with employer-sponsored health insurance. Additional research is needed among other patients (e.g., those enrolled in Medicaid). Second, although our examination of within-individual associations among racially and ethnically minoritized individuals presents a strength compared with prior research, the available race-ethnicity data had notable limitations. The categories were broad, heterogeneous, and subject to possible bias from misclassification (59,60). More research is needed to understand how racial-ethnic marginalization and other social processes contextualize experiences of ADHD, psychiatric treatment, and related health outcomes. Third, although our analyses adjusted for time-invariant confounding factors by design, they remain subject to possible unmeasured time-varying confounding. We addressed some of these confounds by adjusting for the time-varying use of other psychiatric treatments, but there are other important factors [e.g., fluctuating symptom severity (2), life events] for which we could not account. Fourth, studies of health care claims are subject to possible exposure and outcome misclassification. Although we had information on medication prescription fills, we lacked a measure of whether individuals consumed their medication. We also lacked information on treatments not billed to insurance (e.g., those paid for out of pocket) and suicidal behavior events not resulting in emergency or inpatient care. Notably, our outcome excluded deaths by suicide that did not result in claims for medical care [however, see a recent case-control study that did not detect a significant association of stimulant and nonstimulant pharmacotherapy with deaths by suicide (61)]. We may have also missed suicidal behavior events misclassified as unintentional (62), although our sensitivity analysis including events with undetermined intent yielded findings similar to the main

analysis. Our definition of suicidal behavior also included severe self-injuries lacking suicidal intent as these were not defined separately in some ICD-10-CM codes (45). Fifth, only individuals with within-individual variability in psychiatric treatment and at least 1 suicidal behavior event were informative to the estimates in this study. These individuals may differ from the general population of people with ADHD. Finally, this study was focused on concurrent associations of medication treatment with suicidal behavior, not subsequent risk for suicidal behavior. Given limited statistical precision, we were also unable to examine possible differences in associations between short-term and long-term treatment, which future research should explore.

Despite these limitations, this study extends previous research by evaluating associations between multiple types of ADHD pharmacotherapies and suicidal behavior using recent, large-scale U.S. health claims data and a rigorous within-individual comparison design. We observed that risk of suicidal behavior was elevated during periods just before ADHD medication treatment and declined thereafter, while remaining slightly elevated compared with other off-treatment periods (i.e., excluding the 2 months pretreatment). These fluctuations in risk appeared particularly pronounced among individuals using atomoxetine and alpha-2 agonists. If replicated, these findings have important clinical implications. First, they indicate that existing ADHD medication treatments, including nonstimulant treatments, do not appear to substantially increase risk of suicidal behavior. In fact, we observed a 1.5- to 3-fold elevation in risk of suicidal behavior during the 2-month pretreatment period immediately before ADHD medication treatment, and on-treatment periods appeared protective compared with this higher-risk pretreatment period. Additional research is needed to determine whether the modest elevations in suicidal behavior observed during treatment are due to true medication effects or to persistence in the distress that prompted treatment initiation. Finally, the general lack of protective effects observed in this study (with the exceptions of stimulant treatments for adults ages 46–64 years) emphasizes the need to identify additional strategies to support and prevent suicide among individuals with ADHD.

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If you are contemplating suicide, please reach out for help; resources are available at <https://www.iasp.info/suicidalthoughts/>.

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