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*This headline grabbing paper recently came through, and also pops up on the well-known point of care decision support resource, UpToDate when searching ADHD treatment. It reports on an observational study done with Swedish registry data evaluating the impact of treatment for ADHD on mortality in those aged 6-64. The authors reported a protective effect in overall mortality of 0.79 (0.70-0.88), which subgroup analysis suggests was driven by accidental poisoning, i.e., overdose, in men. The authors made efforts to adjust for confounders in the data but the bias introduced when comparing those treated versus not is a notorious cause of bias (*Schneeweiss et al 2007*) that is very possibly in effect here. The authors suggest that because of this, and because of multiple comparisons made, their findings should be considered exploratory.*

Further, with the generous input about validity concerns from our psychiatry research colleague, Dr Lauren Moran, further doubt is cast on these findings. As Dr Moran shared with me, given that the mortality finding was driven by accidental overdose, the study would have to measure and account for important substance use disorder (SUD) features, however those are notoriously underrecognized and missing from data sets such as these, where the groups are defined by those who were treated versus those who weren't. An example is that in this group, the stated rate of tobacco use disorder was 0.4% while epidemiologic data from Sweden suggests 6% of adults and 6-19% of high school kids smoke (Public Health Agency of Sweden, 2021). It is possible that those patients with ADHD who were "non initiators", i.e. not prescribed medication, displayed risks or features for SUD (such as a single positive urine) without be asked for, or coming forth with, DSM criteria for an SUD, making findings due to a "healthy user bias". Other concerns about the methods are described in the commentary below.

In combination with a previous report of ***increased*** *mortality in the setting of new stimulant prescriptions in adults (Westover et al, 2018), the limitations above indicate that data about ADHD impact on mortality remain inconclusive.*

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Title: ADHD Pharmacotherapy Showed a Signal for 2year Mortality Reduction But is Likely Healthy User Bias

Citation: Li L, Zhu N, Zhang L, Kuja-Halkola R, D'Onofrio BM, Brikell I, Lichtenstein P, Cortese S, Larsson H, Chang Z. ADHD Pharmacotherapy and Mortality in Individuals With ADHD. JAMA. 2024 Mar 12;331(10):850-860. doi: 10.1001/jama.2024.0851. PMID: 38470385; PMCID: PMC10936112.

Link: https://pubmed.ncbi.nlm.nih.gov/38470385/ (abstract only)

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METHODS

This study was conducted using Swedish registry data to look at children and adults (6-64

years) who received an ADHD diagnosis after a thorough neuropsychiatric evaluation. **They compared mortality between those who went on to fill prescriptions for pharmacotherapy for ADHD and those who didn't.**

Excluded was any individual who filled a prescription for ADHD pharmacotherapy in the 18months prior to diagnosis. They included only those who adhered to treatment for the full follow-up period in the treatment (initiation group), though in a sensitivity analysis they also included those who adhered to treatment through the initial 3month grace period. They followed individuals for up to two years. The end of follow up was death, emigration, Dec 31, 2020, or 2yrs, whichever came first.

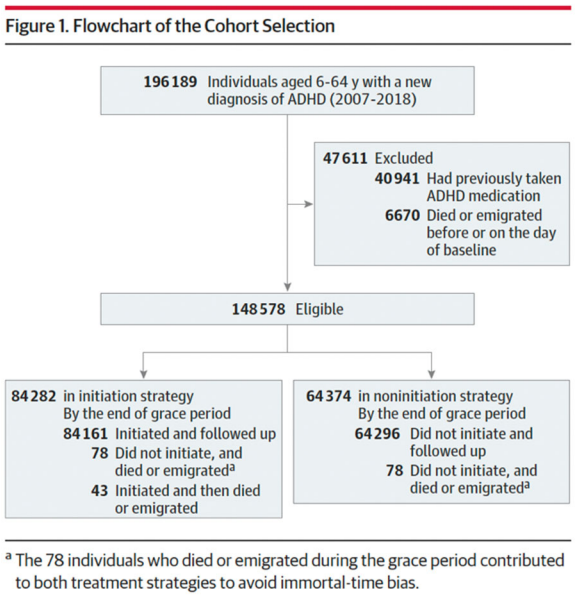
The authors used available information about comorbidities and medications and used this information to adjust for differences in the two groups using regression models. They looked at the association of medication initiation with outcomes of all-cause mortality, subdivided into "natural" (medical) and "unnatural" (accidents,

suicide, accidental poisoning). They use well accepted techniques to conduct the regression but made choices about assignment of individuals that were not always standard and that introduce bias, (see commentary).

Medications included non-stimulants atomoxetine and guanfacine but 92% were initiated with a stimulant. We don't know which stimulants but it is known that the US uses more amphetamine than any other country in the world and prescribes more amphetamine than methylphenidate whereas Sweden favors methylphenidate. (Chan, et al, 2023)

MAIN RESULTS

Patients flowed in or dropped out as follows:



Overall 57% of those with a new diagnosis of ADHD initiated pharmacotherapy. The overall group was young (median age 17yrs (IQR 12-29), 92% Swedish and only 0.4% had a tobacco use disorder. Other notable characteristics are here but a full list of measured characteristics is available in the article.

Characteristic	Overall Group	Initiators	Non Initiators
Age, yrs.	17.6	16.4	19.1

Female, %	41.3	41.1	41.6
Postsecondary education	31.9	33.2	30.2
Accidental Injury	52.9	58.2	57.5
Non alcohol drug use disorder	8.7	7.4	10.3
Alcohol use disorder	8.3	7.3	9.6
Tobacco	0.4	0.3	0.5
Suicide attempt	8.4	7.5	9.5
Anxiety	8	7.2	9.2
Personality disorder	4.9	4.0	5.9
CV disease	3.4	2.7	4.3
On antidepressant therapy	34.7	32.9	37
On anxiolytics	28.6	27.5	30
On antiaddiction medication	5.1	4.6	5.7
On antiepileptics	7.3	6.2	8.7
No prior psychiatric hospitalization	82.3	85.3	78.5

Actual length of follow up was not reported. Nor were number of people who did not fill prescriptions.

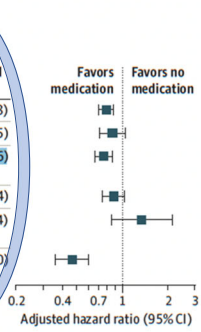
Mortality Results:

- **Overall, mortality events over the two year follow up period were <1%.** I.e., 17/10,000 initiation vs 32/10,000 non-initiation.
- 33% of deaths were natural. 67% were unnatural, of which 55% were suicide
- The driver of the differences between groups was accidental overdose, occurring in 23% of the unnatural deaths
- 1/3 of the natural deaths were cardiovascular

The main findings are here:

Figure 2. Association Between ADHD Medication Initiation and 2-Year Mortality Among Individuals With ADHD

	Crude				Weighted							
	Initiation		Noninitiation		Initiation			Noninitiation				
	Deaths (person-years, 133 201)	Incidence rate per 10 000 person-years	Deaths (person-years, 91 912)	Incidence rate per 10 000 person-years	Deaths (person-years, 310 362)	Incidence rate per 10 000 person-years	2-Year risk (95% CI)[a]	Deaths (person-years, 307 604)	Incidence rate per 10 000 person-years	2-Year risk (95% CI)[a]	2-Year risk difference (95% CI)[a]	Adjusted hazard ratio (95% CI)
All cause	231	17.3	292	31.8	598	19.3	39.1 (33.8-45.4)	731	23.8	48.1 (42.5-54.5)	-8.9 (-17.3 to -0.6)	0.79 (0.70-0.88)
Natural cause	66	5.0	102	11.1	203	6.6	13.1 (10.0-17.3)	226	7.4	14.7 (11.9-18.2)	-1.6 (-6.4 to 3.2)	0.86 (0.71-1.05)
Unnatural cause	165	12.4	190	20.7	395	12.7	25.9 (21.8-30.8)	505	16.4	33.3 (28.5-38.8)	-7.4 (-14.2 to -0.5)	0.75 (0.66-0.86)
Suicide	103	7.7	105	11.4	248	8.0	16.3 (13.0-20.3)	268	8.7	17.7 (14.4-21.8)	-1.4 (-6.6 to 3.7)	0.88 (0.74-1.04)
Accidental injuries	19	1.4	11	1.2	41	1.3	2.7 (1.6-4.3)	33	1.1	2.1 (1.1-4.0)	0.5 (-1.4 to 2.4)	1.34 (0.85-2.14)
Accidental poisoning	38	2.9	68	7.4	92	3.0	6.0 (4.2-8.7)	183	6.0	12.1 (9.4-15.6)	-6.0 (-9.8 to -2.3)	0.47 (0.36-0.60)



Natural-cause mortality among those diagnosed with attention-deficit/hyperactivity disorder (ADHD) included death from somatic diseases and medical conditions (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*], A00-R99, U07) and unnatural-cause mortality included death from suicide, accidental injuries, accidental poisoning, and other external injuries (*ICD-10* codes, S00-T98, V01-Y98).

[a]Two-year absolute risk and 2-year risk difference were calculated per 10 000 individuals.

When adjusted for known possible confounders, initiators experienced significantly lower overall mortality (HR 0.79 (0.7-0.88)), driven by fewer unnaturally caused deaths (0.75 (0.66, 0.86).

When divided by gender, the results were significant for men but not for women. Among women however, there were significantly fewer deaths from natural causes among initiators. The results were similar for groups ages 6-24 and ages 25-64.

Sensitivity analyses (eSupplement 1) were done to assess the impact of certain assumptions and showed:

- **At 5yr fup (eTable5) – there was a lost significance for all cause mortality, but death by unnatural causes remained significant** at 7.4/10,000 fewer in treatment group, driven by higher accidental poisonings.
- When fup was assessed in 2wk intervals (vs one month) (eTable6), results didn't change.
- When those who deviated from treatment after the grace period were kept in/not censored, (eTable7) results didn't change. We don't know how many of these deviations existed.
- When they did NOT exclude competing events (eTable 8): the authors state there was no difference from main results but they don't report the overall mortality difference, and the magnitude and significance of the death from unnatural causes is reduced and almost loses significance 0.78 (0.62, 0.99).

- The case crossover analysis (essentially comparing the person to themselves in and out of treatment) held significance for unnatural and all-cause mortality.

Other findings

- There was **no difference in all-cause mortality for those treated with stimulants vs non stimulants** (eTable 9), 0.96 (0.58, 1.58) but we do not know power to detect this difference given 92% of initiations were with a stimulant.

COMMENTARY

This observational study of Swedish residents with carefully diagnosed ADHD shows a signal for a mortality benefit with ADHD pharmacotherapy driven by accidental poisoning deaths in males. While possible this is a treatment effect there is also a good chance that healthy user bias accounts for this (i.e., those prescribed and initiating treatment were healthier/lower risk than those not prescribed stimulants). This and other caveats mean that the findings should be considered exploratory in nature.

Major things to consider about the validity and applicability of these findings are as follows, again with thanks and attribution to Dr Lauren Moran (LM):

Internal validity

The overall approach was sound *and has been gaining traction because of the work of Miguel Hernan, who is very rigorous****, however there are methodological concerns in the decisions made for assigning people who dropped out, who did not start medication in spite of being prescribed, and in how confounders were adjusted for. (LM) In particular:***

- ***There is a bias favoring the treatment/initiation group related to those who did not initiate in the grace period.*** The 78 patients mentioned in flow chart "did not initiate and died or emigrated" were "assigned to both treatment strategies to avoid immortal time bias". This is wrong – since they did not initiate, the person time within that 3 month period should have been assigned to the non-initiator group to avoid immortal time bias. Also it would be important to know the # emigrated vs # died as this could change conclusions given the total number of deaths in two groups was 231 initiators vs. 292 non-initiators. (LM)

- ***Adjustment for confounders*** was done in an atypical way – typically done before treatment assignment but was done after the grace period. (LM)
- ***Removal of non- adherent people from the treatment group.*** They censored people (removed them from observation) if they did not redeem any dispensation of ADHD medication during grace period, so they are comparing adherent patients with ADHD to those diagnosed but not prescribed medication for ADHD. Comparing treated to untreated people leads to bias (Schneeweiss, et al, 2007) but this was worsened by restricting to those that adhered to treatment. They also censored if they switched to another ADHD treatment, which seems unnecessary given the question being asked, and may introduce more bias as they are removing people who may have not responded to or had adverse events due to ADHD medication. **So essentially, the comparison was between adherent users without side effects to those not prescribed**. They did do a sensitivity analysis where they did not censor/remove people who stopped medication after the grace period but this doesn't capture that early censoring of non-adherent people. (LM)
- Case crossover design was used inappropriately and reported as further evidence that bias was accounted for. Case crossover works with transient phenomena, originally designed for vaccines to show anaphylaxis and other transient events. But overdose deaths are preceded by a period of drug use such that it is a subacute process, not appropriate for case crossover design. (LM)

There is a possibility of unmeasured confounders. This study is comparing people who were offered and took ADHD medication with those who did not. It is clear from the characteristics that there are some differences between the two groups. In particular those with substance use disorders, on psychiatric medications, with history of suicide attempt, personality disorders, and pre-existing cardiovascular disease were less likely to be offered treatment. Those were the documented differences for which adjustments were made, however as stated in the introduction, when the main outcome is accidental poisoning, it is important to carefully adjust for SUD related features and risks which is difficult to do. As such, it is possible that there are other features about these individuals which were not measured that account for the findings (i.e., early substance use disorder not captured in the database, risk taking behavior, poverty, social environment).

Other features that go with pharmacotherapy for ADHD may lead to the observed reduction in risk (i.e., behavioral treatments, monitoring with response to risk response) The observed difference may not be entirely or at all do to the medication.

There was a loss of significance of overall mortality reduction when observation was extended to 5yrs. Given the comprehensive nature of the registries and lack of

reporting about missing data over time, it's unclear why this would be. If anything, we would expect to see more events over time and therefore greater significance. Could it be that the effect of pharmacotherapy is diminished over time? Or that starting pharmacotherapy is marked with a period of doing well and that this was captured in more limited analysis. Note that we don't know the actual length of follow up – they looked at up to two years but when patients had an event or emigrated, they were removed making the actual observation period shorter.

Multiple comparisons were done (i.e., different kinds of mortality were evaluated without an adjustment for these comparisons). In particular, women did not experience an overall reduction in mortality, only in mortality due to natural causes. Its hard to know why this would be, especially in a mostly young population and raises concerns this finding is due to multiple comparisons.

We don't know about doses prescribed, or which type of amphetamine was used (though we know that the US is the world's leader in amphetamine prescribing – with majority of stimulants prescriptions at the end of this study period being amphetamine, compared with Sweden which favored methylphenidate (Chan et al, 2023).

- We also don't know what was the ADHD symptom severity among those treated vs untreated and whether that mediated the effect of treatment.

External validity

This is a **young population (median age 17 with IQR (middle 50%)= 12-29yoa),** applying it to people outside of this range may incorrectly estimate risk and benefit.

The **practice environment in Sweden** is different than in the United States and our understanding of this is, no doubt, incomplete. It appears that in Sweden ADHD diagnoses are made with neuropsychiatric testing, which is quite different than in current US practice. In addition, Sweden has universal access to care which may affect treatment duration and ease of monitoring for harms, as well as access to behavioral health supports. In addition, as above, amphetamines are used less than methylphenidate.

Conclusions

Given the above limitations and previous work suggesting increased overdose risk in US adults new stimulant prescribed stimulants (for mostly off label indications), (Westover, et al, 2018), these findings should be considered exploratory.

References

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