Supplemental Online Content

Hartikainen M, Taipale H, Tanskanen A, Mittendorfer-Rutz E, Lähteenvuo M, Tiihonen J. Association of pharmacological treatments and hospitalization and death in individuals with amphetamine use disorders in a Swedish nationwide cohort of 13 965 patients. *JAMA Psychiatry*. Published online November 16, 2022. doi:10.1001/jamapsychiatry.2022.3788

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This supplemental material has been provided by the authors to give readers additional information about their work.
eMethods

Exposure

Exposure to studied medications was categorized as medications for substance use disorders (SUD), medications for attention-deficit hyperactive disorder (ADHD), mood stabilizers, antidepressants, benzodiazepines and related drugs, and antipsychotics. SUD-medications included disulfiram (N07BB01), acamprosate (N07BB03), naltrexone (N07BB04, only oral available during the study period), methadone (N07BC02) and buprenorphine (N07BC01, N07BC51). ADHD medications were defined as N06BA and specifically as amphetamine, dexamphetamine, modafinil, atomoxetine, methylphenidate and lisdexamphetamine. Mood stabilizers included carbamazepine (N03AF01), valproic acid (N03AG01), lamotrigine (N03AX09) and topiramate (N03AX11). These specific drugs were compared with non-use of the drug class. All specific drugs refer to within-class monotherapies and concomitant use of two or more medication from the class was defined as combination use (e.g. concomitant use of disulfiram and naltrexone). In addition, we analysed the risk of main and secondary outcomes associated with the following drug classes: benzodiazepine and related medications (N05BA, N05CD, N05CF), antidepressants (N06A) and antipsychotics (N05A, including lithium). Sensitivity analyses were conducted for specific antidepressants, including ten most common antidepressants: mirtazapine, sertraline, venlafaxine, escitalopram, bupropion, citalopram, fluoxetine, duloxetine, amitriptyline and paroxetine.

PRE2DUP

Medication use was modelled into drug use periods (when drug use started and ended) based on dispensing data with the PRE2DUP-method (From Prescriptions to Drug Use Periods). The method is based on the calculation of sliding averages of daily dose (in DDDs), the purchased amounts of medications and personal medication use patterns. The method utilizes product level parameters which control the joining of purchases, takes into account hospital stays (when medication use is not recorded in the register) and stockpiling of medications when constructing use periods.1

Dose analyses

Additional analyses were conducted for lisdexamphetamine to inform most beneficial dose range. Temporal dose was estimated at each dispensing based on PRE2DUP-modelled data. Dose estimate was calculated by using two previous dispensings and categorized into dose categories (defined daily doses per day translated into milligrams per day dose, <45, 45-<65, 65-<85 and ≥85 mg/day, designed around tablet strengths available and allowing some variation from strictly everyday use).

Study design

Exposure to medications is modelled as time-varying exposure comparing different medications to non-use of medications. The main study design was within-individual which means that use periods are compared to non-use periods within the same person. The within-individual model is a stratified Cox regression model in which each individual forms his or her own stratum. Within each stratum, time is reset to zero after each outcome event. This reduces selection bias of different treatments, i.e. that non-users may be different than users of a certain medication. The method is described in more detail in: Paul D Allison: Fixed Effects Regression Models2.

Only persons having an event and having variation in exposure status (on medication/off medication) over time contribute to the model in within-individual analysis, whereas all individuals contribute to the between-individual model. Traditional between-individual model was utilized for analyses of mortality, and as sensitivity analyses for the main outcomes. Exposure in between-individual analyses was similarly time-varying and the reference was non-use of the medication class. Dependence between repeated observations was corrected with robust sandwich estimator in between-individual analyses.
### eTable 1. Covariate definitions for within-individual and between individual analyses

The Anatomical Therapeutic Chemical (ATC) classification codes for covariate medications and International Classification of Diseases (ICD) version 10 codes for somatic diseases are described in the table.

- **Covariate Definition Register**

#### Within-individual models

| Covariate                          | Definition                                                                 | Register |
|------------------------------------|---------------------------------------------------------------------------|----------|
| Order of treatments                | Order of treatment continuously updated in the models, categorized as no treatment, 1st, 2nd, 3rd, >3rd | PDR      |
| Time since cohort entry            | Time since first (meth)amphetamine use disorder (MAUD) diagnosis in years, categorized as 0-1, 1-2, 2-3 and >3 years, continuously updated in the models | NPR      |

#### Between-individual models additionally adjusted for the following (in addition to above mentioned covariates)

- **Other medication use:** defined time-dependently during the follow-up (current use vs. no use currently)
  - Opioid analgesics: N02A PDR
  - Non-opioid analgesics: N02BE01, M01A PDR
  - Cardiovascular medications: C01-C10, excl. C04, C05 PDR
  - Alimentary tract and metabolism medications: A02, A04AA, A05, A07, A10 PDR
  - Antiepileptic drugs: N03A excl. valproate, carbamazepine, lamotrigine, lithium PDR
  - The number of previous hospitalizations due to MAUD: Main diagnoses of F15; categorized as ≤1, 2-3, >3, updated time-dependently during the follow-up NPR

- **Comorbidities:** updated continuously in the model as "no" before the first diagnoses and "yes" thereafter
  - Cardiovascular disease: I00-I99 NPR
  - Diabetes: E10-E14, or antidiabetic use A10 NPR, PDR
  - Asthma/COPD: J42-44 NPR
  - Previous cancer: C01-C99 NPR
  - Renal disease: N10-N19 NPR
  - Previous suicide attempt: X60-84, Y10-34 Z728, Z915 NPR
  - Other substance use disorder than MAUD: F10--F14, F16, F19 NPR
  - Depression: F32–F33 NPR
  - Anxiety disorder: F41 NPR
  - ADHD: F90 NPR

- **Sociodemographic factors:** measured at cohort entry
  - Age: ≤35, 36-55, >55 LISA
  - Sex: Male or female LISA
  - Education (years): Low (< 9), medium (10 - 12), high (>12), missing LISA

NPR: National Patient Register, PDR: Prescribed Drug Register, LISA: The Longitudinal Integration Database for Health Insurance and Labor Market Studies

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**Table 2.** Description of the cohort of persons with (meth)amphetamine use disorder (MAUD) (N=13,965), including all residents aged 16–65 living in Sweden with registered first-time diagnosis of MAUD (=cohort entry) during 2005-2016.

| Use of specific drugs at any time after cohort entry | % (n)       |
|------------------------------------------------------|------------|
| **SUD-medications**                                  | 20.5 (2856) |
| Disulfiram                                           | 8.0 (1115)  |
| Acamprosate                                          | 4.1 (579)   |
| Naltrexone                                           | 6.3 (873)   |
| Buprenorphine                                        | 4.7 (652)   |
| Methadone                                            | 2.6 (368)   |
| ≥2 SUD-medications                                   | 4.2 (592)   |
| **Antidepressants**                                  | 54.0 (7543) |
| Tricyclic                                            | 5.0 (700)   |
| SSRI                                                 | 31.6 (4411) |
| SNRI                                                 | 13.1 (1825) |
| Mirtazapin                                           | 19.7 (2752) |
| Bupropion                                            | 6.9 (960)   |
| Other antidepressants                                | 3.6 (505)   |
| ≥2 antidepressants                                   | 20.1 (2800) |
| **Mood stabilizers**                                 | 12.2 (1706) |
| Carbamazepine                                        | 4.3 (605)   |
| Valproic acid                                        | 4.0 (562)   |
| Lamotrigine                                          | 4.6 (642)   |
| Topiramate                                           | 0.8 (117)   |
| ≥2 mood stabilizers                                  | 0.8 (114)   |
| **ADHD-medications**                                 | 28.2 (3941) |
| Amphetamine                                          | 0.1 (19)    |
| Dexamphetamine                                       | 1.9 (268)   |
| Methylphenidate                                      | 21.8 (3043) |
| Modafinil                                            | 0.4 (62)    |
| Atomoxetine                                          | 6.3 (881)   |
| Lisdexamphetamine                                    | 10.8 (1511) |
| ≥2 ADHD-medications                                  | 8.5 (1190)  |
| **Benzodiazepines**                                  | 43.7 (6101) |
| **Antipsychotics**                                   | 36.3 (5067) |
## Description of the cohort

| Description of the cohort                  |       |
|-------------------------------------------|-------|
| Mean age (SD)                              | 34.4 (13.0) |
| Male gender                               | 69.3 (9671) |
| Year of cohort entry                      |       |
| 2006                                      | 5.6 (785) |
| 2007                                      | 5.3 (743) |
| 2008                                      | 5.2 (727) |
| 2009                                      | 5.2 (731) |
| 2010                                      | 4.7 (655) |
| 2011                                      | 4.4 (618) |
| 2012                                      | 11.9 (1662) |
| 2013                                      | 10.3 (1437) |
| 2014                                      | 9.6 (1344) |
| 2015                                      | 10.3 (1441) |
| 2016                                      | 9.4 (1312) |
| 2017                                      | 8.6 (1196) |
| 2018                                      | 9.4 (1315) |
| Country of birth                          |       |
| Sweden                                    | 87.0 (12145) |
| Other Europe                              | 6.2 (869) |
| Rest of the world                         | 6.8 (952) |
| Education                                 |       |
| Low                                       | 45.6 (6365) |
| Medium                                    | 42.6 (5951) |
| High                                      | 6.8 (947) |
| Missing                                   | 5.0 (703) |
| Family situation                          |       |
| Married without children                  | 2.7 (373) |
| Married with children                     | 5.9 (829) |
| Single without children                   | 74.2 (10367) |
| Single with children                      | 3.9 (543) |
| <20 years living at home                  | 11.1 (1543) |
| Missing information                       | 2.2 (311) |
| Any income from work (year before cohort entry) | 29.1 (4059) |
| Unemployment during previous year         |       |
| 1 – 180 days                              | 23.6 (3292) |
| >180 days                                 | 6.4 (890) |
| No unemployment                           | 70.1 (9784) |
| On disability pension at cohort entry     | 14.9 (2082) |
| Sickness absence during a year before cohort entry |       |
| 1-90 days                                 | 9.0 (1258) |
| >90 days                                  | 6.4 (889) |
| No sickness absence                       | 84.6 (11819) |
| Comorbidities at baseline (ICD-10-code)                                      |     |
|---------------------------------------------------------------------------|-----|
| Alcohol use disorder (F10)                                               | 29.2 (4075) |
| Opioid use disorder (F11)                                                | 11.6 (1623) |
| Cannabis use disorder (F12)                                               | 10.8 (1502) |
| Sedative use disorder (F13)                                               | 12.8 (1791) |
| Cocaine use disorder (F14)                                               | 2.6 (360) |
| Hallucinogen use disorder (F16)                                           | 2.1 (299) |
| Other psychoactive substance use disorder (F19)                          | 33.9 (4728) |
| Depression (F32–33)                                                      | 13.2 (1843) |
| Anxiety disorder (F41)                                                   | 19.3 (2690) |
| ADHD (F90)                                                               | 11.9 (1657) |
| Previous suicide attempt (X60–84, Y10–Y34, Z728, Z915)                   | 21.1 (2953) |
| Cardiovascular disease (I00 – I99)                                       | 11.0 (1541) |
| Previous cancer (C01–99)                                                 | 1.0 (142) |
| Diabetes (E10–14, or antidiabetic use, ATC-code A10)                     | 2.6 (362) |
| Asthma/COPD (J42–44)                                                    | 4.0 (553) |
eTable 3. The risk for the main outcomes, when first 30 days of medication use was omitted from the analysis. Bolded results are associated with reduced risk of outcome and results written in red color, indicate the increased risk of the outcome studied.

| Medication(s)        | SUD HOSP (30 days omitted) | ANY HOSP OR DEATH (30 days omitted) |
|----------------------|-----------------------------|-------------------------------------|
| Medication(s)        | Events | HR (95%CI) | Events | HR (95%CI) |
| **SUD-medications**  |        |            |        |            |
| Disulfiram           | 313    | 1.04 (0.90–1.21) | 455    | 1.07 (0.94–1.21) |
| Acamprosate          | 181    | 0.94 (0.78–1.13) | 245    | 0.92 (0.78–1.09) |
| Naltrexone           | 178    | 1.19 (0.98–1.44) | 247    | 1.14 (0.97–1.35) |
| Buprenorphine        | 949    | 1.00 (0.91–1.11) | 1132   | 0.96 (0.88–1.06) |
| Methadone            | 1401   | **1.16 (1.04–1.28)** | 1669   | **1.16 (1.05–1.28)** |
| POLY                 | 151    | 0.86 (0.70–1.06) | 180    | 0.86 (0.71–1.04) |
| **Antidepressants**  |        |            |        |            |
| Carbamazepine        | 707    | 0.91 (0.82–1.02) | 787    | 0.96 (0.88–1.05) |
| Valproic acid        | 505    | **0.87 (0.76–0.99)** | 560    | 1.00 (0.91–1.11) |
| Lamotrigine          | 349    | 0.87 (0.74–1.03) | 389    | 0.97 (0.87–1.09) |
| Topiramate           | 63     | 0.93 (0.66–1.32) | 76     | 1.01 (0.80–1.28) |
| POLY                 | 48     | 1.04 (0.70–1.53) | 59     | 0.99 (0.76–1.29) |
| **Mood stabilizers** |        |            |        |            |
| Carbamazepine        | 707    | 0.91 (0.82–1.02) | 787    | 0.96 (0.88–1.05) |
| Valproic acid        | 505    | **0.87 (0.76–0.99)** | 560    | 1.00 (0.91–1.11) |
| Lamotrigine          | 349    | 0.87 (0.74–1.03) | 389    | 0.97 (0.87–1.09) |
| Topiramate           | 63     | 0.93 (0.66–1.32) | 76     | 1.01 (0.80–1.28) |
| POLY                 | 48     | 1.04 (0.70–1.53) | 59     | 0.99 (0.76–1.29) |
| **ADHD-medications** |        |            |        |            |
| Amphetamine          | 9      | 1.18 (0.30–4.58) | 24     | 0.96 (0.46–2.03) |
| Dexamphetamine       | 97     | 0.91 (0.87–1.23) | 211    | 0.96 (0.78–1.19) |
| Methylphenidate      | 2295   | 0.97 (0.91–1.04) | 3908   | 1.01 (0.96–1.06) |
| Modafinil            | 17     | 0.53 (0.27–1.04) | 47     | 0.76 (0.51–1.13) |
| Lisdexamphetamine    | 443    | **0.84 (0.73–0.96)** | 855    | **0.86 (0.78–0.95)** |
| POLY                 | 203    | 0.83 (0.68–1.00) | 396    | **0.86 (0.75–0.99)** |
| **Benzodiazepines**  |        |            |        |            |
| Chlorpromazine       | 6960   | **1.21 (1.16–1.26)** | 12337  | 1.24 (1.20–1.28) |
| **Antipsychotics**   |        |            |        |            |
| Chlorpromazine       | 6183   | **1.11 (1.06–1.16)** | 9478   | 1.13 (1.09–1.17) |
eTable 4. Events and adjusted hazard ratios (HRs) with nominal p-values for main outcomes related to use vs. no-use of the most common antidepressants.

| Medication     | SUD-hospitalization | Any hospitalization or death |
|----------------|---------------------|------------------------------|
|                | Users (events)      | HR (95%CI)                   | p-value | Users (events) | HR (95%CI) | p-value |
| Mirtazapine    | 2766 (1941)         | 1.08 (1.00–1.15)             | 0.04    | 2752 (2766)   | 1.09 (1.02–1.15) | <0.001 |
| Sertraline     | 2202 (1194)         | 1.03 (0.94–1.12)             | 0.58    | 2192 (1996)   | 1.07 (1.00–1.15) | 0.06   |
| Venlafaxine    | 1325 (990)          | 1.13 (1.02–1.25)             | 0.02    | 1322 (1565)   | 1.17 (1.07–1.26) | <0.001 |
| Escitalopram   | 1162 (576)          | 0.91 (0.80–1.03)             | 0.15    | 1155 (997)    | 1.01 (0.92–1.11) | 0.85   |
| Bupropion      | 972 (317)           | 1.01 (0.86–1.18)             | 0.85    | 960 (501)     | 1.06 (0.94–1.20) | 0.35   |
| Citalopram     | 953 (581)           | 1.14 (1.00–1.29)             | 0.05    | 951 (1070)    | 1.15 (1.05–1.27) | 0.004  |
| Fluoxetine     | 880 (526)           | 1.13 (0.99–1.29)             | 0.07    | 876 (962)     | 1.13 (1.02–1.24) | 0.02   |
| Duloxetine     | 656 (426)           | 1.13 (0.97–1.31)             | 0.11    | 649 (700)     | 1.09 (0.97–1.22) | 0.15   |
| Amitriptyline  | 531 (249)           | 1.11 (0.93–1.32)             | 0.26    | 526 (427)     | 1.12 (0.98–1.28) | 0.11   |
| Paroxetine     | 270 (237)           | 1.14 (0.92–1.42)             | 0.24    | 270 (355)     | 1.19 (1.00–1.43) | 0.05   |

eTable 5. Adjusted Hazard Ratios (HRs) and 95% confidence intervals (CIs) for the risk of hospitalization due to any cause or death during SUD- and ADHD-medication combinations.

| Medication combination | ANY HOSPITALIZATION OR DEATH |
|------------------------|-----------------------------|
|                        | Events | HR (95%CI) |
| Combination, SUD       |        |            |
| Disulfiram and naltrexone | 32     | 0.92 (0.61–1.37) |
| Disulfiram and acamprosate | 71     | 0.76 (0.55–1.05) |
| Disulfiram and buprenorphine | 4      | 0.37 (0.11–1.26) |
| Disulfiram and methadone | 20     | 0.80 (0.44–1.45) |
| Acamprosate and naltrexone | 41     | 0.74 (0.51–1.06) |
| Acamprosate and buprenorphine | 4      | 0.35 (0.10–1.18) |
| Acamprosate and methadone | 12     | 0.74 (0.37–1.46) |
| Buprenorphine and methadone | 18     | 0.98 (0.59–1.63) |
| Other combination       | 16     | 0.79 (0.42–1.48) |
| Combination, ADHD       |        |            |
| Dexamphetamine and methylphenidate | 46     | 1.14 (0.71–1.82) |
| Dexamphetamine and lisdexamphetamine | 82     | 0.74 (0.54–1.00) |
| Methylphenidate and atomoxetine | 107    | 0.85 (0.67–1.09) |
| Methylphenidate and lisdexamphetamine | 135    | 0.86 (0.68–1.08) |
| Atomoxetine and lisdexamphetamine | 16     | 0.99 (0.52–1.87) |
| Other combination       | 42     | 0.95 (0.62–1.45) |
eTable 6. The risk of death due to overdose (ICD-10-codes X40-X49; X60-X69; Y10-Y19) associated with the use of studied medications. Black bolded results indicate the reduced risk of outcome (p-value <0.05), red bolded indicate the increased risk of studied outcome (p-value <0.05).

| Medication(s)          | Events | Users | Person years | HR (95%CI)       |
|------------------------|--------|-------|--------------|------------------|
| **OVERDOSE DEATH**     |        |       |              |                  |
| **Between-individual model** |        |       |              |                  |
| **SUD-medications**    |        |       |              |                  |
| Disulfiram             | 7      | 1125  | 497          | 0.87 (0.40–1.89) |
| Acamprosate            | 3      | 585   | 250          | 0.77 (0.24–2.50) |
| Naltrexone             | 2      | 890   | 285          | 0.50 (0.12–2.06) |
| Buprenorphine          | 6      | 673   | 1163         | **0.32 (0.14–0.73)** |
| Methadone              | 8      | 379   | 974          | **0.44 (0.21–0.93)** |
| POLY                   | 1      | 615   | 199          | 0.24 (0.03–1.78)  |
| **Antidepressants**    | 151    | 7573  | 13 410       | 1.24 (1.00–1.54)  |
| **Mood stabilizers**   |        |       |              |                  |
| Carbamazepine          | 8      | 617   | 698          | 0.77 (0.38–1.57)  |
| Valproic acid          | 10     | 572   | 566          | 1.22 (0.64–2.33)  |
| Lamotrigine            | 9      | 656   | 661          | 1.40 (0.71–2.78)  |
| Topiramate             | 1      | 120   | 117          | 0.80 (0.11–6.15)  |
| POLY                   | 0      | 119   | 53           | -                |
| **ADHD-medication**    |        |       |              |                  |
| Amphetamine            | 0      | 19    | 48           | -                |
| Dexamphetamine         | 0      | 271   | 366          | -                |
| Methylphenidate        | 33     | 3067  | 5336         | **0.60 (0.42–0.85)** |
| Modafinil              | 1      | 62    | 49           | 1.66 (0.22–12.7)  |
| Atomoxetine            | 4      | 895   | 383          | 0.90 (0.34–2.39)  |
| Lisdexamphetamine      | 5      | 1540  | 1446         | **0.34 (0.14–0.82)** |
| POLY                   | 1      | 1211  | 606          | 0.16 (0.02–1.14)  |
| **Benzodiazepines**    | 155    | 6132  | 10 561       | **1.74 (1.40–2.17)** |
| **Antipsychotics**     | 111    | 5102  | 7029         | **1.29 (1.02–1.64)** |

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