Supplementary Online Content

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eTable 1. *ICD-9-CM* and *ICD-10-CM* Codes Used in Outcome Definition
eTable 2. Young People Initiating BZD or Comparator Treatment for Sleep Disorder: Crude and Propensity Score Weighted Cohorts, Full List of Variables
eTable 3. Cumulative Incidence and Hazard Ratio of Overdose Involving BZD Within 6 Months of BZD or Comparator Treatment Initiation in Young People With Sleep Disorders
eFigure 1. Study Flow Diagram
eFigure 2. Survival Curves of Drug Overdose by Initial Treatment: BZD vs Alternative Sleep Medications
eFigure 3. Sensitivity Analysis of Residual Confounding (Rule Out Approach)

This supplementary material has been provided by the authors to give readers additional information about their work.
**eTable 1. ICD-9-CM and ICD-10-CM Codes Used in Outcome Definition**

| ICD-9-CM codes | ICD-10-CM codes |
|----------------|-----------------|
| **Drug overdose** | Codes in the range of T36-T50 that have the 'initial' specification for accidental, intentional, and undetermined poisonings (Excluded codes for 'subsequent encounters' and 'sequela' along with poisonings by assault, adverse effect, and underdosing) |
| • 960-979.x | • T42.4X1A |
| • E850-E858 | • T42.4X2A |
| • E950.0-E950.5 | • T42.4X4A |
| • E980.0-E980.5 | |
| **Overdose involving BZD** | |
| • 969.4 | |
| • E853.2 | |
**Table 2.** Young People Initiating BZD or Comparator Treatment for Sleep Disorder: Crude and Propensity Score Weighted Cohorts, Full List of Variables

| Patient characteristics | Study cohort, unweighted | IPTW |
|--------------------------|--------------------------|------|
|                          | BZD initiators N=23,084 | Comparator group N=66,706 | sdiff |
|                          | No (%)                   | No (%) |       |
| Male                     | 8,640 (37.4)             | 28,260 (42.4) | 0.10 |
| Age at treatment initiation |                         |       |      |
| 10-17y                   | 2,001 (8.7)              | 9,730 (14.6) | 0.19 |
| 18-24y                   | 11,424 (49.5)            | 33,481 (50.2) | 0.01 |
| 25-29y                   | 9,659 (41.8)             | 23,495 (35.2) | 0.14 |
| Unspecified sleep disorder (vs. insomnia) | 2,438 (10.6) | 6,255 (9.4) | 0.04 |

**Comorbid psychiatric diagnoses, 1 year**

| ADHD                      | BZD initiators N=89,515 | Comparator group N=89,814 | sdiff |
|                          | Weighted No (%)         | Weighted No (%) |       |
|                          | No (%)                   | No (%) |       |
| Recent, 0-30d             | 1,275 (5.5)              | 4,815 (7.2) | 0.07 |
| Past (no recent), 31-365d | 880 (3.8)                | 2,626 (3.9) | 0.01 |
| None                     | 20,929 (90.7)            | 59,265 (88.8) | 0.06 |
| Major depressive disorder|                         |       |      |
| Recent, 0-30d             | 4,045 (17.5)             | 12,586 (18.9) | 0.04 |
| Past (no recent), 31-365d | 1,350 (5.8)              | 4,260 (6.4) | 0.02 |
| None                     | 17,689 (76.6)            | 49,860 (74.7) | 0.04 |
| Other depressive disorder| 1,311 (5.7)              | 3,171 (4.8) | 0.04 |
| Anxiety disorder, unspecified |                     |       |      |
| Recent, 0-30d             | 6,897 (29.9)             | 10,193 (15.3) | 0.36 |
| Past (no recent), 31-365d | 1,110 (4.8)              | 3,778 (5.7) | 0.04 |
| None                     | 15,077 (65.3)            | 52,735 (79.1) | 0.31 |
| Generalized anxiety disorder |                     |       |      |
| Recent, 0-30d             | 2,660 (11.5)             | 4,913 (7.4) | 0.14 |
| Past (no recent), 31-365d | 551 (2.4)                | 1,872 (2.8) | 0.03 |
| None                     | 19,873 (86.1)            | 59,921 (89.8) | 0.12 |
| Panic disorder            | 1,357 (5.9)              | 1,361 (2.0) | 0.20 |
| Anxiety disorder, other   | 1,066 (4.6)              | 2,815 (4.2) | 0.02 |
| Adjustment disorder with anxiety or depression | 1,599 (6.9) | 4,102 (6.1) | 0.03 |
| Adjustment disorder, other| 528 (2.3)                | 1,572 (2.4) | 0.01 |
| Obsessive compulsive disorder | 268 (1.2) | 565 (0.8) | 0.03 |
| Post-traumatic stress disorder | 408 (1.8) | 1,138 (1.7) | 0.01 |
| Autism, pervasive developmental disorder | 128 (0.6) | 375 (0.6) | 0.00 |
| Schizophrenia             | 143 (0.6)                | 259 (0.4) | 0.03 |
| Bipolar disorder          | 749 (3.2)                | 1,898 (2.8) | 0.02 |
| Personality disorder      | 109 (0.5)                | 374 (0.6) | 0.01 |
| Other psychoses           | 371 (1.6)                | 826 (1.2) | 0.03 |
| Eating disorder           | 162 (0.7)                | 531 (0.8) | 0.01 |
| Other episodic mood disorder | 633 (2.7) | 2,029 (3.0) | 0.02 |
| Conduct/disruptive disorder | 214 (0.9) | 854 (1.3) | 0.03 |
| Acute stress              | 635 (2.8)                | 923 (1.4) | 0.10 |
| Narcolepsy, cataplexy, hypersomnia | 167 (0.7) | 443 (0.7) | 0.01 |
| Other sleep disorder      | 306 (1.3)                | 846 (1.3) | 0.01 |
| Suicidal ideation diagnosis | 394 (1.7) | 1,894 (2.8) | 0.08 |
|                          | 36,674 (41.0)            | 36,812 (41.0) | 0.00 |

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| Medications, 1 year |          |          |          |          |          |
|---------------------|----------|----------|----------|----------|----------|
|                     | Recent, 0-3mo | Past (no recent), 3-12mo | None | Recent, 0-3mo | Past (no recent), 3-12mo | None |
| SSRI | 8,629 (37.4) | 2,856 (4.3) | 13,528 (58.6) | 8,867 (13.3) | 13,038 (19.5) | 14,927 (64.7) |
| Opioid (prescription) | 2,450 (10.6) | 7,131 (10.7) | 118,716 (65.0) | 9,225 (10.3) | 17,603 (19.7) | 59,095 (66.0) |
| Non-SSRI/SNR antidepressant | 1,164 (5.0) | 2,469 (3.7) | 3,415 (6.1) | 3,970 (4.4) | 2,528 (2.8) | 3,739 (6.5) |
| Stimulant | 2,198 (9.5) | 7,131 (10.7) | 8,912 (15.0) | 9,225 (10.3) | 17,603 (19.7) | 59,095 (66.0) |
| Antipsychotic | 702 (3.0) | 1,923 (2.9) | 5,555 (10.0) | 2,861 (3.2) | 2,338 (2.6) | 465 (0.5) |
| Hypnotic, sedative | 650 (2.8) | 1,650 (2.5) | 3,278 (5.9) | 2,528 (2.8) | 2,338 (2.6) | 465 (0.5) |
| Mood stabilizer, lithium | 92 (0.4) | 449 (0.7) | 79 (0.3) | 510 (0.6) | 527 (0.6) | 465 (0.5) |
| Antidepressant | 3,095 (4.6) | 3,095 (4.6) | 3,095 (4.6) | 3,095 (4.6) | 3,095 (4.6) | 3,095 (4.6) |
| Guanfacine | 79 (0.3) | 393 (0.6) | 79 (0.3) | 393 (0.6) | 393 (0.6) | 393 (0.6) |
| NSAIDs | 4,976 (21.6) | 14,195 (21.3) | 20,759 (90.1) | 19,204 (21.5) | 19,204 (21.5) | 19,204 (21.5) |
| Asthma medication | 4,760 (20.6) | 14,075 (21.1) | 20,759 (90.1) | 19,204 (21.5) | 19,204 (21.5) | 19,204 (21.5) |
| Antihistamine | 1,970 (8.5) | 5,555 (8.3) | 1,970 (8.5) | 5,555 (8.3) | 1,970 (8.5) | 5,555 (8.3) |
| Beta-blockers | 773 (3.3) | 1,953 (2.9) | 773 (3.3) | 1,953 (2.9) | 773 (3.3) | 1,953 (2.9) |
| Cardiovascular medications | 732 (3.2) | 2,240 (3.4) | 732 (3.2) | 2,240 (3.4) | 732 (3.2) | 2,240 (3.4) |
| Other anticonvulsants | 543 (2.4) | 1,497 (2.2) | 543 (2.4) | 1,497 (2.2) | 543 (2.4) | 1,497 (2.2) |
| Gabapentin, pregabalin | 460 (2.0) | 1,431 (2.1) | 460 (2.0) | 1,431 (2.1) | 460 (2.0) | 1,431 (2.1) |
| Antidiabetics | 387 (1.7) | 1,242 (1.9) | 387 (1.7) | 1,242 (1.9) | 387 (1.7) | 1,242 (1.9) |

| Healthcare utilization, 1 year |          |          |          |          |          |
|-------------------------------|----------|----------|----------|----------|----------|
| Inpatient psychiatric admission | 677 (2.9) | 2,953 (4.4) | 12,288 (67.3) | 3,766 (4.2) | 3,565 (4.0) | 4,094 (4.6) |
| Inpatient non-psychiatric admission | 1,222 (5.3) | 2,809 (4.2) | 11,939 (63.3) | 3,565 (4.0) | 4,094 (4.6) | 4,094 (4.6) |
| Emergency department visit | 3,392 (14.7) | 8,499 (12.7) | 14,024 (15.7) | 11,939 (63.3) | 14,024 (15.7) | 11,939 (63.3) |
| Psychotherapy claim | 1,941 (8.4) | 5,786 (8.7) | 8,437 (15.0) | 7,816 (8.4) | 8,437 (15.0) | 7,816 (8.4) |
| Outpatient visit count | 7,487 (32.4) | 22,097 (33.1) | 28,518 (31.9) | 28,497 (31.9) | 28,518 (31.9) | 28,497 (31.9) |

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### Recent provider contact

| Service                        | Count (Rate)          | Count (Rate) | Count (Rate) | Count (Rate) |
|-------------------------------|-----------------------|--------------|--------------|--------------|
| Psychiatry                    | 1,535 (6.6)           | 4,843 (7.3)  | 6,742 (7.5)  | 6,408 (7.1)  |
| Other mental health provider  | 2,041 (8.8)           | 6,029 (9.0)  | 8,680 (9.7)  | 8,124 (9.0)  |
| Neurology                     | 726 (3.1)             | 1,497 (2.2)  | 2,447 (2.7)  | 2,268 (2.5)  |

### Other diagnoses, 1 year

| Disorder                               | Count (Rate)          | Count (Rate) | Count (Rate) | Count (Rate) |
|----------------------------------------|-----------------------|--------------|--------------|--------------|
| Musculoskeletal pain                   | 5,312 (23.0)          | 16,206 (24.3)| 21,829 (24.4)| 21,566 (24.0)|
| Fatigue, malaise                       | 5,228 (22.6)          | 12,528 (18.8)| 17,871 (20.0)| 17,855 (19.9)|
| Migraine, headache                     | 4,112 (17.8)          | 11,590 (17.4)| 16,017 (17.9)| 15,781 (17.6)|
| Joint disorders and dislocations       | 3,457 (15.0)          | 10,857 (16.3)| 14,547 (16.3)| 14,346 (16.0)|
| Allergic rhinitis                      | 2,814 (12.2)          | 8,337 (12.5) | 11,115 (12.4)| 11,185 (12.5)|
| Low back pain                          | 2,243 (9.7)           | 6,486 (9.7)  | 8,837 (9.9)  | 8,741 (9.7)  |
| Nonspecific chest pain                 | 1,890 (8.2)           | 4,373 (6.6)  | 6,484 (7.2)  | 6,338 (7.1)  |
| Asthma                                 | 1,746 (7.6)           | 5,331 (8.0)  | 7,099 (7.9)  | 7,092 (7.9)  |
| Obesity                                | 1,368 (5.9)           | 4,431 (6.6)  | 5,758 (6.4)  | 5,789 (6.4)  |
| Palpitations                           | 1,185 (5.1)           | 1,865 (2.8)  | 3,084 (3.4)  | 3,125 (3.5)  |
| Cancer, malignancy                     | 1,091 (4.7)           | 2,326 (3.5)  | 3,383 (3.8)  | 3,430 (3.8)  |
| Myalgia, fibromyalgia, myositis        | 1,059 (4.6)           | 2,399 (3.6)  | 3,575 (4.0)  | 3,509 (3.9)  |
| Nervous system pain, pain syndromes    | 869 (3.8)             | 2,102 (3.2)  | 3,009 (3.4)  | 2,963 (3.3)  |
| IBS, Crohn’s disease                   | 630 (2.7)             | 1,855 (2.8)  | 2,525 (2.8)  | 2,492 (2.8)  |
| Hypertension                           | 602 (2.6)             | 1,392 (2.1)  | 2,039 (2.3)  | 2,007 (2.2)  |
| Overweight                             | 506 (2.2)             | 1,777 (2.6)  | 2,130 (2.4)  | 2,274 (2.5)  |
| Cardiac dysrhythmias                   | 488 (2.1)             | 1,097 (1.6)  | 1,626 (1.8)  | 1,588 (1.8)  |
| Diabetes                               | 446 (1.9)             | 1,069 (1.7)  | 1,525 (1.7)  | 1,553 (1.7)  |
| Sexually transmitted infection         | 445 (1.9)             | 1,214 (1.8)  | 1,646 (1.8)  | 1,659 (1.8)  |
| Premenstrual dysphoric disorder        | 146 (0.6)             | 292 (0.4)    | 439 (0.5)    | 441 (0.5)    |
| Low blood pressure                     | 118 (0.5)             | 290 (0.4)    | 419 (0.5)    | 419 (0.5)    |
| Pain, unspecified                      | 304 (1.3)             | 806 (1.2)    | 1,168 (1.3)  | 1,114 (1.2)  |
| Scoliosis                              | 291 (1.3)             | 892 (1.3)    | 1,213 (1.4)  | 1,191 (1.3)  |
| Fracture                               | 698 (3.0)             | 2,219 (3.3)  | 3,041 (3.4)  | 2,934 (3.3)  |
| Injury to body (excluding fractures)   | 4,791 (20.8)          | 14,819 (22.2)| 19,836 (22.2)| 19,639 (21.9)|
| Injury, other                          | 2,142 (9.3)           | 5,894 (8.8)  | 8,147 (9.1)  | 8,068 (9.0)  |

### Poisoning, adverse effect

| Type                        | Count (Rate) | Count (Rate) | Count (Rate) | Count (Rate) |
|-----------------------------|--------------|--------------|--------------|--------------|
| Recent, 0-30d               | 203 (0.9)    | 744 (1.1)    | 916 (1.0)    | 925 (1.0)    |
| Past (no recent), 31-365d   | 182 (0.8)    | 564 (0.8)    | 792 (0.9)    | 761 (0.8)    |
| None                        | 22,699 (98.3)| 65,398 (98.0)| 87,806 (98.1)| 88,129 (98.1)|

### Other variables

#### Geographical division

| Region                   | Count (Rate) | Count (Rate) | Count (Rate) |
|--------------------------|--------------|--------------|--------------|
| East North Central       | 3,456 (15.0) | 10,579 (15.9)| 14,269 (15.9)| 14,034 (15.6)|
| East South Central       | 1,435 (6.2)  | 5,170 (7.8)  | 6,526 (7.3)  | 6,612 (7.4)  |
| Mid-Atlantic             | 2,750 (11.9) | 5,843 (8.8)  | 8,478 (9.5)  | 8,597 (9.6)  |
| Mountain                 | 1,872 (8.1)  | 5,684 (8.5)  | 7,379 (8.2)  | 7,541 (8.4)  |
| New England              | 932 (4.0)    | 2,001 (3.0)  | 2,932 (3.3)  | 2,945 (3.3)  |
| Pacific                  | 2,784 (12.1) | 8,317 (12.5) | 11,077 (12.4)| 11,104 (12.4)|
| South Atlantic           | 4,506 (19.5) | 11,684 (17.5)| 16,142 (18.0)| 16,234 (18.1)|
| West North Central       | 970 (4.2)    | 4,059 (6.1)  | 5,028 (5.6)  | 5,003 (5.6)  |
| West South Central       | 3,680 (15.9) | 10,869 (16.3)| 14,408 (16.1)| 14,540 (16.2)|
| Unknown                  | 699 (3.0)    | 2,500 (3.7)  | 3,274 (3.7)  | 3,205 (3.6)  |

#### First new use period in dataset

| Group                      | Count (Rate) |
|----------------------------|--------------|
| Family practitioner        | 10,882 (47.1)|
| MD, not elsewhere classified | 5,018 (21.7)|

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| Provider Type                      | 2009-2010  | 2014-2015  | P-value | 2009-2010  | 2014-2015  | P-value |
|-----------------------------------|-----------|-----------|---------|-----------|-----------|---------|
| Nurse practitioner, Physician’s  | 754 (3.3) | 3,389 (5.1)| 0.09    | 4,102 (4.6)| 4,120 (4.6)| 0.00    |
| Assistant                        |           |           |         |           |           |         |
| Pediatricist                      | 576 (2.5) | 2,687 (4.0)| 0.09    | 3,288 (3.7)| 3,244 (3.6)| 0.00    |
| Acute care hospital              | 592 (2.6)| 1,588 (2.4)| 0.01    | 2,101 (2.3)| 2,173 (2.4)| 0.01    |
| Other                            | 3,420 (14.8)| 10,030 (15.0)| 0.01| 13,801 (15.4)| 13,503 (15.0)| 0.01    |
| Unknown or multiple providers    | 1,842 (8.0)| 5,359 (8.0)| 0.00    | 7,153 (8.0)| 7,191 (8.0)| 0.00    |

ADHD: Attention-deficit/hyperactivity disorder; BZD: benzodiazepine; d: day; ED: Emergency department; IBS: Irritable bowel syndrome; IPTW: Inverse probability of treatment weighting; MD: medical doctor; mo: months; NSAID: Nonsteroidal anti-inflammatory drug; SDIFF: Standardized difference; SSRI: Selective serotonin reuptake inhibitor; SNRI: Serotonin–norepinephrine reuptake inhibitor; y: year

2009-2018 MarketScan commercial claims database

*All variables were included in the propensity score estimation
**eTable 3.** Cumulative Incidence and Hazard Ratio of Overdose Involving BZD Within 6 Months of BZD or Comparator Treatment Initiation in Young People With Sleep Disorders\(^a\)

|                         | Total No. (unweighted) | BZD overdose events\(^b\) | Cumulative incidence 6mo | Difference at 6mo | Hazard ratio (95% CI) |
|-------------------------|------------------------|---------------------------|--------------------------|------------------|-----------------------|
| **Intention-to-treat analysis** |                        |                           |                          |                  |                       |
| Crude                   |                        |                           |                          |                  |                       |
| BZD treatment           | 23,084                 | 70                        | 0.33%                    | 0.25%            | 4.40 (3.03 – 6.38)   |
| Comparator treatment    | 66,706                 | 46                        | 0.08%                    | REF              | REF                   |
| Adjusted                |                        |                           |                          |                  |                       |
| BZD treatment           | 23,084                 | 275.4                     | 0.33%                    | 0.26%            | 4.65 (3.13 – 6.91)   |
| Comparator treatment    | 66,553                 | 59.4                      | 0.07%                    | REF              | REF                   |
| **As-treated analysis** |                        |                           |                          |                  |                       |
| Crude                   |                        |                           |                          |                  |                       |
| BZD treatment           | 23,084                 | 54                        | 0.56%                    | 0.49%            | 7.14 (4.41-11.56)    |
| Comparator treatment    | 66,706                 | 24                        | 0.06%                    | REF              | REF                   |
| Adjusted                |                        |                           |                          |                  |                       |
| BZD treatment           | 23,084                 | 217.9                     | 0.64%                    | 0.58%            | 7.67 (4.61-12.76)    |
| Comparator treatment    | 66,553                 | 32.0                      | 0.06%                    | REF              | REF                   |

BZD: benzodiazepine; CI: confidence interval; mo: months; REF: reference
\(^a\)Young people aged 10-29 years with an insomnia or unspecific sleep disorder diagnosis
\(^b\)Weighted outcome counts displayed for adjusted analyses
eFigure 1. Study Flow Diagram

- Young people aged 10-29 years with benzodiazepine or alternative sleep medication prescription, 2010-2018, N=2,664,947
- New use period of benzodiazepine or alternative sleep medication (all medications and clonidine in washout), N=1,467,632
- Recent (30 day) diagnosis of insomnia or unspecified sleep disorder, N=100,378 (7%)
  - Sequential Exclusions:
    - Contraindication or epilepsy diagnosis (n=5,810, 6%)
    - Combination treatment (n=59, <1%)
    - Trazodone new users with >150 mg/day (n=1,691, 2%)
    - Multiple drugs initiated at index (n=3,028, 3%)
- Full cohort, N=89,790 (90%)
  - Benzodiazepine new users: 23,084 (26%)
  - Alternative sleep medication new users: 66,706 (74%)
    - Trazodone: 27,815 (31%)
    - Hydroxyzine: 10,929 (12%)
    - Z-drug: 27,962 (31%)

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eFigure 2. Survival Curves of Drug Overdose by Initial Treatment: BZD vs Alternative Sleep Medications
A) intention-to-treat analysis and B) as-treated analysis censoring at treatment discontinuation

A) Intention-to-treat

B) As-treated
**eFigure 3.** Sensitivity Analysis of Residual Confounding (Rule Out Approach): Example for RR=1.44 and RR=1.25 assuming unmeasured confounder prevalence at 40%\(^a,b\)

ARR: Observed relative risk; OR\(_{EC}\): Odds ratio between treatment status (benzodiazepine vs. comparator sleep medication) and unmeasured confounder prevalence; RR\(_{CD}\): Association between unmeasured confounder and the study outcome (drug overdose within 6 months).

\(^a\)ARR=1.44 corresponds to the adjusted effect estimate from the primary as-treated analysis and ARR=1.25 corresponds to the adjusted effect estimate from the primary intention-to-treat analysis.

\(^b\)The area to the upper right of each curved line represents the combinations of OR\(_{EC}\) and RR\(_{CD}\) in which confounding by an unmeasured factor would be strong enough to move the point estimate to null (RR=1.00) or below null. The area to the lower-left of each curved line representations the combinations of OR\(_{EC}\) and RR\(_{CD}\) in which the point estimate would remain above null (RR>1.00).

\(^c\)Figure adapted from Schneeweiss S. Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics. *Pharmacoepidemiol Drug Safety*, 2006;15:291-303.