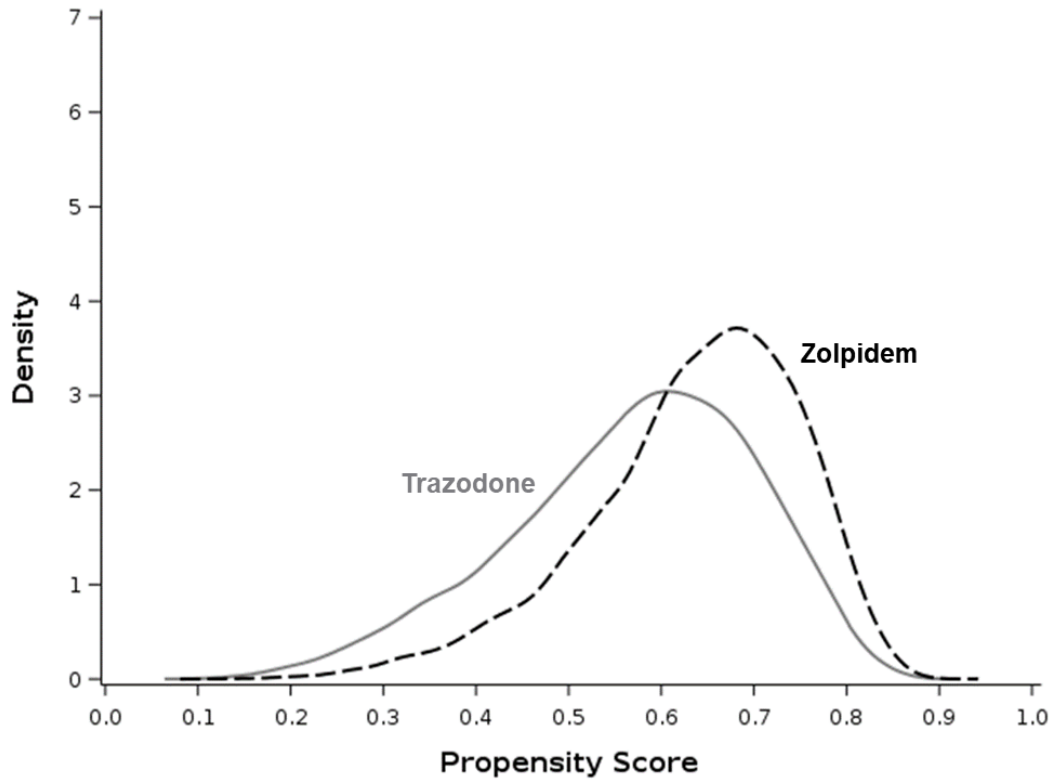


## SUPPLEMENTAL MATERIAL

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## SUPPLEMENTAL FIGURES

### Supplemental Figure 1. Propensity score distribution



The black dashed line is the propensity score distribution for zolpidem initiators and the gray solid line is the propensity score distribution for trazodone initiators.

## SUPPLEMENTAL TABLES

**Supplemental Table 1. Starting doses of zolpidem and trazodone outside of the recommended range for insomnia management**

<b>Medication</b>	<b>Doses outside the recommended range</b>
<b>Zolpidem</b>	
Regular release tablets	> 10 mg/day
Controlled release tablets	> 12.5 mg/day
Sublingual tablets for sleep initiation	> 10 mg/day
Sublingual tablets for middle of the night awakening	> 3.5 mg/day
Oral spray	> 10 mg/day
<b>Trazodone</b>	> 100 mg/day

Abbreviations: mg, milligram.

## Supplemental Table 2. Outcome definitions

Outcome	Specification
Fall-related fracture ( <i>primary outcome</i> )	An inpatient hospital admission for a fall-related fracture defined as: <ul style="list-style-type: none"><li>○ The presence of an ICD-9 <u>or</u> ICD-10 discharge diagnosis code for fracture located in <u>any</u> billing position<sup>a</sup></li></ul> <p style="text-align: center;"><i>PLUS</i></p> <ul style="list-style-type: none"><li>○ The presence of an external cause of injury ICD-9 or ICD-10 discharge diagnosis code for fall located in any billing position<sup>a</sup></li></ul>
Fracture ( <i>alternative outcome</i> )	An inpatient hospital admission for fracture defined as: <ul style="list-style-type: none"><li>○ The presence of an ICD-9 <u>or</u> ICD-10 discharge diagnosis code for fracture located in <u>any</u> billing position<sup>a</sup></li></ul>

<sup>a</sup> Supplemental Table 3 lists all applicable ICD-9 and ICD-10 codes.

Abbreviations: ICD-9, International Classification of Diseases, 9<sup>th</sup> Revision; ICD-10, International Classification of Diseases, 10<sup>th</sup> Revision.

### Supplemental Table 3. ICD-9/10 diagnosis codes used to identify outcome events

#### All-cause fracture

**ICD-9 codes:** 800-829

**ICD-10 codes:** S02.0\*\*A, S02.0\*\*B, S02.1\*\*A, S02.1\*\*B, S02.2\*\*A, S02.2\*\*B, S02.3\*\*A, S02.3\*\*B, S02.4\*\*A, S02.4\*\*B, S02.5\*\*A, S02.5\*\*B, S02.6\*\*A, S02.6\*\*B, S02.8\*\*A, S02.8\*\*B, S02.9\*\*A, S02.9\*\*B, S12.0\*\*A, S12.0\*\*B, S12.1\*\*A, S12.1\*\*B, S12.2\*\*A, S12.2\*\*B, S12.3\*\*A, S12.3\*\*B, S12.4\*\*A, S12.4\*\*B, S12.5\*\*A, S12.5\*\*B, S12.6\*\*A, S12.6\*\*B, S12.8\*\*A, S12.9\*\*A, S22.0\*\*A, S22.0\*\*B, S22.2\*\*A, S22.2\*\*B, S22.3\*\*A, S22.3\*\*B, S22.4\*\*A, S22.4\*\*B, S22.5\*\*A, S22.5\*\*B, S22.9\*\*A, S22.9\*\*B, S32.0\*\*A, S32.0\*\*B, S32.1\*\*A, S32.1\*\*B, S32.2\*\*A, S32.2\*\*B, S32.3\*\*A, S32.3\*\*B, S32.4\*\*A, S32.4\*\*B, S32.5\*\*A, S32.5\*\*B, S32.6\*\*A, S32.6\*\*B, S32.8\*\*A, S32.8\*\*B, S32.9\*\*A, S32.9\*\*B, S42.0\*\*A, S42.0\*\*B, S42.1\*\*A, S42.1\*\*B, S42.2\*\*A, S42.2\*\*B, S42.3\*\*A, S42.3\*\*B, S42.4\*\*A, S42.9\*\*A, S42.9\*\*B, S49.0\*\*A, S49.1\*\*A, S52.0\*\*A, S52.0\*\*B, S52.0\*\*C, S52.1\*\*A, S52.1\*\*B, S52.1\*\*C, S52.2\*\*A, S52.2\*\*B, S52.2\*\*C, S52.3\*\*A, S52.3\*\*B, S52.3\*\*C, S52.5\*\*A, S52.5\*\*B, S52.5\*\*C, S52.6\*\*A, S52.6\*\*B, S52.6\*\*C, S52.9\*\*A, S52.9\*\*B, S52.9\*\*C, S59.0\*\*A, S59.1\*\*A, S59.2\*\*A, S62.0\*\*A, S62.0\*\*B, S62.1\*\*A, S62.1\*\*B, S62.2\*\*A, S62.2\*\*B, S62.3\*\*A, S62.3\*\*B, S62.5\*\*A, S62.5\*\*B, S62.6\*\*A, S62.6\*\*B, S62.9\*\*A, S62.9\*\*B, S72.0\*\*A, S72.0\*\*B, S72.0\*\*C, S72.1\*\*A, S72.1\*\*B, S72.1\*\*C, S72.2\*\*A, S72.2\*\*B, S72.2\*\*C, S72.3\*\*A, S72.3\*\*B, S72.3\*\*C, S72.4\*\*A, S72.4\*\*B, S72.4\*\*C, S72.8\*\*A, S72.8\*\*B, S72.8\*\*C, S72.9\*\*A, S72.9\*\*B, S72.9\*\*C, S79.0\*\*A, S79.1\*\*A, S82.0\*\*A, S82.0\*\*B, S82.0\*\*C, S82.1\*\*A, S82.1\*\*B, S82.1\*\*C, S82.2\*\*A, S82.2\*\*B, S82.2\*\*C, S82.3\*\*A, S82.3\*\*B, S82.3\*\*C, S82.4\*\*A, S82.4\*\*B, S82.4\*\*C, S82.5\*\*A, S82.5\*\*B, S82.5\*\*C, S82.6\*\*A, S82.6\*\*B, S82.6\*\*C, S82.8\*\*A, S82.8\*\*B, S82.8\*\*C, S82.9\*\*A, S82.9\*\*B, S82.9\*\*C, S89.0\*\*A, S89.1\*\*A, S89.2\*\*A, S89.3\*\*A, S92.0\*\*A, S92.0\*\*B, S92.1\*\*A, S92.1\*\*B, S92.2\*\*A, S92.2\*\*B, S92.3\*\*A, S92.3\*\*B, S92.4\*\*A, S92.4\*\*B, S92.5\*\*A, S92.5\*\*B, S92.8\*\*A, S92.8\*\*B, S92.9\*\*A, S92.9\*\*B, S99.0\*\*A, S99.0\*\*B, S99.1\*\*A, S99.1\*\*B, S99.2\*\*A, S99.2\*\*B

#### Fall

**ICD-9 codes:** E880-E888

**ICD-10 codes:** V00, W00-W19

Specified three-digit ICD-9 diagnosis code categories include all existing 4th and 5th digit diagnosis codes, and specified four-digit ICD-9 diagnosis code categories include all existing 5th digit diagnosis codes. Specified three-digit ICD-10 diagnosis code categories include all existing 4th, 5<sup>th</sup>, 6<sup>th</sup>, and 7th digit diagnosis codes. For the specified seven-digit ICD-10 codes, the \* indicates that all existing 4<sup>th</sup> and 5<sup>th</sup> digit code combinations were considered.

**Abbreviations:** ICD-9, International Classification of Diseases, 9<sup>th</sup> Revision; ICD-10, International Classification of Diseases, 10<sup>th</sup> Revision.

**Supplemental Table 4. ICD-9/10 diagnosis codes and HCPCS procedure codes used to identify relevant comorbid conditions and frailty indicators**

Comorbid conditions	
Comorbidity	Diagnosis codes
Anxiety	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 300.0, 309.21, 309.24, 309.28</li> <li>○ ICD-10 codes: F41, F43.22, F43.23, F93.0</li> </ul>
Bipolar disorder	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 296.0, 296.4–296.8</li> <li>○ ICD-10 codes: F30, F31, F32.89</li> </ul>
Delusional disorder	<ul style="list-style-type: none"> <li>○ ICD-9 code: 297</li> <li>○ ICD-10 codes: F22, F23, F24</li> </ul>
Dementia	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 331.0–331.2, 331.7, 331.82, 290.0–290.4, 294.0–294.2, 797</li> <li>○ ICD-10 codes: F01.5, F02.8, F03.9, F04, F05, G13.2, G13.8, G30, G31.0–G31.2, G31.83, G91.4, G94, R41.81, R54</li> </ul>
Depression	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 296.2, 296.3, 296.5, 296.6, 296.82, 300.4, 309.0, 309.1, 309.28, 311</li> <li>○ ICD-10 codes: F31.30–F31.32, F31.4–F31.6, F31.75–F31.78, F32.0–F32.5, F32.89, F32.9, F33.0–F33.9, F34.1, F43.21, F43.23</li> </ul>
Insomnia	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 307.41, 307.42, 327.0, 780.51, 780.52</li> <li>○ ICD-10 codes: F51.0, G47.00, G47.0</li> </ul>
Personality disorder	<ul style="list-style-type: none"> <li>○ ICD-9 code: 301</li> <li>○ ICD-10 codes: F21, F34.0, F34.1, F60, F68.10, F68.12, F68.13, F69</li> </ul>
Schizophrenia	<ul style="list-style-type: none"> <li>○ ICD-9 code: 295</li> <li>○ ICD-10 codes: F20, F25</li> </ul>
Arrhythmia	<ul style="list-style-type: none"> <li>○ ICD-9 code: 427</li> <li>○ ICD-10 codes: I46–I49</li> </ul>
Conduction disorder	<ul style="list-style-type: none"> <li>○ ICD-9 code: 426</li> <li>○ ICD-10 codes: I44–I45</li> </ul>
Dyslipidemia	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 272.0–272.2, 272.4</li> <li>○ ICD-10 codes: E78.0, E78.1, E78.2, E78.4, E78.5</li> </ul>
Heart failure	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 398.91, 402.x1, 404.x1, 404.x3, 428</li> <li>○ ICD-10 codes: I09.81, I11.0, I13.0, I50</li> </ul>
Hypertension	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 401–405</li> <li>○ ICD-10 codes: I10–I16</li> </ul>
Ischemic heart disease	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 410–414</li> <li>○ ICD-10 codes: I20–I25</li> </ul>
Peripheral arterial disease	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 250.7, 440.2–440.9, 443.1, 443.22, 443.81, 443.89, 443.9, 444.22, 444.81, 445.02</li> <li>○ ICD-10 codes: E10.5, E11.5, E13.5, I70.2–I70.9, I73.1, I73.89, I73.9, I74.3–I74.5, I75.02, I77.72, I79.1, I79.8</li> </ul>
Stroke	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 430–438</li> <li>○ ICD-10 codes: G45–G46, I60–I69</li> </ul>
Valvular disease	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 394–397, 424.0–424.3</li> <li>○ ICD-10 codes: I05–I08, I09.1, I34–I37</li> </ul>

Cardiac pacemaker	<ul style="list-style-type: none"> <li>○ ICD-9 codes: V45.01</li> <li>○ ICD-10 codes: Z95.0</li> </ul>
Implantable cardiac defibrillator	<ul style="list-style-type: none"> <li>○ ICD-9 codes: V45.02</li> <li>○ ICD-10 codes: Z95.810</li> </ul>
Asthma or COPD	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 491–494, 496</li> <li>○ ICD-10 codes: J41–J45, J47</li> </ul>
Cancer	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 140–209</li> <li>○ ICD-10 codes: C00–C96, C7A</li> </ul>
Diabetes	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 250</li> <li>○ ICD-10 codes: E10, E11, E13</li> </ul>
Gastrointestinal bleed	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 531.0, 531.2, 531.4, 531.6, 532.0, 532.2, 532.4, 532.6, 533.0, 533.2, 533.4, 533.6, 534.0, 534.2, 534.4, 534.6, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 578.0, 578.1, 578.9</li> <li>○ ICD-10 codes: K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K55.21, K57.01, K57.11, K57.13, K57.21, K57.31, K57.33, K57.41, K57.51, K57.53, K57.81, K57.91, K57.93, K62.5, K92.0, K92.1, K92.2</li> </ul>
Liver disease	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 571</li> <li>○ ICD-10 codes: K70–K76</li> </ul>
Lower limb amputation	<ul style="list-style-type: none"> <li>○ ICD-9 code: V49.7</li> <li>○ ICD-10 codes: Z89.4–Z89.6, Z89.9</li> </ul>
Sleep apnea	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 327.2, 780.51, 780.53, 780.57</li> <li>○ ICD-10 codes: G47.3</li> </ul>
Alcohol abuse or dependence	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 303, 305.0</li> <li>○ ICD-10 codes: F10.10, F10.11, F10.120, F10.129, F10.20, F10.21, F10.220, F10.229</li> </ul>
Drug abuse or dependence	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 304, 305.2–305.9</li> <li>○ ICD-10 codes: F11.10, F11.11, F11.120, F11.129, F11.20–F11.25, F11.28, F11.29, F11.90, F12.10, F12.11, F12.20–F12.25, F12.28, F12.29, F13.10, F13.11, F13.120, F13.20–F13.29, F13.90, F14.10, F14.11, F14.120, F14.20–F14.25, F14.28, F14.29, F14.90, F15.10, F15.11, F15.120, F15.20–F15.25, F15.28, F15.29, F15.90, F16.10, F16.11, F16.120, F16.20–F16.25, F16.28, F16.29, F16.90, F18.10, F18.11, F18.120, F18.20–F18.25, F18.27, F18.28, F18.29, F18.90, F19.10, F19.11, F19.120, F19.20–F19.29, F19.90, F55</li> </ul>
Tobacco use	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 305.1</li> <li>○ ICD-10 codes: F17.200, F17.201, F17.210, F17.211, F17.220, F17.221, F17.290, F17.291</li> </ul>
History of non-compliance	<ul style="list-style-type: none"> <li>○ ICD-9 codes: V15.81, V45.12</li> <li>○ ICD-10 codes: Z91.1</li> </ul>

### Frailty indicators associated with mobility impairment and falls

Frailty indicator	Diagnosis and procedure codes
Abnormal gait	<ul style="list-style-type: none"> <li>○ ICD-9 code: 781.2</li> <li>○ ICD-10 codes: R26.0, R26.1, R26.81, R26.89, R26.9</li> </ul>

Abnormal loss of weight or underweight	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 783.21, 783.22</li> <li>○ ICD-10 codes: R63.4, R63.6</li> </ul>
Cachexia	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 799.4</li> <li>○ ICD-10 code: R64</li> </ul>
Debility	<ul style="list-style-type: none"> <li>○ ICD-9 code: 799.3</li> <li>○ ICD-10 code: R53.81</li> </ul>
Difficulty walking	<ul style="list-style-type: none"> <li>○ ICD-9 code: 719.7</li> <li>○ ICD-10 code: R26.2</li> </ul>
Failure to thrive	<ul style="list-style-type: none"> <li>○ ICD-9 code: 783.7</li> <li>○ ICD-10 code: R62.7</li> </ul>
Fall history	<ul style="list-style-type: none"> <li>○ ICD-9 code: V15.88</li> <li>○ ICD-10 code: Z91.81</li> </ul>
Malaise or fatigue	<ul style="list-style-type: none"> <li>○ ICD-9 code: 780.7</li> <li>○ ICD-10 codes: G93.3, R53</li> </ul>
Muscular wasting or disease atrophy	<ul style="list-style-type: none"> <li>○ ICD-9 code: 728.2</li> <li>○ ICD-10 codes: M62.50–M62.59</li> </ul>
Muscle weakness	<ul style="list-style-type: none"> <li>○ ICD-9 code: 728.87</li> <li>○ ICD-10 codes: M62.81</li> </ul>
Pressure ulcers	<ul style="list-style-type: none"> <li>○ ICD-9 codes: 707.0, 707.2</li> <li>○ ICD-10 codes: L89.000–L89.004, L89.009, L89.010–L89.014, L89.019, L89.020–L89.024, L89.029, L89.100–L89.104, L89.109, L89.110–L89.114, L89.119, L89.120–L89.124, L89.129, L89.130–L89.134, L89.139, L89.140–L89.144, L89.149, L89.150–L89.154, L89.159, L89.200–L89.204, L89.209, L89.210–L89.214, L89.219, L89.220–L89.224, L89.229, L89.300–L89.304, L89.309, L89.310–L89.314, L89.319, L89.320–L89.324, L89.329, L89.40–L89.45, L89.500–L89.504, L89.509, L89.510–L89.514, L89.519, L89.520–L89.520, L89.529, L89.600–L89.604, L89.609, L89.610–L89.614, L89.619, L89.620–L89.624, L89.629, L89.810–L89.814, L89.819, L89.890–L89.894, L89.899, L89.90–L89.95</li> </ul>
Senility	<ul style="list-style-type: none"> <li>○ ICD-9 code: 797</li> <li>○ ICD-10 codes: R41.81, R54</li> </ul>
Using durable medical equipment (cane, walker, bath equipment, or commode)	<ul style="list-style-type: none"> <li>○ HCPCS codes: E0100, E0105, E0130, E0135, E0140, E0141, E0143, E0144, E0147–E0149, E0160–E0171</li> </ul>
Using nursing or personal healthcare services	<ul style="list-style-type: none"> <li>○ HCPCS codes: T1000–T1005, T1019–T1022, T1030, T1031</li> </ul>

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Specified three-digit ICD-9 diagnosis code categories included all existing 4<sup>th</sup> and 5<sup>th</sup> digit diagnosis codes and specified four-digit ICD-9 diagnosis code categories included all existing 5<sup>th</sup> digit diagnosis codes. Specified three-digit ICD-10 diagnosis codes include all existing 4<sup>th</sup>, 5<sup>th</sup>, 6<sup>th</sup> and 7<sup>th</sup> digit diagnosis codes; specified four-digit ICD-10 diagnosis codes include all existing 5<sup>th</sup>, 6<sup>th</sup> and 7<sup>th</sup> digit diagnosis codes; specified five-digit ICD-10 diagnosis codes include all existing 6<sup>th</sup> and 7<sup>th</sup> digit diagnosis codes; and specified six-digit ICD-10 diagnosis codes include all existing 7<sup>th</sup> digit codes.

Abbreviations: COPD, chronic obstructive pulmonary disease; HCPCS, Healthcare Common Procedure Coding System; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision.



## Supplemental Table 5. Lists of relevant medications

### CYP 3A4 inhibitors<sup>a</sup>

Amiodarone, amprenavir, aprepitant, atazanavir, chloramphenicol, clarithromycin, conivaptan, cyclosporine, darunavir, dasatinib, delavirdine, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosamprenavir, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lapatinib, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, quinupristin, saquinavir, tamoxifen, telithromycin, troleandomycin, verapamil, voriconazole

### Medications with strong anticholinergic properties

Disopyramide, amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, nortriptyline, paroxetine, protriptyline, trimipramine, prochlorperazine, promethazine, brompheniramine, carbinoxamine, chlorpheniramine, clemastine, cyproheptadine, dexbrompheniramine, dexchlorpheniramine, dimenhydrinate, diphenhydramine, doxylamine, hydroxyzine, meclizine, clidinium/chlordiazepoxide, dicyclomine, hyoscyamine, methscopolamine, propantheline, pyrilamine, triprolidine, darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, trospium, benztropine, trihexyphenidyl, chlorpromazine, clozapine, loxapine, olanzapine, perphenazine, thioridazine, trifluoperazine, atropine, belladonna alkaloids, scopolamine, cyclobenzaprine, orphenadrine

### Antidepressants

Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, venlafaxine, desvenlafaxine, duloxetine, milnacipran, levomilnacipran, bupropion, mirtazapine, nefazodone, trazodone, vilazodone, vortioxetine, amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine, iproclazide, iproniazid, isocarboxazid, moclobemide, phenelzine, tranylcypromine, selegiline

### Selective serotonin reuptake inhibitors

Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline

### Serotonin norepinephrine reuptake inhibitors

Desvenlafaxine, duloxetine, levomilnacipran, milnacipran, venlafaxine

### Tricyclic antidepressants

Amitriptyline, amoxapine, clomipramine, desipramine, doxepin, imipramine, maprotiline, nortriptyline, protriptyline, trimipramine

### Benzodiazepines

Alprazolam, chlordiazepoxide, clobazam, clonazepam, clorazepate, diazepam, estazolam, flurazepam, halazepam, lorazepam, midazolam, oxazepam, prazepam, quazepam, temazepam, triazolam

### Typical antipsychotics

Chlorpromazine, fluphenazine, haloperidol, loxapine, perphenazine, pimozide, thioridazine, thiothixene, trifluoperazine

### Atypical antipsychotics

Aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, pimavanserin, quetiapine, risperidone, ziprasidone

### Antiepileptics (non-benzodiazepines)

Brivaracetam, cannabidiol, carbamazepine, divalproex, eslicarbazepine, ethosuximide, ethotoin, felbamate, fosphenytoin, gabapentin, lacosamide, lamotrigine, levetiracetam, mephenytoin, mephobarbital, oxcarbazepine, perampanel, phenacemide, phenobarbital, phenytoin, pregabalin, primadone, rufinamide, tiagabine, topiramate, valproate, valproic acid, vigabatrin, zonisamide

### Gabapentinoids

Gabapentin, pregabalin

### Acetylcholinesterase inhibitors

Donepezil, galantamine, rivastigmine

**Opioids**

Alfentanil, buprenorphine, butorphanol, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levomethadyl, levorphanol, meperidine, methadone, morphine, nalbuphine, oxycodone, oxymorphone, pentazocine, propoxyphene, remifentanil, sufentanil, tapentadol, tramadol

**Muscle relaxants**

Baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, tizanidine

**Steroids (oral glucocorticoids)**

Hydrocortisone, cortisone, prednisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone

**Calcimimetic**

Cinacalcet

**Alpha blockers**

Alfuzosin, doxazosin, prazosin, silodosin, terazosin

**Angiotensin converting enzyme inhibitors**

Benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril,trandolapril

**Angiotensin II receptor blockers**

Azilsartan, candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan

**Beta blockers (excluding eye drops)**

Acebutolol, atenolol, betaxolol, bisoprolol, carteolol, carvedilol, esmolol, labetalol, metoprolol, nadolol, nebivolol, oxprenolol, penbutolol, pindolol, propranolol, sotalol, timolol

**Calcium channel blocker**

Amlodipine, clevidipine, diltiazem, felodipine, isradipine, levamlodipine, nicardipine, nifedipine, nimodipine, nisoldipine, verapamil

**Central alpha agonists**

Clonidine, methyl dopa, guanabenz, guanfacine

**Diuretics**

Bumetanide, ethacrynic acid, furosemide, torsemide, bendroflumethiazide, chlorothiazide, hydrochlorothiazide, methyclothiazide, polythiazide, chlorthalidone, indapamide, metolazone, amiloride, triamterene, spironolactone, eplerenone, acetazolamide

**Vasodilators**

Hydralazine, minoxidil

**Long-acting nitrates (oral & transdermal only)**

Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate

**Alpha-1 agonists**

Midodrine

<sup>a</sup> Zolpidem and trazodone are major CYP 3A4 substrates. We obtained lists of CYP 3A4 inhibitors on February 14, 2020 using the Flockhart Table website (<https://drug-interactions.medicine.iu.edu/MainTable.aspx>) and Pharmacy Times website (<https://www.pharmacytimes.com>).

Abbreviations: CYP, cytochrome P450.

**Supplemental Table 6. Definitions of lower and higher zolpidem doses**

<b>Zolpidem formulation</b>	<b>Lower doses</b>	<b>Higher doses</b>
Regular release tablets	$\leq 5$ mg/day	$> 5$ mg/day
Controlled release tablets	$\leq 6.25$ mg/day	$> 6.25$ mg/day
Sublingual tablets for sleep initiation	$\leq 5$ mg/day	$> 5$ mg/day
Sublingual tablets for middle of the night awakening	$\leq 1.75$ mg/day	$> 1.75$ mg/day
Oral spray	$\leq 5$ mg/day	$> 5$ mg/day

Abbreviations: mg, milligram.

**Supplemental Table 7. Baseline characteristics of zolpidem and trazodone initiators**

Characteristic	Unweighted			Weighted		
	Zolpidem n = 18,941	Trazodone n = 12,114	Std diff <sup>a</sup>	Zolpidem n = 18,964	Trazodone n = 12,100	Std diff <sup>a</sup>
<b>Year of study medication initiation</b>						
2013	3,657 (19%)	1,596 (13%)	0.17	3,206 (17%)	2,037 (17%)	0.00
2014	6,264 (33%)	3,448 (28%)	0.10	5,936 (31%)	3,794 (31%)	0.00
2015	5,101 (27%)	3,482 (29%)	0.04	5,215 (28%)	3,323 (27%)	0.00
2016	3,919 (21%)	3,588 (30%)	0.21	4,607 (24%)	2,947 (24%)	0.00
<b>Month of study medication initiation</b>						
January	1,629 (9%)	873 (7%)	0.05	1,531 (8%)	983 (8%)	0.00
February	1,436 (8%)	819 (7%)	0.03	1,381 (7%)	875 (7%)	0.00
March	1,440 (8%)	970 (8%)	0.02	1,471 (8%)	937 (8%)	0.00
April	1,291 (7%)	933 (8%)	0.03	1,370 (7%)	873 (7%)	0.00
May	1,283 (7%)	785 (6%)	0.01	1,252 (7%)	803 (7%)	0.00
June	1,140 (6%)	861 (7%)	0.04	1,228 (6%)	783 (6%)	0.00
July	1,817 (10%)	1,061 (9%)	0.03	1,757 (9%)	1,113 (9%)	0.00
August	1,886 (10%)	1,137 (9%)	0.02	1,839 (10%)	1,172 (10%)	0.00
September	1,844 (10%)	1,183 (10%)	0.00	1,838 (10%)	1,166 (10%)	0.00
October	1,881 (10%)	1,214 (10%)	0.00	1,892 (10%)	1,208 (10%)	0.00
November	1,628 (9%)	1,110 (9%)	0.02	1,666 (9%)	1,070 (9%)	0.00
December	1,666 (9%)	1,168 (10%)	0.03	1,740 (9%)	1,118 (9%)	0.00
<b>Age (years)</b>	59 ± 14	61 ± 15	0.09	60 ± 15	60 ± 15	0.00
<b>Female</b>	8,611 (45%)	5,740 (47%)	0.04	8,794 (46%)	5,620 (46%)	0.00
<b>Race</b>						
Black	7,415 (39%)	4,573 (38%)	0.03	7,291 (38%)	4,655 (38%)	0.00
White	10,420 (55%)	6,962 (57%)	0.05	10,642 (56%)	6,789 (56%)	0.00

Other	1,106 (6%)	579 (5%)	0.05	1,031 (5%)	656 (5%)	0.00
<b>Hispanic</b>	4,024 (21 %)	1,930 (16%)	0.15	3,639 (19%)	2,322 (19%)	0.00
<b>Low income subsidy</b>	14,700 (78%)	9,460 (78 %)	0.01	14,768 (78%)	9,427 (78%)	0.00
<b>Dialysis vintage (years)</b>	3.6 [1.7, 6.7]	3.4 [1.6, 6.3]	0.06	3.5 [1.6, 6.5]	3.5 [1.6, 6.5]	0.00
<b>Cause of dialysis-dependent kidney failure</b>						
Diabetes	8,589 (45%)	5,821 (48%)	0.05	8,814 (46%)	5,637 (47%)	0.00
Hypertension	5,746 (30%)	3,382 (28%)	0.05	5,567 (29 %)	3,544 (29%)	0.00
Glomerular disease	2,220 (12%)	1,287 (11%)	0.04	2,135 (11%)	1,365 (11%)	0.00
Other	2,386 (13%)	1,624 (13%)	0.02	2,448 (13%)	1,554 (13%)	0.00
<b>Anxiety</b>	4,019 (21%)	3,559 (29%)	0.19	4,654 (25%)	2,984 (25%)	0.00
<b>Bipolar disorder</b>	477 (3%)	571 (5%)	0.12	661 (3%)	414 (3%)	0.00
<b>Delusional disorder</b>	54 (0%)	88 (1%)	0.06	92 (0%)	57 (0%)	0.00
<b>Dementia</b>	838 (4%)	1,218 (10%)	0.22	1,268 (7%)	803 (7%)	0.00
<b>Depression</b>	4,738 (25%)	4,592 (38%)	0.28	5,748 (30%)	3,664 (30%)	0.00
<b>Insomnia</b>	2,669 (14%)	2,062 (17%)	0.08	2,899 (15%)	1,855 (15%)	0.00
<b>Personality disorder</b>	147 (1%)	201 (2%)	0.08	218 (1%)	135 (1%)	0.00
<b>Schizophrenia</b>	283 (1%)	345 (3%)	0.09	411 (2%)	255 (2%)	0.00
<b>Arrhythmia</b>	6,370 (34%)	4,262 (35%)	0.03	6,506 (34%)	4,146 (34%)	0.00
<b>Conduction disorder</b>	2,080 (11%)	1,615 (13 %)	0.07	2,280 (12%)	1,468 (12%)	0.00
<b>Dyslipidemia</b>	11,661 (62%)	7,686 (63%)	0.04	11,813 (62%)	7,546 (62%)	0.00
<b>Heart failure</b>	8,907 (47%)	6,128 (51%)	0.07	9,204 (49%)	5,882 (49%)	0.00
<b>Hypertension</b>	17,076 (90%)	11,146 (92 %)	0.07	17,243 (91%)	11,003 (91%)	0.00
<b>Ischemic heart disease</b>	9,137 (48%)	6,102 (50%)	0.04	9,302 (49%)	5,940 (49%)	0.00
<b>Peripheral artery disease</b>	6,652 (35%)	4,640 (38%)	0.07	6,894 (36%)	4,398 (36%)	0.00
<b>Stroke</b>	4,371 (23%)	3,341 (28%)	0.10	4,727 (25%)	3,020 (25%)	0.00
<b>Valvular disease</b>	4,576 (24%)	2,916 (24%)	0.00	4,596 (24%)	2,941 (24%)	0.00
<b>Cardiac pacemaker</b>	1,166 (6%)	735 (6%)	0.00	1,154 (6%)	735 (6%)	0.00

<b>Implantable cardiac defibrillator</b>	833 (4%)	480 (4%)	0.02	807 (4%)	517 (4%)	0.00
<b>Asthma or COPD</b>	6,032 (32%)	4,300 (35%)	0.08	6,335 (33%)	4,054 (34%)	0.00
<b>Cancer</b>	2,034 (11%)	1,288 (11%)	0.00	2,006 (11%)	1,272 (11%)	0.00
<b>Diabetes</b>	13,029 (67%)	8,649 (71%)	0.06	13,249 (70%)	8,456 (70%)	0.00
<b>GI bleed</b>	2,117 (11%)	1,538 (13%)	0.05	2,242 (12%)	1,434 (12%)	0.00
<b>Liver disease</b>	1,551 (8%)	980 (8%)	0.00	1,554 (8%)	988 (8%)	0.00
<b>History of lower limb amputation</b>	1,809 (10%)	1,402 (12%)	0.07	1,980 (10%)	1,260 (10%)	0.00
<b>Sleep apnea</b>	3,080 (16%)	2,112 (17%)	0.03	3,179 (17%)	2,037 (17%)	0.00
<b>Alcohol abuse or dependence</b>	427 (2%)	399 (3%)	0.06	503 (3%)	324 (3%)	0.00
<b>Drug abuse or dependence</b>	1,149 (6%)	988 (8%)	0.08	1,313 (7%)	835 (7%)	0.00
<b>Tobacco use</b>	2,995 (16%)	2,222 (18%)	0.07	3,208 (17%)	2,059 (17%)	0.00
<b>History of non-compliance</b>	2,614 (14%)	2,049 (17%)	0.09	2,860 (15%)	1,831 (15%)	0.00
<b>Number of frailty indicators<sup>b</sup></b>						
0 indicators	9,496 (50%)	5,137 (42%)	0.16	8,902 (47%)	5,665 (47%)	0.00
1 indicator	4,153 (22%)	2,528 (21%)	0.03	4,091 (22%)	2,622 (22%)	0.00
2 indicators	2,083 (11%)	1,478 (12%)	0.03	2,189 (12%)	1,401 (12%)	0.00
3 indicators	1,350 (7%)	1,048 (9%)	0.06	1,459 (8%)	927 (8%)	0.00
4 indicators	883 (5%)	885 (7%)	0.11	1,078 (6%)	690 (6%)	0.00
≥ 5 indicators	976 (5%)	1,038 (9%)	0.14	1,245 (7%)	795 (7%)	0.00
<b>Abnormality of gait</b>	2,516 (13%)	2,170 (18%)	0.13	2,869 (15%)	1,839 (15%)	0.00
<b>Abnormal loss of weight or underweight</b>	651 (3%)	462 (4%)	0.02	680 (4%)	434 (4%)	0.00
<b>Cachexia</b>	188 (1%)	166 (1%)	0.04	218 (1%)	136 (1%)	0.00
<b>Debility</b>	1,620 (9%)	1,563 (13%)	0.14	1,947 (10%)	1,247 (10%)	0.00
<b>Difficulty walking</b>	2,064 (11%)	1,908 (16%)	0.14	2,420 (13%)	1,535 (13%)	0.00
<b>Failure to thrive</b>	327 (2%)	302 (2%)	0.05	390 (2%)	253 (2%)	0.00
<b>Fall history</b>	1,065 (6%)	982 (8%)	0.10	1,262 (7%)	806 (7%)	0.00

<b>Malaise and fatigue</b>	6,025 (32%)	4,520 (37%)	0.12	6,456 (34%)	4,130 (34%)	0.00
<b>Muscular wasting and disease atrophy</b>	644 (3%)	594 (5%)	0.08	763 (4%)	489 (4%)	0.00
<b>Muscle weakness</b>	3,742 (20%)	3,287 (27%)	0.18	4,319 (23%)	2,753 (23%)	0.00
<b>Pressure ulcers</b>	1,584 (8%)	1,339 (11%)	0.09	1,804 (10%)	1,148 (9%)	0.00
<b>Senility</b>	82 (0%)	109 (1%)	0.06	120 (1%)	76 (1%)	0.00
<b>Using of durable medical equipment (e.g. cane, walker)</b>	962 (5%)	686 (6%)	0.03	1,012 (5%)	647 (5%)	0.00
<b>Using nursing or healthcare services</b>	< 11 (0%)	< 11 (0%)	0.00	< 11 (0%)	< 11 (0%)	0.00
<b>Use of <math>\geq 1</math> CYP 3A4 inhibitor<sup>c</sup></b>	1,986 (10%)	1,153 (10%)	0.03	1,940 (10%)	1,244 (10%)	0.00
<b>Use of <math>\geq 1</math> CNS-active medication<sup>d</sup></b>	9,022 (48%)	6,301 (52%)	0.09	9,429 (50%)	6,040 (50%)	0.00
<b>Use of <math>\geq 1</math> strong anticholinergic medication<sup>e</sup></b>	1,876 (10%)	1,305 (11%)	0.03	1,966 (10%)	1,254 (10%)	0.00
<b>Use of any antidepressant</b>	3,561 (19%)	3,030 (25%)	0.15	4,096 (22%)	2,615 (22%)	0.00
<b>SSRI use</b>	2,439 (13%)	2,091 (17%)	0.12	2,801 (15%)	1,786 (15%)	0.00
<b>SNRI use</b>	473 (2%)	404 (3%)	0.05	546 (3%)	344 (3%)	0.00
<b>TCA use</b>	418 (2%)	282 (2%)	0.01	436 (2%)	281 (2%)	0.00
<b>Benzodiazepine use</b>	2,445 (13%)	1,807 (15%)	0.06	2,625 (14%)	1,681 (14%)	0.00
<b>Typical antipsychotic use</b>	63 (0%)	83 (1%)	0.05	95 (1%)	59 (0%)	0.00
<b>Atypical antipsychotic use</b>	528 (3%)	604 (5%)	0.11	714 (4%)	447 (4%)	0.00
<b>Antiepileptic use</b>	3,486 (18%)	2,559 (21%)	0.07	3,714 (20%)	2,371 (20%)	0.00
<b>Gabapentinoid use</b>	2,779 (15%)	1,960 (16%)	0.04	2,923 (15%)	1,865 (15%)	0.00
<b>Acetylcholinesterase inhibitor use</b>	253 (1%)	261 (2%)	0.06	324 (2%)	201 (2%)	0.00
<b>Opioid use</b>	4,172 (22%)	2,542 (21%)	0.03	4,141 (22%)	2,673 (22%)	0.01
<b>Muscle relaxant use</b>	563 (3%)	356 (3%)	0.00	565 (3%)	370 (3%)	0.01
<b>Oral steroid use</b>	765 (4%)	448 (4%)	0.02	743 (4%)	477 (4%)	0.00
<b>Cinacalcet use</b>	3,969 (21%)	2,312 (19%)	0.05	3,842 (20%)	2,457 (20%)	0.00

<b>Alpha blocker use</b>	602 (3%)	402 (3%)	0.01	613 (3%)	397 (3%)	0.00
<b>ACE inhibitor use</b>	3,410 (18%)	2,029 (17%)	0.03	3,321 (18%)	2,129 (18%)	0.00
<b>ARB use</b>	2,381 (13%)	1,297 (11%)	0.06	2,253 (12%)	1,442 (12%)	0.00
<b>Beta blocker use</b>	8,652 (46%)	5,239 (43%)	0.05	8,513 (45%)	5,464 (45%)	0.01
<b>Calcium channel blocker use</b>	6,615 (35%)	3,928 (32%)	0.05	6,465 (34%)	4,126 (34%)	0.00
<b>Central alpha agonist use</b>	2,711 (14%)	1,477 (12%)	0.06	2,571 (14%)	1,654 (14%)	0.00
<b>Diuretic use</b>	1,989 (11%)	1,295 (11%)	0.01	2,020 (11%)	1,293 (11%)	0.00
<b>Vasodilator use</b>	3,035 (16%)	1,718 (14%)	0.05	2,914 (15%)	1,868 (15%)	0.00
<b>Long-acting nitrate</b>	1,640 (9%)	1,102 (9%)	0.02	1,691 (9%)	1,076 (9%)	0.00
<b>Midodrine use</b>	765 (4%)	493 (4%)	0.00	777 (4%)	498 (4%)	0.00
<b>Number of baseline hospital admissions</b>	1 [0, 2]	1 [0, 2]	0.09	1 [0, 2]	1 [0, 2]	0.00
<b>Number of baseline ED visits</b>	1 [0, 3]	2 [0, 4]	0.14	1 [0, 3]	1 [0, 3]	0.00
<b>Hospitalized in the last 30 days of baseline</b>	4,383 (23%)	3,073 (25%)	0.05	4,553 (24%)	2,915 (24%)	0.00
<b>SNF admission during baseline</b>	2,211 (12%)	2,341 (19%)	0.21	2,785 (15%)	1,775 (15%)	0.00
<b>Psychotherapy visit during baseline</b>	994 (5 %)	1,178 (10%)	0.17	1,358 (7%)	857 (7%)	0.00

Values are given as number (%) for categorical variables and as mean  $\pm$  standard deviation or median [quartile 1, quartile 3] for continuous variables. All covariates were measured during the 180-day baseline period. The weighted cohort is the pseudo-population generated by the inverse probability of treatment weighting.

<sup>a</sup> A std diff > 0.10 represents meaningful imbalance between groups.

<sup>b</sup> A total of 14 validated frailty indicators associated with mobility impairment and falls were considered. Frailty indicators included abnormal gait, abnormal loss of weight or underweight, cachexia, debility, difficulty walking, failure to thrive, fall history, malaise or fatigue, muscular wasting or disease atrophy, muscle weakness, pressure ulcers, senility, using durable medical equipment (cane, walker, bath equipment, or commode), and using nursing or healthcare services.

<sup>c</sup> Zolpidem and trazodone are major CYP 3A4 substrates. Lists of relevant CYP 3A4 inhibitors are provided in Supplemental Table 5.

<sup>d</sup> CNS-active medications included antidepressants (selective serotonin re-uptake inhibitors, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants), antipsychotics, benzodiazepines, antiepileptics, and opioids. These medications are associated with a heightened risk of fall according to the 2019 Beers Criteria.

<sup>e</sup> Medications with strong anticholinergic properties were identified using the 2019 Beers Criteria. These medications are associated with a heightened risk of fall.

**Abbreviations:** ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease; CNS, central nervous system; CYP, cytochrome P450; ED, emergency department; GI, gastrointestinal; SNF, skilled nursing facility; SNRI, serotonin-norepinephrine re-uptake inhibitor; SSRI, selective serotonin re-uptake inhibitor; std diff, standardized difference; TCA, tricyclic antidepressant.



**Supplemental Table 8. Association between zolpidem vs. trazodone initiation and 30-day fall-related fracture risk using an intention-to-treat analytic approach**

Fall-related fracture – primary outcome							
Medication	n	No. of events	Rate per 1,000 p-y	Crude HR (95% CI)	Weighted HR (95% CI)	Crude RD (95% CI)	Weighted RD (95% CI)
Trazodone	12,114	33	34.1	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	18,941	68	44.6	1.31 (0.87, 1.99)	1.71 (1.11, 2.63)	0.09% (0.00%, 0.20%)	0.17% (0.07%, 0.29%)

An intention-to-treat analytic approach was used in all analyses. Fine and Gray proportional subdistribution hazards models were used to estimate 30-day HRs and the Aalen-Johansen estimator was used to estimate 30-day RDs. Death was treated as a competing event. Inverse probability of treatment weighting was used for confounding control.

Abbreviations: CI, confidence interval; HR, hazard ratio; No., number; p-y, person-year; RD, risk difference; ref., referent.

**Supplemental Table 9. Association between zolpidem vs. trazodone initiation and 30-day fall-related fracture risk within clinically relevant subgroups using an intention-to-treat analytic approach**

<b>Age subgroups</b>							
<b>Age &lt; 60 years</b>							
<b>Medication</b>	<b>n</b>	<b>No. of events</b>	<b>Rate per 1,000 p-y</b>	<b>Crude HR (95% CI)</b>	<b>Weighted HR (95% CI)</b>	<b>Crude RD (95% CI)</b>	<b>Weighted RD (95% CI)</b>
Trazodone	5,497	< 11	18.1	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	9,333	15	19.9	1.10 (0.47, 2.59)	1.28 (0.56, 2.93)	0.02% (-0.11%, 0.13%)	0.04% (-0.08%, 0.16%)
<b>Age ≥ 60 years</b>							
<b>Medication</b>	<b>n</b>	<b>No. of events</b>	<b>Rate per 1,000 p-y</b>	<b>Crude HR (95% CI)</b>	<b>Weighted HR (95% CI)</b>	<b>Crude RD (95% CI)</b>	<b>Weighted RD (95% CI)</b>
Trazodone	6,617	25	47.4	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	9,608	53	68.7	1.46 (0.90, 2.34)	1.89 (1.14, 3.12)	0.17% (0.01%, 0.38%)	0.29% (0.12%, 0.49%)
<b>Sex subgroups</b>							
<b>Male</b>							
<b>Medication</b>	<b>n</b>	<b>No. of events</b>	<b>Rate per 1,000 p-y</b>	<b>Crude HR (95% CI)</b>	<b>Weighted HR (95% CI)</b>	<b>Crude RD (95% CI)</b>	<b>Weighted RD (95% CI)</b>
Trazodone	6,374	11	21.6	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	10,330	27	32.5	1.51 (0.75, 3.04)	2.29 (1.10, 4.81)	0.09% (-0.03%, 0.21%)	0.18% (0.07%, 0.31%)
<b>Female</b>							
<b>Medication</b>	<b>n</b>	<b>No. of events</b>	<b>Rate per 1,000 p-y</b>	<b>Crude HR (95% CI)</b>	<b>Weighted HR (95% CI)</b>	<b>Crude RD (95% CI)</b>	<b>Weighted RD (95% CI)</b>
Trazodone	5,740	22	47.8	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	8,611	41	59.1	1.24 (0.73, 2.08)	1.45 (0.85, 2.46)	0.09% (-0.09%, 0.27%)	0.16% (-0.03%, 0.35%)

### Frailty indicator subgroups

#### 0 frailty indicators

Medication	n	No. of events	Rate per 1,000 p-y	Crude HR (95% CI)	Weighted HR (95% CI)	Crude RD (95% CI)	Weighted RD (95% CI)
Trazodone	5,137	12	29.0	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	9,496	18	23.5	0.81 (0.39, 1.68)	0.91 (0.43, 1.91)	-0.04% (-0.18%, 0.09%)	-0.02% (-0.15%, 0.10%)

#### 1 frailty indicator

Medication	n	No. of events	Rate per 1,000 p-y	Crude HR (95% CI)	Weighted HR (95% CI)	Crude RD (95% CI)	Weighted RD (95% CI)
Trazodone	2,528	< 11	29.6	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	4,153	15	44.8	1.51 (0.59, 3.90)	1.89 (0.74, 4.81)	0.12% (-0.09%, 0.33%)	0.20% (-0.03%, 0.47%)

#### ≥ 2 frailty indicators

Medication	n	No. of events	Rate per 1,000 p-y	Crude HR (95% CI)	Weighted HR (95% CI)	Crude RD (95% CI)	Weighted RD (95% CI)
Trazodone	4,449	15	42.5	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	5,292	35	82.9	1.96 (1.07, 3.58)	2.50 (1.28, 4.89)	0.33% (0.07%, 0.56%)	0.43% (0.19%, 0.68%)

### CNS active med subgroups

#### Using 0 CNS-active medications

Medication	n	No. of events	Rate per 1,000 p-y	Crude HR (95% CI)	Weighted HR (95% CI)	Crude RD (95% CI)	Weighted RD (95% CI)
Trazodone	5,813	16	34.4	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	9,919	26	32.6	0.95 (0.51, 1.77)	1.28 (0.67, 2.42)	-0.01% (-0.15%, 0.13%)	0.07% (-0.06%, 0.21%)

**Using ≥ 1 CNS-active medication**

<b>Medication</b>	<b>n</b>	<b>No. of events</b>	<b>Rate per 1,000 p-y</b>	<b>Crude HR (95% CI)</b>	<b>Weighted HR (95% CI)</b>	<b>Crude RD (95% CI)</b>	<b>Weighted RD (95% CI)</b>
Trazodone	6,301	17	33.7	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	9,022	42	57.9	1.72 (0.98, 3.02)	2.15 (1.19, 3.88)	0.20% (0.04%, 0.37%)	0.27% (0.11%, 0.46%)

An intention-to-treat analytic approach was used in all analyses. Fine and Gray proportional subdistribution hazards models were used to estimate 30-day HRs and the Aalen-Johansen estimator was used to estimate 30-day RDs. Death was treated as a competing event. Inverse probability of treatment weighting was used for confounding control.

Abbreviations: CI, confidence interval; CNS, central nervous system; HR, hazard ratio; med, medication; No., number; p-y, person-years; ref., referent.

**Supplemental Table 10. Proportion of patients in clinically relevant subgroups initiating zolpidem therapy at higher doses**

<b>Subgroup</b>	<b>No. of zolpidem initiators<sup>a</sup></b>	<b>Higher dose zolpidem initiators<sup>b</sup></b>
<b>Age</b>		
≥ 60 years	9,608	2,848 (30%)
< 60 years	9,333	3,711 (40%)
<b>Sex</b>		
Female	8,611	2,620 (30%)
Male	10,330	3,939 (38%)
<b>≥ 1 frailty indicator</b>		
Yes	9,445	3,017 (32%)
No	9,496	3,542 (37%)
<b>≥ 1 CNS-active medication</b>		
Yes	9,022	3,398 (38%)
No	9,919	3,161 (32%)

Values given are number (%).

<sup>a</sup> No. of zolpidem initiators includes new-users of higher and lower dose zolpidem initiators.

<sup>b</sup> Higher zolpidem doses were formulation dependent and defined as: > 1.75 mg/day for sublingual tablets used to treat middle of the night awakening; > 5 mg/day for regular release tablets, the oral spray formulation, and sublingual tablets used to treat sleep initiation; and > 6.25 mg/day for controlled release tablets.

Abbreviations: CNS, central nervous system; No., number.

**Supplemental Table 11. Association between zolpidem vs. trazodone initiation and 60- and 90-day fall-related fracture risk using an intention-to-treat analytic approach**

<b>Intention-to-treat analysis with a 60-day follow-up period</b>							
<b>Medication</b>	<b>n</b>	<b>No. of events</b>	<b>Rate per 1,000 p-y</b>	<b>Crude HR (95% CI)</b>	<b>Weighted HR (95% CI)</b>	<b>Crude RD (95% CI)</b>	<b>Weighted RD (95% CI)</b>
Trazodone	12,114	67	35.6	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	18,941	122	40.9	1.15 (0.86, 1.56)	1.40 (1.03, 1.89)	0.09% (-0.05%, 0.23%)	0.20% (0.05%, 0.35%)
<b>Intention-to-treat analysis with a 90-day follow-up period</b>							
<b>Medication</b>	<b>n</b>	<b>No. of events</b>	<b>Rate per 1,000 p-y</b>	<b>Crude HR (95% CI)</b>	<b>Weighted HR (95% CI)</b>	<b>Crude RD (95% CI)</b>	<b>Weighted RD (95% CI)</b>
Trazodone	12,114	98	35.7	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	18,941	171	39.1	1.10 (0.86, 1.41)	1.35 (1.05, 1.74)	0.08% (-0.09%, 0.26%)	0.26% (0.10%, 0.45%)

An intention-to-treat analytic approach was used in all analyses. Fine and Gray proportional subdistribution hazards models were used to estimate 60- and 90-day HRs and the Aalen-Johansen estimator was used to estimate 60- and 90-day RDs. Death was treated as a competing event. Inverse probability of treatment weighting was used for confounding control.

Abbreviations: CI, confidence interval; HR, hazard ratio; No., number; p-y, person-years; RD, risk difference; ref., referent

**Supplemental Table 12. Association between zolpidem vs. trazodone initiation and fall-related fracture risk using an on-treatment analytic approach**

On-treatment analysis							
Medication	n	No. of events	Rate per 1,000 p-y	Crude HR (95% CI)	Weighted HR (95% CI)	Crude RD (95% CI) <sup>a</sup>	Weighted RD (95% CI) <sup>a</sup>
Trazodone	12,114	102	35.6	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	18,941	124	40.6	1.14 (0.87, 1.49)	1.34 (1.02, 1.75)	1.12% (-0.16%, 2.53%)	1.38% (0.05%, 2.90%)

An on-treatment analytic approach was used in all analyses. In these analyses, all possible follow-up time was considered. Additional censoring events included index study medication discontinuation (using a 7-day grace period), switching to a non-index study medication (e.g. if the patient initiated zolpidem therapy and switched to trazodone), or switching to another z-drug (eszopiclone, zaleplon). Fine and Gray proportional subdistribution hazards models were used to estimate HRs using and the Aalen-Johansen estimator was used to estimate RDs. Death was treated as a competing event. Inverse probability of treatment weighting was used for confounding control. The maximum follow-up time observed in our on-treatment cohort was 1,279 days and the median [quartile 1, quartile 3] length of follow-up was 37 [37, 67] days.

<sup>a</sup> 365-day RDs are presented.

Abbreviations: CI, confidence interval; HR, hazard ratio; No., number; p-y, person-years; RD, risk difference; ref., referent.

**Supplemental Table 13. Association between zolpidem vs. trazodone initiation and 30-day fracture risk using an intention-to-treat analytic approach**

Fracture – alternative outcome							
Medication	n	No. of events	Rate per 1,000 p-y	Crude HR (95% CI)	Weighted HR (95% CI)	Crude RD (95% CI)	Weighted RD (95% CI)
Trazodone	12,114	43	44.4	1.00 (ref.)	1.00 (ref.)	0.00% (ref.)	0.00% (ref.)
Zolpidem	18,941	85	55.8	1.26 (0.87, 1.82)	1.56 (1.07, 2.27)	0.09% (-0.01%, 0.22%)	0.18% (0.07%, 0.31%)

Fine and Gray proportional subdistribution hazards models were used to estimate 30-day HRs and the Aalen-Johansen estimator was used to estimate 30-day RDs. Death was treated as a competing event. Inverse probability of treatment weighting was used for confounding control.

Abbreviations: CI, confidence interval; HR, hazard ratio; No., number; p-y, person-years; RD, risk difference; ref., referent.