Supplementary Table 1. Exposure and outcome definitions.

| Variable                                      | Definition                                                                                                                                 |
|-----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| **Medications**                               |                                                                                                                                           |
| Alcohol use disorder drug                     | ATC code beginning with N07BB appearing at least once in prescription claims                                                              |
| Anticholinergic                               | ATC code beginning with N04AA, N04AB, N04AC appearing at least once in prescription claims                                               |
| Anticonvulsant                                | ATC code beginning with N03A, excluding N03AE01 (clonazepam) appearing at least once in prescription claims                               |
| Antidepressant                                | ATC code beginning with N06A appearing at least once in prescription claims                                                               |
| Antidiabetic drug                             | ATC code beginning with A10A, A10B, A10X appearing at least once in prescription claims                                                 |
| Antihyperlipidemic drug                       | ATC code beginning with C10A, C10B appearing at least once in prescription claims                                                         |
| Antipsychotic                                | ATC code beginning with N05A, excluding ATC N05AN01 (lithium) appearing at least once in prescription claims                               |
| Anxiolytic                                    | ATC code beginning with N05BA; ATC codes N03AE01, N05BE01 appearing at least once in prescription claims                                |
| Dementia drug                                 | ATC code beginning with N06DA, N06DX appearing at least once in prescription claims                                                       |
| Long-acting injectable antipsychotic          | ATC code beginning with N05A, excluding ATC N05AN01 (lithium) and route intramuscular or subcutaneous, excluding non-LAIA injectables (DINs 00017574, 00808652, 02366010, 00743518, 01929984, 00497509, 01927698, 00028002, 01927795, 02162946, 02230405, 00439819, 02169991, 02247099, 01933272, 00627615, 02382016, 02167832, 02232966, 02406411, 02416522, 02232449) appearing at least once in prescription claims |
| Mood stabilizer                               | ATC codes N03AF01, N03AF02, N03AG01, N03AX09, N05AN01 appearing at least once in prescription claims                                      |
| Opioid                                        | ATC code beginning with N02A; ATC codes N07BC02, R05DA01, R05DA03-06, R05DA12, R05DA20, R05FA01, R05FA02 appearing at least once in prescription claims |
| Opioid agonist therapy                        | ATC code beginning with N07BC appearing at least once in prescription claims                                                               |
| Sedative-hypnotic                             | ATC code beginning with N05C, R06AA; ATC codes N05BB01, R06AD02, N06AX02, N05CH01 appearing at least once in prescription claims          |
| Smoking cessation aid                         | ATC codes N07BA01, N07BA03; DIN 02238441 appearing at least once in prescription claims                                                   |
| **Diagnoses**                                 |                                                                                                                                           |
| Attention deficit/hyperactivity disorder      | ICD-9-CM code 314 or ICD-10-CA code F90 appearing at least once in hospital claims; or ICD-9-CM code 314 appearing at least once in medical claims; or ATC code N06BA appearing at least twice in prescription claims without ICD-9-CM 312, 313, 347 or ICD-10-CA F63, F91, F92, F93, F94, G47.4 in hospital or medical claims; or ATC code N06BA appearing at least once in prescription claims and ICD-9-CM code 314 or ICD-10-CA code F90 appearing at least once in hospital or medical claims in the previous 3 years |
| Autism spectrum disorder                      | ICD-9-CM code 299.0, 299.1, 299., 299.9 or ICD-10-CA code F84.0, F84.1, F84.2, F84.3, F84.4, F84.5, F84.8, F84.9 appearing at least once in hospital claims; or ICD-9-CM code 299 appearing at least once in medical claims |
| Condition                        | ICD-9-CM Codes                                                                 |
|---------------------------------|-------------------------------------------------------------------------------|
| Dementia                        | ICD-9-CM code 290, 291.1, 292.2, 292.82, 294, 331, 797 or ICD-10-CA code F00, F01, F02, F03, F04, F05.1, F06.5, F06.6, F06.8, F06.9, F09, F10.7, F11.7, F12.7, F14.7, F15.7, F18.7, F19.7, G30, G31.1, G31.9, G32.8, G91, G93.7, G94, R54 appearing at least once in hospital claims; or ICD-9-CM code 290, 294, 331, 797 appearing at least once in medical claims |
| Intellectual disability/developmental disorder | ICD-9-CM code 299, 317, 318, 319, 758.0, 758.1, 758.2, 758.3, 759.81, 759.82, 759.84, 759.85, 759.86, 759.87, 759.88, 759.89, 760.71 or ICD-10-CA code F00, F01, F02, F03, F04, F05.1, F06.5, F06.6, F06.8, F06.9, F09, F10.7, F11.7, F12.7, F14.7, F15.7, F18.7, F19.7, G30, G31.1, G31.9, G32.8, G91, G93.7, G94, R54 appearing at least once in hospital claims; or ICD-9-CM code 299, 317, 318, 319 appearing at least once in medical claims |
| Mood or anxiety disorder        | ICD-9-CM code 296, 300.0, 300.2, 300.3, 300.4, 300.7, 309, 311 or ICD-10-CA code F31, F32, F33, F34.1, F38.0, F38.1, F40, F41.0, F41.1, F41.2, F41.3, F41.8, F41.9, F42, F43.1, F43.2, F43.8, F45.2, F53.0, F93.0 appearing at least once in hospital claims; or ICD-9-CM code 300 or ICD-10-CA code F41, F44, F45.0, F45.1, F68.0 or F99 appearing at least once in hospital claims and ATC code N05AN01, N05BA or N06A appearing at least once in prescription claims; or ICD-9-CM code 296, 311 appearing at least once in medical claims; or ICD-9-CM code 300 appearing at least once in medical claims and ATC code N05AN01, N05BA or N06A appearing at least once in prescription claims; or ICD-9-CM code 300, 309 appearing at least 3 times in medical claims |
| Personality disorder            | ICD-9-CM code 301 or ICD-10-CA code F34.0, F60, F61, F62, F68.1, F68.8, F69 appearing at least once in hospital claims; or ICD-9-CM code 301 appearing at least once in medical claims |
| Psychotic disorder              | ICD-9-CM code 295, 297, 298 or ICD-10-CA code F11.5, F12.5, F13.5, F14.5, F15.5, F16.5, F18.5, F19.5, F20, F22, F23, F24, F25, F28 or F29 appearing at least once in hospital claims; or ICD-9-CM code 295, 297, 298 appearing at least once in medical claims |
| Schizophrenia                   | ICD-9-CM code 295 or ICD-10-CA code F20 appearing at least once in hospital claims; or ICD-9-CM code 295 appearing at least once in medical claims |
| Substance use disorder          | ICD-9-CM code 291, 292, 303, 304, 305 or ICD-10-CA code F10, F11, F12, F13, F14, F15, F16, F17, F18, F19, F55, Z50.2, Z50.3 appearing at least once in hospital claims; or ICD-9-CM code 291, 292, 303, 304, 305 appearing at least once in medical claims |
| Suicide attempt                 | ICD-9-CM code E95.0-E95.9 or ICD-10-CA code X60-84 appearing at least once in hospital claims; or ICD-9-CM code 965, 967, 969, 977.9, 986, E850-854, E858, E862, E868 or ICD-10-CA code T39, T40, T42.3, T42.4, T42.7, T43, T50.9, T58, X40-42, X44, X46, X47, Y10-12, Y16, Y17 appearing at least once in hospital claims and tariff code 8444, 8446, 8447, 8472, 8475, 8476, 8503, 8504, 8553, 8554, 8581, 8584, 8588, 8596, 8580, 8587 or 8589 appearing in hospital claims during admission or in medical claims within 30 days of hospital separation |
| Other baseline variables         |                                                                                   |
| **Accused of a crime** | Identified in the Prosecutions Information and Scheduling Management database as having been accused of a crime, excluding offenses under the Highway Traffic Act |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| **Income quintile**    | Area-level income based on postal code of residence                                                                                                                                 |
| **Victim of a crime**  | Identified in the Prosecutions Information and Scheduling Management database as having been victim of a crime, excluding offenses under the Highway Traffic Act |
| **Outcomes**           |                                                                                                                                                                                                 |
| **Completed suicide**  | Primary cause of death self-inflicted injury or poisoning, or poisoning of undetermined intent (ICD-9-CM code E950-952, E953-958, E959 or ICD-10-CA code X40-42, X46, X47, X70-X84, Y10-12, Y16-17, Y87.0) |
| **Incarceration**      | Identified in the Corrections Offender Management System database as having been taken into custody, excluding probation and intoxicated persons detention |
| **Psychiatric hospitalization** | Hospitalization for a mood or anxiety disorder, substance use disorder, psychotic disorder, schizophrenia or attempted suicide (ICD-9-CM codes 296, 311, 309, 300, 291, 292, 303, 304.3 05, 295, 301, E95.0-95.9 or ICD-10-CA F30, F31, F32, F33, F34, F38, F40, F41.0, F41.1, F41.2, F41.3, F41.8, F41.9, F42, F43, F53.0, F10-19, F55, Z50.2, Z50.3, F20, F21, F60-62, F69, X60-84; or ICD-9-CM code 965, 967, 969, 977.9, 986, E850-854, E858, E862, E868 or ICD-10-CA code T39, T40, T42.3, T42.4, T42.7, T43, T50.9, T58, X40-42, X44, X46, X47, Y10-12, Y16, Y17 and tariff code 8444, 8446, 8472, 8475, 8476, 8503, 8504, 8553, 8554, 8581, 8584, 8588, 8596, 8580, 8587 or 8589 appearing in hospital claims during admission or in medical claims within 30 days of hospital separation) |
| **Treatment discontinuation** | Gap of >90 days between consecutive dispensations in prescription claims data |

ATC=anatomical therapeutic chemical; DIN=drug identification number; ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CA=International Classification of Diseases, Tenth Revision, with Canadian Enhancements; LAIA=long-acting injectable antipsychotic
Supplementary Table 2. Antipsychotics used by cohort members prior to and upon cohort entry.

| Characteristics                  | Before matching                                                                 | After matching                                                                 |
|----------------------------------|--------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
|                                  | SG-LAIA New Users, n=1,681 | Antipsychotic Users, n=1,681 | Standardized Difference | SG-LAIA New Users, n=1,182 | Antipsychotic Users, n=1,182 | Standardized Difference |
|                                  | n or mean | % or SD | n or mean | % or SD | n or mean | % or SD | n or mean | % or SD | n or mean | % or SD |
| Prevalent antipsychotic used prior to cohort entry† | | | | | | | | | | |
| SGA                              | 1258 | 74.8% | 1168 | 69.5% | 0.16 | 881 | 74.5% | 862 | 72.9% | 0.06 |
| Aripiprazole                     | 117 | 7.0% | 29 | 1.7% | 0.28 | 80 | 6.8% | 30 | 2.5% | 0.22 |
| Brexpiprazole                    | S | S | S | S | 0.04 | S | S | 0 | 0.0% | 0.04 |
| Clozapine                        | 83 | 4.9% | 66 | 3.9% | 0.05 | 52 | 4.4% | 36 | 3.0% | 0.08 |
| Lurasidone                       | S | S | S | S | 0.03 | S | S | S | S | 0.02 |
| Olanzapine                       | 360 | 21.4% | 309 | 18.4% | 0.08 | 252 | 21.3% | 239 | 20.2% | 0.03 |
| Paliperidone                     | 6 | 0.4% | S | S | 0.09 | S | S | S | S | 0.04 |
| Quetiapine                       | 274 | 16.3% | 378 | 22.5% | 0.17 | 190 | 16.1% | 277 | 23.4% | 0.21 |
| Risperidone                      | 402 | 23.9% | 384 | 22.8% | 0.03 | 290 | 24.5% | 277 | 23.4% | 0.03 |
| Ziprasidone                      | 11 | 0.7% | S | S | 0.12 | S | 10 | 0.8% | 0 | 0.0% | 0.14 |
| FGA                              | 221 | 13.1% | 311 | 18.5% | 0.16 | 114 | 9.6% | 133 | 11.3% | 0.06 |
| Chlorpromazine                   | 7 | 0.4% | 42 | 2.5% | 0.19 | S | S | 10 | 0.8% | 0.07 |
| Flupentixol                      | 10 | 0.6% | 15 | 0.9% | 0.04 | S | S | S | S | 0.04 |
| Flupentixol LAI                  | 35 | 2.1% | 52 | 3.1% | 0.07 | 18 | 1.5% | 22 | 1.9% | 0.03 |
| Fluphenazine                     | S | S | 7 | 0.4% | 0.08 | 0 | 0.0% | S | S | 0.09 |
| Fluphenazine LAI                 | 38 | 2.3% | 37 | 2.2% | 0.00 | 22 | 1.9% | 11 | 0.9% | 0.09 |
| Haloperidol                      | 38 | 2.3% | 27 | 1.6% | 0.05 | 25 | 2.1% | 15 | 1.3% | 0.07 |
| Haloperidol LAI                  | 38 | 2.3% | 26 | 1.5% | 0.06 | 12 | 1.0% | 13 | 1.1% | 0.01 |
| Antipsychotic                             | 
|------------------------------------------|
| Loxapine 8 0.5% 8 0.5% 0.00 S S 8 0.7% 0.05 |
| Methotrimeprazine 10 0.6% 48 2.9% 0.19 6 0.5% 17 1.4% 0.10 |
| Perphenazine 6 0.4% S S S 0.02 S S S S S 0.04 |
| Pipotiazine palmitate LAI S S S S 0.04 S S S 0 0.0% 0.08 |
| Thiothixene S S S 0 0.0% 0.04 0 0.0% 0 0.0% 0.00 |
| Trifluoperazine S S 20 1.2% 0.12 S S S 7 0.6% 0.07 |
| Zuclopenthixol 6 0.4% S S 0.07 S S S 0 0.0% 0.06 |
| Zuclopenthixol LAI 15 0.9% 20 1.2% 0.03 6 0.5% 15 1.3% 0.09 |
| None 202 12.0% 202 12.0% 0.00 187 15.8% 187 15.8% 0.00 |

Antipsychotic dispensed on t₀

SG-LAIA

| Antipsychotic LAI | - | - | - | - | 140 | 11.8% | - | - | - |
|--------------------|---|---|---|---|-----|-------|---|---|---|
| Paliperidone LAI‡  | - | - | - | - | -  | 455  | 38.5%| - | - | - |
| Risperidone LAI   | - | - | - | - | -  | 587  | 49.7%| - | - | - |
| SGA               | - | - | - | - | -  | -    | -  | 1027 | 86.9%| - |
| Aripiprazole      | - | - | - | - | -  | -    | -  | 44   | 3.7%| - |
| Brexpiprazole     | - | - | - | - | -  | -    | -  | S    | S  | - |
| Clozapine         | - | - | - | - | -  | -    | -  | 36   | 3.0%| - |
| Lurasidone        | - | - | - | - | -  | -    | -  | S    | S  | - |
| Olanzapine        | - | - | - | - | -  | -    | -  | 290  | 24.5%| - |
| Paliperidone      | - | - | - | - | -  | -    | -  | S    | S  | - |
| Quetiapine        | - | - | - | - | -  | -    | -  | 309  | 26.1%| - |
| Antipsychotic | Count | Percentage | G1 LAIA |
|---------------|-------|------------|---------|
| Risperidone   | 344   | 29.1%      |         |
| Ziprasidone   | S     | S          | -       |
| FGA           | 155   | 13.1%      |         |
| Chlorpromazine| 11    | 0.9%       |         |
| Flupentixol   | 6     | 0.5%       |         |
| Flupentixol LAI | 24  | 2.0%       |         |
| Fluphenazine  | S     | S          |         |
| Fluphenazine LAI | 13  | 1.1%       |         |
| Haloperidol   | 25    | 2.1%       |         |
| Haloperidol LAI | 16  | 1.4%       |         |
| Loxapine      | 9     | 0.8%       |         |
| Methotrimeprazine | 19 | 1.6%       |         |
| Pimozide      | S     | S          |         |
| Perphenazine  | S     | S          |         |
| Trifluoperazine| 7    | 0.6%       |         |
| Zuclopenthixol| 0     | 0.0%       |         |
| Zuclopenthixol LAI | 16 | 1.4%     |         |

Total G1 LAIA: 69 (5.8%)

* Cohort before matching consisted of SG-LAIA new users and antipsychotic users in the exposure set of an SG-LAIA new user. Exposure sets were based on calendar time, prior duration of continuous antipsychotic use, prior year use of clozapine, prior use of FG-LAIA and prior year number of unique antipsychotic medications dispensed. Characteristics of a random sample of one antipsychotic user per exposure set are reported. SG-LAIA users were matched 1:1 with an antipsychotic user on time-conditional propensity score.

†If multiple prior antipsychotics were used, the antipsychotic with longest duration of continuous use was selected
‡Includes once-monthly and 3-monthly formulations of paliperidone

FGA=first-generation antipsychotic; FG-LAIA=first-generation long-acting injectable antipsychotic; LAI=long-acting injectable; S=suppressed due to count <6; SD=standard deviation; SGA=second-generation antipsychotic; SG-LAIA=second-generation long-acting injectable antipsychotic; t₀=cohort entry date
Supplementary Table 3. Baseline characteristics of incident and prevalent new user cohort members before and after matching.

| Characteristics                  | Before Matching | After Matching |
|----------------------------------|-----------------|---------------|
|                                 | Incident New Users, n=1,681 | Incident New Users, n=1,872 |
|                                 | Antipsychotic Users, n=1,681* | Antipsychotic Users, n=1,872* |
|                                 | Standardized Difference | Standardized Difference |
|                                 | Incident Users, n=203 | Incident Users, n=203* |
|                                 | Incident Users, n=1,479 | Incident Users, n=1,479* |
|                                 | Prevalent Users, n=201* | Prevalent Users, n=201* |
|                                 | Prevalent Users, n=1,477 | Prevalent Users, n=1,477* |
| Females (years)                  | 79 39.1% 525 35.5% | 79 39.6% 361 36.3% |
| Age (years)                      | 37 17.1 36 16.2 | 37 17.2 37 17.2 |
| Age group (years)                |                              |                              |
| <18                              | 5 5 44 3.0% | 5 5 44 3.0% |
| 18-30                            | 96 47.5% 661 44.7% | 86 46.0% 380 38.2% |
| 31-40                            | 29 14.4% 293 19.8% | 26 13.9% 190 19.1% |
| 41-50                            | 22 10.9% 196 13.3% | 20 10.7% 128 12.9% |
| 51-60                            | 27 13.4% 150 10.1% | 25 13.4% 104 10.5% |
| 61-70                            | 12 5.9% 78 5.3% | 10 5.3% 55 5.5% |
| 71-80                            | 6 3.0% 30 2.0% | 5 5 28 2.8% |
| >80                              | 5 5 27 1.8% | 5 5 24 2.4% |
| Income quintile                  |                              |                              |
| 1 (lowest)                       | 76 37.6% 546 36.9% | 73 39.0% 376 37.8% |
| 2                                | 35 17.3% 311 21.0% | 34 18.2% 218 21.9% |
| 3                                | 25 12.4% 189 12.8% | 24 12.8% 128 12.9% |
| 4                                | 26 12.9% 166 11.2% | 25 13.4% 115 11.6% |
| 5 (highest)                      | 14 6.9% 113 7.6% | 13 7.0% 80 8.0% |
| Missing                          | 26 12.9% 154 10.4% | 18 9.6% 78 7.8% |
| Year of cohort entry             |                              |                              |
| 2005/2006                        | 6 3.0% 39 2.6% | 5 5 36 3.6% |
| 2007/2008                        | 8 4.0% 73 4.9% | 5 5 52 5.2% |
| 2009/2010                        | 13 6.4% 92 6.2% | 11 5.9% 63 6.3% |
| 2011/2012                        | 22 10.9% 171 11.6% | 22 11.8% 102 10.3% |
| 2013/2014                        | 25 12.4% 181 12.2% | 23 12.3% 106 10.7% |
| Year          | Medication                  | Count | Percentage |
|---------------|----------------------------|-------|------------|
| 2015/2016     | Mood stabilizer             | 7     | 3.5%       |
|               | Antidepressant              | 28    | 13.9%      |
|               | Antihistamine               | 26    | 12.9%      |
|               | Sedative-hypnotic           | 18    | 8.9%       |
|               | Anticonvulsant              | 13    | 6.4%       |
|               | Psychostimulant             | 5     | 3.3%       |
|               | Anticholinergic             | 13    | 6.4%       |
|               | Opioid                      | 23    | 11.4%      |
|               | Opioid agonist therapy      | 5     | 2.2%       |
|               | Smoking cessation aid       | 5     | 2.2%       |

| Year          | Count | Percentage |
|---------------|-------|------------|
| 2017/2018     | 100.0%| 100.0%     |
| 2019/2020     | 100.0%| 100.0%     |

**Prior Year Antipsychotic Medications**

| Year | Medication                  | Count | Percentage |
|------|----------------------------|-------|------------|
| 0-1  | Clozapine                  | 0     | 0.0%       |
| >1   | Clozapine                  | 133   | 9.0%       |

**Prior Year Number of Medication Classes Dispensed**

| Year | Medication                  | Count | Percentage |
|------|----------------------------|-------|------------|
| 0-1  | Mood stabilizer             | 7     | 3.5%       |
|      | Antidepressant              | 28    | 13.9%      |
|      | Antihistamine               | 26    | 12.9%      |
|      | Sedative-hypnotic           | 18    | 8.9%       |
|      | Anticonvulsant              | 13    | 6.4%       |
|      | Psychostimulant             | 5     | 3.3%       |
|      | Anticholinergic             | 13    | 6.4%       |
|      | Opioid                      | 23    | 11.4%      |
|      | Opioid agonist therapy      | 5     | 2.2%       |
|      | Smoking cessation aid       | 5     | 2.2%       |
| Drug Class                        | Exposure Set | Number of New Users | Number of Users | Drug Use | Drug Use % | Number of New Users | Number of Users | Drug Use | Drug Use % |
|----------------------------------|--------------|---------------------|----------------|----------|------------|---------------------|----------------|----------|------------|
| Alcohol use disorder             | 0            | 0                   | 0              | S        | 0.0%       | S                   | 0              | 0.0%     | 0.0%       |
| Dementia drug                    | S            | S                   | S              | S        | 7.9%       | S                   | 7.9%           | 262      | 17.7%      |
| Antidiabetic drug                | S            | S                   | S              | S        | 10.8%      | S                   | 9.7%           | 97       | 9.7%       |
| Antihyperlipidemic drug          | S            | S                   | S              | S        | 8.5%       | S                   | 8.5%           | 81       | 8.5%       |
| Comorbidities                    |              |                     |                |          |            |                     |                |          |            |
| Mood or anxiety disorder         | 121          | 95.9%               | 1162           | 78.6%    | 146        | 27.3%               | 1225           | 82.8%    | 0.29       | 0.29       |
| Personality disorder             | 45           | 12.3%               | 440            | 12.9%    | 87         | 45.0%               | 876            | 59.2%    | 0.09       | 0.09       |
| Substance use disorder          | 91           | 45.0%               | 876            | 59.2%    | 82         | 40.6%               | 644            | 43.5%    | 0.32       | 0.32       |
| Dementia                         | 20           | 9.9%                | 181            | 12.2%    | 63         | 31.2%               | 376            | 25.4%    | 0.55       | 0.55       |
| Autism spectrum disorder        | S            | S                   | S              | S        | 3.9%       | S                   | 2.6%           | 0.08     | 0.08       |
| Intellectual disability/         | 14           | 6.9%                | 185            | 12.5%    | 10         | 5.0%                | 128            | 8.7%     | 0.08       | 0.08       |
| Developmental disorder          | S            | S                   | S              | S        | 228        | 15.4%               | 137            | 13.8%    | 0.04       | 0.04       |
| Suicide attempt                  | 14           | 6.9%                | 170            | 11.5%    | 5          | 9.2%                | 136            | 7.5%     | 0.13       | 0.13       |
| Prior year hospitalizations      | 0            | 20.8%               | 432            | 29.2%    | 105        | 52.0%               | 959            | 46.8%    | 0.69       | 0.69       |
| Prior year physician visits      | 1-2          | 75.2%               | 821            | 55.5%    | 5          | 45.8%               | 431            | 31.0%    | 0.64       | 0.64       |
|                                | >2           | 4.0%                | 226            | 15.3%    | 5          | 62%                 | 4.2%           | 0.08     | 0.08       |
| Incidents where accused          | 0            | 67.8%               | 1019           | 68.9%    | 154        | 76.2%               | 1321           | 89.3%    | 0.31       | 0.31       |
| of a crime                       | 1-2          | 19.9%               | 204            | 13.8%    | 23         | 11.4%               | 90             | 6.1%     | 0.07       | 0.07       |
|                                | >2           | 18.3%               | 256            | 17.3%    | 15         | 7.4%                | 68             | 4.6%     | 0.33       | 0.33       |
| Incidents where victim           | 0            | 95.5%               | 1392           | 94.1%    | 5          | 1432                | 96.8%          | 0.14     | 0.14       |
| of a crime                       | >0           | 4.5%                | 87             | 5.9%     | 5          | 47                  | 3.2%           | 0.14     | 0.14       |

* Cohort before matching consisted of SG-LAIA new users and antipsychotic users in the exposure set of an SG-LAIA new user. Exposure sets were based on calendar time, prior duration of continuous antipsychotic use, prior year use of clozapine, prior use of FG-LAIA and prior year number of unique antipsychotic medications dispensed. Characteristics of a random sample of one antipsychotic user per exposure set are reported. SG-LAIA users were matched 1:1 with an antipsychotic user on time-conditional propensity score.
Supplementary Table 4. Baseline characteristics of matched cohort members included in monotherapy subgroup.

| Characteristics          | After matching |        |        | Standardized Difference |
|-------------------------|----------------|--------|--------|-------------------------|
|                         | SG-LAIA New Users, n=519 | Antipsychotic Users, n=519 |        |
|                         | n or mean | % or SD | n or mean | % or SD |                      |
| Females                 | 187       | 36.0%   | 214       | 41.2%   | 0.11                  |
| Age (years)             | 36.4      | 16.7%   | 36.2      | 17.6%   | 0.01                  |
| Age group (years)       |           |        |          |          |                       |
| <18                     | 45        | 8.7%    | 12        | 2.3%    | 0.28                  |
| 18-30                   | 206       | 39.7%   | 240       | 46.2%   | 0.13                  |
| 31-40                   | 104       | 20.0%   | 96        | 18.5%   | 0.04                  |
| 41-50                   | 67        | 12.9%   | 58        | 11.2%   | 0.05                  |
| 51-60                   | 39        | 7.5%    | 60        | 11.6%   | 0.14                  |
| 61-70                   | 26        | 5.0%    | 32        | 6.2%    | 0.05                  |
| 71-80                   | 13        | 2.5%    | 11        | 2.1%    | 0.03                  |
| >80                     | 19        | 3.7%    | 10        | 1.9%    | 0.11                  |
| Income quintile         |           |        |          |          |                       |
| 1 (lowest)              | 203       | 39.1%   | 198       | 38.2%   | 0.11                  |
| 2                       | 100       | 19.3%   | 85        | 16.4%   | 0.08                  |
| 3                       | 50        | 9.6%    | 76        | 14.6%   | 0.15                  |
| 4                       | 73        | 14.1%   | 74        | 14.3%   | 0.01                  |
| 5 (highest)             | 53        | 10.2%   | 44        | 8.5%    | 0.06                  |
| Missing                 | 40        | 7.7%    | 42        | 8.1%    | 0.01                  |

Year of cohort entry
| Year            | Count | Percentage | Count | Percentage | Difference |
|-----------------|-------|------------|-------|------------|------------|
| 2005/2006       | 19    | 3.7%       | 19    | 3.7%       | 0.00       |
| 2007/2008       | 25    | 4.8%       | 25    | 4.8%       | 0.00       |
| 2009/2010       | 37    | 7.1%       | 40    | 7.7%       | 0.02       |
| 2011/2012       | 54    | 10.4%      | 54    | 10.4%      | 0.00       |
| 2013/2014       | 52    | 10.0%      | 49    | 9.4%       | 0.02       |
| 2015/2016       | 103   | 19.8%      | 103   | 19.8%      | 0.00       |
| 2017/2018       | 137   | 26.4%      | 133   | 25.6%      | 0.02       |
| 2019/2020       | 92    | 17.7%      | 96    | 18.5%      | 0.02       |
| Time since psychotic disorder diagnosis (years) | 6.9 | 6.6 | 6.4 | 6.4 | 0.07 |
| <1              | 132 | 25.4%      | 106   | 20.4%      | 0.12       |
| 1-4.9           | 152  | 29.3%      | 167   | 32.2%      | 0.06       |
| 5-10            | 92   | 17.7%      | 83    | 16.0%      | 0.05       |
| >10             | 142  | 27.4%      | 163   | 31.4%      | 0.09       |
| Prior FG-LAIA use | 59  | 11.4%      | 59    | 11.4%      | 0.00       |
| Prior year antipsychotic medications | 381 | 73.4% | 381 | 73.4% | 0.00 |
| 0-1             | 381  | 73.4%      | 381   | 73.4%      | 0.00       |
| >1              | 120  | 23.1%      | 120   | 23.1%      | 0.00       |
| Clozapine       | 18   | 3.5%       | 18    | 3.5%       | 0.00       |
| Prior year number of medication classes dispensed | 179 | 34.5% | 161 | 31.0% | 0.07 |
| 0-1             | 179  | 34.5%      | 161   | 31.0%      | 0.07       |
| 2-5             | 186  | 35.8%      | 177   | 34.1%      | 0.04       |
| >5              | 154  | 29.7%      | 181   | 34.9%      | 0.11       |
## Prior year medication use

| Category               | N   | %      | N   | %      | P-value |
|------------------------|-----|--------|-----|--------|---------|
| Mood stabilizer        | 62  | 11.9%  | 51  | 9.8%   | 0.07    |
| Antidepressant         | 151 | 29.1%  | 184 | 35.5%  | 0.14    |
| Anxiolytic             | 152 | 29.3%  | 163 | 31.4%  | 0.05    |
| Sedative-hypnotic      | 86  | 16.6%  | 90  | 17.3%  | 0.02    |
| Anticonvulsant         | 28  | 5.4%   | 30  | 5.8%   | 0.02    |
| Psychostimulant        | 9   | 1.7%   | 19  | 3.7%   | 0.12    |
| Anticholinergic        | 93  | 17.9%  | 81  | 15.6%  | 0.06    |
| Opioid                 | 80  | 15.4%  | 112 | 21.6%  | 0.16    |
| Opioid agonist therapy | S   | S      | 6   | 1.2%   | 0.09    |
| Alcohol use disorder   | S   | S      | S   | S      | 0.04    |
| Antidiabetic drug      | S   | S      | S   | S      | 0.08    |
| Antihyperlipidemic drug| 34  | 6.6%   | 35  | 6.7%   | 0.07    |

## Comorbidities

| Category                          | N   | %      | N   | %      | P-value |
|-----------------------------------|-----|--------|-----|--------|---------|
| Mood or anxiety disorder          | 381 | 73.4%  | 410 | 79.0%  | 0.13    |
| Personality disorder              | 133 | 25.6%  | 135 | 26.0%  | 0.01    |
| Substance use disorder            | 278 | 53.6%  | 260 | 50.1%  | 0.07    |
| Dementia                          | 64  | 12.3%  | 57  | 11.0%  | 0.04    |
| Autism spectrum disorder          | 12  | 2.3%   | 15  | 2.9%   | 0.04    |
| Intellectual disability/developmental disorder | 51  | 9.8%   | 49  | 9.4%   | 0.01    |
| ADHD                              | 65  | 12.5%  | 67  | 12.9%  | 0.01    |
| Incident Type                          | Count | %   | Count | %   | %   | SD  |
|---------------------------------------|-------|-----|-------|-----|-----|-----|
| Suicide attempt                       | 45    | 8.7%| 51    | 9.8%| 0.04|     |
| Prior year hospitalizations            |       |     |       |     |     |     |
| 0                                     | 180   | 34.7%| 167   | 32.2%| 0.05|     |
| 1-2                                   | 303   | 58.4%| 307   | 59.2%| 0.02|     |
| >2                                    | 36    | 6.9% | 45    | 8.7% | 0.06|     |
| Prior year physician visits           |       |     |       |     |     |     |
| 0-2                                   | 23    | 4.4% | 32    | 6.2% | 0.08|     |
| 3-5                                   | 52    | 10.0%| 48    | 9.2% | 0.03|     |
| >5                                    | 444   | 85.5%| 439   | 84.6%| 0.03|     |
| Incidents where accused of a crime    |       |     |       |     |     |     |
| 0                                     | 361   | 69.6%| 389   | 75.0%| 0.12|     |
| 1-2                                   | 69    | 13.3%| 61    | 11.8%| 0.05|     |
| >2                                    | 89    | 17.1%| 69    | 13.3%| 0.11|     |
| Incidents where victim of a crime     |       |     |       |     |     |     |
| 0                                     | 495   | 95.4%| 497   | 95.8%| 0.02|     |
| >0                                    | 24    | 4.6% | 22    | 4.2% | 0.02|     |

ADHD=attention-deficit hyperactivity disorder; FGA=first-generation antipsychotic; FG-LAIA=first-generation long-acting injectable antipsychotic; LAI=long-acting injectable; S=suppressed due to count <6; SD=standard deviation; SGA=second-generation antipsychotic; SG-LAIA=second-generation long-acting injectable antipsychotic
Supplementary Table 5. Antipsychotics used as monotherapy by cohort members prior to and upon cohort entry.

| Matched cohort | Matched cohort | Matched cohort | Matched cohort | Matched cohort |
|----------------|----------------|----------------|----------------|----------------|
| Characteristics | SG-LAIA New Users, n=519 | Antipsychotic Users, n=519 | Standardized Difference |
| Prevalent antipsychotic used prior to cohort entry† | n or mean | % or SD | n or mean | % or SD |  |
| SGA | 360 | 69.4% | 359 | 69.2% | 0.01 |
| Aripiprazole | 36 | 6.9% | 25 | 4.8% | 0.10 |
| Brexpiprazole | 0 | 0.0% | 0 | 0.0% | 0.00 |
| Clozapine | 14 | 2.7% | 8 | 1.5% | 0.09 |
| Lurasidone | S | S | S | S | 0.07 |
| Olanzapine | 110 | 21.2% | 101 | 19.5% | 0.05 |
| Paliperidone | S | S | S | S | 0.00 |
| Quetiapine | 69 | 13.3% | 86 | 16.6% | 0.11 |
| Risperidone | 128 | 24.7% | 138 | 26.6% | 0.05 |
| Ziprasidone | S | S | 0 | 0.0% | 0.07 |
| FGA | 41 | 7.9% | 42 | 8.1% | 0.01 |
| Chlorpromazine | S | S | S | S | 0.10 |
| Flupentixol | 0 | 0.0% | 0 | 0.0% | 0.00 |
| Flupentixol LAI | 9 | 1.7% | 7 | 1.3% | 0.04 |
| Fluphenazine | 0 | 0.0% | 0 | 0.0% | 0.00 |
| Fluphenazine LAI | 7 | 1.3% | S | S | 0.15 |
| Haloperidol | S | S | 9 | 1.7% | 0.08 |
| Haloperidol LAI | 6 | 1.2% | 9 | 1.7% | 0.06 |
| Antipsychotic | Usage | %t0 | No. | %t0 |
|---------------|-------|-----|-----|-----|
| Loxapine      | S     | S   | S   | S   | 0.00 |
| Methotrimeprazine | S     | S   | S   | S   | 0.00 |
| Perphenazine  | S     | S   | S   | S   | 0.07 |
| Pimozide      | S     | S   | S   | S   | 0.07 |
| Pipotiazine palmitate LAI | 0 | 0.0% | 0 | 0.0% | 0.00 |
| Thiothixene   | 0     | 0.0% | 0   | 0.0% | 0.00 |
| Trifluoperazine | S     | S   | S   | 0.0% | 0.10 |
| Zuclopenthixol | S     | 2.0%| S   | S   | 0.04 |
| Zuclopenthixol LAI | S | S   | S   | S   | 0.00 |
| None          | 118   | 22.7% | 118 | 22.7% | 0.00 |

Antipsychotic dispensed on t0

SG-LAIA

| Antipsychotic   | Usage | %t0 | No. | %t0 |
|-----------------|-------|-----|-----|-----|
| Aripiprazole LAI | 58 | 11.2% | -   | -   |
| Paliperidone LAI | 198 | 38.2% | -   | -   |
| Risperidone LAI | 263 | 50.7% | -   | -   |

SGA

| Antipsychotic | Usage | %t0 | No. | %t0 |
|---------------|-------|-----|-----|-----|
| Aripiprazole  | -     | -   | 33  | 6.4%|
| Brexpiprazole | -     | -   | S   | S   |
| Clozapine     | -     | -   | S   | S   |
| Lurasidone    | -     | -   | S   | S   |
| Olanzapine    | -     | -   | 136 | 26.2%|
| Paliperidone  | -     | -   | S   | S   |
| Quetiapine    | -     | -   | 105 | 20.2%|
| Antipsychotic          | Count | SD | Count | SD |
|------------------------|-------|----|-------|----|
| Risperidone            | 179   | 34.5% | 0.0% |
| Ziprasidone            | -     | 56  | 10.8% | -  |
| FGA                    | -     | 13  | 2.5%  | -  |
| Chlorpromazine         | -     | 9   | 1.7%  | -  |
| Flupentixol            | -     | 0   | 0.0%  | -  |
| Fluphenazine           | -     | 0   | 0.0%  | -  |
| Fluphenazine LAI       | -     | 0   | 0.0%  | -  |
| Haloperidol            | -     | 13  | 2.5%  | -  |
| Haloperidol LAI        | -     | 11  | 2.1%  | -  |
| Loxapine               | -     | 0   | 0.0%  | -  |
| Methotrimeprazine      | -     | 0   | 0.0%  | -  |
| Perphenazine           | -     | 0   | 0.0%  | -  |
| Pimozide               | -     | 0   | 0.0%  | -  |
| Trifluoperazine        | -     | 0   | 0.0%  | -  |
| Zuclopenthixol         | -     | 0   | 0.0%  | -  |
| Zuclopenthixol LAI     | -     | 0   | 0.0%  | -  |
| **Total FG-LAIA**      | -     | 27  | 5.2%  | -  |

†If multiple prior antipsychotics were used, the antipsychotic with longest duration of continuous use was selected
‡Includes once-monthly and 3-monthly formulations of paliperidone
FGA=first-generation antipsychotic; FG-LAIA=first-generation long-acting injectable antipsychotic; LAI=long-acting injectable; S=suppressed due to count <6; SD=standard deviation; SGA=second-generation antipsychotic; SG-LAIA=second-generation long-acting injectable antipsychotic; t=cohort entry date
Supplementary Table 6. Sensitivity analysis: Antipsychotics used as monotherapy by cohort members prior to and upon cohort entry, with inclusion of previous antipsychotic in time-conditional propensity score.

| Matched cohort | Characteristics | SG-LAIA New Users, n=1,164 | Antipsychotic Users, n=1,164 | Standardized Difference |
|----------------|----------------|-----------------------------|-------------------------------|-------------------------|
|                | Prevalent antipsychotic used prior to cohort entry† | n or mean | % or SD | n or mean | % or SD |                      |
| SGA            | 864 | 74.2% | 848 | 72.9% | 0.05 |
| Aripiprazole   | 64  | 5.5%  | 57  | 4.9%  | 0.03 |
| Brexpiprazole  | 0   | 0.0%  | 0   | 0.0%  | 0.00 |
| Clozapine      | 44  | 3.8%  | 36  | 3.1%  | 0.04 |
| Lurasidone     | S   | S     | S   | S     | 0.02 |
| Olanzapine     | 257 | 22.1% | 237 | 20.4% | 0.05 |
| Paliperidone   | S   | S     | S   | S     | 0.00 |
| Quetiapine     | 205 | 17.6% | 220 | 18.9% | 0.04 |
| Risperidone    | 284 | 24.4% | 294 | 25.3% | 0.02 |
| Ziprasidone    | 7   | 0.6%  | 0   | 0.0%  | 0.12 |
| FGA            | 113 | 9.7%  | 129 | 11.1% | 0.05 |
| Chlorpromazine | S   | S     | 10  | 0.9%  | 0.06 |
| Flupentixol    | S   | S     | S   | S     | 0.05 |
| Flupentixol LAI| 17  | 1.5%  | 15  | 1.3%  | 0.02 |
| Fluphenazine   | 0   | 0.0%  | S   | S     | 0.05 |
| Fluphenazine LAI| 22  | 1.9%  | 18  | 1.5%  | 0.03 |
| Haloperidol    | 24  | 2.1%  | 27  | 2.3%  | 0.02 |
| Haloperidol LAI| 12  | 1.0%  | 14  | 1.2%  | 0.02 |
| Loxapine | 7 | 0.6% | 8 | 0.7% | 0.01 |
|----------|---|------|---|------|-----|
| Methotrimazole | 9 | 0.8% | 11 | 0.9% | 0.02 |
| Perphenazine | S | S | S | S | 0.05 |
| Pimozide | S | S | S | S | 0.02 |
| Pipotiazine palmitate LAI | 0 | 0.0% | 0 | 0.0% | 0.00 |
| Thiothixene | 0 | 0.0% | 0 | 0.0% | 0.00 |
| Trifluoperazine | S | S | S | S | 0.02 |
| Zuclopenthixol | S | S | S | S | 0.06 |
| Zuclopenthixol LAI | 8 | 0.7% | 7 | 0.6% | 0.01 |
| None | 187 | 16.1% | 187 | 16.1% | 0.00 |

Antipsychotic dispensed on t<sub>0</sub>

SG-LAIA

| Aripiprazole LAI | 128 | 11.0% | - | - | - |
| Paliperidone LAI‡ | 445 | 38.2% | - | - | - |
| Risperidone LAI | 591 | 50.8% | - | - | - |
| SGA | - | - | 1013 | 87.0% | - |
| Aripiprazole | - | - | 71 | 6.1% | - |
| Brexpiprazole | - | - | S | S | - |
| Clozapine | - | - | 36 | 3.1% | - |
| Lurasidone | - | - | S | S | - |
| Olanzapine | - | - | 288 | 24.7% | - |
| Paliperidone | - | - | S | S | - |
| Quetiapine | - | - | 253 | 21.7% | - |
| Antipsychotic | Start Count | End Count | Count | Percentage |
|---------------|-------------|-----------|-------|------------|
| Risperidone   | -           | -         | 360   | 30.9%      |
| Ziprasidone   | -           | -         | 0     | 0.0%       |
| FGA           | -           | -         | 151   | 13.0%      |
| Chlorpromazine| -           | -         | 11    | 0.9%       |
| Flupentixol   | -           | -         | S     | S          |
| Flupentixol LAI| -          | -         | 17    | 1.5%       |
| Fluphenazine  | -           | -         | S     | S          |
| Fluphenazine LAI| -       | -         | 24    | 2.1%       |
| Haloperidol   | -           | -         | 37    | 3.2%       |
| Haloperidol LAI| -         | -         | 17    | 1.5%       |
| Loxapine      | -           | -         | 9     | 0.8%       |
| Methotrimeprazine | -   | -         | 13    | 1.1%       |
| Perphenazine  | -           | -         | 0     | 0.0%       |
| Pimozide      | -           | -         | S     | S          |
| Trifluoperazine| -         | -         | S     | S          |
| Zuclopenthixol| -           | -         | S     | S          |
| Zuclopenthixol LAI| -     | -         | 8     | 0.7%       |
| Total FG-LAIA | -           | -         | 66    | 5.7%       |

†If multiple prior antipsychotics were used, the antipsychotic with longest duration of continuous use was selected
‡Includes once-monthly and 3-monthly formulations of paliperidone
FGA=first-generation antipsychotic; FG-LAIA=first-generation long-acting injectable antipsychotic; LAI=long-acting injectable; LAI=long-acting injectable antipsychotic; SD=standard deviation; SGA=second-generation antipsychotic; SGLAIA=second-generation long-acting injectable antipsychotic; t=cohort entry date
Supplementary Table 7. Sensitivity analysis: Association between second-generation long-acting injectable antipsychotics versus oral antipsychotics and treatment failure, psychiatric hospitalization, incarceration, treatment discontinuation and all-cause mortality with inclusion of previous antipsychotic in time-conditional propensity score.

| Treatment failure | Number of events | Person years | Crude incidence rate per 100 person years | Crude Hazard Ratio (95% CI) | Adjusted Hazard Ratio* (95% CI) |
|-------------------|-----------------|--------------|------------------------------------------|-----------------------------|--------------------------------|
| SG-LAIA New Users | 905             | 1,491        | 60.7                                     | 1.15 (1.11-1.19)            | 1.05 (0.97-1.13)               |
| Matched Antipsychotic Users | 787         | 1,717        | 45.8                                     | 1.00 (Reference)            | 1.00 (Reference)               |

| Psychiatric hospitalization | Number of events | Person years | Crude incidence rate per 100 person years | Crude Hazard Ratio (95% CI) | Adjusted Hazard Ratio* (95% CI) |
|-----------------------------|-----------------|--------------|------------------------------------------|-----------------------------|--------------------------------|
| SG-LAIA New Users | 572             | 2,792        | 20.5                                     | 1.21 (1.14-1.29)            | 1.35 (1.21-1.51)               |
| Matched Antipsychotic Users | 471        | 2,890        | 16.3                                     | 1.00 (Reference)            | 1.00 (Reference)               |

| Incarceration | Number of events | Person years | Crude incidence rate per 100 person years | Crude Hazard Ratio (95% CI) | Adjusted Hazard Ratio* (95% CI) |
|---------------|-----------------|--------------|------------------------------------------|-----------------------------|--------------------------------|
| SG-LAIA New Users | 173             | 4,396        | 3.9                                      | 1.18 (1.02-1.36)            | 0.99 (0.75-1.30)               |
| Matched Antipsychotic Users | 147         | 3,904        | 3.8                                      | 1.00 (Reference)            | 1.00 (Reference)               |

| Treatment discontinuation | Number of events | Person years | Crude incidence rate per 100 person years | Crude Hazard Ratio (95% CI) | Adjusted Hazard Ratio* (95% CI) |
|---------------------------|-----------------|--------------|------------------------------------------|-----------------------------|--------------------------------|
| SG-LAIA New Users | 797             | 2,148        | 37.1                                     | 1.21 (1.16-1.26)            | 1.01 (0.93-1.10)               |
| Matched Antipsychotic Users | 658        | 2,197        | 29.9                                     | 1.00 (Reference)            | 1.00 (Reference)               |

| All-cause mortality | Number of events | Person years | Crude incidence rate per 100 person years | Crude Hazard Ratio (95% CI) | Adjusted Hazard Ratio* (95% CI) |
|---------------------|-----------------|--------------|------------------------------------------|-----------------------------|--------------------------------|
| SG-LAIA New Users | 95              | 5,184        | 1.8                                      | 0.99 (0.82-1.19)            | 1.10 (0.77-1.57)               |
| Matched Antipsychotic Users | 96         | 4,383        | 2.2                                      | 1.00 (Reference)            | 1.00 (Reference)               |

*Adjusted for time-varying use of additional antipsychotic medications in each 3-month period of follow-up time, and baseline variables age, sex, time since psychotic disorder diagnosis, decile of time-conditional propensity score, prior year hospital admissions, being accused of a crime, diagnosis of personality disorder, substance use disorder, mood/anxiety disorder

SG-LAIA=second-generation long-acting injectable antipsychotic
Supplementary Figure 1. Outcome comparison in a cohort with psychotic disorder versus a cohort with schizophrenia.
Supplementary Figure 2. Outcome comparison during monotherapy in a cohort with psychotic disorder versus a cohort with schizophrenia.