Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.
### eTable 1. Details of Eligibility Criteria

| Eligibility Criteria | Implementation in MarketScan | Rationale |
|----------------------|-----------------------------|-----------|
| **Inclusion Criteria** |                             |           |
| Age 20-65 years for adult trial | Age assessed on the date of treatment initiation | Both children and adults were included because patients are treated with anticonvulsant mood stabilizers across the life course |
| Age 10-19 years for pediatric trial |                             |           |
| Continuous enrollment in a health plan for at least 1 year | Require continuous pharmacy and medical enrollment during the year prior to treatment initiation | To ensure complete capture of the claims data |
| **Exclusion Criteria** |                             |           |
| No anticonvulsant medication use (including those not used as mood stabilizers) during the prior year | Exclude patients with a dispensing of any anticonvulsant mood stabilizer in the year prior to treatment initiation | New users only |
| No diagnosis of diabetes (type 1, type 2, secondary or gestational diabetes) or antidiabetic medication use (oral hypoglycemics or insulin) during the prior year | Exclude patients with a diagnosis of diabetes (type 1, type 2, secondary or gestational diabetes) or dispensing of an antidiabetic medication (except metformin*) during the year prior to treatment initiation | Exclude patients with the outcome at baseline; Minimize reverse causation |
| *Since metformin is used to treat conditions besides diabetes, patients who were treated with metformin but were not diagnosed with diabetes were eligible for inclusion in the study |                             |           |
| No evidence of pregnancy during the prior year | Exclude patients with a diagnosis or procedure code suggesting pregnancy or delivery of infant in the year prior to treatment initiation | Treatment decisions differ for pregnant women |
| No evidence of bariatric surgery during the prior year | Exclude patients with a procedure code for bariatric surgery in the year prior to treatment initiation | Patterns of weight gain and metabolic risk differ substantially for patients who recently had bariatric surgery |
Table 2. Study Definitions for Treatment Strategies

| Treatment Strategy | Generic Name                                      |
|--------------------|---------------------------------------------------|
| Carbamazepine      | carbamazepine                                     |
| Lamotrigine        | lamotrigine                                       |
| Oxcarbazepine      | oxcarbazepine                                     |
| Valproate          | divalproex sodium, valproic acid, valproate sodium |

To define treatment groups, generic names were mapped to NDC codes.
### Table 3. List of Baseline and Time-Varying Covariates

| **Baseline Covariates**                              | **Other Comorbidities**                                      |
|------------------------------------------------------|-------------------------------------------------------------|
| Demographics                                        | Asthma                                                      |
| Age at initiation                                    | Cancer                                                      |
| Female                                               | Chronic kidney disease*                                     |
| Year of initiation                                   | Essential tremor*                                            |
| Comorbidity index (combined score for adults, pediatric comorbidity index for children)² | Fibromyalgia                                                |
| Treatment Indications                                | Sleep disorders                                             |
| Bipolar disorder                                     | Lifestyle Factors                                           |
| Epilepsy or convulsions                              | Alcohol abuse or dependence                                 |
| Migraine/headache                                    | Drug abuse or dependence                                    |
| Neuropathic pain                                     | Smoking                                                     |
| Metabolic Conditions                                 | Lab Tests Ordered                                           |
| Obesity or overweight                                | Glucose test                                                |
| Weight management                                    | Hemoglobin A1C test                                         |
| Abnormal weight gain                                 | Lipid test                                                  |
| Abnormal glucose/Prediabetes                         | Medications                                                 |
| Metabolic syndrome                                   | Lithium                                                     |
| Hyperinsulinemia                                     | Antipsychotics                                              |
| Growth conditions                                    | Antidepressants                                             |
| Hyperlipidemia                                       | Stimulants                                                  |
| Hyperthyroidism                                      | Oral corticosteroids                                        |
| Hypothyroidism                                       | Weight loss medications*                                    |
| Nonalcoholic fatty liver disease                     | Antihypertensives**                                         |
| Polycystic ovary syndrome                            | Angiotensin-converting-enzyme inhibitors*                  |
| Psychiatric Conditions                               | Angiotensin II receptor blockers*                           |
| Attention-deficit/hyperactivity disorder             | Beta blockers*                                              |
| Anxiety                                              | Thiazides*                                                  |
| Autism and pervasive developmental disorders         | Calcium channel blockers*                                   |
| Delirium                                             | Statins and lipid lowering drugs*                           |
| Depression                                           | Healthcare Utilization                                      |
| Eating disorders                                     | Number of outpatient visits                                 |
| Psychotic disorders                                  | Number of mental health outpatient visits                   |
| Cardiovascular Conditions                            | Number of distinct generic drugs dispensed                  |
| Acute myocardial infarction *                        | Number of emergency department visits                       |
| Coronary artery disease *                            | Number of hospitalizations                                  |
| Heart failure*                                       | Any mental health hospitalization                            |
| Hemorrhagic stroke*                                  | Days hospitalized                                           |
| Hypertension                                         |                                                             |
| Ischemic stroke*                                     |                                                             |

| **Time-Varying Covariates**                          | **Treatment Indications**                                   |
|------------------------------------------------------|-------------------------------------------------------------|
| Factors Associated With Weight Change or Type 2 Diabetes |                                             |
| Depression                                           | Bipolar disorder                                            |
| Psychotic disorders                                  | Epilepsy or convulsions                                     |
| Lithium                                              | Migraine/headache                                           |
| Antipsychotics                                       | Neuropathic pain                                            |
| Antidepressants                                       | Healthcare Utilization                                      |
| Stimulants                                           | Any outpatient visit                                        |
| Oral corticosteroids                                 | Any emergency department visit                              |
| Weight loss medications*                             | Any hospitalization                                         |
| Antihypertensives                                    | Any generic drugs dispensed, excluding anticonvulsants      |
| Statins and lipid lowering drugs*                    | Lifestyle factors                                           |
| Pregnancy                                            | Alcohol abuse or dependence                                 |
| Bariatric surgery                                    | Drug abuse or dependence                                    |
| Smoking                                              |                                                             |

* Indicates covariate was only included in the adult trial emulation.
** Indicates covariate was only included in the pediatric trial emulation.
eMethods. Details on Estimating Inverse Probability Weights and Treatment Effects

We used inverse probability weights to adjust for confounding due to lack of baseline randomization, as well as selection bias due to loss to follow-up [ITT and PP] and treatment nonadherence [PP only]. The analytic dataset was structured so that each patient had one record for each two-week interval of follow up. In the ITT analysis, follow up ended at the two-week interval of T2D incidence, loss to follow-up, or 5 years, whichever came first. In the PP analysis, we additionally censored patients in the first interval where patients reached the end of the grace period without refilling their initiated medication (treatment discontinuation) or switched treatments (the date a different anticonvulsant medication was dispensed). Therefore, follow up ended at the 2-week interval of T2D incidence, loss to follow up, 5 years, treatment discontinuation, or treatment switch, whichever came first.

Treatment Weights

In both the intention-to-treat and per-protocol analyses, we applied inverse probability of treatment weights (IPTW) to account for baseline confounding. Specifically, we defined the numerator of the weight for a particular individual as the marginal probability of initiating treatment and the denominator of the weight as the probability of initiating that treatment conditional on that individual’s levels of the measured baseline covariates. We used multinomial logistic regression to estimate these initiation probabilities. These weights were time-fixed, so each patient had the same IPTW for each 2-week interval of follow up. More details and SAS code for implementation available elsewhere.

Censoring Weights

Intention-to-Treat Analysis

In the intention-to-treat analysis, we applied inverse probability of censoring weights (IPCW) to account for potential selection bias due to loss to follow-up. Probabilities needed for these weights were estimated separately for each treatment group. These weights varied for each individual over time. Therefore, the weight for an individual in a particular 2-week interval of follow-up t, who was still uncensored by t, is a product, over all prior intervals k < t, of a ratio of probabilities indexed by interval k: the numerator was an estimate of the marginal probability of remaining uncensored by loss to follow-up through k and the denominator was an estimate of this probability conditional on that individual’s level of measured baseline covariates. We used logistic regression to estimate these probabilities, with the censoring indicator as the dependent variable. Patients received a weight of zero once they were censored. Therefore, censored individuals contributed information to the probabilities used for the weight construction up until their censoring time. More details and SAS code for implementation available elsewhere.

Per-Protocol Analysis

In the per-protocol analysis, we applied IPCW to account for potential selection bias due to censoring by treatment discontinuation (C1k), treatment switching (C2k), or loss to follow-up (C3k) by a particular interval k. The same approach above to constructing IPCW for the ITT analysis was used here with a few exceptions.

First, we constructed ICPW separately for each type of censoring (C1, C2, C3). The final IPCW at a particular time was defined as the product of these three weights at that time (C1k*C2k*C3k), for individuals still uncensored by that time. As in the ITT analysis, individuals receive a weight of zero at the time of censoring, but they still contribute information to the analysis up until their censoring time. Separate models were used for each censorship reason to allow better prediction of these different types of censorship events.

Second, the denominator of each of the three weights depended not only on baseline covariates (V), but also the history of time-varying covariates to account for potential time-varying confounding. To estimate the probability of remaining uncensored for a given reason in an interval k conditional on baseline and time-varying covariates, we additionally included the values of time-varying covariates corresponding to the current 2-week interval (Lk), the previous 2-week interval (Llag[Lk]), and an interaction term between these measurements (Lk*lag[Lk]). For time-varying covariates that were chronic conditions, the presence of a diagnosis code was carried forward for the remainder of the follow up period. For example, a patient diagnosed with depression during the 2nd week of follow up was flagged as having depression for each subsequent 2-week interval over follow up. Because we defined treatment discontinuation using the grace period algorithm described in the main text, censoring by treatment discontinuation was only possible during time intervals where a patient’s grace period (i.e., allowable gap between prescription fills) would expire if no medication refill were dispensed (Gk=1). Therefore, the weights were not updated during these intervals (as the contribution to the product mentioned above was 1). This approach minimizes model misclassification by incorporating knowledge that this form of censoring was not possible during certain intervals for certain patients. The time k contribution to the denominator of the censoring weights can be summarized as follows:
Treatment discontinuation:
\[ \Pr(C_1 = 0 | L_k, \text{lag}[L_k], L_k \ast \text{lag}[L_k], V, G_k = 1), \text{if } G_k = 1 \]
\[ 1, \text{if } G_k = 0 \]

Treatment switch:
\[ \Pr(C_2 = 0 | L_k, \text{lag}[L_k], L_k \ast \text{lag}[L_k], V) \]

Loss to follow up:
\[ \Pr(C_3 = 0 | L_k, \text{lag}[L_k], L_k \ast \text{lag}[L_k], V) \]

Third, the numerator of the weights further depended on a subset of the baseline covariates (Z) which were conditioned on in the weighted outcome regression model described below. This provided further weight stabilization at the expense of the assumption that this conditional outcome model was correctly specified. The time k contribution to the numerator of the censoring weights can be summarized as follows:

Treatment discontinuation:
\[ \Pr(C_1 = 0 | Z, G_k = 1), \text{if } G_k = 1 \]
\[ 1, \text{if } G_k = 0 \]

Treatment switch:
\[ \Pr(C_2 = 0 | Z) \]

Loss to follow up:
\[ \Pr(C_3 = 0 | Z) \]

Estimating Treatment Effects

We estimated the absolute risks of type 2 diabetes for each treatment group using weighted pooled logistic regression models. The weight for each 2-week person-time record in the data was defined as the product of a time-fixed IPTW (i.e., weight remains the same for each person) and time-updated IPCW (i.e., weight changes for each 2-week interval of follow up). The weights were truncated at the 1st and 99th percentiles to prevent outliers from influencing the analysis. The dependent variable in this pooled over interval model was T2D and the independent variables were indicators for which treatment the patient initiated and a function of time (modelled flexibly as linear and quadratic terms, as well as interactions terms with treatment to minimize misclassification of the baseline hazard). In the PP analysis, the independent variables also included subset of the baseline covariates Z that were included in the numerator of the censoring weights described above.

From these models, we predicted the hazard of T2D under each treatment strategy for each 2-week interval of follow up, which can be used to estimate the cumulative survival under initiation of or adherence to each treatment strategy. We generated adjusted survival curves for the probability of remaining free of type 2 diabetes over follow up. In the per-protocol analysis, these survival curves were standardized by the subset of baseline covariates Z that were used to estimate the numerator of the censoring weights. We estimated 95% confidence intervals for the 2-year and 5-year risk (complement of survival) differences using nonparametric bootstrapping of 400 samples. The desired interpretation of our estimates relied on the assumptions that our weight models were correctly specified, the hazard models were a correctly specified function of time (and Z), and that measured baseline and time-varying covariates were sufficient to control confounding due to lack of baseline randomization and selection bias due to loss to follow-up. Additional details on these analyses and how to implement them are available elsewhere.
eFigure 1. Flow Diagram of Cohort Assembly

A. Adult Target Trial
- Adults (20-65 years) with >1 year of enrollment in MarketScan, n=64,381,602
- Excluded: 63,656,031
  - 63,266,354 Did not receive an anticonvulsant mood stabilizer
  - 388,677 Without continuous enrollment during the year prior to treatment initiation
- Received an anticonvulsant mood stabilizer medication, n=706,571
  - Excluded: 432,365
    - 394,882 Received an anticonvulsant medication (including those not used as mood stabilizers) in the previous year
    - 30,027 Diagnosed with diabetes or dispensed an antidiabetic medication in the previous year
    - 6,781 Pregnant during the previous year
    - 675 Received bariatric surgery in the previous year
- Final study population, n=274,206

B. Pediatric Target Trial
- Children (10-19 years) with >1 year of enrollment in MarketScan, n=12,886,608
- Excluded: 12,752,487
  - 12,662,859 Did not receive an anticonvulsant mood stabilizer
  - 69,628 Without continuous enrollment during the year prior to treatment initiation
- Received an anticonvulsant mood stabilizer medication, n=134,121
  - Excluded: 60,116
    - 58,456 Received an anticonvulsant medication (including those not used as mood stabilizers) in the previous year
    - 1,038 Diagnosed with diabetes or dispensed an antidiabetic medication in the previous year
    - 613 Pregnant during the previous year
    - 9 Received bariatric surgery in the previous year
- Final study population, n=74,005
Table 4. Unadjusted Baseline Characteristics of Adults Who Initiated Anticonvulsant Mood Stabilizer Treatment in MarketScan

| Characteristic                        | Carbamazepine | Lamotrigine | Oxcarbazepine | Valproate |
|---------------------------------------|---------------|-------------|---------------|-----------|
|                                       | N            | %           | N            | %         | N          | %           | N          | %         |
| No. of patients                       | 26641        | 100.0       | 132739       | 100.0     | 24226      | 100.0       | 90600      | 100.0     |
| **Demographics**                      |              |             |              |           |            |             |            |           |
| Age at initiation, years              |              |             |              |           |            |             |            |           |
| mean (SD)                             | 45.45        | 12.5        | 38.02        | 12.8      | 39.49      | 13.4        | 41.04      | 13.3      |
| 20-39 years                           | 8339         | 31.3        | 73698        | 55.5      | 12204      | 50.4        | 41544      | 45.9      |
| 40-54 years                           | 10566        | 39.7        | 41448        | 31.2      | 7835       | 32.3        | 30810      | 34.0      |
| 55-65 years                           | 7736         | 29          | 17593        | 13.3      | 4187       | 17.3        | 18246      | 20.1      |
| Female                                | 16069        | 60.3        | 87039        | 65.6      | 14418      | 59.5        | 41902      | 46.2      |
| Year of initiation                    |              |             |              |           |            |             |            |           |
| 2011                                  | 4839         | 18.2        | 19910        | 15.0      | 3525       | 14.6        | 25739      | 28.4      |
| 2012                                  | 5141         | 19.3        | 22776        | 17.2      | 4194       | 17.3        | 17027      | 18.8      |
| 2013                                  | 3878         | 14.6        | 17784        | 13.4      | 3222       | 13.3        | 11272      | 12.4      |
| 2014                                  | 3314         | 12.4        | 16195        | 12.2      | 3037       | 12.5        | 9560       | 10.6      |
| 2015                                  | 2663         | 10.0        | 13228        | 10.0      | 2438       | 10.1        | 7555       | 8.3       |
| 2016                                  | 2386         | 9.0         | 13589        | 10.2      | 2512       | 10.4        | 7085       | 7.8       |
| 2017                                  | 2026         | 7.6         | 12753        | 9.6       | 2378       | 9.8         | 5521       | 6.1       |
| 2018                                  | 1907         | 7.2         | 12773        | 9.6       | 2259       | 9.3         | 5342       | 5.9       |
| 2019                                  | 487          | 1.8         | 3731         | 2.8       | 661        | 2.7         | 1499       | 1.7       |
| Combined comorbidity index; mean (SD) | 0.51         | 1.2         | 0.95         | 1.0       | 0.92       | 1.2         | 0.88       | 1.3       |
| **Treatment Indications**             |              |             |              |           |            |             |            |           |
| Bipolar disorder                      | 3669         | 13.8        | 51393        | 38.7      | 8445       | 34.9        | 32447      | 35.8      |
| Epilepsy or convulsions               | 2156         | 8.1         | 5715         | 4.3       | 1680       | 6.9         | 9458       | 10.4      |
| Migraine/headache                     | 6917         | 26.0        | 19657        | 14.8      | 4298       | 17.7        | 25769      | 28.4      |
| Neuropathic pain                      | 10876        | 40.8        | 13913        | 10.5      | 4913       | 20.3        | 10156      | 11.2      |
| **Metabolic Conditions**              |              |             |              |           |            |             |            |           |
| Obesity or overweight                | 2931         | 11.0        | 15097        | 11.4      | 2971       | 12.3        | 8258       | 9.1       |
| Weight management                    | 313          | 1.2         | 2142         | 1.6       | 335        | 1.4         | 861        | 1.0       |
| Abnormal weight gain                 | 446          | 1.7         | 3337         | 2.5       | 466        | 1.9         | 1356       | 1.5       |
| Abnormal glucose/Prediabetes          | 1251         | 4.7         | 5096         | 3.8       | 1031       | 4.3         | 3556       | 3.9       |
| Metabolic syndrome                   | 154          | 0.6         | 801          | 0.6       | 144        | 0.6         | 391        | 0.4       |
| Hyperinsulinemia                      | 13           | 0.0         | 130          | 0.1       | 21         | 0.1         | 84         | 0.1       |
| Growth conditions                    | 213          | 0.8         | 1008         | 0.8       | 200        | 0.8         | 759        | 0.8       |
| Hyperlipidemia                        | 6325         | 23.7        | 22000        | 16.6      | 4603       | 19.0        | 19469      | 21.5      |
| Hyperthyroidism                       | 161          | 0.6         | 844          | 0.6       | 157        | 0.6         | 628        | 0.7       |
| Hypothyroidism                        | 2725         | 10.2        | 12644        | 9.5       | 2350       | 9.7         | 8518       | 9.4       |
| Nonalcoholic fatty liver disease      | 284          | 1.1         | 1018         | 0.8       | 229        | 0.9         | 813        | 0.9       |
| Polycystic ovary syndrome             | 144          | 0.5         | 1532         | 1.2       | 218        | 0.9         | 344        | 0.4       |
| **Lab Tests Ordered**                 |              |             |              |           |            |             |            |           |
| Glucose test                          | 1854         | 7.0         | 8243         | 6.2       | 1574       | 6.5         | 6474       | 7.1       |
| Hemoglobin A1C test                   | 3496         | 13.1        | 17938        | 13.5      | 3323       | 13.7        | 10567      | 11.7      |
| Lipid test                            | 11052        | 41.5        | 50344        | 37.9      | 9359       | 38.6        | 35261      | 38.9      |
| **Psychiatric Conditions**           |              |             |              |           |            |             |            |           |
| ADHD                                  | 840          | 3.2         | 13104        | 9.9       | 2032       | 8.4         | 4610       | 5.1       |
| Anxiety                               | 5868         | 22.0        | 61497        | 46.3      | 9560       | 39.5        | 27069      | 29.9      |
| Autism and pervasive developmental disorders | 105    | 0.4         | 641          | 0.5       | 245        | 1.0         | 953        | 1.1       |
| Delirium                              | 223          | 0.8         | 753          | 0.6       | 225        | 0.9         | 1473       | 1.6       |
| Depression                            | 6416         | 24.1        | 77693        | 58.5      | 11144      | 46.0        | 33280      | 36.7      |
| Eating disorders                      | 96           | 0.4         | 2142         | 1.6       | 223        | 0.9         | 405        | 0.4       |
| Psychotic disorders                   | 915          | 3.4         | 5403         | 4.1       | 1745       | 7.2         | 9770       | 10.8      |
| **Cardiovascular Conditions**         |              |             |              |           |            |             |            |           |

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### Days hospitalized

| Days hospitalized | Count |
|-------------------|-------|
| 0                 | 22542 |
| 1 to 5            | 1725  |
| ≥6                | 2374  |

### Number of ED visits

| Number of ED visits | Count |
|---------------------|-------|
| 0                   | 17070 |
| 1                   | 5528  |
| ≥2                  | 4043  |

### Number of hospitalizations

| Number of hospitalizations | Count |
|---------------------------|-------|
| 0                         | 22542 |
| 1                         | 2892  |
| ≥2                        | 1207  |

### Any mental health hospitalization

| Any mental health hospitalization | Count |
|----------------------------------|-------|
| 0                                | 2456  |

### Number of distinct generic drugs dispensed; median (IQR)

| Number of distinct generic drugs dispensed; median (IQR) | Count |
|---------------------------------------------------------|-------|
| 0                                                       | 7     |
| 1                                                       | 7     |
| ≥2                                                      | 7     |

### Number of mental health outpatient visits; median (IQR)

| Number of mental health outpatient visits; median (IQR) | Count |
|--------------------------------------------------------|-------|
| 0                                                      | 0     |
| 1                                                      | 4     |

### Number of outpatient visits; median (IQR)

| Number of outpatient visits; median (IQR) | Count |
|------------------------------------------|-------|
| 9                                        | 5     |
| 12                                       | 5     |

### Lifestyle Factors

| Lifestyle Factors | Count |
|-------------------|-------|
| Alcohol abuse or dependence | 1791  |
| Drug abuse or dependence   | 2006  |

### Smoking

| Smoking | Count |
|---------|-------|
| 3145    | 11.8  |

### Medications

| Medications | Count |
|-------------|-------|
| Lithium     | 630   |
| Antipsychotics | 3121 |
| Antidepressants | 8318 |
| Stimulants | 2152 |
| Oral corticosteroids | 7161 |
| Weight loss medications | 143  |
| ACE inhibitors | 2796 |
| ARBs        | 1673 |
| Beta blockers | 3342 |
| Thiazides | 2899 |
| Calcium channel blockers | 1831 |
| Statins and lipid lowering drugs | 4375 |

### Comorbidities

| Comorbidities | Count |
|---------------|-------|
| Asthma        | 1899  |
| Cancer        | 967   |
| Chronic kidney disease | 321  |
| Essential tremor | 136  |
| Fibromyalgia | 1562  |
| Sleep disorders | 3730 |
| Alcohol abuse or dependence | 1791 |
| Drug abuse or dependence   | 2006 |

### Medications

| Medications                      | Count |
|----------------------------------|-------|
| Statins and lipid lowering drugs | 4375  |
| ACE inhibitors                   | 2796  |
| ARBs                             | 1673  |
| Beta blockers                    | 3342  |
| Thiazides                        | 2899  |
| Calcium channel blockers         | 1831  |
| Oral corticosteroids             | 7161  |
| Weight loss medications         | 143   |
| Antipsychotics                   | 3121  |
| Antidepressants                  | 8318  |
| Stimulants                       | 2152  |
| Smoking                          | 3145  |

### Healthcare Utilization

| Healthcare Utilization | Count |
|------------------------|-------|
| Number of outpatient visits; median (IQR) | 9  |
| Number of mental health outpatient visits; median (IQR) | 0  |
| Number of distinct generic drugs dispensed; median (IQR) | 7  |

### Abbreviations

- ACE = Angiotensin-converting-enzyme
- ARBs = Angiotensin II receptor blockers
- ADHD = Attention-deficit/hyperactivity disorder
- ED = Emergency department
- IQR = Interquartile range
- SD = Standard deviation

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### Table 5. Unadjusted Baseline Characteristics of Children Who Initiated Anticonvulsant Mood Stabilizer Treatment in MarketScan

| Characteristic                          | Carbamazepine | Lamotrigine | Oxcarbazepine | Valproate |
|----------------------------------------|---------------|-------------|---------------|-----------|
| No. of patients                        | N             | %           | N             | %         | N          | %     | N          | %     |
| Demographics                           |               |             |               |           |            |       |            |       |
| Age at initiation (years)              |               |             |               |           |            |       |            |       |
| mean (SD)                              | 15.63         | 2.7         | 16.01         | 2.4       | 14.69      | 2.7   | 15.51      | 2.7   |
| 10-12 years                            | 386           | 15.2        | 3564          | 9.8       | 3100       | 24.9  | 3761       | 16.6  |
| 13-17 years                            | 1369          | 54.1        | 20949         | 57.6      | 7070       | 56.9  | 12382      | 54.7  |
| 18-19 years                            | 777           | 30.7        | 11881         | 32.6      | 2264       | 18.2  | 6502       | 28.7  |
| Female                                 | 1193          | 47.1        | 24273         | 66.7      | 6023       | 48.4  | 7183       | 31.7  |
| Year of initiation                     |               |             |               |           |            |       |            |       |
| 2011                                   | 547           | 21.6        | 4902          | 13.5      | 1854       | 14.9  | 6110       | 27.0  |
| 2012                                   | 531           | 21.0        | 5642          | 15.5      | 2056       | 16.5  | 4329       | 19.1  |
| 2013                                   | 366           | 14.5        | 4767          | 13.1      | 1572       | 12.6  | 2853       | 12.6  |
| 2014                                   | 318           | 12.6        | 4468          | 12.3      | 1619       | 13.0  | 2454       | 10.8  |
| 2015                                   | 231           | 9.1         | 3781          | 10.4      | 1277       | 10.3  | 1837       | 8.1   |
| 2016                                   | 218           | 8.6         | 3877          | 10.7      | 1335       | 10.7  | 1761       | 7.8   |
| 2017                                   | 151           | 6.0         | 3882          | 10.7      | 1233       | 9.9   | 1520       | 6.7   |
| 2018                                   | 135           | 5.3         | 3921          | 10.8      | 1140       | 9.2   | 1403       | 6.2   |
| 2019                                   | 35            | 1.4         | 1154          | 3.2       | 348        | 2.8   | 378        | 1.7   |
| Pediatric comorbidity index; mean (SD) | 5.97          | 4.3         | 6.51          | 3.8       | 6.06       | 3.9   | 5.83       | 4.1   |
| Treatment Indications                  |               |             |               |           |            |       |            |       |
| Bipolar disorder                       | 968           | 38.2        | 14723         | 40.5      | 4556       | 36.6  | 8840       | 39.0  |
| Epilepsy or convulsions                | 344           | 13.6        | 2204          | 6.1       | 1862       | 15.0  | 3627       | 16.0  |
| Migraine/headache                      | 415           | 16.4        | 4679          | 12.9      | 1403       | 11.3  | 4835       | 21.4  |
| Neuropathic pain                       | 176           | 7.0         | 1155          | 3.2       | 279        | 2.2   | 569        | 2.5   |
| Metabolic Conditions                   |               |             |               |           |            |       |            |       |
| Obesity or overweight                 | 161           | 6.4         | 2649          | 7.3       | 862        | 6.9   | 1117       | 4.9   |
| Weight management                     | 62            | 2.4         | 1488          | 4.1       | 498        | 4.0   | 669        | 3.0   |
| Abnormal weight gain                   | 45            | 1.8         | 689           | 1.9       | 235        | 1.9   | 253        | 1.1   |
| Abnormal glucose/Prediabetes           | 22            | 0.9         | 315           | 0.9       | 92         | 0.7   | 175        | 0.8   |
| Metabolic syndrome                     | 7             | 0.3         | 134           | 0.4       | 40         | 0.3   | 61         | 0.3   |
| Growth conditions                      | 23            | 0.9         | 210           | 0.6       | 100        | 0.8   | 175        | 0.8   |
| Hyperlipidemia                         | 54            | 2.1         | 734           | 2.0       | 226        | 1.8   | 408        | 1.8   |
| Hyperthyroidism or Hypothyroidism      | 58            | 2.3         | 1010          | 2.8       | 249        | 2.0   | 543        | 2.4   |
| Lab Tests Ordered                      |               |             |               |           |            |       |            |       |
| Glucose test                           | 164           | 6.5         | 2081          | 5.7       | 795        | 6.4   | 1418       | 6.3   |
| Hemoglobin A1C test                    | 156           | 6.2         | 2798          | 7.7       | 830        | 6.7   | 1382       | 6.1   |
| Lipid test                             | 453           | 17.9        | 7248          | 19.9      | 2198       | 17.7  | 4108       | 18.1  |
| Psychiatric Conditions                 |               |             |               |           |            |       |            |       |
| ADHD                                   | 439           | 17.3        | 7155          | 19.7      | 2880       | 23.2  | 4024       | 17.8  |
| Anxiety                                | 714           | 28.2        | 17075         | 46.9      | 4235       | 34.1  | 5976       | 26.4  |
| Autism and pervasive developmental disorders | 209       | 8.3         | 1878          | 5.2       | 1262       | 10.1  | 2458       | 10.9  |
| Delirium                               | 38            | 1.5         | 375           | 1.0       | 159        | 1.3   | 331        | 1.5   |
| Depression                             | 975           | 38.5        | 22100         | 60.7      | 5477       | 44.0  | 8123       | 35.9  |
| Eating disorders                       | 44            | 1.7         | 1537          | 4.2       | 195        | 1.6   | 208        | 0.9   |
| Psychotic disorders                    | 257           | 10.2        | 2694          | 7.4       | 1092       | 8.8   | 2755       | 12.2  |
| Other Comorbidities                    |               |             |               |           |            |       |            |       |
| Asthma                                 | 309           | 12.2        | 3813          | 10.5      | 1428       | 11.5  | 2510       | 11.1  |
| Cancer                                 | 19            | 0.8         | 102           | 0.3       | 65         | 0.5   | 103        | 0.5   |
| Fibromyalgia                           | 62            | 2.4         | 641           | 1.8       | 167        | 1.3   | 313        | 1.4   |

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| Hypertension | 42  | 1.7 | 459  | 1.3  | 181  | 1.5  | 451  | 2.0  |
|--------------|-----|-----|-------|------|------|------|------|------|
| Sleep disorders | 221 | 8.7 | 3647  | 10.0 | 1042 | 8.4  | 1886 | 8.3  |
| **Lifestyle Factors** | | | | | | | | |
| Alcohol abuse or dependence | 147 | 5.8 | 1463 | 4.0  | 479  | 3.9  | 1060 | 4.7  |
| Drug abuse or dependence | 364 | 14.4 | 3675 | 10.1 | 1306 | 10.5 | 3023 | 13.3 |
| Smoking | 189 | 7.5 | 1709 | 4.7  | 626  | 5.0  | 1457 | 6.4  |
| **Medications** | | | | | | | | |
| Lithium | 117  | 4.6 | 1519 | 4.2  | 332  | 2.7  | 847  | 3.7  |
| Antipsychotics | 913 | 36.1 | 12898 | 35.4 | 4527 | 36.4 | 9089 | 40.1 |
| Antidepressants | 1001 | 39.5 | 21777 | 59.8 | 5760 | 46.3 | 8272 | 36.5 |
| Stimulants | 807  | 31.9 | 11306 | 31.1 | 4793 | 38.5 | 8010 | 35.4 |
| Oral corticosteroids | 329  | 13.0 | 4210 | 11.6 | 1319 | 10.6 | 2706 | 11.9 |
| Antihypertensives | 468  | 18.5 | 5679 | 15.6 | 2750 | 22.1 | 4681 | 20.7 |
| **Healthcare Utilization** | | | | | | | | |
| Number of outpatient visits; median (IQR) | 9   | (5-19) | 13  | (7-26) | 11  | (5-21) | 9   | (5-18) |
| Number of mental health outpatient visits; median (IQR) | 3   | (0-9)  | 6   | (2-17) | 4   | (1-12) | 3   | (0-10) |
| Number of distinct generic drugs dispensed; median (IQR) | 5   | (2-8)  | 5   | (3-8)  | 4   | (2-7)  | 5   | (3-8)  |
| Number of ED visits | | | | | | | | |
| 0  | 1299 | 51.3 | 21279 | 58.5 | 6810 | 54.8 | 12229 | 54.0 |
| 1  | 634  | 25.0 | 8455  | 23.2 | 3067 | 24.7 | 5396  | 23.8 |
| ≥2 | 599  | 23.7 | 6660  | 18.3 | 2557 | 20.6 | 5020  | 22.2 |
| Number of hospitalizations | | | | | | | | |
| 0  | 1733 | 68.4 | 27510 | 75.6 | 8752 | 70.4 | 15993 | 70.6 |
| 1  | 554  | 21.9 | 6368  | 17.5 | 2600 | 20.9 | 4573  | 20.2 |
| ≥2 | 245  | 9.7  | 2516  | 6.9  | 1082 | 8.7  | 2079  | 9.2  |
| Any mental health hospitalization | 681 | 26.9 | 8074 | 22.2 | 3096 | 24.9 | 5528 | 24.4 |
| Days hospitalized | | | | | | | | |
| 0  | 1733 | 68.4 | 27510 | 75.6 | 8752 | 70.4 | 15993 | 70.6 |
| 1 to 5 | 209 | 8.3  | 2588  | 7.1  | 1084 | 8.7  | 1704  | 7.5  |
| ≥6 | 590  | 23.3 | 6296  | 17.3 | 2598 | 20.9 | 4948  | 21.9 |

Abbreviations: ADHD=Attention-deficit/hyperactivity disorder; ED=Emergency department; IQR=Interquartile range; SD=Standard deviation
Table 6. Baseline Characteristics of Adults Who Initiated Anticonvulsant Mood Stabilizer Treatment in MarketScan After Accounting for Baseline Confounding

| Characteristic                        | Carbamazepine | Lamotrigine | Oxcarbazepine | Valproate |
|---------------------------------------|---------------|-------------|---------------|-----------|
|                                       | N      | %    | N      | %    | N      | %    | N      | %    |
| No. of patients                       | 26806  | 100.0| 130670 | 100.0| 24712  | 100.0| 89831  | 100.0|
| **Demographics**                      |         |      |         |      |         |      |         |      |
| Age at initiation, years              |         |      |         |      |         |      |         |      |
| mean (SD)                             | 39.52  | 13.1 | 39.67  | 13.0 | 39.77  | 13.5 | 39.78  | 13.1 |
| 20-39 years                           | 13507  | 50.4 | 65468  | 50.1 | 12298  | 49.8 | 44877  | 50.0 |
| 40-54 years                           | 8892   | 33.2 | 43373  | 33.2 | 8014   | 32.4 | 29336  | 32.7 |
| 55-65 years                           | 4408   | 16.4 | 21829  | 16.7 | 4401   | 17.8 | 15619  | 17.4 |
| Female                                | 15123  | 56.4 | 75729  | 58.0 | 14417  | 58.3 | 51569  | 57.4 |
| Year of initiation                    |         |      |         |      |         |      |         |      |
| 2011                                  | 5516   | 20.6 | 25525  | 19.5 | 4848   | 19.6 | 17827  | 19.8 |
| 2012                                  | 5143   | 19.2 | 23618  | 18.1 | 4475   | 18.1 | 16296  | 18.1 |
| 2013                                  | 3667   | 13.7 | 17224  | 13.2 | 3290   | 13.3 | 11978  | 13.3 |
| 2014                                  | 3306   | 12.3 | 15365  | 11.8 | 2897   | 11.7 | 10568  | 11.8 |
| 2015                                  | 2509   | 9.4  | 12334  | 9.4  | 2314   | 9.4  | 8481   | 9.4  |
| 2016                                  | 2387   | 8.9  | 12150  | 9.3  | 2298   | 9.3  | 8249   | 9.2  |
| 2017                                  | 1993   | 7.4  | 10862  | 8.3  | 2027   | 8.2  | 7268   | 8.1  |
| 2018                                  | 1790   | 6.7  | 10556  | 8.1  | 1985   | 8.0  | 7098   | 7.9  |
| 2019                                  | 495    | 1.8  | 3036   | 2.3  | 578    | 2.3  | 2066   | 2.3  |
| Combined comorbidity index; mean (SD) | 1.01   | 1.3  | 0.91   | 1.1  | 0.9    | 1.2  | 0.91   | 1.2  |
| **Treatment Indications**             |         |      |         |      |         |      |         |      |
| Bipolar disorder                      | 10829  | 40.4 | 48095  | 36.8 | 8973   | 36.3 | 33303  | 37.1 |
| Epilepsy or convulsions               | 2329   | 8.7  | 9649   | 7.4  | 1763   | 7.1  | 6393   | 7.1  |
| Migraine/headache                     | 6083   | 22.7 | 26740  | 20.5 | 5205   | 21.1 | 18972  | 21.1 |
| Neuropathic pain                      | 3596   | 13.4 | 18084  | 13.8 | 3819   | 15.5 | 12792  | 14.2 |
| **Metabolic Conditions**              |         |      |         |      |         |      |         |      |
| Obesity or overweight                | 2923   | 10.9 | 14290  | 10.9 | 2660   | 10.8 | 9816   | 10.9 |
| Weight management                     | 341    | 1.3  | 1767   | 1.4  | 325    | 1.3  | 1176   | 1.3  |
| Abnormal weight gain                  | 570    | 2.1  | 2740   | 2.1  | 516    | 2.1  | 1850   | 2.1  |
| Abnormal glucose/Prediabetes          | 1209   | 4.5  | 5284   | 4.0  | 993    | 4.0  | 3648   | 4.1  |
| Metabolic syndrome                    | 167    | 0.6  | 723    | 0.6  | 139    | 0.6  | 484    | 0.5  |
| Hyperinsulinemia                      | 34     | 0.1  | 129    | 0.1  | 23     | 0.1  | 79     | 0.1  |
| Growth conditions                     | 258    | 1.0  | 1091   | 0.8  | 200    | 0.8  | 721    | 0.8  |
| Hyperlipidemia                        | 5324   | 19.9 | 24995  | 19.1 | 4752   | 19.2 | 17327  | 19.3 |
| Hyperthyroidism                       | 198    | 0.7  | 875    | 0.7  | 166    | 0.7  | 614    | 0.7  |
| Hypothyroidism                        | 2613   | 9.7  | 12573  | 9.6  | 2371   | 9.6  | 8558   | 9.5  |
| Nonalcoholic fatty liver disease      | 289    | 1.1  | 1173   | 0.9  | 214    | 0.9  | 797    | 0.9  |
| Polycystic ovary syndrome             | 231    | 0.9  | 1087   | 0.8  | 211    | 0.9  | 695    | 0.8  |
| **Lab Tests Ordered**                 |         |      |         |      |         |      |         |      |
| Glucose test                          | 1887   | 7.0  | 8767   | 6.7  | 1668   | 6.7  | 6047   | 6.7  |
| Hemoglobin A1C test                   | 3580   | 13.4 | 17202  | 13.2 | 3222   | 13.0 | 11730  | 13.1 |
| Lipid test                            | 10296  | 38.4 | 50624  | 38.7 | 9589   | 38.8 | 34818  | 38.8 |
| **Psychiatric Conditions**            |         |      |         |      |         |      |         |      |
| ADHD                                  | 2046   | 7.6  | 10181  | 7.8  | 1917   | 7.8  | 6928   | 7.7  |
| Anxiety                               | 10898  | 40.7 | 51181  | 39.2 | 9602   | 38.9 | 35189  | 39.2 |
| Autism and pervasive developmental disorders | 216  | 0.8  | 965    | 0.7  | 181    | 0.7  | 663    | 0.7  |
| Delirium                              | 420    | 1.6  | 1314   | 1.0  | 255    | 1.0  | 933    | 1.0  |
| Depression                            | 13280  | 49.5 | 63468  | 48.6 | 11824  | 47.8 | 43411  | 48.3 |
| Eating disorders                      | 263    | 1.0  | 1411   | 1.1  | 282    | 1.1  | 863    | 1.0  |
| Psychotic disorders                   | 2274   | 8.5  | 8904   | 6.8  | 1712   | 6.9  | 6077   | 6.8  |
| **Cardiovascular Conditions**         |         |      |         |      |         |      |         |      |

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| Condition                        | Number of Patients | Mean (IQR) |
|---------------------------------|--------------------|------------|
| Acute myocardial infarction     | 85                 | 0.3 (0-1.5)|
| Coronary artery disease         | 706                | 2.6 (1.4-3.5)|
| Heart failure                   | 305                | 1.1 (0.7-1.7)|
| Hemorrhagic stroke              | 244                | 0.9 (0.5-1.3)|
| Hypertension                    | 6052               | 22.6 (20.7-22.7)|
| Ischemic stroke                 | 413                | 1.5 (1.4-1.7)|
| **Other Comorbidities**         |                    |            |
| Asthma                          | 2267               | 8.5 (7.8-9.2)|
| Cancer                          | 724                | 2.7 (2.4-3.0)|
| Chronic kidney disease          | 382                | 1.4 (1.2-1.6)|
| Essential tremor                | 164                | 0.6 (0.5-0.7)|
| Fibromyalgia                    | 1625               | 6.1 (5.1-6.7)|
| Sleep disorders                 | 5380               | 20.1 (18.4-20.3)|
| **Lifestyle Factors**           |                    |            |
| Alcohol abuse or dependence     | 2699               | 10.1 (7.9-10.7)|
| Drug abuse or dependence        | 3478               | 13.0 (10.0-13.0)|
| Smoking                         | 4022               | 15.0 (12.9-15.7)|
| **Medications**                 |                    |            |
| Lithium                         | 1689               | 6.3 (5.1-6.6)|
| Antipsychotics                  | 8547               | 31.9 (27.4-35.8)|
| Antidepressants                 | 14684              | 54.8 (52.8-68.9)|
| Stimulants                      | 4453               | 16.6 (15.2-18.8)|
| Oral corticosteroids            | 5664               | 21.1 (20.1-22.9)|
| Weight loss medications         | 147                | 0.5 (0.6-0.7)|
| ACE inhibitors                  | 2256               | 8.4 (8.0-8.8)|
| ARBs                            | 1202               | 4.5 (4.4-10.9)|
| Beta blockers                   | 3526               | 13.2 (11.8-15.4)|
| Thiazides                       | 2175               | 8.1 (7.7-10.0)|
| Calcium channel blockers        | 1571               | 5.9 (5.3-6.9)|
| Statins and lipid lowering drugs| 3468               | 12.9 (12.5-13.9)|
| **Healthcare Utilization**      |                    |            |
| Number of outpatient visits; median (IQR) | 12 (6-23) | 12 (6-22) | 11 (6-21) | 11 (5-21) |
| Number of mental health outpatient visits; median (IQR) | 3 (0-9) | 3 (1-9) | 3 (0-8) | 3 (0-8) |
| Number of distinct generic drugs dispensed; median (IQR) | 8 (4-12) | 7 (4-12) | 7 (4-11) | 7 (4-11) |
| Number of ED visits             | 0                  | 16247 (60.6-83639) | 64.0 | 15946 (64.5-57133) | 63.6 |
|                                | 1                  | 5422 (20.2-25778) | 19.7 | 4798 (19.4-17936) | 20.0 |
|                                | ≥2                 | 5139 (19.2-21253) | 16.3 | 3969 (16.1-14763) | 16.4 |
| Number of hospitalizations      | 0                  | 20629 (77.0-106890) | 81.8 | 20356 (82.4-73396) | 81.7 |
|                                | 1                  | 4268 (15.9-17261) | 13.2 | 3161 (12.8-11899) | 13.2 |
|                                | ≥2                 | 1910 (7.1-6519) | 5.0 | 1196 (4.8-4537) | 5.1 |
| Any mental health hospitalization | 4299   | 16.0 (16.0-16171) | 12.4 | 2934 (11.9-11137) | 12.4 |
| Days hospitalized              | 0                  | 20629 (77.0-106890) | 81.8 | 20356 (82.4-73396) | 81.7 |
|                                | 1 to 5             | 2321 (8.7-9576) | 7.3 | 1744 (7.1-6663) | 7.4 |
|                                | ≥6                 | 3857 (14.4-14204) | 10.9 | 2612 (10.6-9772) | 10.9 |

Abbreviations: ACE=Angiotensin-converting enzyme; ARBs=Angiotensin II receptor blockers; ADHD=Attention-deficit/hyperactivity disorder; ED=Emergency department; IQR=Interquartile range; SD=Standard deviation

Estimates weighted by the inverse probability of treatment.
**Table 7. Baseline Characteristics of Children Who Initiated Anticonvulsant Mood Stabilizer Treatment in MarketScan After Accounting for Baseline Confounding**

| Characteristic                        | Carbamazepine | Lamotrigine | Oxcarbazepine | Valproate |
|---------------------------------------|---------------|-------------|---------------|-----------|
|                                       | N            | %           | N             | %         | N          | %          | N            | %          |
| No. of patients                       | 2548         | 100.0       | 36136         | 100.0     | 12495      | 100.0      | 21922        | 100.0      |
| **Demographics**                      |               |             |               |           |            |            |               |            |
| Age at initiation (years) mean (SD)   | 15.67        | 2.7         | 15.62         | 2.6       | 15.64      | 2.6        | 15.59        | 2.6        |
| 10-12 years                           | 372          | 14.6        | 5297          | 14.7      | 1818       | 14.5       | 3352         | 15.3       |
| 13-17 years                           | 1373         | 53.9        | 20374         | 56.4      | 7109       | 56.9       | 12145        | 55.4       |
| 18-19 years                           | 804          | 31.5        | 10467         | 29        | 3568       | 28.6       | 6432         | 29.3       |
| Female                                | 1320         | 51.8        | 18975         | 52.5      | 6627       | 53.0       | 11058        | 50.4       |
| Year of initiation                    | 2011         | 18.3        | 6484          | 17.9      | 2290       | 18.3       | 4107         | 18.7       |
|                                      | 2012         | 17.2        | 6233          | 17.2      | 2124       | 17.0       | 3929         | 17.9       |
|                                      | 2013         | 13.2        | 4713          | 13.0      | 1620       | 13.0       | 2892         | 13.2       |
|                                      | 2014         | 11.9        | 4349          | 12.0      | 1497       | 12.0       | 2616         | 11.9       |
|                                      | 2015         | 9.9         | 3429          | 9.5       | 1176       | 9.4        | 2096         | 9.6        |
|                                      | 2016         | 9.7         | 3543          | 9.8       | 1255       | 10.0       | 2082         | 9.5        |
|                                      | 2017         | 9.0         | 3272          | 9.1       | 1123       | 9.0        | 1890         | 8.6        |
|                                      | 2018         | 8.4         | 3200          | 8.9       | 1084       | 8.7        | 1821         | 8.3        |
|                                      | 2019         | 2.4         | 913           | 2.5       | 326        | 2.6        | 489          | 2.2        |
| Pediatric comorbidity index; mean (SD)| 6.41         | 4.2         | 6.25          | 4.0       | 6.34       | 4.0        | 6.29         | 4.0        |
| **Treatment Indications**             |               |             |               |           |            |            |               |            |
| Bipolar disorder                      | 1073         | 42.1        | 14461         | 40.0      | 5110       | 40.9       | 8960         | 40.9       |
| Epilepsy or convulsions               | 277          | 10.9        | 3838          | 10.6      | 1310       | 10.5       | 2514         | 11.5       |
| Migraine/headache                     | 378          | 14.8        | 5535          | 15.3      | 1904       | 15.2       | 3539         | 16.1       |
| Neuropathic pain                      | 79           | 3.1         | 1070          | 3.0       | 388        | 3.1        | 644          | 2.9        |
| **Metabolic Conditions**              |               |             |               |           |            |            |               |            |
| Obesity or overweight                | 160          | 6.3         | 2377          | 6.6       | 834        | 6.7        | 1387         | 6.3        |
| Weight management                     | 85           | 3.3         | 1318          | 3.6       | 454        | 3.6        | 745          | 3.4        |
| Abnormal weight gain                  | 39           | 1.5         | 624           | 1.7       | 200        | 1.6        | 375          | 1.7        |
| Abnormal glucose/Prediabetes          | 22           | 0.9         | 300           | 0.8       | 95         | 0.8        | 188          | 0.9        |
| Metabolic syndrome                    | 7            | 0.3         | 123           | 0.3       | 41         | 0.3        | 74           | 0.3        |
| Growth conditions                     | 16           | 0.6         | 257           | 0.7       | 88         | 0.7        | 171          | 0.8        |
| Hyperlipidemia                        | 47           | 1.8         | 704           | 1.9       | 245        | 2.0        | 421          | 1.9        |
| Hyperthyroidism or Hypothyroidism     | 73           | 2.9         | 908           | 2.5       | 313        | 2.5        | 530          | 2.4        |
| **Lab Tests Ordered**                 |               |             |               |           |            |            |               |            |
| Glucose test                          | 145          | 5.7         | 2205          | 6.1       | 768        | 6.1        | 1366         | 6.2        |
| Hemoglobin A1C test                   | 176          | 6.9         | 2554          | 7.1       | 880        | 7.0        | 1531         | 7.0        |
| Lipid test                            | 464          | 18.2        | 6902          | 19.1      | 2400       | 19.2       | 4176         | 19.0       |
| **Psychiatric Conditions**           |               |             |               |           |            |            |               |            |
| ADHD                                  | 503          | 19.7        | 7175          | 19.9      | 2509       | 20.1       | 4328         | 19.7       |
| Anxiety                               | 969          | 38.0        | 13810         | 38.2      | 4846       | 38.8       | 8048         | 36.7       |
| Autism and pervasive development      | 201          | 7.9         | 3003          | 8.3       | 1015       | 8.1        | 1844         | 8.4        |
| disorders                             | Delirium      | 35          | 1.4           | 445       | 1.2        | 153        | 1.2         | 277         | 1.3        |
| Depression                            | 1289         | 50.6        | 18137         | 50.2      | 6352       | 50.8       | 10715        | 48.9       |
| Eating disorders                      | 78           | 3.1         | 978           | 2.7       | 346        | 2.8        | 475          | 2.2        |
| Psychotic disorders                   | 241          | 9.4         | 3347          | 9.3       | 1169       | 9.4        | 2078         | 9.5        |
| **Other Comorbidities**               |               |             |               |           |            |            |               |            |
| Asthma                                | 282          | 11.1        | 3939          | 10.9      | 1364       | 10.9       | 2391         | 10.9       |
| Cancer                                | 10           | 0.4         | 125           | 0.3       | 47         | 0.4        | 93           | 0.4        |
| Fibromyalgia                          | 43           | 1.7         | 588           | 1.6       | 203        | 1.6        | 345          | 1.6        |
| Hypertension   | 44  | 1.7 | 534  | 1.5 | 192  | 1.5 | 338  | 1.5 |
|---------------|-----|-----|------|-----|------|-----|------|-----|
| Sleep disorders| 239 | 9.4 | 3428 | 9.5 | 1172 | 9.4 | 2112 | 9.6 |

**Lifestyle Factors**

| Alcohol abuse or dependence | 114 | 4.5 | 1566 | 4.3 | 576  | 4.6 | 973  | 4.4 |
| Drug abuse or dependence    | 311 | 12.2| 4163 | 11.5| 1489 | 11.9| 2569 | 11.7|
| Smoking                     | 139 | 5.4 | 1979 | 5.5 | 708  | 5.7 | 1228 | 5.6 |

**Medications**

| Lithium                      | 114 | 4.5 | 1460 | 4.0 | 493  | 3.9 | 954  | 4.4 |
| Antipsychotics               | 998 | 39.1| 13727| 38.0| 4818 | 38.6| 8435 | 38.5|
| Antidepressants              | 1297| 50.9| 18251| 50.5| 6360 | 50.9| 10819| 49.4|
| Stimulants                   | 878 | 34.4| 12355| 34.2| 4306 | 34.5| 7551 | 34.4|
| Oral corticosteroids         | 304 | 11.9| 4170 | 11.5| 1463 | 11.7| 2545 | 11.6|
| Antihypertensives            | 471 | 18.5| 6764 | 18.7| 2344 | 18.8| 4079 | 18.6|

**Healthcare Utilization**

| Number of outpatient visits; median (IQR) | 11 (6-23) | 12 (6-23) | 12 (6-23) | 11 (5-22) |
| Number of mental health outpatient visits; median (IQR) | 5 (1-14) | 5 (1-14) | 5 (1-14) | 4 (1-12) |
| Number of distinct generic drugs dispensed; median (IQR) | 5 (3-8) | 5 (3-8) | 5 (3-8) | 5 (3-8) |
| Number of ED visits | 0 | 1412 | 55.4 | 20211 | 55.9 | 6973 | 55.8 | 12020 | 54.8 |
|                      | 1 | 621  | 24.4 | 8643  | 23.9 | 2968 | 23.8 | 5289  | 24.1 |
|                      | ≥2 | 516  | 20.3 | 7281  | 20.1 | 2554 | 20.4 | 4613  | 21.0 |
| Number of hospitalizations | 0 | 1845 | 72.4 | 26484 | 73.3 | 9040 | 72.3 | 15899 | 72.5 |
|                         | 1 | 495  | 19.4 | 6801  | 18.8 | 2412 | 19.3 | 4199  | 19.2 |
|                         | ≥2 | 208  | 8.2  | 2850  | 7.9  | 1043 | 8.4  | 1824  | 8.3  |
| Any mental health hospitalization | 614 | 24.1 | 8457 | 23.4 | 3017 | 24.1 | 5191 | 23.7 |

| Days hospitalized | 0 | 1845 | 72.4 | 26484 | 73.3 | 9040 | 72.3 | 15899 | 72.5 |
|                  | 1 to 5 | 196 | 7.7  | 2716  | 7.5  | 948  | 7.6  | 1705  | 7.8  |
|                  | ≥6       | 507 | 19.9 | 6935  | 19.2 | 2508 | 20.1 | 4318  | 19.7 |

Abbreviations: ADHD=Attention-deficit/hyperactivity disorder; ED=Emergency department; IQR=Interquartile range; SD=Standard deviation

Estimates weighted by the inverse probability of treatment.
| Treatment Group      | No. of patients | No. of events | Total follow up in person-years | Mean follow up in person-years (SD) | Incidence rate per 1,000 person-years |
|----------------------|-----------------|---------------|----------------------------------|-------------------------------------|--------------------------------------|
| **Adult Trial**      |                 |               |                                  |                                     |                                      |
| **Intention-to-treat** |                |               |                                  |                                     |                                      |
| Carbamazepine        | 26,641          | 932           | 52,438                           | 2.0 (1.6)                           | 17.77                               |
| Lamotrigine          | 132,739         | 3,377         | 237,867                          | 1.8 (1.5)                           | 14.20                               |
| Oxcarbazepine        | 24,226          | 752           | 43,874                           | 1.8 (1.5)                           | 17.14                               |
| Valproate            | 90,600          | 3,371         | 175,972                          | 1.9 (1.6)                           | 19.16                               |
| **Per-protocol**     |                 |               |                                  |                                     |                                      |
| Carbamazepine        | 26,641          | 220           | 9,193                            | 0.35 (0.59)                         | 23.93                               |
| Lamotrigine          | 132,739         | 1,160         | 79,091                           | 0.60 (0.79)                         | 14.67                               |
| Oxcarbazepine        | 24,226          | 202           | 9,998                            | 0.41 (0.60)                         | 20.20                               |
| Valproate            | 90,600          | 803           | 36,988                           | 0.41 (0.66)                         | 21.71                               |
| **Pediatric Trial**  |                 |               |                                  |                                     |                                      |
| **Intention-to-treat** |                |               |                                  |                                     |                                      |
| Carbamazepine        | 2,532           | 14            | 5,547                            | 2.2 (1.7)                           | 2.52                                |
| Lamotrigine          | 36,394          | 160           | 75,561                           | 2.1 (1.6)                           | 2.12                                |
| Oxcarbazepine        | 12,434          | 54            | 26,073                           | 2.1 (1.6)                           | 2.07                                |
| Valproate            | 22,645          | 105           | 50,455                           | 2.2 (1.7)                           | 2.08                                |
| **Per-protocol**     |                 |               |                                  |                                     |                                      |
| Carbamazepine        | 2,532           | 6             | 1,084                            | 0.43 (0.63)                         | 5.54                                |
| Lamotrigine          | 36,394          | 57            | 22,463                           | 0.62 (0.79)                         | 2.54                                |
| Oxcarbazepine        | 12,434          | 17            | 6,812                            | 0.55 (0.75)                         | 2.50                                |
| Valproate            | 22,645          | 30            | 7,990                            | 0.35 (0.58)                         | 3.75                                |
Table 9. Hazard Ratios and 95% Confidence Intervals Comparing the Incidence of Type 2 Diabetes Across Mood Stabilizer Treatment, By Level of Adjustment

| Level of Adjustment       | Carbamazepine     | Lamotrigine     | Oxcarbazepine    | Valproate     |
|---------------------------|-------------------|-----------------|------------------|--------------|
| **Adult Trial**           |                   |                 |                  |              |
| **Intention-to-treat**    |                   |                 |                  |              |
| Crude                     | 1.26 (1.17-1.35)  | ref             | 1.21 (1.12-1.31) | 1.36 (1.29-1.42) |
| Fully adjusted for baseline covariates | 1.07 (0.96-1.19) | ref             | 1.07 (0.98-1.17) | 1.15 (1.09-1.22) |
| **Per-protocol**          |                   |                 |                  |              |
| Crude                     | 1.55 (1.34-1.79)  | ref             | 1.31 (1.13-1.53) | 1.44 (1.31-1.57) |
| Partially adjusted for baseline covariates | 1.25 (0.99-1.59) | ref             | 1.05 (0.89-1.24) | 1.20 (1.06-1.36) |
| Fully adjusted for baseline and time-varying covariates | 1.17 (0.93-1.46) | ref             | 1.08 (0.91-1.29) | 1.14 (1.01-1.28) |
| **Pediatric Trial**       |                   |                 |                  |              |
| **Intention-to-treat**    |                   |                 |                  |              |
| Crude                     | 1.21 (0.70-2.09)  | ref             | 0.98 (0.72-1.34) | 1.00 (0.78-1.27) |
| Fully adjusted for baseline covariates | 1.04 (0.58-1.84) | ref             | 1.11 (0.78-1.56) | 1.18 (0.87-1.60) |
| **Per-protocol**          |                   |                 |                  |              |
| Crude                     | 1.87 (0.81-4.34)  | ref             | 0.94 (0.54-1.61) | 1.23 (0.79-1.92) |
| Partially adjusted for baseline covariates | 1.38 (0.55-3.46) | ref             | 1.18 (0.56-2.50) | 1.46 (0.77-2.76) |
| Fully adjusted for baseline and time-varying covariates | 1.23 (0.48-3.14) | ref             | 0.84 (0.44-1.61) | 1.39 (0.75-2.56) |

Estimates were weighted by the inverse probability of treatment and the inverse probability or censoring. We truncated weights at the 1st and 99th percentiles.
eTable 10. Adjusted Hazard Ratios and 95% Confidence Intervals Comparing the Incidence of Type 2 Diabetes Across Mood Stabilizer Treatment in Adults, Stratified by Age and Treatment Indication

| Subgroup                  | Carbamazepine | Lamotrigine | Oxcarbazepine | Valproate |
|---------------------------|---------------|-------------|---------------|-----------|
| **Intention-to-treat**    |               |             |               |           |
| Total population          | 1.07 (0.96-1.20) | ref         | 1.07 (0.98-1.17) | 1.16 (1.09-1.22) |
| Age 20-39 years           | 1.21 (0.95-1.52) | ref         | 1.09 (0.92-1.30) | 1.25 (1.12-1.39) |
| Age 40-54 years           | 1.10 (0.94-1.28) | ref         | 1.06 (0.93-1.21) | 1.13 (1.04-1.23) |
| Age 55-65 years           | 0.93 (0.77-1.12) | ref         | 1.07 (0.90-1.27) | 1.12 (1.01-1.25) |
| Bipolar disorder          | 1.15 (0.94-1.41) | ref         | 1.10 (0.95-1.27) | 1.24 (1.14-1.36) |
| Epilepsy                  | 1.06 (0.72-1.57) | ref         | 1.08 (0.72-1.63) | 1.33 (1.04-1.70) |
| **Per-protocol**          |               |             |               |           |
| Total population          | 1.17 (0.93-1.46) | ref         | 1.08 (0.91-1.29) | 1.14 (1.01-1.28) |
| Age 20-39 years           | 1.54 (0.97-2.44) | ref         | 0.98 (0.66-1.44) | 1.21 (0.95-1.55) |
| Age 40-54 years           | 1.27 (0.91-1.79) | ref         | 1.06 (0.82-1.36) | 1.23 (1.04-1.46) |
| Age 55-65 years           | 0.82 (0.57-1.17) | ref         | 1.20 (0.90-1.60) | 1.04 (0.95-1.26) |
| Bipolar disorder          | 1.44 (0.96-2.17) | ref         | 1.08 (0.81-1.44) | 1.16 (0.97-1.38) |
| Epilepsy                  | 0.94 (0.48-1.86) | ref         | 0.75 (0.35-1.59) | 1.54 (0.96-2.46) |

Adjusted estimates were weighted by the inverse probability of treatment and the inverse probability or censoring. Subgroup analyses were not conducted in the pediatric trial emulation due to lack of power.
eFigure 2. Sensitivity Analysis Evaluating the Potential Role of Unmeasured Confounding on Observed Point Estimates in the Intention-to-Treat Analysis

Under the assumptions of the E-value, to nullify the adjusted estimate for valproate in the adult or pediatric trial emulation, an unmeasured confounder would need to be associated with both the choice of mood stabilizer treatment and the onset of T2D by a magnitude of at least 1.6-fold, above and beyond the measured confounders.

Sensitivity analysis was conducted on the adjusted hazard ratio comparing valproate treatment to lamotrigine treatment, where the strongest magnitude of association was observed. The plots illustrate the magnitude of confounding needed to explain away the observed association. The x-axis reflects the range of risk ratios for the association between an unmeasured confounder and the choice of mood stabilizer treatment (exposure). The y-axis reflects the range of risk ratios for the association between an unmeasured confounder and type 2 diabetes (outcome). The E-value is the minimum strength of association (on the risk ratio scale) that an unmeasured confounder would need to have on both the choice of mood stabilizer treatment and the onset of type 2 diabetes (conditional on measured covariates) to fully explain away the observed association in the intention-to-treat analysis. While the E-value was originally proposed for the risk ratio, the same formula can be applied to hazard ratios with a rare outcome. Results were generated using the online E-value calculator.9

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Table 11. Sensitivity Analysis Evaluating the Potential Impact of Truncating Inverse Probability Weights

| Treatment Group | Distribution of Weights | Adjusted Hazard Ratio (95% Confidence Interval) |
|-----------------|-------------------------|-----------------------------------------------|
|                 | Mean (SD) | Minimum | Maximum | Carbamazepine | Oxcarbazepine | Valproate |
| **Adult Trial** |           |         |         |               |               |          |
| **Intention-to-treat** |           |         |         |               |               |          |
| No truncation | 1.02 (1.03) | 0.12 | 91.84 | 1.02 (0.89-1.17) | 1.06 (0.97-1.16) | 1.14 (1.07-1.21) |
| 0.5<sup>th</sup> and 99.5<sup>th</sup> percentile | 1.00 (0.71) | 0.17 | 5.86 | 1.07 (0.95-1.20) | 1.07 (0.98-1.17) | 1.15 (1.09-1.22) |
| 1<sup>st</sup> and 99<sup>th</sup> percentile | 0.99 (0.65) | 0.18 | 4.37 | 1.07 (0.96-1.20) | 1.07 (0.98-1.17) | 1.16 (1.09-1.22) |
| 5<sup>th</sup> and 95<sup>th</sup> percentile | 0.94 (0.46) | 0.41 | 2.19 | 1.13 (1.03-1.24) | 1.09 (1.00-1.19) | 1.19 (1.13-1.26) |
| **Per-protocol** |           |         |         |               |               |          |
| No truncation | 1.00 (1.88) | 1.37 x 10<sup>-5</sup> | 1117.98 | 1.15 (0.80-1.66) | 1.06 (0.89-1.27) | 1.11 (0.97-1.26) |
| 0.5<sup>th</sup> and 99.5<sup>th</sup> percentile | 0.97 (0.74) | 0.12 | 6.17 | 1.18 (0.92-1.49) | 1.08 (0.91-1.28) | 1.13 (1.00-1.27) |
| 1<sup>st</sup> and 99<sup>th</sup> percentile | 0.96 (0.67) | 0.16 | 4.50 | 1.17 (0.93-1.46) | 1.08 (0.91-1.29) | 1.14 (1.01-1.28) |
| 5<sup>th</sup> and 95<sup>th</sup> percentile | 0.92 (0.47) | 0.35 | 2.21 | 1.18 (0.98-1.43) | 1.12 (0.95-1.32) | 1.17 (1.05-1.31) |
| **Pediatric Trial** |           |         |         |               |               |          |
| **Intention-to-treat** |           |         |         |               |               |          |
| No truncation | 1.00 (0.70) | 0.16 | 24.98 | 1.01 (0.57-1.81) | 1.09 (0.77-1.55) | 1.19 (0.86-1.64) |
| 0.5<sup>th</sup> and 99.5<sup>th</sup> percentile | 1.00 (0.63) | 0.37 | 4.78 | 1.02 (0.58-1.82) | 1.10 (0.78-1.55) | 1.20 (0.87-1.64) |
| 1<sup>st</sup> and 99<sup>th</sup> percentile | 0.99 (0.59) | 0.39 | 3.79 | 1.04 (0.58-1.84) | 1.11 (0.78-1.56) | 1.18 (0.87-1.60) |
| 5<sup>th</sup> and 95<sup>th</sup> percentile | 0.95 (0.46) | 0.46 | 2.17 | 1.07 (0.60-1.89) | 1.09 (0.78-1.52) | 1.11 (0.84-1.46) |
| **Per-protocol** |           |         |         |               |               |          |
| No truncation | 1.04 (7.78) | 8.18 x 10<sup>-6</sup> | 1783.72 | 1.17 (0.45-3.01) | 0.78 (0.40-1.53) | 1.36 (0.73-2.52) |
| 0.5<sup>th</sup> and 99.5<sup>th</sup> percentile | 0.96 (0.80) | 0.03 | 6.51 | 1.19 (0.46-3.06) | 0.83 (0.43-1.60) | 1.41 (0.76-2.67) |
| 1<sup>st</sup> and 99<sup>th</sup> percentile | 0.94 (0.73) | 0.06 | 4.70 | 1.23 (0.48-3.14) | 0.84 (0.44-1.61) | 1.39 (0.75-2.56) |
| 5<sup>th</sup> and 95<sup>th</sup> percentile | 0.90 (0.53) | 0.25 | 2.30 | 1.38 (0.55-3.46) | 0.87 (0.46-1.63) | 1.37 (0.78-2.41) |

This analysis explored the bias-variance tradeoff in weight truncation. More truncation results in more biased point estimates, but smaller variance. In general, well behaved-weights have a mean of 1 and small range. In the primary analysis, we truncated weights at the 1<sup>st</sup> and 99<sup>th</sup> percentile. Adjusted hazard ratios were weighted by the inverse probability of treatment and the inverse probability of censoring (adjusted for baseline covariates in the intention-to-treat analysis, adjusted for baseline and time-varying covariates in the per-protocol analysis).
Table 12. Sensitivity Analysis Evaluating the Potential Role of Different Grace Periods in the Per-Protocol Analysis

|                | No. of patients | No. of events | Total follow up in person-years | Mean follow up in person-years (SD) | Incidence rate per 1,000 person-years | Crude HR (95% CI) | Adjusted HR (95% CI) |
|----------------|----------------|---------------|---------------------------------|-------------------------------------|---------------------------------------|-------------------|----------------------|
| **Adult Trial**|                |               |                                 |                                     |                                       |                   |                      |
| 100% Grace Period (Primary Analysis) |                |               |                                 |                                     |                                       |                   |                      |
| Carbamazepine  | 26,641         | 220           | 9,193                           | 0.35 (0.59)                         | 23.93                                 | 1.55 (1.34-1.79) | 1.17 (0.93-1.46)     |
| Lamotrigine    | 132,739        | 1160          | 79,091                          | 0.60 (0.79)                         | 14.67                                 | ref               | ref                  |
| Oxcarbazepine  | 24,226         | 202           | 9,998                           | 0.41 (0.60)                         | 20.20                                 | 1.31 (1.13-1.53) | 1.08 (0.91-1.29)     |
| Valproate      | 90,600         | 803           | 36,988                          | 0.41 (0.66)                         | 21.71                                 | 1.44 (1.31-1.57) | 1.14 (1.01-1.28)     |
| **200% Grace Period (Sensitivity Analysis) |                |               |                                 |                                     |                                       |                   |                      |
| Carbamazepine  | 26,641         | 277           | 12,179                          | 0.46 (0.70)                         | 22.74                                 | 1.53 (1.35-1.75) | 1.22 (1.00-1.49)     |
| Lamotrigine    | 132,739        | 1406          | 99,578                          | 0.75 (0.91)                         | 14.12                                 | ref               | ref                  |
| Oxcarbazepine  | 24,226         | 248           | 13,024                          | 0.54 (0.72)                         | 19.04                                 | 1.29 (1.13-1.48) | 1.09 (0.93-1.26)     |
| Valproate      | 90,600         | 940           | 44,811                          | 0.49 (0.74)                         | 20.98                                 | 1.44 (1.32-1.56) | 1.16 (1.05-1.29)     |
| **Pediatric Trial** |            |               |                                 |                                     |                                       |                   |                      |
| 100% Grace Period (Primary Analysis) |                |               |                                 |                                     |                                       |                   |                      |
| Carbamazepine  | 2,532          | 6             | 1,084                           | 0.43 (0.63)                         | 5.54                                  | 1.87 (0.81-4.34) | 1.23 (0.48-3.14)     |
| Lamotrigine    | 36,394         | 57            | 22,463                          | 0.62 (0.79)                         | 2.54                                  | ref               | ref                  |
| Oxcarbazepine  | 12,434         | 17            | 6,812                           | 0.55 (0.75)                         | 2.50                                  | 0.94 (0.54-1.61) | 0.84 (0.44-1.61)     |
| Valproate      | 22,645         | 30            | 7,990                           | 0.35 (0.58)                         | 3.75                                  | 1.23 (0.79-1.92) | 1.39 (0.75-2.56)     |
| **200% Grace Period (Sensitivity Analysis) |                |               |                                 |                                     |                                       |                   |                      |
| Carbamazepine  | 2,532          | 8             | 1,464                           | 0.58 (0.80)                         | 5.46                                  | 1.98 (0.95-4.12) | 1.44 (0.66-3.15)     |
| Lamotrigine    | 36,394         | 71            | 29,083                          | 0.80 (0.92)                         | 2.44                                  | ref               | ref                  |
| Oxcarbazepine  | 12,434         | 21            | 8,739                           | 0.70 (0.87)                         | 2.40                                  | 0.94 (0.57-1.52) | 0.90 (0.51-1.59)     |
| Valproate      | 22,645         | 33            | 9,811                           | 0.43 (0.67)                         | 3.36                                  | 1.14 (0.75-1.72) | 1.28 (0.73-2.25)     |

One of the censorship events in the per-protocol analysis was treatment discontinuation. In the primary analysis, we allowed a gap between the end of supply and the next prescription filled that was equal to the days supplied of the current dispensing (e.g., for a 30-day dispensing, we allowed an additional 30 days between the end of supply and the next prescription filled; “100% grace period”). Treatment episodes were considered discontinued if the next prescription was not filled by the end of this allowable gap. In a sensitivity analysis, we allowed a gap that was equal to twice the days supplied of the current dispensing (e.g., for a 30-day dispensing, we allowed an additional 60 days between the end of supply and the next prescription filled; “200% grace period”). Inverse probability weights were truncated at the 1st and 99th percentiles. In the sensitivity analysis, the mean (SD)/range of the inverse probability weights were 0.96 (0.63)/0.18 to 4.27 in the adult trial emulation and 0.93 (0.66)/0.10 to 4.15 in the pediatric trial emulation.
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