

Table S1. Medications categorized as NSAIDs

**NSAID – all (Warner-Schmidt)** includes all (NSAIDs, Salicytes, and Cox-2 inhibitors)

**Nonsteroidal anti-inflammatory agents**

Bromfenac  
Diclofenac  
Diclofenac-misoprostol  
Etodolac  
Fenoprofen  
Flurbiprofen  
Ibuprofen  
Indomethacin  
Ketoprofen  
Ketorolac  
Meclofenamate  
Mefenamic acid  
Nabumetone  
Naproxen  
Oxaprozin  
Phenylbutazone  
Piroxicam  
Sulindac  
Tolmetin

**Salicylates**

Al hydroxide/ASA/Ca carbonate/Mg hydroxide  
ASA/citric acid/Na bicarb  
Aspirin  
Choline salicylate  
Choline salicylate-magnesium salicylate  
Diflunisal  
Salsalate  
Sodium salicylate

**Cox-2 inhibitors**

Celecoxib (Celebrex)  
Meloxicam (Mobic)  
Rofecoxib (Vioxx)  
Valdecoxib (Bextra)  
Zompirac (Zomax)

Table S2a: Demographics and clinical features in i2b2-Treatment-Resistant Depression cohort

|                                                 | NSAID<br>chronic<br>exposure (++) | NSAID<br>intermittent<br>exposure (+) | NSAID<br>Unexposed (-) | Test<br>statistic† | p-value |
|-------------------------------------------------|-----------------------------------|---------------------------------------|------------------------|--------------------|---------|
| <b>N</b>                                        | 1,012                             | 233                                   | 283                    |                    |         |
| <b>Demographics</b>                             |                                   |                                       |                        |                    |         |
| Age, mean years ± SD                            | 53.4 ± 15.0                       | 51.3 ± 16.7                           | 46.9 ± 17.6            | t=5.71             | < 0.001 |
| Gender, no. (% female)                          | 765 (75.6)                        | 149 (63.9)                            | 175 (61.8)             | $\chi^2 = 20.3$    | < 0.001 |
| Race/ethnicity <sup>§§</sup> , no. (% of group) |                                   |                                       |                        | $\chi^2 = 54.5$    | < 0.001 |
| White                                           | 655 (64.7)                        | 186 (79.8)                            | 236 (83.4)             |                    |         |
| African American                                | 80 (8.0)                          | 12 (5.2)                              | 8 (2.8)                |                    |         |
| Hispanic                                        | 243 (24.0)                        | 29 (12.5)                             | 21 (7.4)               |                    |         |
| Asian                                           | 10 (1.0)                          | 4 (1.7)                               | 6 (2.1)                |                    |         |
| Other                                           | 24 (2.4)                          | 2 (0.9)                               | 12 (4.2)               |                    |         |
| Insurance, % of group                           |                                   |                                       |                        | $\chi^2 = 47.5$    | < 0.001 |
| Public                                          | 556 (54.9)                        | 95 (40.8)                             | 85 (30.0)              |                    |         |
| Private                                         | 429 (42.4)                        | 129 (55.4)                            | 176 (62.2)             |                    |         |
| Other / unknown                                 | 27 (2.7)                          | 9 (3.9)                               | 22 (7.7)               |                    |         |
| <b>Utilization, median (IQR)</b>                |                                   |                                       |                        |                    |         |
| Medical facts recorded                          | 710 (434-1,116)                   | 364 (222-588)                         | 228 (106-386)          | W = 242821         | < 0.001 |
| <b>Comorbidities, no. (% of group)</b>          |                                   |                                       |                        |                    |         |
| Age-adjusted Charlson index                     | 6 (3-10)                          | 4 (1-6)                               | 2 (0-5)                | W = 206310         | < 0.001 |
| Body mass index (kg/m <sup>2</sup> )            | 33.1 ± 8.3                        | 29.0 ± 7.0                            | 28.2 ± 7.1             | t=8.1              | < 0.001 |
| History of hypertension                         | 608 (60.1)                        | 85 (36.5)                             | 80 (28.3)              | $\chi^2 = 88.6$    | < 0.001 |
| History of hyperlipidemia                       | 671 (66.3)                        | 106 (45.5)                            | 101 (35.7)             | $\chi^2 = 84.8$    | < 0.001 |
| History of myocardial infarction                | 109 (10.8)                        | 5 (2.1)                               | 2 (0.7)                | $\chi^2 = 27.3$    | < 0.001 |
| History of stroke                               | 153 (15.1)                        | 14 (6.0)                              | 9 (3.2)                | $\chi^2 = 27.7$    | < 0.001 |
| History of type 2 diabetes                      | 336 (33.2)                        | 35 (15.0)                             | 26 (9.2)               | $\chi^2 = 62.1$    | < 0.001 |
| <b>Psychiatry visits, median (IQR)</b>          |                                   |                                       |                        |                    |         |
| All psychiatric visits                          | 12 (6-24)                         | 10 (4-19)                             | 9 (4-18)               | W = 163790         | < 0.001 |
| Depressed visits                                | 2 (0-6)                           | 1 (0-4)                               | 1 (0-4)                | W = 172907         | < 0.001 |
| Well visits                                     | 1 (0-4)                           | 2 (0-5)                               | 2 (1-5)                | W = 127681         | < 0.001 |

† Comparing chronic exposure (++) to unexposed (-); t: Student's t-test, W: Mann-Whitney U,  $\chi^2$ : Pearson's chi-square

<sup>§§</sup> Race and ethnicity are collected using a single field in the electronic medical record, so subjects who identify as Hispanic are not further characterized

Table S2b: NSAID and Anti-depressant use in i2b2-Treatment-Resistant Depression cohort

|                                                     | NSAID<br>chronic<br>exposure (++) | NSAID<br>intermittent<br>exposure (+) | NSAID<br>Unexposed (-) | Test statistic† | p-value |
|-----------------------------------------------------|-----------------------------------|---------------------------------------|------------------------|-----------------|---------|
| <b>N</b>                                            | 1,012                             | 233                                   | 283                    |                 |         |
| <b>NSAID use, no. (% of group)</b>                  |                                   |                                       |                        |                 |         |
| NSAID                                               | 895 (88.4)                        | 142 (60.9)                            | -                      | n/a             | n/a     |
| Cox-2 inhibitors                                    | 190 (18.8)                        | 12 (5.2)                              | -                      | n/a             | n/a     |
| Salicylates                                         | 505 (49.9)                        | 89 (38.2)                             | -                      | n/a             | n/a     |
| NSAID or Cox-2 or Salicylates<br>( Warner-Schmidt ) | 1,106 (100)                       | 233 (100)                             | -                      | n/a             | n/a     |
| NSAID and Cox-2                                     | 169 (16.7)                        | 2 (0.9)                               | -                      | n/a             | n/a     |
| NSAID and Salicylates                               | 428 (42.3)                        | 16 (6.9)                              | -                      | n/a             | n/a     |
| Cox-2 and Salicylates                               | 123 (12.2)                        | 3 (1.3)                               | -                      | n/a             | n/a     |
| NSAID and Cox-2 and Salicylates                     | 110 (10.9)                        | 1 (0.4)                               | -                      | n/a             | n/a     |
| <b>Antidepressant use, median (IQR)</b>             |                                   |                                       |                        |                 |         |
| Unique antidepressants                              | 3 (2-5)                           | 2 (1-4)                               | 2 (1-3)                | W = 197670      | < 0.001 |
| Refills per antidepressant                          | 8 (2-20)                          | 4 (1-10)                              | 3 (1-9)                | W = 193636      | < 0.001 |
| <b>Antidepressant response, no. (% of group)</b>    |                                   |                                       |                        |                 |         |
| Treatment-resistant (TRD)                           | 499 (49.3)                        | 87 (37.3)                             | 103 (36.4)             | $\chi^2 = 14.3$ | < 0.001 |
| Treatment-responsive                                | 513 (50.7)                        | 146 (62.7)                            | 180 (63.6)             |                 |         |

† Comparing chronic exposure (++) to unexposed (-); t: Student's t-test, W: Mann-Whitney U,  $\chi^2$ : Pearson's chi-square

Table S3: Unadjusted and adjusted odds ratios for treatment-resistance, by medication class in i2b2-Treatment-Resistant Depression

| <b>Medication Class</b>                         | <b>Unadjusted<br/>TRD OR (95% CI)</b> | <b>Model 1*<br/>TRD OR (95% CI)</b> | <b>Model 2**<br/>TRD OR (95% CI)</b> |
|-------------------------------------------------|---------------------------------------|-------------------------------------|--------------------------------------|
| NSAID + Cox-2 + Salicylates<br>(Warner-Schmidt) | 1.75 (1.35-2.29)                      | 1.68 (1.27-2.24)                    | 1.36 (0.93-2.00)                     |
| NSAID only                                      | 1.88 (1.47-2.41)                      | 1.76 (1.36-2.28)                    | 1.47 (1.06-2.05)                     |
| Cox-2 inhibitors only                           | 0.79 (0.58-1.08)                      | 0.89 (0.63-1.23)                    | 0.79 (0.54-1.15)                     |
| Salicylates only                                | 0.82 (0.64-1.02)                      | 1.22 (0.94-1.62)                    | 1.24 (0.89-1.75)                     |

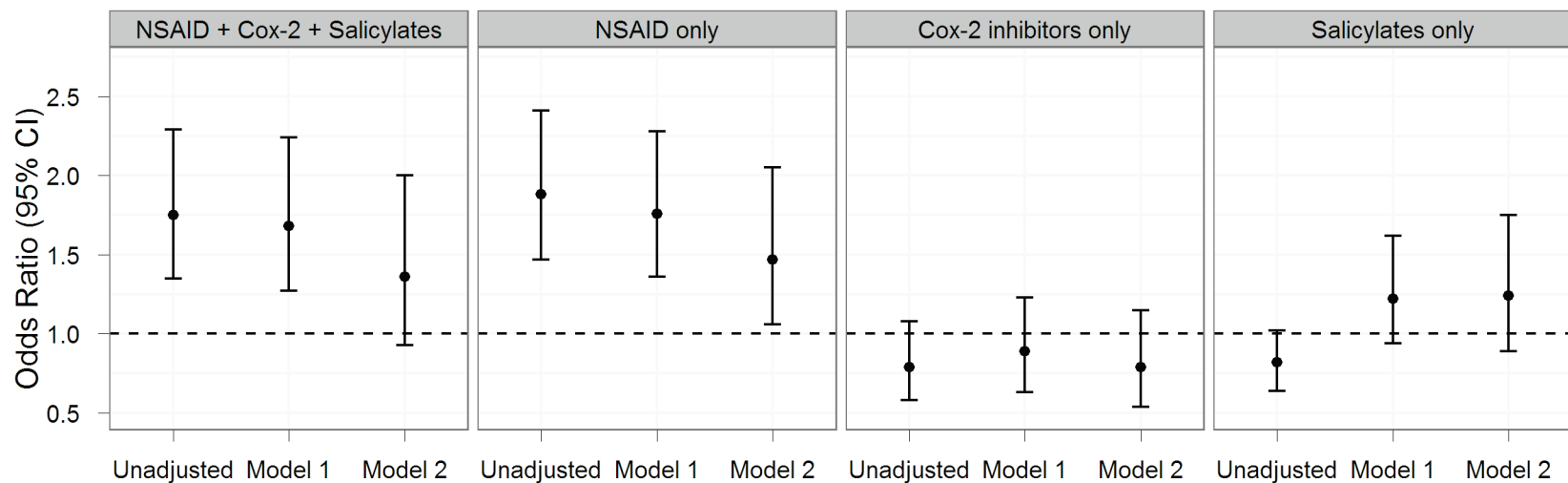
§ Reference group is treatment-responsive. By likelihood-ratio test, fit for model 2>model 1>unadjusted ( $p<0.001$  for all comparisons).

\*Model 1 includes age, gender, race, and payor

\*\*Model 2 includes age, gender, race, payor, log-transformed fact count, age-adjusted Charlson comorbidity index, history of hypertension, history of hyperlipidemia, history of myocardial infarction, history of stroke and history of type 2 diabetes mellitus.

Figure S1

(a) Unadjusted and adjusted odds ratios of treatment-resistance by medication class in i2b2-Treatment-Resistant Depression cohort secondary analysis excluding intermittent NSAID exposed patients



\*Model 1 includes age, gender, race, and payor

\*\*Model 2 includes age, gender, race, payor, log-transformed fact count, age-adjusted Charlson comorbidity index, history of hypertension, history of hyperlipidemia, history of myocardial infarction, history of stroke and history of type 2 diabetes mellitus.