SUPPLEMENTAL MATERIAL FOR PAPER:

“GENOMEWIDE PHARMACOGENOMIC STUDY OF CITALOPRAM-INDUCED SIDE EFFECTS IN STAR*D”

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A. Sensitivity analyses for factor analyses of side effect indicators

Side effect presence and tolerance was measured by the Patient Rated Inventory of Side Effects (PRISE) (Rush et al., 2004). For each of eight biological systems, patients were asked two types of questions, one relating to specific side effects (e.g., dizziness, anorgasmia) and one relating to the overall tolerability of side effects for a given biological system. For the specific side effects, patients were asked to indicate whether the side effect was present. For the tolerability measures, an overall score of side effect tolerability was given for each of the eight biological systems as a trichotomous item, scored as none, tolerable, or distressing (Wisniewski et al., 2006). Using Mplus 6.0 (Muthen and Muthen, 1998-2010), exploratory factor analyses were conducted to examine the factor structure of the 34 side effect indicators of the PRISE scale. As reported in Table 1 of the main text, of the several potential factors emerging from the exploratory analysis, five were retained based on overall fit to the data, interpretability, and having a Cronbach’s alpha greater than 0.70, which indicates good reliability for the factor (Nunnally and Bernstein, 1994). The five factors were: 1) a general side effect burden factor in which all of the 26 symptom measures served as factor indicators, 2) an overall tolerability factor based on the eight system-specific tolerability indicators, 3) a sexual factor, 4) a dizziness factor, and 5) a factor relating to vision/hearing (i.e., ocular/auricular) side effects.

After identifying the five side effect dimensions that could be reliably measured in the PRISE data, we conducted various sensitivity analyses to make certain that these factor structures were robust. First, given former research showing that the prevalence of
side effects may vary by number of days taking a particular antidepressant (Demyttenaere et al., 2005), additional factor analyses were performed stratifying the STAR*D sample based on the number of days on the treatment. This was done to confirm that the factor solution was robust across treatment duration and not artifactual due to heterogeneity across time. Specifically, we split the repeated assessment data into five quintiles depending on how long the subjects had been taking the current trial drug (q1: 0-14 days; q2: 15-28 days; q3: 29-44 days; q4: 45-70 days; q5: 70+ days). Results of these sensitivity analyses are presented, by quintile, below and confirm that the latent side effect variables were generally consistent regardless of the duration of treatment (Supplemental Tables A1-A5).
Table A1. Factor analyses of side effect indicators, first quintile (days 0-14)

| Area          | Item                        | Symptom | Tolerability | Sex | Eye/Ear | Dizziness |
|---------------|-----------------------------|---------|--------------|-----|---------|-----------|
| GI            | Diarrhea                    | 0.22    |              |     |         |           |
|               | Constipation                | 0.21    |              |     |         |           |
|               | Dry Mouth                   | 0.35    |              |     |         |           |
|               | Nausea/Vomiting             | 0.29    |              |     |         |           |
|               | GI Tolerability             |         | 0.51         |     |         |           |
| Dizziness     | Palpitations                | 0.25    | 0.36         |     |         |           |
|               | Dizziness on Standing       | 0.58    | 0.63         |     |         |           |
|               | Chest Pain                  | 0.25    | 0.39         |     |         |           |
|               | Dizziness Tolerability      |         | 0.57         |     |         | 0.86      |
| Skin          | Rash                        | 0.23    |              |     |         |           |
|               | Increased Perspiration      | 0.25    |              |     |         |           |
|               | Itching                     | 0.37    |              |     |         |           |
|               | Dry Skin                    | 0.36    |              |     |         |           |
|               | Skin Tolerability           |         | 0.45         |     |         |           |
| CNS           | Headache                    | 0.33    | 0.45         |     |         |           |
|               | Tremors                     | 0.3     |              |     |         |           |
|               | Poor Coordination           | 0.41    |              |     |         |           |
|               | Dizziness                   | 0.55    |              |     |         |           |
|               | CNS Tolerability            |         | 0.57         |     |         | 0.62      |
| Eyes\Ears     | Blurred Vision              | 0.4     | 0.63         |     |         |           |
|               | Ringing in Ears             | 0.3     | 0.62         |     |         |           |
|               | Eyes\Ear Tolerability      |         | 0.49         |     |         | 0.91      |
| Gen\Urin.     | Difficulty Urinating        | 0.27    |              |     |         |           |
|               | Painful Urination           | 0.18    |              |     |         |           |
|               | Menstrual Irregularity      | 0.11    |              |     |         |           |
|               | Frequent Urination          | 0.28    |              |     |         |           |
|               | Gen\Urin. Tolerability     |         | 0.43         |     |         |           |
| Sleep         | Difficulty Sleeping         | 0.25    |              |     |         |           |
|               | Sleeping too much           | 0.08    |              |     |         |           |
|               | Sleep Tolerability          |         | 0.40         |     |         |           |
| Sex           | Loss of Sexual Desire       | 0.25    | 0.68         |     |         |           |
|               | Trouble achieving orgasm    | 0.21    | 0.54         |     |         |           |
|               | Trouble with erections     | 0.14    | 0.41         |     |         |           |
|               | Sex Tolerability            |         | 0.32         |     | 0.88    |           |
|               | Alpha                       | 0.7     | 0.69         | 0.71| 0.74    | 0.7       |
Table A2. Factor analyses of side effect indicators, second quintile (days 15-28)

| Area    | Item                          | Symptom | Tolerability | Sex   | Eye/Ear | Dizziness |
|---------|-------------------------------|---------|--------------|-------|---------|-----------|
| GI      | Diarrhea                      | 0.25    | 0.24         | 0.36  | 0.28    | 0.52      |
|         | Constipation                  |         |              |       |         |           |
|         | Dry Mouth                     |         |              |       |         |           |
|         | Nausea/Vomiting               |         |              |       |         |           |
|         | GI Tolerability               |         |              |       |         |           |
| Dizziness| Palpitations                  | 0.3     | 0.41         | 0.64  | 0.41    | 0.86      |
|         | Dizziness on Standing         | 0.57    | 0.64         | 0.41  | 0.41    |           |
|         | Chest Pain                    | 0.32    | 0.41         | 0.41  | 0.41    |           |
|         | Dizziness Tolerability        | 0.6     | 0.86         | 0.41  | 0.41    |           |
| Skin    | Rash                          | 0.21    |              | 0.48  | 0.48    |           |
|         | Increased Perspiration        | 0.26    |              |       |         |           |
|         | Itching                       | 0.35    |              |       |         |           |
|         | Dry Skin                      | 0.32    |              |       |         |           |
|         | Skin Tolerability             | 0.45    |              |       |         |           |
| CNS     | Headache                      | 0.34    | 0.48         |       |         |           |
|         | Tremors                       | 0.33    |              |       |         |           |
|         | Poor Coordination             | 0.4     |              |       |         |           |
|         | Dizziness                     | 0.54    |              |       |         |           |
|         | CNS Tolerability              | 0.61    | 0.64         | 0.64  | 0.64    |           |
| Eyes\Ears| Blurred Vision                | 0.43    | 0.65         |       |         |           |
|         | Ringing in Ears               | 0.34    | 0.61         | 0.61  | 0.61    |           |
|         | Eyes\Ear Tolerability         | 0.53    | 0.91         | 0.91  | 0.91    |           |
| Gen\Urin.| Difficulty Urinating          | 0.26    |              |       |         |           |
|         | Painful Urination             | 0.16    |              |       |         |           |
|         | Menstrual Irregularity        | 0.11    |              |       |         |           |
|         | Frequent Urination            | 0.28    |              |       |         |           |
|         | Gen\Urin. Tolerability       | 0.41    |              |       |         |           |
| Sleep   | Difficulty Sleeping           | 0.24    |              |       |         |           |
|         | Sleeping too much             | 0.05    |              |       |         |           |
|         | Sleep Tolerability            | 0.38    |              |       |         |           |
| Sex     | Loss of Sexual Desire         | 0.23    | 0.65         |       |         |           |
|         | Trouble achieving orgasm     | 0.16    | 0.55         |       |         |           |
|         | Trouble with erections       | 0.21    | 0.45         |       |         |           |
|         | Sex Tolerability              | 0.32    | 0.88         | 0.88  | 0.88    |           |
|         | Alpha                         | 0.7     | 0.68         | 0.71  | 0.74    | 0.72      |
Table A3. Factor analyses of side effect indicators, third quintile (days 29-44)

| Area         | Item                              | Symptom | Tolerability | Sex | Eye/Ear | Dizziness |
|--------------|-----------------------------------|---------|--------------|-----|---------|-----------|
| GI           | Diarrhea                          | 0.26    |              |     |         |           |
|              | Constipation                      | 0.26    |              |     |         |           |
|              | Dry Mouth                         | 0.37    |              |     |         |           |
|              | Nausea/Vomiting                   | 0.32    |              |     |         |           |
|              | GI Tolerability                   |         | 0.56         |     |         |           |
| Dizziness    | Palpitations                      | 0.33    | 0.4          |     |         |           |
|              | Dizziness on Standing             | 0.59    | 0.66         |     |         |           |
|              | Chest Pain                        | 0.4     | 0.47         |     |         |           |
|              | Dizziness Tolerability            |         | 0.61         | 0.88|         |           |
| Skin         | Rash                              | 0.25    |              |     |         |           |
|              | Increased Perspiration            | 0.31    |              |     |         |           |
|              | Itching                           | 0.4     |              |     |         |           |
|              | Dry Skin                          | 0.36    |              |     |         |           |
|              | Skin Tolerability                 |         | 0.47         |     |         |           |
| CNS          | Headache                          | 0.41    | 0.54         |     |         |           |
|              | Tremors                           | 0.29    |              |     |         |           |
|              | Poor Coordination                 | 0.45    |              |     |         |           |
|              | Dizziness                         | 0.58    |              |     |         |           |
|              | CNS Tolerability                  |         | 0.63         | 0.69|         |           |
| Eyes\Ears    | Blurred Vision                    | 0.44    | 0.64         |     |         |           |
|              | Ringing in Ears                   | 0.37    | 0.66         |     |         |           |
|              | Eyes\Ear Tolerability             |         | 0.52         | 0.92|         |           |
| Gen\Ur.     | Difficulty Urinating              | 0.25    |              |     |         |           |
|              | Painful Urination                 | 0.21    |              |     |         |           |
|              | Menstrual Irregularity            | 0.12    |              |     |         |           |
|              | Frequent Urination                | 0.32    |              |     |         |           |
|              | Gen\Urination Tolerability        |         | 0.44         |     |         |           |
| Sleep        | Difficulty Sleeping               | 0.29    |              |     |         |           |
|              | Sleeping too much                 | 0.08    |              |     |         |           |
|              | Sleep Tolerability                |         | 0.42         |     |         |           |
| Sex          | Loss of Sexual Desire             | 0.27    | 0.64         |     |         |           |
|              | Trouble achieving orgasm          | 0.2     | 0.56         |     |         |           |
|              | Trouble with erections           | 0.23    | 0.46         |     |         |           |
|              | Sex Tolerability                  |         | 0.37         | 0.88|         |           |
|              | Alpha                             | 0.75    | 0.73         | 0.72| 0.76    | 0.76      |
Table A4. Factor analyses of side effect indicators, fourth quintile (days 45-70)

| Area     | Item                          | Symptom | Tolerability | Sex | Eye/Ear | Dizziness |
|----------|-------------------------------|---------|--------------|-----|---------|-----------|
| GI       | Diarrhea                      | 0.21    |              |     |         |           |
|          | Constipation                  | 0.28    |              |     |         |           |
|          | Dry Mouth                     | 0.4     |              |     |         |           |
|          | Nausea/Vomiting               | 0.33    |              |     |         |           |
|          | GI Tolerability               |         | 0.53         |     |         |           |
| Dizziness| Palpitations                  | 0.28    | 0.38         |     |         |           |
|          | Dizziness on Standing         | 0.56    | 0.63         |     |         |           |
|          | Chest Pain                    | 0.4     | 0.47         |     |         |           |
|          | Dizziness Tolerability        |         | 0.59         |     |         | 0.86      |
| Skin     | Rash                          | 0.21    |              |     |         |           |
|          | Increased Perspiration        | 0.33    |              |     |         |           |
|          | Itching                       | 0.41    |              |     |         |           |
|          | Dry Skin                      | 0.37    |              |     |         |           |
|          | Skin Tolerability             |         | 0.5          |     |         |           |
| CNS      | Headache                      | 0.38    | 0.53         |     |         |           |
|          | Tremors                       | 0.32    |              |     |         |           |
|          | Poor Coordination             | 0.46    |              |     |         |           |
|          | Dizziness                     | 0.56    |              |     |         |           |
|          | CNS Tolerability              |         | 0.6          |     |         | 0.67      |
| Eyes\Ears| Blurred Vision                | 0.44    | 0.66         |     |         |           |
|          | Ringing in Ears               | 0.35    | 0.63         |     |         |           |
|          | Eyes\Ear Tolerability         |         | 0.5          |     |         | 0.92      |
| Gen\Ur. | Difficulty Urinating          | 0.23    |              |     |         |           |
|          | Painful Urination             | 0.23    |              |     |         |           |
|          | Menstrual Irregularity        | 0.12    |              |     |         |           |
|          | Frequent Urination            | 0.37    |              |     |         |           |
|          | Gen\Urination Tolerability    |         | 0.48         |     |         |           |
| Sleep    | Difficulty Sleeping           | 0.32    |              |     |         |           |
|          | Sleeping too much             | 0.06    |              |     |         |           |
|          | Sleep Tolerability            |         | 0.42         |     |         |           |
| Sex      | Loss of Sexual Desire         | 0.26    | 0.64         |     |         |           |
|          | Trouble achieving orgasm     | 0.16    | 0.56         |     |         |           |
|          | Trouble with erections       | 0.24    | 0.41         |     |         |           |
|          | Sex Tolerability              |         | 0.36         | 0.88 |         |           |
|          | Alpha                         | 0.74    | 0.73         | 0.71 | 0.75    | 0.74      |
Table A5. Factor analyses of side effect indicators, second quintile (days 70+)

| Area        | Item                      | Symptom | Tolerability | Sex | Eye/Ear | Dizziness |
|-------------|---------------------------|---------|--------------|-----|---------|-----------|
| GI          | Diarrhea                  | 0.25    |              |     |         |           |
|             | Constipation              | 0.35    |              |     |         |           |
|             | Dry Mouth                 | 0.39    |              |     |         |           |
|             | Nausea/Vomiting           | 0.33    |              |     |         |           |
|             | GI Tolerability           |         | 0.58         |     |         |           |
| Dizziness   | Palpitations              | 0.29    | 0.38         |     |         |           |
|             | Dizziness on Standing     | 0.59    | 0.64         |     |         |           |
|             | Chest Pain                | 0.35    | 0.42         |     |         |           |
|             | Dizziness Tolerability    |         | 0.58         |     |         | 0.85      |
| Skin        | Rash                      | 0.28    |              |     |         |           |
|             | Increased Perspiration    | 0.34    |              |     |         |           |
|             | Itching                   | 0.41    |              |     |         |           |
|             | Dry Skin                  | 0.36    |              |     |         |           |
|             | Skin Tolerability         |         | 0.54         |     |         |           |
| CNS         | Headache                  | 0.38    | 0.53         |     |         |           |
|             | Tremors                   | 0.3     |              |     |         |           |
|             | Poor Coordination         | 0.44    |              |     |         |           |
|             | Dizziness                 | 0.58    |              |     |         |           |
|             | CNS Tolerability          |         | 0.6          |     |         | 0.67      |
| Eyes\Ears  | Blurred Vision            | 0.47    | 0.64         |     |         |           |
|             | Ringing in Ears           | 0.36    | 0.64         |     |         |           |
|             | Eyes\Ear Tolerability     |         | 0.52         |     |         | 0.92      |
| Gen\Ur.    | Difficulty Urinating      | 0.27    |              |     |         |           |
|             | Painful Urination         | 0.23    |              |     |         |           |
|             | Menstrual Irregularity    | 0.12    |              |     |         |           |
|             | Frequent Urination        | 0.35    |              |     |         |           |
|             | Gen\Ur. Tolerability      |         | 0.47         |     |         |           |
| Sleep       | Difficulty Sleeping       | 0.33    |              |     |         |           |
|             | Sleeping too much         | 0.1     |              |     |         |           |
|             | Sleep Tolerability        |         | 0.46         |     |         |           |
| Sex         | Loss of Sexual Desire     | 0.27    | 0.66         |     |         |           |
|             | Trouble achieving orgasm  | 0.18    | 0.58         |     |         |           |
|             | Trouble with erections   | 0.2     | 0.46         |     |         |           |
|             | Sex Tolerability          |         | 0.5          |     |         | 0.89      |
|             | Alpha                     | 0.76    | 0.74         | 0.72| 0.75    | 0.73      |
Another potentially confounding issue in evaluating side effects to antidepressant treatment is the presence of somatoform symptoms, which sometimes co-occur with depression and may influence perception of the presence and severity of side effects, independently of actual side effects (Barbee, 1998; Regier et al., 1998). Thus, factor analyses were repeated controlling for baseline somatoform and hypochondriasis diagnoses, assessed using the Psychiatric Diagnostic Screening (PDS) Questionnaire (Zimmerman and Mattia, 1999). This was done to eliminate the possibility that the estimation of a given side effect factor (particularly the 2 general factors—General symptoms and Overall tolerability) was artifactual due to some subjects’ tendency to perceive and report side effects that were not physically present. As shown in Table A6, adjusting for the influence of somatoform and hypochondriasis did, in fact, improve model fit, with the best fitting model being the one in which somatoform and hypochondriasis status influence the side effect factor directly (Models II and VI), compared to no influence (Models I and V) or an indirect influence through effecting the factor indicators (Models III and VII). This conclusion is indicated by the values shown for the BIC—a robust index of comparative model fit, which is essentially a function of the log likelihood adjusted for model complexity/number of estimated parameters (Bollen, 1989; Schwarz, 1978).
Table A6. Model fit indices. Considering whether somatoform and hypochondriasis symptoms influence factor structure

| Model | Items                              | LL     | # par. | BIC     |
|-------|------------------------------------|--------|--------|---------|
| I     | No Covariates                      | -134784| 52     | 270060  |
| II    | Direct Effect on factor            | -133043| 54     | 266595  |
| III   | Indirect effect on factor through items | -132890| 104    | 266761  |

**Tolerability**

|   |                                      | LL     | # par. | BIC     |
|---|--------------------------------------|--------|--------|---------|
| V | No Covariates                        | -82683 | 24     | 165593  |
| VI| Direct Effect on factor              | -81518 | 26     | 163282  |
| VII| Indirect effect on factor through items | -81475 | 40     | 163327  |

In Table A7, the factor loadings and structural effects of somatoform and hypochondriasis status are shown for Models 1-6 in Table A6 (for models III and VII, the individual structural effects of somatoform and hypochondriasis status on individual side effect indicators has been omitted for clarity). Here it is shown that while somatoform and hypochondriasis diagnoses do have significant effects on the General symptom and Overall tolerability factors, they do not substantially alter the factor loadings. Thus, while modest improvements to measurement of the side effect factors can be made by adjusting for somatoform symptoms (which we do, as discussed below in Supplemental Material B), the factor structure for the general side effect latent variables is not driven primarily by somatoform and/or hypochondriasis symptoms. In short, the factor structures remain robust after adjusting for the influence of somatoform and hypochondriasis.
Table A7. Factor loadings and structural effects. Considering the influence of somatoform and hypochondriasis on side effect factor structures.

| Area                  | Symptom Items                  | Tolerability |       |       |       |
|-----------------------|--------------------------------|--------------|-------|-------|-------|
|                       |                                | I            | II    | III   | V     | VI    | VII   |
| **GI**                | Diarrhea                       | 0.62         | 0.61  | 0.62  |       |       |       |
|                       | Constipation                   | 0.77         | 0.76  | 0.74  |       |       |       |
|                       | Dry Mouth                      | 0.95         | 0.94  | 0.94  |       |       |       |
|                       | Nausea/Vomiting                | 0.99         | 0.99  | 0.99  |       |       |       |
|                       | GI Tolerability                |              |       |       | 1.48  | 1.45  | 1.45  |
| **Heart**             | Palpitations                   | 1.02         | 1.01  | 0.98  |       |       |       |
|                       | Dizziness on Standing          | 2.14         | 2.07  | 2.17  |       |       |       |
|                       | Chest Pain                     | 1.28         | 1.25  | 1.26  |       |       |       |
|                       | Heart Tolerability             |              |       |       | 1.88  | 1.84  | 1.86  |
| **Skin**              | Rash                           | 0.9          | 0.88  | 0.88  |       |       |       |
|                       | Increased Perspiration         | 0.84         | 0.83  | 0.82  |       |       |       |
|                       | Itching                        | 1.07         | 1.06  | 1.03  |       |       |       |
|                       | Dry Skin                       | 0.91         | 0.9   | 0.88  |       |       |       |
|                       | Skin Tolerability              |              |       |       | 1.22  | 1.21  | 1.18  |
| **CNS**               | Headache                       | 0.96         | 0.95  | 0.95  |       |       |       |
|                       | Tremors                        | 0.99         | 0.99  | 0.98  |       |       |       |
|                       | Poor Coordination              | 1.6          | 1.58  | 1.59  |       |       |       |
|                       | Dizziness                      | 2.05         | 1.99  | 2.09  |       |       |       |
|                       | CNS Tolerability               |              |       |       | 1.75  | 1.71  | 1.74  |
| **Eyes\Ears**         | Blurred Vision                 | 1.35         | 1.33  | 1.3   |       |       |       |
|                       | Ringing in Ears                | 0.97         | 0.96  | 0.97  |       |       |       |
|                       | Eyes\Ear Tolerability         |              |       |       | 1.42  | 1.38  | 1.39  |
| **Gen\Ur.**          | Difficulty Urinating           | 1.11         | 1.09  | 1.12  |       |       |       |
|                       | Painful Urination              | 1.24         | 1.23  | 1.16  |       |       |       |
|                       | Menstrual Irregularity         | 0.58         | 0.56  | 0.55  |       |       |       |
|                       | Frequent Urination             | 0.89         | 0.88  | 0.86  |       |       |       |
|                       | Gen\Urin. Tolerability        |              |       |       | 1.16  | 1.15  | 1.12  |
| **Sleep**             | Difficulty Sleeping            | 0.71         | 0.71  | 0.7   |       |       |       |
|                       | Sleeping too much              | 0.21         | 0.2   | 0.22  |       |       |       |
|                       | Sleep Tolerability             |              |       |       | 0.93  | 0.91  | 0.92  |
| **Sex**               | Loss of Sexual Desire          | 0.63         | 0.63  | 0.62  |       |       |       |
|                       | Trouble achieving orgasm      | 0.44         | 0.44  | 0.45  |       |       |       |
|                       | Trouble with erections        | 0.7          | 0.69  | 0.72  |       |       |       |
|                       | Sex Tolerability               |              |       |       | 0.72  | 0.71  | 0.72  |
|                       | F ON Hypo                      | 0.643*       |       |       | 0.747*|       |       |
|                       | F ON SOMA                      | 0.677*       |       |       | 0.700*|       |       |

* P < 0.05
B. Estimating treatment effects for citalopram-induced side effects

To develop measures of citalopram-induced adverse drug reactions, we employed a mixed model approach conceptualizing individual differences in drug response as random effects (Goldstein, 1995; Searle et al., 1992). Specifically, we used a multi-step model fitting procedure to: 1) determine the correct functional form of longitudinal, citalopram-induced change in side effects, and 2) screen 55 potentially relevant covariates to identify those that improve the precision of the treatment effect measures (Adkins et al., 2011; van den Oord et al., 2009). After identifying the optimal functional form and covariate set, we estimated linear mixed models predicting citalopram side effects with fixed and random effects. Separate model fitting procedures were conducted for each of the 5 following side effect indicators: general side effect burden, overall tolerability, sexual side effects, dizziness and vision/hearing side effects.

Linear mixed models are a generalization of linear regression allowing for the inclusion of individual-level random deviations (effects) other than those associated with the overall residual term. In matrix notation,

\[ y = X\beta + Zu + \varepsilon \]

where \( y \) is the \( n \times 1 \) vector of responses, \( X \) is a \( n \times p \) design/covariate matrix for the fixed effect \( \beta \), and \( Z \) is the \( n \times q \) design/covariate matrix for the random effects \( u \). The \( n \times 1 \) vector of residuals \( \varepsilon \), is assumed to be multivariate normal with mean zero and variance matrix \( \sigma_e^2 I_n \).

The fixed portion, \( X\beta \), is equivalent to the linear predictor of OLS regression. For the random portion, \( Zu + \varepsilon \), it is assumed that the \( u \) has variance-covariance matrix \( G \) and that \( u \) is orthogonal to \( \varepsilon \) so that
The random effects $u$ are not directly estimated (although, as described below, they are predicted), but instead are characterized by the elements of $G$, known as the variance components, that are estimated along with the residual variance $\sigma^2_e$. Considering $Zu + \epsilon$ the combined error, we see that $y$ is multivariate normal with mean $X\beta$ and $n \times n$ variance-covariance matrix

$$V = ZGZ' + \sigma^2_e I_n$$  \hspace{1cm} \text{Eq. 3}$$

In the current analysis, our model fitting procedure begins with identifying the correct functional form of longitudinal antidepressant-induced change in side effect severity. That is, we determine how long it takes for antidepressant-induced side effect change to reach its maximum and plateau out. For instance, based on the clinical trial data, the procedure indicates after how many days on citalopram, on average, subjects’ general side effect burden stops worsening and plateaus out. This is vital to developing high-quality measures of treatment effects, because to the extent the assumed functional form deviates from the actual one, noise is introduced into the measure and the power to detect associations in the GWAS is proportionately diminished. For this reason, we estimate a series of models in which the number of days until antidepressant-induced side effect change plateaus varies systematically, beginning with a model that assumes maximal response at day 1, and then increasing the number of days, in 5 day increments, until 141 days on drug.

This procedure is achieved using the equation:

$$y_{ij} = \beta_0 + \beta_1 D_{ij} + u_{0i} + u_{1i} D_{ij} + e_{ij}$$  \hspace{1cm} \text{Eq. 4}$$
where \( i \) and \( j \) denote the subject and assessment levels, respectively; \( y \) is the side effect outcome for subject \( i \) at assessment \( j \); \( \beta_0 \) is the overall sample intercept; \( \beta_1 \) is the sample mean coefficient (i.e., fixed effect) of antidepressant treatment; \( u_{0i} \) is the subject-specific deviation (i.e., random effect) from that overall sample intercept; \( u_{1i} \) is the random effect of the mean antidepressant treatment coefficient; \( e_{ij} \) is the residual for subject \( i \) at assessment \( j \). Most importantly, \( D \) is a variable that describes how long the subject has been on the current antidepressant. \( D \) is recoded in each model of the series to specify a different number of days until maximal response (i.e., a plateau) is achieved. Thus, for the first model in the series, which assumes maximal effect at day 1, \( D \) is coded 0 if the subject isn’t on a trial antidepressant, 1 at day 1, and 1 each day thereafter. In the second model which assumes maximal effect at day 6, \( D \) is coded 0 if the subject isn’t on the antidepressant, 1 if they have been on for 1 day, 2 for 2 days, and so on, until day 6, after which \( D \) is coded equal to 6 for the duration of treatment with that antidepressant. For each outcome, indices of model fit (log likelihoods) were collected for each model in the \( D \) series, and then these values were minimized to determine the optimal response functional form. Figure B1 presented the graphed log likelihood values for each outcome with the optimal plateau values marked with red vertical lines.

After determining the optimal functional forms of the antidepressant treatment effects, we then screened 55 covariates (shown in Table B1) to identify those that improved the precision of the treatment effects. More specifically, we sought covariates that accounted for error in the model, but did not mediate the treatment effects. Thus, we employed a decision rule specifying that covariate must: 1) explain a significant amount
of variance in the outcome (i.e., coefficient p-value > .05), and 2) reduce the residual variance (VAR(e)) significantly more than the treatment effect variance (VAR(u1)). The

Figure B1. Identifying optimal plateau function forms citalopram-induced side effect change (i.e., treatment effects)
55 covariates considered were selected from three domains: 1) Design characteristics – which captured the characteristics of the trial structure such as what phase the subject was currently in and when a given phase ended; 2) Clinical factors – including age at first major depressive episode (MDE), number of year since MDE, physical health, and co-morbid psychiatric conditions; 3) Socio-demographic information – this included information on age, gender, race/ethnicity employment, marital status and insurance status; and 4) Reasons given for early study exit.

Table B1. List of screened covariates

| Design characteristics | Clinical Information | Socio-demographics | Reason, Early Study Exit |
|------------------------|----------------------|--------------------|-------------------------|
| Level 1                | Age at 1st MDE       | Gender             | Unacceptable side effects |
| Level 2                | Years since 1st MDE  | Age                | Emergent GMC            |
| Level 2b               | Months in current episode | White   | Failed to return to clinic |
| Level 3                | CIRS total score     | Black              | Moved from the area     |
| Level 4                | Total number of CIRS categories | Other race/ethnicity | Non-adherence to protocol |
| End of Level (any)     | CIRS severity index  | Employment         | Non-adherence to study medication |
| End of Level 1         | PDS alcohol abuse (count) | Unemployed | Found research too burdensome |
| End of Level 2         | PDS alcohol abuse (binary) | Retired   | Patient withdrew with no reason |
| End of Level 2a        | PDS drug abuse (count) | Married           | Patient became pregnant |
| End of Level 3         | PDS drug abuse (binary) | Never married     | Not randomized due to GMC |
| End of Level 4         | PDS OCD (count)      | Divorced           | Not randomized due to concomitant medication |
|                        | PDS OCD (binary)     | Widowed            | Other                   |
|                        | PDS Hypochondriasis (count) | Private insurance |                         |
|                        | PDS Hypochondriasis (binary) | Public insurance |                         |
|                        | PDS Somatoform (count) | No insurance       |                         |
|                        | PDS Somatoform (binary) |                     |                         |
|                        | PDS Bulimia nervosa (count) |                     |                         |
|                        | PDS Bulimia nervosa (binary) |                     |                         |

MDE: major depressive episode; CIRS: Cumulative Illness Rating Scale; PDS: Psychiatric Diagnostic Screening Questionnaire; GMC: generalized medical condition
The number of selected covariates was 6 for vision/hearing and sexual side effects, 7 for general side effect burden, overall tolerability, and 8 for dizziness. Similar sets of covariates were indicated for all measures, with design characteristics and concurrent psychiatric diagnoses (particularly drug abuse and hypochondriasis) comprising the vast majority of selected covariates. Table 2 lists the covariates retained for each outcome.

Table B2. Covariates included in treatment effect generating models

| Outcome                  | Selected Covariates                                                                 |
|--------------------------|-------------------------------------------------------------------------------------|
| General side effect burden | Level 1, Level 2, Level 4, End of level (any), End of level 1, PDS drug abuse (binary), PDS hypochondriasis (count) |
| Overall Tolerability     | Level 1, Level 2, Level 4, End of level (any), End of level 1, PDS drug abuse (binary), PDS hypochondriasis (count) |
| Dizziness                | Widowed, Level 2, Level 3, PDS drug abuse (binary), PDS drug abuse (count), PDS hypochondriasis (binary), PDS hypochondriasis (count), PDS somatoform (count) |
| Sexual                   | Widowed, Level 1, Level 2, Level 4, End of level 1, End of level 2                   |
| Vision/hearing           | Level 1, Level 2, PDS drug abuse (binary), PDS OCD (binary), PDS OCD (count), hypochondriasis (count) |

After determining the proper functional form of the over-time treatment effects and identifying the precision-enhancing covariates, we then output the random effects for citalopram side effect severity measures for each of the 5 side effect indicators. These measures quantify the deviation of each subject’s citalopram-induced side effect change from the overall sample mean change and thus, serve as our treatment effect measures in the subsequent GWAS. Specifically, they are estimated with the equation:

$$y_{ij} = \beta_0 + \beta_1 D_{ij} + \beta_2 O_{kij} + \beta_{l+1} C_{ij} + u_{0i} + u_{1i} D_{ij} + u_{2i} O_{kij} + e_{ij}$$  \hspace{1cm} \text{Eq.5}$$

where $i$ and $j$ denote the subject and assessment levels, respectively; $y$ is the side effect outcome for subject $i$ at assessment $j$; $\beta_0$ is the overall sample intercept; $D$ is citalopram;
$\beta_1$ is the sample mean coefficient (i.e., fixed effect) for citalopram; $O$ is all trial antidepressants other than citalopram, indexed 1-6 by $k$; $\beta_k$ are the fixed effect for $O$; $l$ indexes the number of covariates $C$ included in the model; $\beta_{l+k}$ are the fixed effects for $C_l$; for $u_{0i}$ is the subject-specific deviation (i.e., random effect) from that overall sample intercept; $u_{1i}$ is the random effect of citalopram; $u_{2i}$ is the random effect of $O_k$; $e_{ij}$ is the residual for subject $i$ at assessment $j$. The parameter of interest, $u_{1i}$, maybe more intuitively described as the subject-specific effect of citalopram on the given side effect outcome.

In each model, the covariance structure of the 3 random effects was modeled as independent:

$$
\begin{bmatrix}
  u_{0i} \\
  u_{1i} \\
  u_{2i}
\end{bmatrix}
\sim N(0,G)
\quad \text{with } G =
\begin{bmatrix}
  \sigma_{u0}^2 & 0 & 0 \\
  0 & \sigma_{u1}^2 & 0 \\
  0 & 0 & \sigma_{u2}^2
\end{bmatrix}
$$

Eq.6

Thus, the random parameters are multivariate normal distributed with means of zero and variance-covariance matrix $G$. The variances of the parameters are on the diagonal and the covariances, constrained equal to zero, are in the off-diagonal cells of $G$. The residual is assumed to be normally distributed with a mean of zero and variance of $\sigma_e^2$.

Because random effects are not directly estimated by the mixed model, they must be predicted in an additional post-estimation step (Robinson, 1991). Best linear unbiased predictors (BLUPs) of the random effects $u$ were obtained as

$$
\tilde{u} = \tilde{G}Z'\tilde{V}^{-1}(y - X\hat{\beta})
$$

Eq.7

where $\tilde{G}$ and $\tilde{V}$ are $G$ and $V$ with estimates of the variance components plugged in. The EM algorithm was used for maximum likelihood estimation (Pinheiro and Bates, 2000).
C. Ethnically stratified results for top GWAS findings in full sample

Table C1. African-American-only subsample: GWAS results with \( q \)-value less than 0.5 in full, ethnically heterogeneous analysis

| Side Effect       | Chr | Position  | SNP ID   | Gene       | N  | BETA | STAT | P        |
|-------------------|-----|-----------|----------|------------|----|------|------|----------|
| Vision\Hearing    | 7   | 100902714 | rs17135437 | EMID2      | 260| 0.105| 23.00| 2.83E-06|
| Overall Tolerability | 18 | 6931108   | rs4398173  | LAMA1      | 260| 0.040| 6.05 | 0.015    |
| Overall Tolerability | 18 | 6931662   | rs3810046  | LAMA1      | 260| 0.044| 7.31 | 0.007    |
| Overall Tolerability | 16 | 13564386  | rs2903308  |            | 260| 0.016| 0.95 | 0.331    |
| GSE               | 5   | 38488651  | rs7715172  | EGFLAM     | 262| 0.041| 13.90| 2.41E-04|
| GSE               | 3   | 59896060  | rs4502542  | FHIT       | 262| 0.064| 12.70| 4.39E-04|
| GSE               | 13  | 83028233  | rs6563353  |            | 262| 0.025| 3.82 | 0.052    |
| GSE               | 13  | 104605024 | rs16965962 |            | 262| 0.069| 27.40| 3.41E-07|
| GSE               | X   | 116106291 | rs6646773  |            | 262| 0.055| 12.90| 3.97E-04|
| GSE               | 4   | 187575329 | rs11935103 |            | 262| 0.008| 0.38 | 0.536    |
| GSE               | 3   | 188896685 | rs6764050  | RPT2       | 262| 0.060| 14.20| 2.00E-04|
| Dizziness         | 20  | 11105011  | rs6040399  |            | 261| 0.132| 24.30| 1.46E-06|
| Dizziness         | 2   | 201356884 | rs13430864 | AOX2P      | 261| 0.102| 14.20| 2.01E-04|
| Dizziness         | 2   | 201360698 | rs13423450 | AOX2P      | 261| 0.117| 17.90| 3.33E-05|
Table C2. European-American-only subsample: GWAS results with $q$-value less than 0.5 in full, ethnically heterogeneous analysis

| SIDE EFFECT      | Chr  | Position | SNP ID     | Gene    | N    | BETA | STAT    | P        |
|------------------|------|----------|------------|---------|------|------|---------|----------|
| Vision\Hearing   | 7    | 100902714| rs17135437 | EMID2   | 1347 | 0.066| 2.11    | 0.146    |
| Overall Tolerability | 18  | 6931108  | rs4398173  | LAMA1   | 1344 | 0.029| 21.50   | 3.97E-06 |
| Overall Tolerability | 18  | 6931662  | rs3810046  | LAMA1   | 1344 | 0.028| 21.00   | 5.10E-06 |
| Overall Tolerability | 16  | 13564386 | rs2903308  |         | 1344 | 0.026| 18.50   | 1.86E-05 |
| GSE              | 5    | 38488651 | rs7715172  | EGFLAM  | 1348 | 0.061| 5.47    | 0.020    |
| GSE              | 3    | 59896060 | rs4502542  | FHIT    | 1348 | 0.091| 7.17    | 0.008    |
| GSE              | 13   | 83028233 | rs6563353  |         | 1348 | 0.023| 17.20   | 3.53E-05 |
| GSE              | 13   | 104605024| rs16965962 | EGFLAM  | 1348 | -0.011| 0.06    | 0.806    |
| GSE              | X    | 116106291| rs6646773  |         | 1348 | 0.027| 5.67    | 0.017    |
| GSE              | 4    | 187575329| rs11935103 |         | 1348 | 0.023| 22.50   | 2.35E-06 |
| GSE              | 3    | 188896685| rs6764050  | RPT2    | 1348 | 0.184| 8.17    | 0.004    |
| Dizziness        | 20   | 11105011 | rs6040399  |         | 1346 | 0.038| 12.00   | 5.60E-04 |
| Dizziness        | 2    | 201356884| rs13430864 | AOX2P   | 1346 | 0.195| 7.45    | 0.006    |
| Dizziness        | 2    | 201360698| rs13423450 | AOX2P   | 1346 | 0.227| 9.37    | 0.002    |
D. Regional Plots for \textit{EGFLAM}, \textit{FHIT}, \textit{RPT2} and intergenic top associations

Figure D1. Regional plots for GWAS results of A) \textit{EGFLAM}, B) \textit{FHIT}, C) \textit{RPT2} and D) intergenic rs11935103 associations. Points represent $-\log_{10}(p)$-values for association tests and are color coded to denote linkage disequilibrium to the target SNP in the HapMap Phase II reference data. Recombination rate is represented by the light blues lines. The plots’ bottom panels show the names and locations of genes in the UCSC Genome Browser, with exon positions denoted by cross-hatches and transcription direction by arrows (Pruim et al., 2010).
Figure D2. Regional plots for GWAS results of A) rs6563353, B) rs6646773, C) rs2903308 and D) rs6040399 associations. Points represent $-\log_{10}(p$-values) for association tests and are color coded to denote linkage disequilibrium to the target SNP in the HapMap Phase II reference data. Recombination rate is represented by the light blues lines. The plots’ bottom panels show the names and locations of genes in the UCSC Genome Browser, with exon positions denoted by cross-hatches and transcription direction by arrows.
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