# Antidepressant Response and Side Effects in the Genetic Links to Anxiety and Depression (GLAD) Study

## Study Information

### Title (required)

**Provide the working title of your study. It may be the same title that you submit for publication of your final manuscript, but it is not a requirement.**

Predictors of Antidepressant Repose and Side Effects in the Genetic Links to Anxiety and Depression (GLAD) study

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### Description (optional)

**Please give a brief description of your study, including some background, the purpose of the study, or broad research questions.**

Antidepressants are a class of psychiatric medications primarily aimed at treating major depressive disorders, but which are also prescribed for other conditions such as anxiety, sleep disorders and bipolar disorder (Olfson and Marcus 2009). In addition, they have various uses for treatment of physiological illnesses, such as pain management in headache and neuropathic pain (Olfson and Marcus 2009). In the UK, 70.9 million prescriptions for antidepressants were given out in 2018 (Iacobucci 2019). Given that antidepressants are a treatment for a wide range of conditions with a high prescription rate, understanding the nature of antidepressant treatment is crucial.

Selective serotonin reuptake inhibitors (SSRIs), one of the most widely prescribed class of antidepressants in various countries (Abbing-Karahagopian et al. 2014; Haller et al. 2019; Olfson and Marcus 2009), are reported to increase both risks on serious and non-serious side effects in a systematic review summarising 161 randomized controlled trials of SSRIs for major depressive disorder. There are a wide range of common side effects assciated with antidepressant treatments, including but not restricted to gastrointestinal disturbances (e.g., nausea and vomiting), hepatotoxicity, metabolic disturbance (e.g., weight gain/loss) and sexual dysfunction (Carvalho et al. 2016). About 43% of patients discontinue their antidepressant because of side effects (Bull et al. 2002). In a telephone survey involving 401 patients, even the most common and less severe side effects, such as drowsiness (17%), weight gain (11%) and sexual dysfunction (17%) were all considered bothersome by participants (Hu et al. 2004).

Although substantial side effects are reported in clinical trials, the generalizability of these findings to naturalistic settings are unclear as trial participants represent a group of highly selected individuals receiving treatments in controlled settings (van der Lem et al. 2011). In addition, typical trial duration with antidepressant treatments last from 6 to 12 weeks, (Rutherford et al. 2013), thus the relatively short time frame of trials insufficiently assesses side effects experienced during long-term usage.

A series of characteristics, such as symptom severity and treatment types, are associated with the number of reported side effects of antidepressants. Bet et al. Assessed patient characteristics in a two-year time frame and found that the side effect burden is higher in patients suffering from more severe depressive symptoms, with higher numbers of comorbid psychiatric disorders, receiving tricyclic antidepressants, and who are on higher doses of antidepressants. In turn, older individuals and individuals with longer medication history report fewer side effects (Bet et al. 2013). Additionally, depressive individuals with clinically significant anxiety symptoms as assessed by psychometric scales report more side effects than those without (see Ionescu et al. 2014 for a review).

Antidepressants exert their effects via several central nervous neurotransmitter receptor systems. There are theoretical underpinnings that these receptors might be responsible for side effects as well as the intended drug effect of lowering anxious and depressive symptoms (Carvalho et al. 2016). Moreover, antidepressants bind to several receptors concurrently (e.g., serotonin, dopamine, histamine and acetylcholine) which impacts several down-stream biological functions. For instance, serotonin receptors mediate a number of systems, including sleep, appetite, and sexual behaviour (Ferguson 2001). All of these biological functions can get disturbed during a treatment with antidepressants leading to a variety of commonly reported side effects, such as insomnia, weight gain/loss, and sexual dysfunction (Williams 2018). These side effects represent a serious burden for individuals taking antidepressants and are associated with lower adherence to treatment complicating successful treatment of depressive episodes.

There has been ongoing research to find correlates of response to antidepressants. Most research centers around using biomarkers from physiological data from, for example, neuroimaging and pharmacogenetics (Labermaier, Masana, and Müller 2013; Sambataro and Wolf 2019). There are several investigations into non-physiological correlates of antidepressant treatment response based on clinical trial data (Chekroud et al. 2016; Rajpurkar et al. 2020; Kautzky et al. 2019; Howland et al. 2008). A similar set of variables that are also assocaited with side effect severity were identified to be assocaited with poorer treatment outcome such as inital depression severity, duration of depressive symptoms, and comorbid symptoms of other psychiatric disorders, especially those concerning anxiety. However, the conclusion of these studies are also limited by the lack of generalizability and the short time frame inherent in trial data, as well as small sample sizes (N < 600).

In the current study, we collect self-report data through a large online questionnaire survey from a total of more than 6,000 patients treated with antidepressants. Participants report a comprehensive set of side effects and effectiveness measures for a wide range of antidepressants that they took during their lifetime. Given the body of research indicating an association between psychiatric diagnoses and treatment experience including side effect severity, we measure a range of psychiatric diagnoses and individual medication history. In addition, we measure family psychiatric diagnostic history as a proxy for genetic/familial load. We investigate associations of side effect severity and treatment intolerance with the length of medication history, lifetime psychiatric diagnoses, family psychiatric diagnostic history and the type of antidepressant, and examine if side effect severity and treatment intolerance are associated with antidepressant effectiveness. We also explore whether specific side effects are particularly associated with effectiveness.

### Hypotheses (required)

**List specific, concise, and testable hypotheses. Please state if the hypotheses are directional or non-directional. If directional, state the direction. A predicted effect is also appropriate here. If a specific interaction or moderation is important to your research, you can list that as a separate hypothesis.**

We hypothesize that 1) the length medication history and lifetime psychiatric diagnoses are positively associated with side effect severity ; 2) these factors are also positively associated with treatment intolerance; 3) side effect severity and treatment intolerance are negatively associated with antidepressant effectiveness. 4) We exploratory analyse if specific side effects are associated with effectiveness.

## Design Plan

**In this section, you will be asked to describe the overall design of your study. Remember that this research plan is designed to register a single study, so if you have multiple experimental designs, please complete a separate preregistration.**

### Study type (required)

Observational Study.

### Blinding (required)

**Blinding describes who is aware of the experimental manipulations within a study. Mark all that apply.**

No blinding is involved in this study as it is observational.

### Study design (required)

**Describe your study design. Examples include two-group, factorial, randomized block, and repeated measures. Is it a between (unpaired), within-subject (paired), or mixed design? Describe any counterbalancing required. Typical study designs for observation studies include cohort, cross sectional, and case-control studies.**

Cross-sectional and retrospective.

## Sampling Plan

**In this section we’ll ask you to describe how you plan to collect samples, as well as the number of samples you plan to collect and your rationale for this decision. Please keep in mind that the data described in this section should be the actual data used for analysis, so if you are using a subset of a larger dataset, please describe the subset that will be used in your study.**

### Existing Data (required)

**Preregistration is designed to make clear the distinction between confirmatory tests, specified prior to seeing the data, and exploratory analyses conducted after observing the data. Therefore, creating a research plan in which existing data will be used presents unique challenges. Please select the description that best describes your situation. Please see https://cos.io/prereg for more information.**

### Data collection procedures (required)

**Please describe the process by which you will collect your data. If you are using human subjects, this should include the population from which you obtain subjects, recruitment efforts, payment for participation, how subjects will be selected for eligibility from the initial pool (e.g. inclusion and exclusion rules), and your study timeline. For studies that don’t include human subjects, include information about how you will collect samples, duration of data gathering efforts, source or location of samples, or batch numbers you will use.**

Participants will be derived from data collected in the Genetic Links to Anxiety and Depression (GLAD) study. The GLAD study was started in 2018 and aims to recruit 40,000 participants with lifetime depression and/or anxiety disorders. Phenotypic data collection is ongoing through an online survey incorporating a wide range of questionnaires regarding psychiatric disorders and behavioural traits. The genetic data is collected using saliva samples. For greater detail regarding recruitment and participant eligibility, see Davies et al. (2019). The current study consists of a subsample from the initial pool of the GLAD study participants who completed the supplementary questionnaire related to medications.

### Sample size (required)

**Describe the sample size of your study. How many units will be analysed in the study? This could be the number of people, birds, classrooms, plots, interactions, or countries included. If the units are not individuals, then describe the size requirements for each unit. If you are using a clustered or multilevel design, how many units are you collecting at each level of the analysis?**

This study will draw on a sample of over 6000 people who completed the medication supplementary questionnaire in the GLAD study.

## Variables

**In this section you can describe all variables (both manipulated and measured variables) that will later be used in your confirmatory analysis plan. In your analysis plan, you will have the opportunity to describe how each variable will be used. If you have variables that you are measuring for exploratory analyses, you are not required to list them, though you are permitted to do so.**

### Measured variables (required)

**Describe each variable that you will measure. This will include outcome measures, as well as any predictors or covariates that you will measure. You do not need to include any variables that you plan on collecting if they are not going to be included in the confirmatory analyses of this study.**

### Indices (optional)

**If any measurements are going to be combined into an index (or even a mean), what measures will you use and how will they be combined? Include either a formula or a precise description of your method. If you are using a more complicated statistical method to combine measures (e.g. a factor analysis), you can note that here but describe the exact method in the analysis plan section.**

#### Current depressive and anxiety symptoms

We computed sum scores of all items in The Patient Health Questionnaire (PHQ-9) (Kroenke, Spitzer, and Williams 2001) and in GAD-7 (Spitzer et al. 2006) to measures current depressive symptoms and current anxiety symptoms, respectively.

#### Number of panic disorder symptoms

The panic disorder questionnaire was adapted from the Australian Genetics of Depression Study (Byrne et al. 2019), where the items concerning panic disorder symptoms were used to calculate a total sum score. A typical such item is presented as follows: “Have you ever been afraid that you were going to lose control/go crazy?”. A complete list of items used can be found in the appendix.

#### Number of first-degree relatives with psychiatric disorders

We adapted the assessment for family history of psychiatric disorders from the Australian Genetics of Depression Study, from which we computed a sum score of the numbers of relatives having suffered from a range of psychiatric disorders. The exact diagnoses included can be found in the appendix.

#### Psychiatric diagnoses

##### Total number of psychiatric diagnoses

Participants self-report if they have been diagnosed or been treated for psychiatric disorders. The total number of endorsed diagnoses were calculated for each participant. A complete list of psychiatric disorders can be found in the appendix.

##### Individual psychiatric diagnoses

A series of individual psychiatric diagnoses that participants self-report are included. In addition we include a variant of the diagnoses for major depressive disorder and anxiety disorder, as assesses by our questionnaire-adpated Composite International Diagnostic Interview (Kessler et al. 2004), the diagnostic algorithms can be found in the appendix.

#### Length of medication history

##### Age at first treatment with antidepressant

Participants indicate for each antidepressant they had taken during their lifetime the age at which they started the treatment. For instance, “How old were you when you started taking Citalopram (e.g. Cipramil)?” Based on all ages at treatment onset for each antidepressant, we extracted the youngest treatment start age.

##### Total duration of antidepressant treatment

Participants indicate for each antidepressant taken the duration of the treatment. A typical such item is presented as: “How long did you take/have you been taking Citalopram (e.g. Cipramil)?” We calculated the total duration by summing the durations for all antidepressants a participant has taken.

#### Side effect severity

##### Average number of experienced side effects

Participants indicate for each antidepressant taken whether they experienced a range of possible side effects. A complete list of side effect items can be found in the appendix. We compute the average number of experienced side effects by averaging the number of total side effects experienced by the number of antidepressants taken. For instance, a participant may have taken four antidepressants during their lifetime and had in total twenty experiences of side effects. Participants may have experienced the same side effect more than once when taking different antidepressants. Such side effects are counted multiple times. In this case, the side effect severity index is expressed with a value of 5, calculated by twenty total side effect experiences divided by the four antidepressants taken during their lifetime.

##### Side effect severity rating

Participants rate the severity of side effects of antidepressant(s) on a 1 to 5 scale, where 1 indicates “very bad” side effects and 5 indicates no or only very mild side effects.

#### Likelihood of treatment intolerance

Participants indicate for each antidepressant taken whether they had to stop taking it because of side effects. We compute the likelihood of treatment intolerance by averaging the number of instances of treatment intolerance by the number of antidepressants taken. For instance, a participant may have taken four antidepressants during their lifetime and had to discontinue two of them because of side effects. In this case, the likelihood of treatment intolerance is expressed with a value of 0.5, calculated by two intolerance experiences divided by the four antidepressants taken during their lifetime.

#### Effectiveness

##### Average effectiveness

Participants indicate for each antidepressant taken how well the antidepressant “worked” by choosing one of the following answer options: 1) “Not at all well”, 2) “Moderately well” , 3) “Very well” or 4) “Don’t know”. We compute the average effectiveness index by averaging the sum of this rating across the number of antidepressants. For instance, a participant may have taken four antidepressants during their lifetime and rate their effectiveness respectively as 2, 2, 3, 3. In this case, the average effectiveness is expressed with a value of 2.5, calculated by the sum of all ratings, ten, divided by the four antidepressants taken during their lifetime.

##### Benefit rating

Participants rate the benefit of side effects of antidepressant(s) on a 1 to 5 Likert scale where 1 indicates the worst rating and 5 the best rating.

##### Number of best aspects of antidepressant treatment

Participants report the best aspects of taking the antidepressant(s) by choosing all of the following that applied: 1) “Relief of depressive symptoms”, 2) “Relief of other key symptoms”, 3) “Reduction in suicidal thinking or actions”, 4) “Return of normal emotions”, 5) “Improved relationships”, 6) “Getting back to normal daily activities”, 7) “Restored control over my mood and actions”. We comput the number of best aspects of antidepressant treatment by counting the number of options endorsed by the participant.

##### Likelihood of remission

Participants indicate for each antidepressant taken whether they experienced any further symptoms after taking antidepressant for “a period of time”. We compute the likelihood of remission by averaging the number of instances where no further symptoms were experienced by the number of antidepressants taken during their lifetime. For instance, a participant may have taken four antidepressants during their lifetime and did not experience further symptoms after taking two of them. In this case, the likelihood of remission is expressed with a value of 0.5, calculated by two remission experiences divided by the four antidepressants taken during their lifetime.

##### Average improvement duration

Participants report for each antidepressant for how long the improvement has been lasting “after treatment” by choosing one of the following that applied: 1) “Less than a month”, 2) “1 to 2 months”, 3) “3 to 6 months”, 4) “7 to 12 months”, 5) “More than 12 months”, 6) “I didn’t have any improvement in symptoms” and 7) “Not sure”. We computed the average improvement duration by averaging the improvement duration ratings across the number of antidepressants taken during their lifetime. For instance, a participant may have taken four antidepressants during their lifetime and indicate their improvement duration as 2, 2, 3, 3. In this case, the average effectiveness is expressed with a value of 2.5, calculated by the sum of all duration ratings, ten, divided by the four antidepressants taken during their lifetime.

#### Type of antidepressants

We cluster antidepressants based on their receptor affinity and compute how many medications per category a participant has taken during their lifetime. The details of statistical methods used are described in the next section.

#### Medication type

## Analysis Plan

**You may describe one or more confirmatory analysis in this preregistration. Please remember that all analyses specified below must be reported in the final article, and any additional analyses must be noted as exploratory or hypothesis-generating.**

**A confirmatory analysis plan must state up front which variables are predictors (independent) and which are the outcomes (dependent), otherwise it is an exploratory analysis. You can describe any exploratory work here, but a clear confirmatory analysis is required.**

### Statistical models (required)

**What statistical model will you use to test each hypothesis? Please include the type of model (e.g. ANOVA, multiple regression, SEM, etc) and the specification of the model (this includes each variable that will be included as predictors, outcomes, or covariates). Please specify any interactions, subgroup analyses, pairwise or complex contrasts, or follow-up tests from omnibus tests. If you plan on using any positive controls, negative controls, or manipulation checks you may mention that here. Remember that any test not included here must be noted as an exploratory test in your final article.**

#### Descriptives

Means, standard deviations, maximums and minimums will be computed and presented for all variables in the data.

#### Antidepressant classification

We cluster antidepressants based on their receptor affinity measured by the equilibrium dissociation constant (Ma, Yang, and He 2018). The data of receptor affinity of antidepressants used were gathered from official publications (Tatsumi et al. 1997; Owens et al. 1997; Brunton, Chabner, and Knollman 2011; Essentials of Clinical Psychopharmacology 2001; Cusack, Nelson, and Richelson 1994).

We apply X-means clustering algorithm (Pelleg and Moore 2000), an extension of K-means clustering with an unspecified number of clustering centroids. Starting from one centroid, the algorithm repeatedly attempts to divide one of the centroids into two and keeps the best split by comparing the resulting AIC (Akaike information criterion) (Akaike (1998)) and BIC (Bayesian information criterion) (Schwarz 1978).

After clustering the medications into categories, we compute how many medications per category a participant has taken during their lifetime.

#### Patient characteristics associated with side effect severity and treatment intolerance

The first analysis examines patient characteristics that may be associated with side effect severity. Variables on the length of medication history and psychiatric diagnoses and the type of antidepressant are included as explanatory variables, as they are associated with the number of reported side effects (RSE) (Bet et al. 2013). We use age at first treatment with antidepressant and total duration on antidepressant as measures for the length of medication history. Our two measures for psychiatric diagnoses, the total number of psychiatric diagnoses and individual psychiatric diagnoses are included in separate models as they measure similar constructs.

We include in the model the number of antidepressants taken per derived antidepressant category, as antidepressant type is associated with the average number of RSE. **We investigate the association of antidepressant type with side effects and effectiveness ratings by first classifying antidepressants by receptor affinity using x-means clustering and subsequently associating these derived antidepressant categories with our outcomes of interest.** As genotype data is not yet available for study participants, we include the number of first relatives with a psychiatric diagnoses as a proxy for genetic/familial load.

Our outcome variables are the average number of reported side effects, the side effect severity rating, and the likelihood of intolerance. We examine each in a separate model.

We **plan** to adjust all models for sex, age. Current depressive and anxiety symptoms and the number of panic disorder symptoms are also included as covariates to adjust for potential negative reporting bias.

#### Effectiveness and side effect severity and treatment Intolerance

The second analysis examines the association between antidepressant effectiveness and side effect severity. We combine three different explanatory variables with five outcome variables, resulting in fifteen models. The explanatory variables include the average number of reported side effect , side effect severity rating, and the likelihood of intolerance. The outcome variables are average effectiveness, benefit rating, the likelihood of remission, the number of best treatment aspects, and the average improvement duration. We adjust the models for age, sex, age at first treatment with antidepressant, and total duration of antidepressant treatment **(both as measures for medication history)**, number of psychiatric diagnoses, current depressive and anxiety symptom scores, the total number of panic disorder symptoms, **number of first-degree relatives with psychiatric diagnoses (i.e., approximation of genetic/familial load)**, and the number of antidepressants taken per derived antidepressant category. All these covariates have been shown to be associated with side effect severity of side effects. **We further investigate their potential association with effectiveness.**

#### Subgroup analysis

We divide paritipants into subgroups by the type of antidepressants. Note that the subgroups can have overlapping paritipants because an individual can take multiple types of antidepressants. Variables relevant to individual antidepressants are recomputed by restricting the antidepressants to those belong to a certain type. For instance, we will recompute the total duration of antidepressant treatment by only considering the duration of taking a specific type of antidepressants. We use the newly computed variables to reconduct the two analyses.

### Inference criteria (optional)

**What criteria will you use to make inferences? Please describe the information you’ll use (e.g. specify the p-values, Bayes factors, specific model fit indices), as well as cut-off criterion, where appropriate. Will you be using one or two tailed tests for each of your analyses? If you are comparing multiple conditions or testing multiple hypotheses, will you account for this?**

We will use the Benjamini–Hochberg procedure (Benjamini and Hochberg 1995) to control the false discovery rate at < 0.05.

### Data exclusion (optional)

**How will you determine which data points or samples if any to exclude from your analyses? How will outliers be handled? Will you use any awareness check?**

### Exploratory analysis (optional)

**If you plan to explore your data set to look for unexpected differences or relationships, you may describe those tests here. An exploratory test is any test where a prediction is not made up front, or there are multiple possible tests that you are going to use. A statistically significant finding in an exploratory test is a great way to form a new confirmatory hypothesis, which could be registered later.**

#### Effectiveness and Individual Side Effects

The explanatory analysis examines if any specific side effect shows a particular association with antidepressant effectiveness. More specifically, we investigate if a participant who is more likely to experience a specific side effect reports higher effectiveness. The likelihood of suffering from a side effect is defined as the average number of its occurrences across antidepressants taken. For instance, a participant may have taken four antidepressants in lifetime and had headaches from two of these antidepressants, this would be expressed with a value of 0.5 calculated by 2 occurrences of the side effect divided by the four antidepressants taken in lifetime. The outcome variables and the planned covariates to adjust for will be the same as those in the second analysis examining the association between effectiveness and side effect severity.

***Table 1.*** Outcome variable: side effect rating, average number of experienced side effects and likelihood of intolerance

|  |  |
| --- | --- |
| Models | Explanatory variables |
| Model 1 | Total duration of antidepressant treatment + age at first treatment with antidepressant + number of first relatives with psychiatric disorders |
| Model 2 | Model 1 + age + sex |
| Model 3 | Model 2 + current depression + current anxiety + number of panic disorder symptoms |

***Table 2.*** Outcome variable: Average effectiveness index, average improvement duration, likelihood of remission, benefit rating and the number of best treatment aspects

|  |  |
| --- | --- |
| Models | Explanatory variables |
| Model 1 | Average number of side effects / side effect severity rating / likelihood of intolerance |
| Model 2 | Model 1 + age + sex |
| Model 3 | Model 2 + current depression + current anxiety + number of panic disorder symptoms |
| Model 4 | Model 3 + the total number of psychiatric diagnoses / individual psychiatric diagnoses |
| Model 5 | Model 4 + total duration of antidepressant treatment + age at first treatment with antidepressant |
| Model 6 | Model 5 + number of first relatives with psychiatric disorders |

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