Analysis Plan

Participant characteristics associated with antidepressant treatment outcomes

Authors: A. Walker, B.L Mitchell, C.A. Hartman, J. Bos, H. van Loo, E. Hak, N.R. Wray

Scientific background

Antidepressants serve as the primary pharmaceutical intervention for Major Depressive Disorder (MDD), a psychiatric condition impacting ~15% of the population throughout their lifetime (1). Antidepressants, which primarily target monoamine transmitters, are designed to alleviate MDD-induced symptoms, including primary symptoms of depressed mood and anhedonia. According to a network meta-analysis, all 21 antidepressants from >522 double-blind studies in people with MDD were found to be more effective than placebo (2). However, despite their widespread use, antidepressants do not guarantee a therapeutic effect for everyone. The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial reported that only one-third of participants achieved remission after the first treatment, and only half achieved remission after completing two treatments (3), with some considering to be treatment-resistant depression (TRD) cases.

As indicated by its complex pathophysiology (4), diverse clinical features (5), and high comorbidity (i.e., ~75% of patient with depression meeting criteria for at least one additional psychiatric disorder (6)), the heterogeneity of MDD is likely a major contributor of the high rates of first-line treatment failure. Translating the complexity of MDD into a universally effective treatment is likely to be a challenging path. Consequently, identifying predictors associated with response to a specific treatment could help optimise therapy with the drugs at hand and reduce instances of TRD in clinical practice. Several clinical, treatment, and patient characteristics have been associated with poor depression treatment response or adverse side-effects. These include factors such as: a longer duration of illness (7), earlier age of onset (8), childhood maltreatment (8), greater symptom severity (9), lower levels of patient engagement (10), lower educational attainment (11), higher levels of neuroticism (12), evening chronotype (13), higher rates of allergies, autoimmune diseases and low grade inflammation (14), and comorbid conditions such as ADHD (15) and substance use disorder (SUD) (16). However, despite the identification of a large number of clinical factors associated with treatment outcomes, predicting individual treatment response (including machine-learning based approaches) remains suboptimal (17, 18).

Genetic factors also contribute to individual differences in antidepressant response, with genome-wide association studies (GWAS) estimating 13-42% of the variance in remission attributable to common genetic variation (SNP-based heritability) (19-21). Despite sizeable heritability estimates, GWAS analyses have had limited success in identifying individual genome-wide significant (GW-sig) genetic variants, implying the need for larger sample sizes in future research. Even with increased sample sizes, recent meta-analyses of GWASs for antidepressant response have faced difficulties in identifying GW-sig variants (22, 23). The impact of participant ascertainment, environmental influences, and genetic heterogeneity between studies likely introduces discrepancies (24, 25). Nevertheless, there is potential for capturing antidepressant response through a polygenic score (PGS), which aggregates the small effect sizes of common variants into a risk score for each individual. PGS has demonstrated clinical utility, as seen with the PGS for schizophrenia showing a significant association with a less favourable response to lithium in bipolar disorder (26). Considering the genetic heterogeneity of MDD (with genetic correlations within MDD subtypes ranging from 0.55-0.86 (24)), and the high comorbidity of MDD, utilising PGS for various traits holds promise for effective treatment stratification based on

biology. A study has already indicated that a greater genetic loading for MDD and neuroticism is somewhat associated with a less favourable antidepressant response (27).

Genetic variation in the polymorphic drug metabolism cytochrome (CYP) P450 enzyme genes have also been linked to variability in efficacy of antidepressants and risk for adverse side effects (28, 29). In 2023, the Clinical Pharmacogenetics Implementation Consortium (CPIC) updated its 2015 guidelines for CYP genotypes, specifically suggesting that the *CYP2D6*/*2C19*/*2B6* variants inform antidepressant prescribing (30). Evidence suggests that pharmacogenetic (PGx)-guided decisions may enhance remission in MDD, with a meta-analysis reporting a significant improvement (pooled cohort-level RRR: 1.71, CI: 1.17-2.48) (31). Despite widespread recognition of Drug-Gene Interactions (DGIs) and PGx, and the high-rates of first-line antidepressant treatment failure, implementing PGx in clinical psychiatry remains limited and challenging. Historically, low-specificity prescribing by doctors, relying on guidelines, family history, and symptoms, has been common. In the Netherlands, primary care guidelines (32) recommend initial treatment with selective serotonin re-uptake inhibitors (SSRIs) or tricyclic antidepressants (TCAs), with a slight preference for SSRIs due to better tolerability. The second treatment step involves switching within the same class, while the third step recommends augmentation or combination therapy, including the addition of lithium or an atypical antipsychotic to ongoing treatment (32). Additional data on DGIs are crucial to advancing PGx, enabling informed drug and dose selection to improve patient outcomes.

In the modern era, large Electronic Health Record (EHR) databases provide abundant data not only for exploring the genetic factors influencing variations in antidepressant response but also for examining genetic interactions related to commonly used medications with potential antidepressant properties. For example, recent research has demonstrated that low-dose prucalopride, a highly selective 5-HT4 receptor agonist, enhances connectivity between brain regions associated with cognitive functions (33). This is particularly significant as conventional antidepressants often fail to effectively address cognitive impairments, which are prevalent in mental illnesses (34). Moreover, additional heterogeneity in antidepressant response may also be attributed to the involvement of innate and adaptive immune-based mechanisms in the development of MDD (35, 36). Meta-analyses have indicated an association between MDD and elevated levels of peripheral pro-inflammatory cytokines, particularly interleukin-6 (IL-6) (37, 38), IL-1β (38) and tumour necrosis factor-α (TNF-α) (37). Dysregulation of the immune system has been implicated in affecting neurotransmitter systems (39), that some antidepressants may not therapeutically target. However, recent findings suggest that immunomodulatory drugs, like statins, antibiotic minocycline, various pro-inflammatory cytokine inhibitors, non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids, can alleviate depressive symptoms (40-42). This discovery paves the way for exploring novel immune-based and pro-cognitive therapeutic agents in combination with antidepressants to meet the clinical needs of MDD patients. Randomized controlled trials (RCTs) are already underway to investigate such combination therapies (43, 44). Thus, exploring the relationship between treatment outcomes and drug-drug-gene interactions (DDGIs) involving these novel therapeutic agents and conventional antidepressants holds promise in advancing personalised medicine for MDD.

Lifelines (45), with its large sample size, detailed phenotyping, family structure, genome-wide genetic data, and linkage to pharmaceutical dispensing records from the IADB.nl database (46) through the Pharmlines initiative, uniquely enables exploration of clinical and genetic factors influencing treatment response. A prior Pharmlines study has focused on the CYP genes, exploring DGIs with SSRI (es)citalopram (47). However, at the time of the study, the cohort comprised only 15,000 individuals with both (es)citalopram usage and DNA data, and so lacked power to draw robust conclusions. With Lifelines set to expand its genetic data to 90,000 individuals and IADB.nl data growth, we anticipate identifying more (es)citalopram users, as well as similar numbers associated with other antidepressants. This expansion will enhance the statistical power to detect DGIs and DDGIs in antidepressant treatment outcomes.

Methods

Hypotheses

1. That there is a genetic contribution to antidepressant response.
    i. Primary hypothesis: That there is an association between drug-gene interactions (DGIs) and response to antidepressant treatment, as proxied by individual-level EHR dispensing patterns. Specifically, DGIs between antidepressants and the highly polymorphic CYP drug metabolism enzymes (*CYP2C19*, *CYP2D6,* and *CYP2B6*), or the PGS for various traits, including:
        a. Mental disorders (MDD, schizophrenia (SCZ), bipolar disorder (BPD), ADHD, SUD)
        b. Educational attainment
        c. Personality (e.g., neuroticism)
        d. Sleep traits (e.g., chronotype, insomnia)
        e. Body Mass Index (BMI)
        f. Inflammation (e.g., high-sensitivity C-reactive protein (hsCRP)).
    ii. Secondary hypothesis: That there is an association between drug-drug-gene interactions (DDGIs) and response to antidepressant augmentation. Specifically, DDGIs between antidepressants, novel immunomodulatory therapeutic agents, or prucalopride, and genetic phenotypes.
2. That the likelihood of responding well to an antidepressant treatment runs in families. The risk of taking antidepressant A is significantly greater in relatives of probands taking antidepressant A.

Data sources

The Lifelines cohort is a prospective three-generational study that includes over 167,000 participants from the northern provinces of the Netherlands. The cohort was established with the objective of examining the intricate interplay among environmental, phenotypic, and genetic factors in the progression of chronic illnesses and the promotion of good ageing (45).

The IADB.nl database, sourced from the University of Groningen, contains prescription details filled at pharmacies in the northern Netherlands (46). The data spans from 1994 to 2023. Gender, birthdate, and four-digit postal codes from patients are provided for linkage. Due to the high patient-pharmacy commitment in the Netherlands, the medication records for each patient are virtually complete, except for over-the-counter drugs and medication dispensed during hospitalisation. Every participant's prescription data is documented, encompassing the dispensing date, the number of units (e.g., the number of pills) delivered (aantal), the dose in milligrams of 1 unit (gpinst), the daily dose in units (dagdos), the number of DDD (defined daily dose), the Anatomical Therapeutic Chemical code (ATC code), the unique identifier for the prescribed drug, the medication brand, and the type of prescriber (GP or specialist). Using these variables, two additional variables will be derived: the theoretical number of days a dispensed drug will be used (calculated as NDGN = aantal/dagdos), and the daily dose in milligrams (calculated as daggpinst = dagdos x gpinst).

Study design and linkage

As part of the Pharmlines initiative, pharmaceutical dispensing data from the IADB.nl database is linked with adult participants from the Lifelines cohort. Linkage of lifelines and IADB.nl will be done at the individual-level in the Netherland's Central Bureau of Statistics (CBS) secure computing environment. Only a proportion of Lifelines participants are currently represented in the IADB.nl database (the remainder are likely to access prescriptions from pharmacies not linked into IADB.nl). However, given the number of participating pharmacies this proportion is expected to be high (65%). The study will

further link the Pharmlines data with a CBS dataset which provides the date and cause of death. Following linkage, data analysis will take place in the CBS.

The primary aim of the study under the Pharmlines initiative is to identify associations between the predicted drug metabolism phenotypes of the *CYP2C19/2D6/2B6* genes and various PGS traits with antidepressant treatment outcomes. The PGS will be of traits (e.g., BMI, sleep disorders, inflammation) that have previously been associated with antidepressant treatment outcomes. Different criteria on EHR dispensing patterns (i.e., duration, switching, adherence, and the dosage levels) will be used to describe various outcomes, including TRD, treatment response, lack of response, augmentation therapy (with various immunomodulatory drugs or prucalopride) and changes in dosage. These outcomes will be measured within a 4-year period centred on the Lifelines individual-level 1A baseline assessment dates. These assessment dates range from 2007 to 2014.

Inclusion criteria for analysis data sets

Phenotype data set: Lifelines' phenotype data, for which adulthood (18 years or older) at the Lifelines individual-level 1A baseline assessment date (index date) and presence in the IABD.nl database within the 4-year window centred on the individual's index date are the primary inclusion criteria. This Lifelines phenotype data set ensures we capture healthy people as controls and includes all possible family relationships.

Prescription data set: A subset of the phenotype data set will also have data from the IADB.nl database if they have at least one psychoanaleptics (N06), statins (C10AA), minocycline (J01AA08), NSAIDs (M01), cytokine inhibitors (L04AB targeting TNF and L04AC targeting IL), glucocorticoids (H02AB) or prucalopride (A06AX05) present in the IABD.nl database within the 4-year window centred on the individual's index date. The prescription dataset will also include data for drugs used as proxy for co-morbidities (e.g., cardiovascular, type 2 diabetes, etc.) as well for CYP genotypes modulators. The inclusion of drugs additional to N06 are required to interpret some aspect of antidepressant usage and response. To ensure the specificity of the analysis concerning antidepressant (N06A) outcomes, individuals with a dispensing record for a psychostimulant (N06B), psycholeptics and psychoanaleptics used in combination (N06C), or an anti-dementia drug (N06D) may be excluded for sensitivity analyses, but are eligible for inclusion in the primary analyses.

GWAS data set: A subset of the Phenotype data set that includes Lifelines' participants with genome-wide genetic data.

Prescription and GWAS data set: A subset of the Phenotype data set included in both the Prescription and GWAS data sets.

MDD data set: A subset of the phenotype data set who completed a follow-up digital questionnaire called "The Lifetime Depression Assessment Self-Report" (LIDAS), within the context of an additional assessment called BIONIC, conducted in 2016 and 2018 (48, 49). In addition, this subset of individuals will include those that record lifetime MDD in the Mini International Neuropsychiatric Interview (MINI) conducted in Lifelines waves 1, 2 and 3. This subset allows the identification of those with lifetime MDD and other psychiatric disorders.

Antidepressant treatment outcome definitions

Individuals will be assigned to antidepressant treatment outcomes based on their unique dispensing patterns within their unique 4-year window centred on their Lifelines baseline index date. Treatment outcomes include:

a. Treatment response
    - Dispense of the same antidepressant for at least 90 days.
b. Treatment lack of response

- Discontinuation of an antidepressant within 90 days.

c. Treatment Resistant Depression (TRD)
    - Dispense of two treatments for at least 45 days with discontinuation within 90 days AND
    - one treatment is an antidepressant, and the other treatment is an antidepressant with a different mechanism of action, lithium, or an atypical antipsychotic AND
    - the two failed treatments could be:
        - separated by a drug free period, prescribed sequentially (switching), in which the time between the dispense of the consecutive treatments is < 90 days OR
        - dispensed with a time overlap (combination/augmentation therapy).
            - Combination therapy: the two treatments are antidepressants
            - Augmentation therapy: antidepressant monotherapy in augmentation with lithium or an atypical antipsychotic.

d. Treatment augmentation response
    - Dispense of the same antidepressant for at least 90 days AND
    - dispense of an immunomodulatory drug or prucalopride for at least 28 days AND
    - the two treatments are dispensed with a time overlap of at least 14 days (augmentation therapy).

e. Treatment augmentation lack of response
    - Discontinuation of an antidepressant within 90 days AND
    - dispense of an immunomodulatory drug or prucalopride for at least 28 days AND
    - the two treatments are dispensed with a time overlap of at least 14 days (augmentation therapy).

Where treatment outcome d) is a subset of a), and likewise, treatment outcome e) is a subset of b). Utilising all the above classification rules, an individual can indicate treatment 'response' to multiple drugs of different types, with or without augmentation. Even if those differing treatments are dispensed with a time overlap, their corresponding treatment periods will be regarded as separate treatment responses. Moreover, individuals may record multiple treatment periods for the same drug, some as a response and some as a lack of response. In this case, at least one instance of 'response' to the drug will classify the individual as a responder to the drug. There is currently no standardised definition for TRD. In this study, TRD was defined based on recommendations achieving moderate consensus (75%) through a Delphi-method-based consensus approach in a prior publication (50).

Typically, a treatment is prescribed for approximately 4-6 weeks (or at least 42 days) at a minimally effective dosage before considering a switch in case of a lack of response. The choice of 90-day time criteria to categorise each treatment outcome is justified, considering the common clinical practice of drug dosage adjustments. However, we acknowledge the potential for misclassification of responders as non-responders due to the lenient 90-day time criteria, as some individuals may stop taking the drug upon recovery within this timeframe rather than due to a lack of response or adverse side effects. To address this, as sensitivity analyses, the time criteria for each treatment outcome will be shortened from 90 days to 60 days and 45 days, however, also increased to 180 days to reduce the likelihood of misclassifying non-response as a response to treatment.

As part of further sensitivity analyses, the treatment period will require good treatment stability (defined as an 80% drug possession ratio) as non-adherence to treatment is a major contributor to pseudo-resistance (51), with poor adherence reported in a median of 40% of patients with depression (52). The treatment stability ratio will be calculated by dividing the total theoretical number of days the dispensed drug will cover within a treatment period (total NDGN) by the total number of days in the treatment period (the difference between the last and the first drug dispensing date of the treatment period). The resulting treatment stability ratio ranges from 0 to >1. Moreover, the treatment period will require

compliance with a treatment-specific dosage criterion. The treatment-specific dosage criterion will exclude prescriptions dispensed for indications other than depression (and anxiety). For instance, TeCA mirtazapine administered at a low dose (<15-30mg) has been associated with increased sedative effects (53, 54), and it has been recommended to initiate mirtazapine at a higher dosage of 30mg to ensure its therapeutic effect for depression (55). Furthermore, low dose (25mg) TCA amitriptyline has been shown to be an effective treatment for pain, such as chronic low back pain (56).

Genotyping and definition of genetic exposures

Genetic data are available for only a subset of lifeline participants and were derived from blood samples. One of the genetic exposure groups of interest (based on 2023 CPIC guidelines to inform antidepressant prescribing) includes the drug metabolism *CYP2D6*, *CYP2C19* and *CYP2B6* genotypes. These genotypes are translated into haplotypes, which, in turn, are used to predict drug metabolism phenotypes based on information from CPIC. Corresponding predicted phenotypes for *CYP2D6* listed in order of lowest functioning to highest include PM (poor metaboliser), IM (intermediate metaboliser), NM (normal metaboliser) and UM (ultra-rapid metaboliser). *CYP2C19's* extensive metaboliser (EM) corresponds to IM, while *CYP2B6* adds rapid metaboliser (RM) between NM and UM. For statistical power reasons, IM/EM and PM groups may be pooled into a combined IM/EM/PM group. In clinical practice, although change in dose or therapy may not be warranted based on results on a single CYP gene, genotype test results may only be available for single genes, thus each CYP phenotype will be tested independently with antidepressant treatment outcomes. However, treatment modification may be warranted given the combination of more than one non-normal CYP phenotype, so in addition, the *CYP* phenotypes for each individual will be amalgamated into various genetic exposures of interest (e.g., *CYP2C19* EM + *CYP2CD6* NM + *CYP2B6* RM or *CYP2C19* EM + *CYP2CD6* NM, etc.).

A second set of genetic exposures includes the PGS for various somatic and psychiatric traits derived from the most powered GWAS available per trait, with SNP weights determined from a state-of-the art method such as SBayesR (57). Another category of genetic exposure involves variations in genes affecting the metabolism of immunomodulatory medications. CPIC guidelines recommend phenotyping *CYP2C9* for NSAID use (58), and *SLCO1B1*, *ABCG2*, and *CYP2D6* for statin use (59). For antidepressants augmented with NSAIDs, the *CYP2C9* phenotype will be combined with the other *CYP* variants in various ways into genetic exposure groups, and likewise for statins, the *SLCO1B1*, *ABCG2*, and *CYP2D6* phenotypes will be combined with the *CYP2C19/2D6/2B6* phenotypes into various genetic exposure groups. Regarding glucocorticoids, minocycline, cytokine inhibitors, and prucalopride, several polymorphisms have been suggested to impact their metabolic sensitivity, though currently, none of them have CPIC drug-gene pairs that achieve a high level of evidence favouring changes in prescribing. Lastly, the phenomenon of 'phenoconversion' in the predicted phenotypes of the *CYP*, *SLCO1B1*, and *ABCG2* genotypes will be considered due to the prevalence of commonly used drugs inhibiting these genotypes (60, 61).

Statistical analyses

All statistical analyses will be conducted in SQL and R in the CBS environment.

1) Investigating participant characteristics across treatment outcome groups and analysis datasets

Within the 4-year period centred on the Lifelines individual-level 1A baseline assessment dates, descriptive and association statistics across treatment outcome groups, the analysis data subsets (with differing inclusion criteria), and treatment stability groups will be reported for:

i. demographic characteristics (gender/genetically inferred sex, age, education, socioeconomic status, income, nationality, death)
ii. presence of depression (lifetime - DSM-5 MDD diagnoses, recent 2-week episodes)

iii. mental health characteristics (generalised anxiety disorder, neuroticism, stress, suicidal ideation levels, adverse childhood experiences, ADHD, SCZ, BPD, obsessive compulsive disorder (OCD))
iv. co-medication usage and co-morbidities (e.g., diabetes, cancer, cardiovascular disease, and SUDs)
v. lifestyle and environmental characteristics (alcohol use, sleep scores, chronotype, smoking)
vi. clinical characteristics (pain levels, inflammation –proxied by baseline hsCRP levels, BMI)
vii. dispensing patterns of medications
viii. PGS for various traits previously associated with antidepressant treatment response
ix. frequency of *CYP2C1/2D6/2B6* predicted drug metabolism phenotypes (i.e., PM, IM, NM, RM, UM).

We aim to assess the representativeness of each subset in comparison to the Lifelines and IADB.nl data from which they are derived to identify any potential biases. For example, we aim to describe those who have prescriptions dispensed by an IADB.nl pharmacy compared to those that don't. We also would like to compare those with a lifetime MDD diagnosis and those without.

2) Analyses to test hypotheses

Hypothesis 1: That there is a genetic contribution to treatment outcomes.

These analyses with use the data set "GWAS and prescription data". We will use multivariable logistic regression to estimate the Odds Ratio (OR) of any defined genetic exposure (i.e., any PGS trait or any drug metabolism phenotype) on any binary treatment outcome, including;

Primary hypothesis (investigating DGIs):

a. response to antidepressant A vs. lack of response to antidepressant A
b. response to antidepressant A vs. response to antidepressant B
c. response to any antidepressant vs. TRD.

Secondary hypothesis (investigating DDGIs):

d. response to antidepressant A augmented with agent C vs. lack of response to antidepressant A augmented with agent C
e. response to antidepressant A augmented with agent C vs. lack of response to antidepressant B augmented with agent C.

Age, sex, number of pre-defined drugs as proxy for certain co-existing co-morbidities (such as cardiovascular disease, diabetes, etc.) will be used as covariates within the logistic regression model. Treatment users need to have had at least two prescriptions of these proxy medications within their treatment period. For analyses a-c) the dispense of an immunomodulatory drug or prucalopride will be used as a covariate within the model.

A basic sanity check analysis will contrast PGS for MDD between those that have dispensed a N06A drug (putative MDD cases) to those with no N06A dispense (MDD controls) but are still within the IADB.nl database. As evidenced from many other studies, the PGS for major depression should be significantly different between these groups.

To enhance the statistical power of analyses, the antidepressants for treatment outcome excluding TRD may be grouped based on their mechanisms of action (i.e., SSRIs, TCAs, etc). These antidepressant groups include: SSRIs (N06AB), SNRIs (N06AX16; N06AX21), NDRIs (N06AX12), TCAs (N06AA), TeCAs (N06AX03; N06AX11), MAOI (N06AF, N06AG), MAs (N06AX22), SARIs (N06AX05; N06AX06), and SMSs (N06AX26). For analyses investigating DDGIs on treatment outcomes, different immunomodulatory therapeutic agents used to augment antidepressants may also be grouped together.

Lifetime depression has only been assessed in a subset of Lifelines participants, so separate genetic associations with treatment outcomes will be performed for both the entire Pharmlines sample and for the subset of individuals with lifetime depression. To increase the specificity of the TRD outcome definition, the TRD treatment outcome may be split into subgroups, e.g., combination therapy or augmentation therapy. Furthermore, within all individuals that respond to a treatment, genetic association analyses will be performed with a change in dose as the treatment outcome. Regarding association estimations between PGS traits and treatment outcome groups, specific hypotheses will be tested based on outcomes of analyses of similarly define groups within the Australian Genetics of Depression Study (AGDS) (62).

Hypotheses 2: the likelihood of responding well to a specific antidepressant runs in families.

This analysis will use the "Phenotype data set". We will first identify relative pairs (parent-offspring, grandparent-grand offspring, full-siblings, maternal half-siblings, paternal half-siblings, cousins, avuncular). Where possible these are checked with GWAS data. From these pairs we will take one individual as the proband, and then we will calculate the risk of taking antidepressant A in relatives of probands taking antidepressant A. We will also calculate the risk of taking antidepressant B in relatives of probands taking antidepressant A. These risk in relatives describe the data, age and sex will be included in analysis model. From risk in relatives, we can estimate heritability of antidepressant treatment response.

Multiple Testing

Our analysis plan includes many tests. Significance will be declared for tests conducted as primary hypotheses (i.e., the tests investigating DGIs) by using a Bonferroni corrected significance threshold, i.e., 0.05/n where n is the number of tests. This correction is conservative if tests are correlated. The number of statistical tests and the analysis plan may be updated based on power calculations given the number of responders/non-responders in each antidepressant treatment group. Secondary analyses, including the investigation of DDGIs, are considered exploratory. The tests conducted as sensitivity analyses will not contribute to the n number of tests, but are used to understand robustness of results. For all tests for which there is evidence of a significant result we will seek independent data sets for replication. Data sets with measures of depression, prescriptions of antidepressants, and genetic data are becoming increasingly available. Each data set is likely to have different study designs, limitations and ascertainment biases, but nonetheless we will seek data sets that best fit the Pharmlines design. In particular, this study has been designed with the knowledge of the 4-year prescription window available form participants in the AGDS (62).

Code and data availability

All statistical code will be publicly available at https://github.com/walkeralicia for downloading.

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Authorship and final remarks

This analysis plan will be hosted on Open Science Framework and logged with a date stamp. Project participants can make decisions to amend or change this analysis plan (any updates will be posted and date stamped on Open Science Framework). Publications based on this analysis plan will include the listed authors and additional authors.

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