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ORIGINAL ARTICLE

CYP2C19 loss-of-function alleles are not associated with higher prevalence of gastrointestinal bleeds in those who have been prescribed antidepressants: Analysis in a British-South Asian cohort

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Aims: CYP2C19 is a hepatic enzyme involved in the metabolism of antidepressants associated with increased gastrointestinal bleed (GIB) risk. The aim of our study was to explore a possible association between loss-of-function *CYP2C19* genotypes and GIB in South Asian ancestry participants prescribed antidepressants.

Methods: Genes & Health participants with a record in Barts Health NHS Trust (N 22 753) were studied using a cross-sectional approach. *CYP2C19* diplotypes were assessed and metabolizer type inferred from consortia guidance. Fisher's exact test was used to compare the prevalence of GIB in different metabolizer categories. Multivariable regression was used to test for association between antidepressant prescriptions and GIB, and between CYP2C19 metabolizer state and GIB in the subcohort prescribed antidepressants.

Results: Antidepressants were frequently prescribed (47%, $N = 10\,612$). A total of 864 participants (4%) had a GIB; 534 (62%) had been prescribed a CYP2C19 metabolized antidepressant. There was an independent association between antidepressant prescriptions and GIB events (odds ratio 1.8, confidence interval 1.5-2.0, $P < 0.0001$). There was no relationship between CYP2C19 inferred poor (*P* 0.56) or intermediate (*P* 0.53) metabolizer status and GIB in those prescribed an antidepressant in unadjusted analysis. A multivariable logistic regression model did not show an independent association between poor (*P* 0.54) or intermediate (*P* 0.62) CYP2C19 metabolizers and GIB in the subcohort prescribed antidepressants.

Conclusions: CYP2C19 dependent antidepressants are associated with increased GIB prevalence. GIB appeared independent from *CYP2C19* metabolizer genotype in individuals who had been prescribed antidepressants. Precision dosing based on *CYP2C19* genetic information alone is unlikely to reduce GIB prevalence.

KEYWORDS
antidepressants, cytochrome P450 enzymes, pharmacogenomics, pharmacotherapy

1 | INTRODUCTION

Genetic polymorphism can explain some of the variation in medication response and predisposition to adverse drug reactions (ADRs).[1] This is referred to as pharmacogenomics (PGx). Evidence generated from PGx research has resulted in guidance of varying strength from regulators and international consortia.[2] There can be significant trans-ethnic differences in the prevalence of pharmacogene polymorphisms impacting medication efficacy and adverse drug events.[2] Cytochrome P450 family 2 subfamily C, polypeptide 19 (CYP2C19) is a hepatic enzyme that is principally responsible for metabolizing several serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs).[2] Asian populations are known to have high prevalence of poor and intermediate CYP2C19 metabolizers due to high prevalence of the *2 and *3 *CYP2C19* loss-of-function (LOF) alleles.[2,3]

As previously shown, the *2 allele is very common in the Genes & Health (G&H) population cohort of UK-South Asian ancestry participants (56% of the population having at least one copy).[4] This contributes to a high percentage of poor (13%) and intermediate (44%) CYP2C19 metabolizers.[4] 2.7% are inferred ultra-rapid metabolizers (homozygous for the *17 gain of function [GOF] allele).[4]

SSRIs have been reproducibly associated with increased risk of gastrointestinal bleed (GIB) in observational studies and meta-analysis.[5] The mechanism is postulated to be the effect of serotonin on platelet aggregation. TCAs also block the reuptake of serotonin, but there has been conflicting evidence regarding TCA association with GIB.[6] Tertiary amines, such as amitriptyline, have serotonergic activity and are metabolized to secondary amines, which have less serotonergic activity, by CYP2C19.[7] GIBs are a significant cause of morbidity and mortality, and associated healthcare costs.[8–10]

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidance suggests initiation of lower doses of these medications for poor CYP2C19 metabolizers (classification of recommendation moderate or optional) based on pharmacokinetic data.[7,11] The effect of metabolizer state on GIB risk for patients taking CYP2C19-dependent SSRIs and TCAs has never been studied. Therefore it remains unknown if this potentially serious adverse effect might be mitigated by a precision approach to prescribing based on *CYP2C19* diplotype, in which lower doses of these antidepressants are prescribed to those with LOF alleles. This is increasingly relevant as there is more uptake of *CYP2C19* point-of-care testing in the context of antiplatelet use and therefore more patients who may know their genotype and inferred metabolizer phenotype at the point of prescribing antidepressants.

The aim of our study was to explore a possible association between genetically inferred CYP2C19 metabolizer status and GIB in individuals exposed to antidepressants.

What is already known about this subject

- CYP2C19-metabolized antidepressants have been associated with increased risk of gastrointestinal bleed in observational studies and meta-analysis.
- *CYP2C19* loss-of-function polymorphisms are associated with higher plasma concentrations of antidepressants and are highly prevalent in people of Asian ancestry.
- The Clinical Pharmacogenetics Implementation Consortium guidance suggests initiation of lower doses of these antidepressants for poor CYP2C19 metabolizers.

What this study adds

- This study agrees with prior studies showing a significant association, with a clinically meaningful effect, between CYP2C19-dependent antidepressants and gastrointestinal bleed.
- In a large South Asian ancestry cohort with nearly one in every two participants prescribed a CYP2C19-dependent antidepressant, there was no significant association between gastrointestinal bleed prevalence and *CYP2C19* loss-of-function alleles.
- These data suggest that gastrointestinal bleed risk would not be mitigated by precision dosing based on *CYP2C19* testing.

2 | METHODS

2.1 | The G&H cohort

The G&H cohort data was accessed for this study after approval by the study executive committee. G&H has obtained ethical approval, 14/LO/1240, from the London South-East NRES Committee of the Health Research Authority, dated 16 September 2014.

Data collection methods for the G&H biobank have been described previously.[12] More than 44 000 volunteers provided saliva for DNA extraction, answered questionnaires and consented to link study data with electronic health records.[12] As previously described, participants were subsequently genotyped using the Illumina GSAMD-24v3-0-EA chip.[13] The TOPMED-r2 dataset was used for imputation using human build 38 of the genome research consortium.[13] Detailed clinical characteristics of the G&H cohort have been published.[12]

2.2 | Characterization of CYP2C19 genotype and inferred phenotype in the G&H cohort

These methods have been characterized in a prior study.[4] The *CYP2C19* genotype was assessed by characterizing the known PGx *2 (LOF), *3 (LOF) and *17 (gain-of-function [GOF]) alleles influencing enzymatic function.[4] Single nucleotide polymorphisms (SNPs) were extracted from the data set using PLINK 2.0.[14,15] The *2 allele was defined as c.681G>A, rs4244285 (chr10:94781859). The *3 allele was defined as c.636G>A, rs4986893 (chr10:94780653). The *17 allele was defined as (c.-806C>T), rs12248560 (chr10:94761900).

Subsequent analysis was done in Rstudio.[16] Participants with one LOF SNP (either *2 or *3) were inferred intermediate CYP2C19 metabolizers. Those with two LOF SNPs were inferred poor metabolizers. Participants with one *17 allele (in the absence of a *2 or *3 allele) were inferred rapid metabolizers, and those with two *17 alleles were inferred ultra-rapid metabolizers.

2.3 | Medication data from primary care

Medication data were obtained from primary care via linkage with participating clinical commissioning groups (CCGs), including Barking, Havering and Redbridge (BHR), Tower Hamlets (TH), Waltham Forest (WF) and Newham (N). Participants who had medication data available from these CCGs were included in our analyses (99.5% of participants with records in Barts Health NHS Trust system [22 753/22 864]) (-Figure 1). The CYP2C19-dependent SSRIs studied were sertraline, citalopram and escitalopram. The CYP2C19-dependent TCAs studied were amitriptyline, clomipramine, doxepin, imipramine and trimipramine. As there were fewer medications in the SSRI group, these were associated with outcomes independently and as a pooled group. Due to the higher number of medications in the TCA group these mediations were pooled for exposure. Exposure to medication was defined by one or more prescription for a medication being used chronically rather than acutely from primary care records.

2.4 | Ascertainment of environmental exposures

Smoking status was defined in primary care records as described in prior analysis by using SNOMED codes to distinguish never-smokers from those who had ever smoked.[4] Participants were identified as never having smoked if they had a never-smoked or current nonsmoker code and had no codes associated with current smoker, ex-smoking or smoking cessation. Alcohol use was defined by the presence of ICD 10 code Z721, "alcohol use" or ICD10 code Z714 "alcohol abuse counselling" and was found by searching Barts Health electronic data from the research database in the G&H trusted research environment (TRE).

2.5 | Linking CYP2C19 inferred phenotypes with GIB

The Barts Health NHS trust secondary care data linkage was used to study the relationship between CYP2C19 inferred phenotype and inpatient GIB. GIB occurrence was defined by ICD10 codes K920 (hematemesis), K921 (melaena) and K922 (gastrointestinal haemorrhage, unspecified).

Due to the association of alcoholic liver disease and liver failure with GIB risk and phenoconversion, we also controlled for these phenotypes. Curated data sets from G&H were used for clinical phenotypes, including alcoholic liver disease (ALD) (ICD10 code K70) and fibrosis and cirrhosis of liver (chronic liver disease [CLD]) (K74). These phenotypes were defined using ICD10 codes, SNOMED codes, and Office of Population Censuses and Surveys (OPCS) codes from linkage with electronic health records, including Barts Health, NHS digital, Bradford teaching hospitals and primary care clinical commissioning groups (CCGs). The methods have previously been described and are based on those used by Biobank UK.[4,17] The G&H website contains detailed information and links to the code used.[17,18] In summary, ICD-10 codes were identified from secondary care, NHS Digital hospital episode and mortality statistics. SNOMED codes from primary and secondary care were then mapped to the ICD-10 code lists to capture the first recording of the code.

The presence of conditions which are common indications, or associated with common indications, for SSRIs/TCAs was ascertained using the G&H curated phenotypes. These included diabetes (ICD10 codes E10, E11, E13, E14), depressive episode (ICD10 code F32), recurrent depressive disorder (ICD10 code F33), anxiety disorders (ICD10 code F41), reaction to severe stress and adjustment disorders (ICD10 code F43), and obsessive-compulsive disorder (ICD10 code F42).

2.6 | G&H curated principal components

G&H has made available to all users in the TRE curated principal components as published in a prior analysis.[13] The first two of these were used to control for population stratification in our analysis.

2.7 | Statistical methods

Multivariable logistic regression was used to test for association between prevalence of GIB and SSRI/TCA use. Alcoholic liver disease, chronic liver disease, gender and age at enrolment were controlled for (all were significant in univariable and multivariable regression). The cohort prescribed a SSRI or TCA was stratified by inferred metabolizer phenotype and Fisher's exact test was performed to look for differences in prevalence of GIB. This was done without adjusting for any other variables to simulate the potential use of diplotype stratification

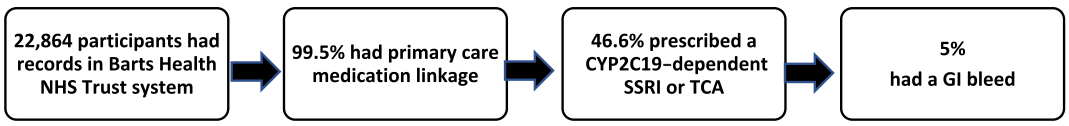

FIGURE 1 Study overview. Overview of cohort and CYP2C19-dependent SSRI and TCA prescriptions. 5% of the cohort prescribed a CYP2C19 dependent SSRI or TCA had a GI. GI, gastrointestinal; NHS, National Health Service; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

in clinical practice. Fisher's exact test was also used to compare binary characteristics between those who were and were not prescribed CYP2C19 metabolized SSRIs and TCAs. A *t*-test was used to compare the mean age of participants at enrolment.

Multivariable logistic regression was used to test for association between CYP2C19 phenotypes and GIB in the cohort who had been prescribed antidepressants, adjusting for age at recruitment, gender, CLD and ALD. The first two principal components were controlled for to avoid bias from population stratification. Four levels were used for the CYP2C19 inferred metabolizer type variable: poor, intermediate, and ultra-rapid metabolizers, with normal and rapid metabolizers as the reference group.

Sensitivity analyses were undertaken to control for lifetime prescription of other medications which may impact on GIB risk, including direct oral anticoagulants (DOACs), coumarins, nonsteroidal anti-inflammatory agents (NSAIDs), aspirin, clopidogrel and proton pump inhibitors (PPIs), as well as for smoking and alcohol use.

2.8 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2021).[19]

3 | RESULTS

3.1 | Prevalence of TCA and SSRI prescriptions

In total 10 612 participants, 47% of the cohort, had been prescribed at least one CYP2C19-dependent SSRI or TCA (Table 1). CYP2C19-dependent TCAs were prescribed to 37% of the cohort, while 22% had been prescribed a CYP2C19-dependent SSRI. Of the individual SSRIs, escitalopram was prescribed less frequently than sertraline and citalopram. Table 2 shows participant characteristics and prevalence of prescribing indication diagnoses. Diabetes mellitus has been included as TCAs may be used to treat neuropathic pain. Women are over-represented in the cohort prescribed antidepressants, at 68%. Anxiety (35%) and diabetes mellitus (31%) were highly prevalent in the cohort prescribed antidepressants. Only 19% of the cohort prescribed antidepressants had a diagnosis of a depressive episode or recurrent depression.

3.2 | Association of SSRIs and TCAs with GIB

A total of 864 participants (4%) had a GIB. A total of 534 of the participants with a GIB had been prescribed a CYP2C19 metabolized SSRI or TCA (62%). Logistic regression was used to study the association between SSRI and TCA prescriptions and GIB. ALD, CLD, age at enrolment and gender were controlled for. All three CYP2C19-dependent SSRIs as well as pooled TCAs and pooled TCA or SSRI prescription were significantly associated with GIB (Table 1). The odds ratios (ORs) were very similar, ranging from 1.5 to 1.7 in the individual SSRI class medications, and 1.8 (confidence interval [CI] 1.5-2.0, $P < 0.00001$) in the pooled SSRI or TCA group (Table 1). The ORs for pooled SSRI (1.7) and pooled TCA (1.6) association with GIB were similar with overlapping CIs.

3.3 | GIB risk stratified by CYP2C19 metabolizer state for those prescribed a CYP2C19-dependent SSRI or TCA

Stratification by CYP2C19 metabolizer state in those prescribed a SSRI or TCA did not show any significant association of metabolizer state with GIB risk (p 0.56 for poor metabolizers and p 0.53 for intermediate metabolizers) (Table 3A).

Multivariable logistic regression in the subcohort prescribed antidepressants, adjusting for CLD, ALD, age at recruitment, gender and principal components, showed no significant association between poor or intermediate CYP2C19 metabolizer status and GIB prevalence (p 0.54 for poor metabolizers, p 0.62 intermediate metabolizers) (Table 3B).

TABLE 1 Association of SSRI/TCAs with GIB.

Medication	N prescribed medication (total $N = 22\,753$)	OR	CI	*P* value
Sertraline	12.3% (2 800)	1.6	1.3-1.9	<0.0001
Citalopram	14.5% (3 301)	1.5	1.3-1.8	<0.0001
Escitalopram	1.2% (271)	1.7	1.0-2.7	0.04
SSRIs pooled	22.3% (5 064)	1.7	1.4-1.9	<0.0001
TCAs[a]	37.2% (8 463)	1.6	1.4-1.8	<0.0001
SSRIs and TCAs pooled	46.6% (10 612)	1.8	1.5-2.0	<0.0001

Note: Multivariable logistic regression analyses controlled for age at enrolment, gender, chronic liver disease and alcoholic liver disease.
Abbreviations: CI, confidence interval; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.
[a]TCAs studied included amitriptyline, clomipramine, doxepin, imipramine, trimipramine.

TABLE 2 Participant characteristics stratified by exposure to CYP2C19-dependent SSRI/TCA.

Characteristic	Cohort not prescribed a CYP2C19-dependent SSRI or TCA (*N* = 12 141)	Cohort prescribed a CYP2C19-dependent SSRI or TCA (*N* = 10 612)	*P* value
Female sex	62% (7 517)	68% (7 179)	<0.0001
Diabetes	18% (2 140)	31% (3 262)	<0.0001
Depression	3% (317)	19% (2 037)	<0.0001
Anxiety	9% (1 119)	35% (3 755)	<0.0001
Stress/adjustment disorder	6% (697)	18% (1 876)	<0.0001
Obsessive compulsive disorder	0.2% (19)	1% (102)	<0.0001
Chronic liver disease	0.4% (54)	1% (101)	<0.0001
Alcoholic liver disease	0.1% (6)	0.2% (17)	0.01
Average age at recruitment	39 years old (±14)	46 years old (±14)	<0.0001

Abbreviations: SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

TABLE 3A No significant association between poor or intermediate CYP2C19 metabolizer status and GIB risk.

CYP2C19 status	Total (*N* = 10 612)	No bleed (*N* = 10 078)	Bleed (*N* = 534)	*P* value
Poor metabolizer	13.4% (1 424)	13.4% (1 348)	14.2% (76)	0.56
Intermediate metabolizer	44.9% (4 770)	44.9% (4 523)	46.3% (247)	0.53
Ultra-rapid metabolizer	2.4% (255)	2.5% (249)	1.1% (6)	0.06

Note: Fisher's exact test stratified by metabolizer status for the subcohort prescribed SSRIs or TCAs (*N* = 10 612).
Abbreviations: GIB, gastrointestinal bleed; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

TABLE 3B No significant independent association between poor or intermediate CYP2C19 metabolizer status and GIB in cohort prescribed antidepressants.

Variable	OR	CI	*P*
Poor metabolizer	1.1	0.8-1.4	0.54
Intermediate metabolizer	1.0	0.9-1.3	0.62
Ultra-rapid metabolizer	0.5	0.2-1.0	0.08
Age at enrolment (per year)	1.02	1.01-1.02	<0.0001
Female sex	0.6	0.5-0.8	<0.0001
ALD	4.5	1.4-12.8	0.007
CLD	2.6	1.4-4.4	0.0009

Note: Multivariable logistic regression analysis for the relationship between metabolizer state and GIB in the subcohort prescribed SSRI/TCAs. Controlled for age at enrolment, gender, CLD, ALD and two principal components.
Abbreviations: ALD, alcoholic liver disease; CI, confidence interval; CLD, chronic liver disease; GIB, gastrointestinal bleed; OR, odds ratio; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

Sensitivity analyses controlling for lifetime use of medications known to be CYP2C19 metabolized (clopidogrel, PPIs) and other commonly prescribed medications likely to impact on GIB risk (aspirin, NSAIDs, DOACs) did not change the results (results shown in Supporting Information Table S2).

4 | DISCUSSION

This study finds a strong association between SSRI/TCA use and GIB. This agrees with prior published studies regarding SSRIs and confirms bleed prevalence associated with CYP2C19-dependent TCAs. Several SSRIs and TCAs are metabolized principally by the CYP2C19 enzyme and international consortia recommend lower starting doses in poor metabolizers as they may suffer adverse events disproportionately due to increased levels of active metabolite.[7,11] This is the first study to look for an association between genetically inferred poor CYP2C19 metabolizer state and GIB in patients prescribed a CYP2C19-metabolized SSRI or TCA. Our study on a cohort of 22 753 participants found no association between CYP2C19 poor or intermediate inferred metabolizer status and GIB in those prescribed antidepressants (Figure 2).

This study also shows, for the first time to our knowledge, the vast scale of prescribing of these CYP2C19-dependent therapeutic agents in the British Pakistani and Bangladeshi ancestry population. While the nature of this secondary care data is not well suited to undertake association studies with nonsevere adverse drug reactions (ADRs) (which may impact quality of life and compliance) or therapeutic inefficacy, other research has suggested that a precision medicine approach to prescribing may mitigate ADRs.[20,21] This study shows the vast number of people in this cohort who would benefit from a precision approach if such a conclusion is confirmed in clinical trials. As two in every three participants (7 179/10 612) prescribed one of these medications was

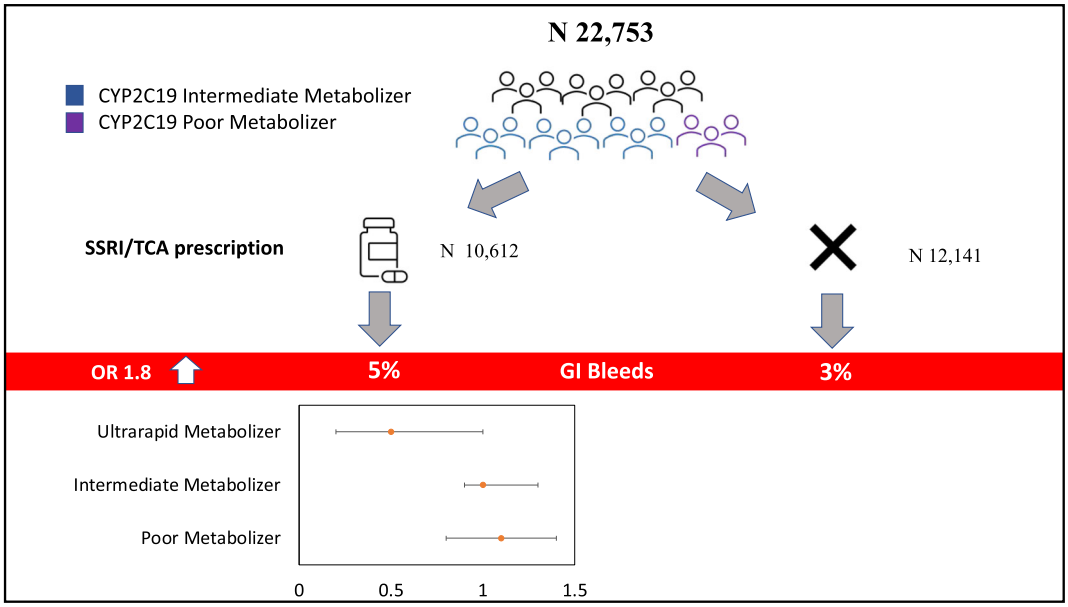

FIGURE 2 Study results: no increased proportion of GIB in participants with *CYP2C19* loss of function alleles in the cohort prescribed SSRI/TCA. SSRI/TCA use was associated with a higher risk of GIB. 5% of participants who were prescribed a CYP2C19-metabolized SSRI/TCA had a GIB compared with 3% of the cohort who were not prescribed a CYP2C19-metabolized SSRI/TCA. Poor metabolizers, who would be given a lower dose of medication based on precision prescribing guidelines, were not more likely to have had a GIB among those taking antidepressants. GI, gastrointestinal; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

female, any benefit of a precision prescribing approach would be disproportionately impactful in the female population. Since women are underrepresented generally in research it is quite likely that any ADR disproportionately affecting women would be underdetected.

5 | CLINICAL IMPLICATIONS

Precision dosing of antidepressants based on *CYP2C19* diplotype is not likely to mitigate any GIB risk associated with use of antidepressants.[11]

6 | LIMITATIONS

Our study is cross-sectional and the timing of the GIB and the relationship with the length of medication exposure was largely unknown due to the way the GP prescriptions and bleed events were recorded. Due to this limitation, we were not able to assess the potential interaction between antidepressants and other medications or environmental exposures such as alcohol intake or cigarette smoking at the time of the GIB. Very few participants were recorded as using or abusing alcohol in Barts Health NHS Trust records, which is partly a result of limitations of recording in secondary care records and partly a result of the fact that many of the cohort are assumed to be practicing Muslims.[12] However, ALD and CLD were controlled for in our analysis. Attempts to quantify lifetime use of aspirin, NSAID and PPI use from primary care prescription records only may be incomplete as these medications are available over the counter.

While the SSRIs included do not have guidance from CPIC dependent on *CYP2D6*, the tricyclic antidepressant guidance would be impacted by CYP2D6 metabolizer status as well, if known, which we are not able to assess from the array data. However, due to the difficulties in characterizing *CYP2D6* genotypes and ready availability of *CYP2C19* as a point of care test it is clinically relevant to ask if *CYP2C19* genotype knowledge implemented as PGx for antidepressants is likely to impact on any associated bleed risk. Furthermore, the tertiary amines have more serotonergic activity than the secondary amines resulting from CYP2C19 metabolism.[7] This serotonergic activity was the mechanism of interest in associating TCAs with GIB risk in the context of published literature associating SSRIs with GIB.

7 | CONCLUSIONS

Our findings are in agreement with prior studies showing a significant association, with a clinically meaningful effect, between CYP2C19-dependent SSRI and TCA use and GIB. This seems to be a class effect. In the cohort who had been prescribed antidepressants there was no difference in GIB prevalence between different CYP2C19 metabolizer groups, therefore our data suggest that GIB risk would not be mitigated by precision dosing based on *CYP2C19* testing. This data should be interpreted in the context of methodologic limitations and further, more granular, studies are needed.

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DATA AVAILABILITY STATEMENT

All Genes & Health data can be accessed by application to the study access team https://www.genesandhealth.org/research/scientists-using-genes-health-scientific-research.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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