

# Genetic risk for chronic pain is associated with lower antidepressant effectiveness: Converging evidence for a depression subtype

Australian & New Zealand Journal of Psychiatry  
2022, Vol. 56(9) 1177–1186  
DOI: 10.1177/00048674211031491

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## Abstract

**Introduction:** Chronic pain and depression are highly comorbid and difficult-to-treat disorders. We previously showed this comorbidity is associated with higher depression severity, lower antidepressant treatment effectiveness and poorer prognosis in the Australian Genetics of Depression Study.

**Objective:** The current study aimed to assess whether a genetic liability to chronic pain is associated with antidepressant effectiveness over and above the effect of genetic factors for depression in a sample of 12,863 Australian Genetics of Depression Study participants.

**Methods:** Polygenic risk scores were calculated using summary statistics from genome-wide association studies of multisite chronic pain and major depression. Cumulative linked regressions were employed to assess the association between polygenic risk scores and antidepressant treatment effectiveness across 10 different medications.

**Results:** Mixed-effects logistic regressions showed that individual genetic propensity for chronic pain, but not major depression, was significantly associated with patient-reported chronic pain (Pain<sup>PRS</sup> OR = 1.17 [1.12, 1.22]; MD<sup>PRS</sup> OR = 1.01 [0.98, 1.06]). Significant associations were also found between lower antidepressant effectiveness and genetic risk for chronic pain or for major depression. However, a fully adjusted model showed the effect of Pain<sup>PRS</sup> (adjOR = 0.93 [0.90, 0.96]) was independent of MD<sup>PRS</sup> (adjOR = 0.96 [0.93, 0.99]). Sensitivity analyses were performed to assess the robustness of these results. After adjusting for depression severity measures (i.e. age of onset; number of depressive episodes; interval between age at study participation and at depression onset), the associations between Pain<sup>PRS</sup> and patient-reported chronic pain with lower antidepressant effectiveness remained significant (0.95 [0.92, 0.98] and 0.84 [0.78, 0.90], respectively).

**Conclusion:** These results suggest genetic risk for chronic pain accounted for poorer antidepressant effectiveness, independent of the genetic risk for major depression. Our results, along with independent converging evidence from other studies, point towards a difficult-to-treat depression subtype characterised by comorbid chronic pain. This finding warrants further investigation into the implications for biologically based nosology frameworks in pain medicine and psychiatry.

## Keywords

Depression, chronic pain, antidepressant, polygenic risk score, pharmacogenetics

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## Introduction

Over the past three decades, chronic pain and depression have remained in the top three leading causes of global disability (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018). Both disorders are highly comorbid – having one condition substantially increases the risk of developing the other (Viana et al., 2018), with around one-third of depression patients presenting with severe pain (Stubbs et al., 2017), and 23–60% of chronic pain patients manifesting depression (Orhurhu et al., 2019). The presence of pain is also strongly associated with depression onset and relapse (DeVeugh-Geiss et al., 2010; Gerrits et al., 2014a, 2014b; Means-Christensen et al., 2008). Furthermore, comorbid chronic pain and depression is typically more difficult to treat than either primary condition alone. However, virtually all clinical guidelines and recommendations for either condition (Bates et al., 2019; Brueckle et al., 2020; Haibach et al., 2014; IsHak et al., 2018; Moore et al., 2015; Urits et al., 2019) have failed to adequately address treatment options for this common comorbidity. This major evidence gap can be attributed (in part) to the reliance on pharmacotherapeutic and other interventional trials excluding specific comorbidities (Baune et al., 2019; Cipriani et al., 2018; Kendrick et al., 2019), and are thus not representative of the inherent clinical heterogeneity across psychiatric populations.

We recently reported on a large pharmacoepidemiological study of comorbid chronic pain and depression (Roughan et al., 2021). This data-driven methodological approach (Bates et al., 2019; IsHak et al., 2018; Moore et al., 2015; Urits et al., 2019) took into account the wide individual variation to examine comorbid chronic pain and depression risk factors and antidepressant treatment effectiveness in the Australian Genetics of Depression Study (AGDS). The main findings concerning disease severity and treatment response were as follows: (1) higher pain severity (intensity) was associated with longer durations of pain and an increased number of depressive episodes; (2) patient-reported effectiveness from taking particular antidepressants (i.e. sertraline, escitalopram, venlafaxine) were significantly lower compared to those without chronic pain; (3) individuals prescribed particular antidepressants (i.e. sertraline, escitalopram, citalopram) for chronic pain (among other indications) reported significantly lower effectiveness compared to those taking the same medications but for a different indication; (4) the vast majority of participants with chronic pain (i.e. 75–98% across antidepressants) reported their antidepressant prescription was not for chronic pain; and (5) individuals with comorbid chronic pain reported fewer positive functional benefits from taking antidepressants (e.g. ‘*relief of depressive symptoms*’, ‘*return of normal emotions*’, ‘*getting back to normal daily activities*’). We therefore provided independent converging evidence that comorbid pain is a strong predictor of non-remission with antidepressant medication treatment as

found in previous clinical trials and observational studies (Bair et al., 2004; Fishbain et al., 2014)).

Here, we continued this work by leveraging genotype data in AGDS to investigate whether the phenotypic association between chronic pain and a poorer antidepressant effectiveness is genetically mediated. The relationship between depression severity and lower antidepressant effectiveness is established (Gueorguieva et al., 2011). We previously reported an association between chronic pain and lower patient-reported antidepressant effectiveness (Roughan et al., 2021). However, this negative association could be confounded by the (dose-dependent) correlation between chronic pain and depression severity (DeVeugh-Geiss et al., 2010), and by the expected relationship between depression severity and antidepressant effectiveness. Using genome-wide association study (GWAS) summary statistics for multi-site chronic pain (Johnston et al., 2019) and major depression (MD) (Wray et al., 2018), polygenic risk scores (PRS) (Wray et al., 2020) were generated for each of these conditions. We examined whether Pain<sup>PRS</sup> and MD<sup>PRS</sup> were associated with patient-reported chronic pain, and antidepressant treatment response. We further examined whether any associations between patient-reported chronic pain and Pain<sup>PRS</sup> with lower antidepressant effectiveness are robust to measures of MD severity and liability. These analyses aim to disentangle the confounding associations and determine whether genetic risk for chronic pain predicts antidepressant treatment response independently of the genetic risk for depression.

## Methods

### Sample recruitment

The AGDS sample was recruited through two main streams: (1) a mailout by the Australian Department of Human Services (DHS) on our behalf, targeted at people who had been prescribed antidepressants at least four times in the past 4.5 years; and (2) a national media publicity campaign. Interested participants were directed to a website where they provided informed consent prior to participating through online questionnaires. Upon completion of the core questionnaire, participants were mailed a GeneFix GFX-02 2 mL saliva DNA extraction kit (Isohelix plc) to use at home and then returned through the post for subsequent genotyping. The package included a consent form specific to genetic information to be signed by participants. Sample recruitment has been extensively described elsewhere (Byrne et al., 2020). All protocols and questionnaires were approved by the QIMR Berghofer Medical Research Institute’s Human Research Ethics Committee.

### Phenotype ascertainment

This study focuses on patient-reported antidepressant effectiveness ( $N=12,863$ ) (Byrne et al., 2020). Participants were

first asked to confirm whether they had been prescribed any of the 10 most commonly prescribed antidepressants in Australia (i.e. sertraline, escitalopram, venlafaxine, fluoxetine, citalopram, desvenlafaxine, duloxetine, mirtazapine, amitriptyline, paroxetine). For each antidepressant participants had taken, they were asked to rate its effectiveness using the item: ‘How well does/did [name of the antidepressant] work for you?’. The possible responses were as follows: ‘not at all well’, ‘moderately well’ and ‘very well’. Participants failing to self-report a diagnosis of major depressive disorder (MDD) were excluded from the current study. Data on chronic pain were gathered through the general health and lifestyle module of our online survey ( $N=11,370$ ) (Roughan et al., 2021). Participants were asked whether they experienced pain in their daily life and to rank its intensity on a scale from 0 to 10. Only those reporting pain (i.e. rating  $> 0$ ) progressed to the remainder of the pain module, which included questions about pain duration and location. We defined chronic pain according to the International Association for the Study of Pain (IASP) as pain persisting or recurring for longer than 3 months (Treede et al., 2015, 2019). We have previously reported on the comorbidity between chronic pain, depression severity and their phenotypic association with antidepressant treatment response in this sample (Roughan et al., 2021).

### Genotyping and QC

Genotyping was performed using the Illumina Global Screening Array (GSA V2.0.) across three genotyping centres. A common set of high-quality markers between the different genotyping centres was identified prior to joint imputation. Pre-imputation marker exclusion criteria consisted of unknown or ambiguous map position, strand alignment in a BLAST search, missingness  $> 5\%$ ,  $p(\text{HWE test}) < 10^{-6}$ ,  $\text{MAF} < 1\%$  and GenTrain score  $< 0.6$ . The Michigan imputation server was used to impute the genotypes using the HRCr1.1 reference panel. Individuals were excluded based on high missingness (missing rate  $> 3\%$ ), inconsistent (and unresolvable) sex, or if they were deemed ancestry outliers from the European population (i.e.  $> 6$  SD from the first two genetic principal components).

### Polygenic risk scoring

We employed a recently developed method, SBayesR (Lloyd-Jones et al., 2019; Ni et al., 2020) to estimate conditional (i.e. simultaneously fitting all genetic variants) GWAS summary statistics for both multisite chronic pain (Johnston et al., 2019) and MD (Wray et al., 2018). This process prevents inflation arising from using correlated single-nucleotide polymorphisms (SNPs) due to linkage disequilibrium (LD) (Lloyd-Jones et al., 2019). Prior to PRS calculations, we excluded insertion/deletion variants, those with strand ambiguity or low-imputation quality

( $R^2 < 0.6$ ). We then used the resulting GWAS effect sizes to estimate multisite chronic pain PRS (Pain<sup>PRS</sup>) and MD PRS (MD<sup>PRS</sup>) with PLINK 1.9 (Chang et al., 2015) on the AGDS imputed genetic dosages.

### Statistical analyses

All analyses were performed on a subset of unrelated participants with European Ancestry. Mixed-effects logistic regressions were used to examine the association between patient-reported chronic pain and Pain<sup>PRS</sup> or MD<sup>PRS</sup>. The regressions were adjusted for sex, age at study enrolment, and the first 20 genetic principal components to adjust for potential population stratification. Cumulative linked mixed models (CLMM; also known as mixed ordered logistic regressions) were used to assess the association between the main variables of interest (i.e. Pain<sup>PRS</sup>, MD<sup>PRS</sup>) and overall treatment effectiveness. This more complex modelling was warranted given the ordinal nature in which antidepressant effectiveness was measured. A fully adjusted regression with both Pain<sup>PRS</sup> and MD<sup>PRS</sup> was used to assess whether any association between MD<sup>PRS</sup> and antidepressant effectiveness is mediated by a genetic correlation between MD and chronic pain. To assess overall treatment response, repeated measures from participants taking more than one antidepressant were adjusted by including a random effect intercept for each participant. CLMM were also used to assess the association between the effectiveness of specific antidepressants with Pain<sup>PRS</sup> and MD<sup>PRS</sup>. Statistical significance was defined with Bonferroni multiple-testing correction per PRS of interest, adjusting for the repeated testing of 10 antidepressants ( $p < 0.005$ ). These analyses were performed in R using the *base* and *ordinal* libraries.

### Results

The final sample consisted of 12,863 participants with genotype and patient-reported antidepressant effectiveness data. Of these, 5809 (45%) participants reported having chronic pain; 3784 (30%) did not report chronic pain; and 3270 (25%) had missing data from the pain module survey. Participants with missing data from the pain module had similar demographics to the other subgroups (Table 1) and were used for polygenic risk scoring as they had genotype data available. Mean age was 43.7 (SD=15.1) years and approximately 76% were female. Of the participants with available data on pain, 60% fulfilled the current IASP definition (Treede et al., 2019) used for chronic pain. We found Pain<sup>PRS</sup> was significantly associated with chronic pain ( $\text{OR}=1.17$  [1.12, 1.22]), whereas MD<sup>PRS</sup> was *not* associated with chronic pain ( $\text{OR}=1.01$  [0.98, 1.06]).

PRS for chronic pain and for MD were both associated with lower antidepressant treatment response (Pain<sup>PRS</sup>  $\text{OR}=0.93$  [0.90, 0.96]; MD<sup>PRS</sup>  $\text{OR}=0.95$  [0.92, 0.99]). However, the fully adjusted model suggests the association

**Table 1.** AGDS sample composition.

		Controls	Chronic pain	No chronic pain data
Age, mean (SD)		41 (15.0)	46 (14.6)	43 (15.2)
Female, <i>n</i> (%)		2488 (66)	4372 (75)	2507 (76)
Total, <i>n</i> (%)		3784 (30)	5809 (45)	3270 (25)
Antidepressant response, <i>n</i> (%)				
Sertraline	Poor	500 (0.33)	988 (0.38)	522 (0.38)
	Moderate	559 (0.36)	946 (0.36)	498 (0.36)
	Well	476 (0.31)	670 (0.26)	371 (0.27)
Escitalopram	Poor	367 (0.29)	603 (0.32)	356 (0.33)
	Moderate	465 (0.37)	734 (0.39)	379 (0.35)
	Well	430 (0.34)	542 (0.29)	335 (0.31)
Venlafaxine	Poor	337 (0.32)	677 (0.37)	306 (0.31)
	Moderate	355 (0.34)	632 (0.34)	365 (0.37)
	Well	347 (0.33)	524 (0.29)	305 (0.31)
Amitriptyline	Poor	100 (0.47)	414 (0.46)	179 (0.47)
	Moderate	72 (0.34)	326 (0.36)	135 (0.36)
	Well	42 (0.20)	158 (0.18)	66 (0.17)
Mirtazapine	Poor	222 (0.42)	422 (0.47)	217 (0.46)
	Moderate	187 (0.35)	282 (0.31)	137 (0.29)
	Well	118 (0.22)	194 (0.22)	113 (0.24)
Desvenlafaxine	Poor	218 (0.30)	344 (0.32)	204 (0.32)
	Moderate	233 (0.32)	353 (0.33)	215 (0.34)
	Well	274 (0.38)	377 (0.35)	217 (0.34)
Citalopram	Poor	239 (0.35)	419 (0.36)	242 (0.41)
	Moderate	247 (0.37)	449 (0.38)	216 (0.36)
	Well	190 (0.28)	308 (0.26)	135 (0.23)
Fluoxetine	Poor	385 (0.39)	668 (0.41)	362 (0.40)
	Moderate	330 (0.33)	558 (0.34)	314 (0.34)
	Well	272 (0.28)	392 (0.24)	236 (0.26)
Duloxetine	Poor	161 (0.33)	345 (0.36)	176 (0.36)
	Moderate	166 (0.34)	331 (0.35)	180 (0.37)
	Well	161 (0.33)	282 (0.29)	130 (0.27)
Paroxetine	Poor	147 (0.37)	316 (0.41)	143 (0.42)
	Moderate	142 (0.35)	247 (0.32)	124 (0.37)
	Well	113 (0.28)	203 (0.27)	70 (0.21)

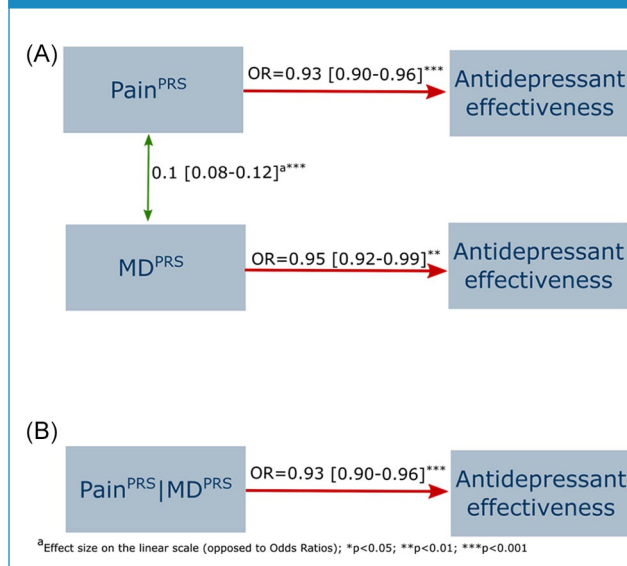
Demographics of the AGDS sample comprising unrelated individuals of European ancestry used in the current study. Participants with no chronic pain data were used for PRS analyses to predict antidepressant treatment response but were excluded from analyses to predict chronic pain.

with Pain<sup>PRS</sup> (adjOR=0.93 [0.90, 0.96]) is independent from the effect of MD<sup>PRS</sup> (adjOR=0.96 [0.93, 0.99]) (Figure 1). Fully adjusted models stratified by antidepressant type also showed significant associations between (1) MD<sup>PRS</sup>

with higher effectiveness of amitriptyline and suggestively lower effectiveness of venlafaxine; and (2) Pain<sup>PRS</sup> with lower effectiveness of sertraline and suggestively lower effectiveness of escitalopram (Table 2 and Figure 2).



**Figure 1.** Association between MD<sup>PRS</sup> and (chronic) Pain<sup>PRS</sup> with antidepressant effectiveness across all medications.



The relationship between MD<sup>PRS</sup> and Pain<sup>PRS</sup> (green double-headed arrow) was modelled using linear regression. The unadjusted results (A) and fully adjusted results (B) are shown in the top and bottom panels, respectively. Note that the effect size and significance of the association between MD<sup>PRS</sup> and antidepressant effectiveness is reduced in the fully adjusted model, which suggests it is mediated in part by Pain<sup>PRS</sup>. MD: major depression; PRS: polygenic risk scores.

Sensitivity analyses were performed to assess the robustness of these results by adjusting for two measures of depression severity – age of depression onset and number of depressive episodes. We also adjusted for the interval between age of onset of depression and age at participation as we expect a positive relationship between this interval

and number of episodes. These analyses showed that only the relationship between Pain<sup>PRS</sup> and overall lower antidepressant effectiveness was sustained (OR=0.95 [0.92, 0.98]). The same was true for patient-reported chronic pain (OR=0.84 [0.78, 0.90]), but not for MD<sup>PRS</sup> (OR=0.98 [0.94, 1.01]). Thus, genetic risk for chronic pain is associated with poorer antidepressant effectiveness and a mediator of treatment response that is independent of the genetic risk and severity of MD. The sensitivity analyses further revealed significant associations were also sustained between (1) Pain<sup>PRS</sup> and lower effectiveness of sertraline; (2) MD<sup>PRS</sup> and higher effectiveness of amitriptyline; and (3) MD<sup>PRS</sup> and lower effectiveness of venlafaxine (Table 3 and Figure 3).

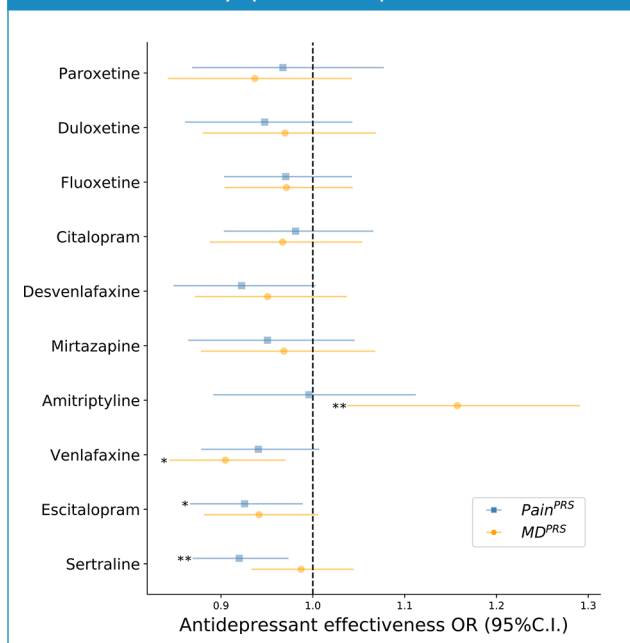
## Discussion

We recently demonstrated in a sample of more than 11,000 participants that comorbid pain is a significant risk factor for poor treatment response with antidepressant medications (Roughan et al., 2021). This finding corroborated previous clinical trials and observational studies showing that pain has a significant negative impact on antidepressant treatment response (Fishbain et al., 2014). Here, we showed the increased risk of poor antidepressant response is genetically mediated using a PRS analytical approach (Wray et al., 2020). The current study has presented the first evidence for predicting antidepressant treatment response in comorbid chronic pain and depression using PRS. Our findings point towards a *difficult-to-treat* depression (DTD) subtype characterised by comorbid pain. The 2020 Royal Australian and New Zealand clinical practice guidelines (CPGs) for mood disorders suggests the use of ‘DTD’ to describe depression subtypes where treatment, which also

**Table 2.** Treatment response association results for each antidepressant with Pain<sup>PRS</sup> and MD<sup>PRS</sup>.

	N	Pain <sup>PRS</sup>			MD <sup>PRS</sup>		
		Effect size	SE	p	Effect size	SE	p
Sertraline	4139	−0.084	0.029	0.004	−0.013	0.029	0.655
Escitalopram	3141	−0.077	0.034	0.022	−0.060	0.034	0.073
Venlafaxine	2872	−0.061	0.035	0.079	−0.100	0.036	0.005
Amitriptyline	1112	−0.004	0.056	0.940	0.146	0.056	0.009
Mirtazapine	1425	−0.051	0.049	0.297	−0.032	0.050	0.520
Desvenlafaxine	1799	−0.081	0.043	0.059	−0.051	0.044	0.254
Citalopram	1852	−0.019	0.042	0.653	−0.033	0.044	0.445
Fluoxetine	2605	−0.030	0.037	0.412	−0.029	0.037	0.426
Duloxetine	1446	−0.054	0.049	0.271	−0.031	0.050	0.535
Paroxetine	1168	−0.033	0.055	0.546	−0.065	0.054	0.231

**Figure 2.** Treatment effectiveness associated with Pain<sup>PRS</sup> or MD<sup>PRS</sup> stratified by specific antidepressant.



This forest plot depicts the odds ratios (ORs) and 95% confidence intervals derived from ordered logistic regressions showing antidepressant effectiveness for MD<sup>PRS</sup> and (chronic) Pain<sup>PRS</sup>. MD<sup>PRS</sup> is associated with higher effectiveness of amitriptyline and suggestively lower effectiveness of venlafaxine. Pain<sup>PRS</sup> is associated with lower effectiveness of sertraline and suggestively lower effectiveness of escitalopram. These results are based on a fully adjusted model using age, sex, Pain<sup>PRS</sup>, MD<sup>PRS</sup> and patient-reported chronic pain (in AGDS) as covariates (\* $p < 0.005$ ; \* $p < 0.05$ ). ORs  $< 1$  indicate a negative association (i.e. PRS left of the vertical dashed line is associated with poorer antidepressant effectiveness of venlafaxine, escitalopram and sertraline). See Table 2 for the corresponding descriptive statistics (i.e. samples size, effect size, standard error [SE] and  $p$ -value) of treatment response association results for each antidepressant with Pain<sup>PRS</sup> and MD<sup>PRS</sup>.

could include other types of pharmacological and non-pharmacological therapies, is challenging but not unachievable (Malhi et al., 2021). This proposed subtype warrants replication in large independent samples with pain, genotype and treatment response data. We suggest that a distinct advantage of such large-scale data-driven studies – through the application of PRS analyses – is their utility in predicting medication response risk for population-level trans diagnostic stratification and disease classification (Shah et al., 2020). This work also provides further evidence for the universally recognised clinical reality that patients presenting with psychiatric and/or physical comorbidities are the rule (Gold et al., 2020; Momen et al., 2020; Viana et al., 2018), rather than the exception.

Further evidence consistent with a comorbid pain subtype was the finding of MD<sup>PRS</sup> not being associated with chronic pain, even though a phenotypic association between depression and chronic pain had been demonstrated using the same sample (Roughan et al., 2021). In the current study,

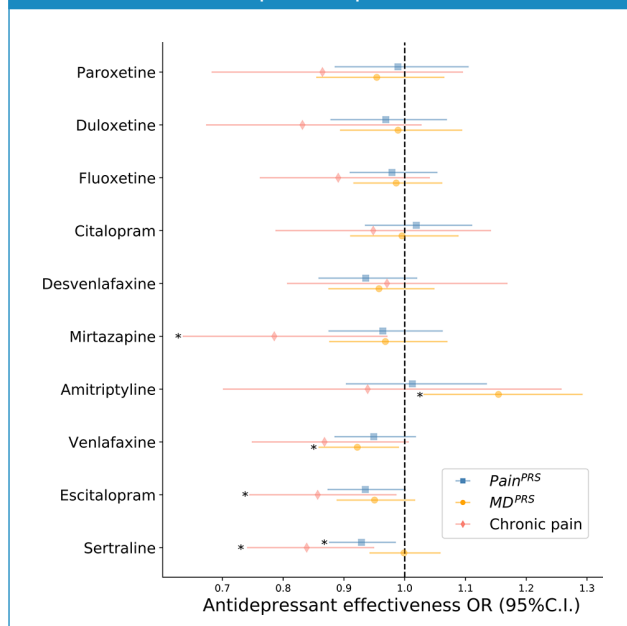
we generated PRS for chronic pain based on GWAS summary statistics from an earlier report using UK Biobank pain data (Johnston et al., 2019). That report also applied Mendelian Randomisation analyses and found a causal effect of chronic pain on MD, but not vice versa. This causal direction finding is corroborated by our sensitivity analyses showing that Pain<sup>PRS</sup> but not MD<sup>PRS</sup> predicts poor antidepressant response after adjusting for depression severity measures. Our results are also complemented by a recent study – notably, in a psychiatric patient cohort – which identified gene expression blood biomarkers that predicted pain state and future emergency department visits for pain, as well as new potential therapeutic targets for pain using existing antidepressant medications (e.g. amoxapine) (Niculescu et al., 2019). Furthermore, a study of medication use in the UK Biobank found depression increased the likelihood of taking analgesics (anilides) (Wu et al., 2019), thus presenting another direction to further investigate treatment-response subtypes in large genotyped samples.

A recent study that also examined PRS for depression in relation to pain and other common comorbidities used summary statistics from UK Biobank and other large population cohorts (Shen et al., 2020). They reported that MD<sup>PRS</sup> predicted recent pain along with other complex traits which showed the largest effect sizes (e.g. sleep, smoking behaviour, cardiovascular conditions). MD<sup>PRS</sup> was not reported to predict chronic pain (i.e. pain for 3+ months), which is consistent with our results. Notably, we have shown that Pain<sup>PRS</sup> predicts patient-reported chronic pain. Altogether, these results support an underlying genetic difference between short-term pain and chronic pain. However, the current consensus-based IASP and ICD-11 diagnostic criteria for defining ‘chronic pain’ rests on a purely temporal and arbitrary cutoff of ‘pain persisting or recurring for longer than three months’ (Treede et al., 2019), while also failing to account for comorbidities such as depression. Furthermore, despite decades of enormous effort put into pain research, there has been no objective biological evidence found for this critical criterion. Our results on the other hand present the first evidence to support a genetic transdiagnostic subtype of depression with comorbid chronic pain. This unexpected finding has major implications, for example, on diagnostics, disease classification and early intervention approaches (e.g. screening, education, prevention) in pain medicine (Davis et al., 2020) and occupational rehabilitation (e.g. after injury/trauma) – and correspondingly – for biologically mechanisms-based nosology frameworks in psychiatry (i.e. RDoC).

In the current study, Pain<sup>PRS</sup> was associated with poorer antidepressant effectiveness overall. However, when stratifying per antidepressant, we found statistically significant lower effectiveness for sertraline only. This result is likely explained by the fact that sertraline was the most commonly reported antidepressant taken and therefore had the greatest statistical power. Consistently, the effect of associations

**Table 3.** Sensitivity analysis association results for each antidepressant treatment response with Pain<sup>PRS</sup>, MD<sup>PRS</sup> and patient-reported chronic pain.

	N	Pain <sup>PRS</sup>			MD <sup>PRS</sup>			Chronic Pain		
		Effect size	SE	p	Effect size	SE	p	Effect size	SE	p
Sertraline	3867	−0.074	0.030	0.014	−0.001	0.030	0.969	−0.176	0.064	0.006
Escitalopram	2954	−0.067	0.035	0.057	−0.051	0.035	0.142	−0.155	0.072	0.032
Venlafaxine	2733	−0.052	0.036	0.146	−0.081	0.037	0.027	−0.142	0.076	0.061
Amitriptyline	1049	0.012	0.058	0.830	0.144	0.058	0.013	−0.063	0.149	0.673
Mirtazapine	1352	−0.037	0.050	0.460	−0.032	0.051	0.527	−0.242	0.109	0.026
Desvenlafaxine	1687	−0.066	0.044	0.134	−0.043	0.046	0.352	−0.030	0.095	0.755
Citalopram	1727	0.019	0.044	0.669	−0.005	0.046	0.921	−0.053	0.095	0.575
Fluoxetine	2465	−0.021	0.038	0.572	−0.014	0.038	0.709	−0.116	0.080	0.147
Duloxetine	1374	−0.032	0.050	0.530	−0.011	0.052	0.831	−0.184	0.108	0.088
Paroxetine	1111	−0.011	0.057	0.843	−0.047	0.056	0.403	−0.145	0.121	0.229

**Figure 3.** Sensitivity analyses for antidepressant effectiveness results after adjusting for age of depression onset and number of depressive episodes.

Patient-reported chronic pain and Pain<sup>PRS</sup> – but not MD<sup>PRS</sup> – remained significantly associated with lower antidepressant effectiveness. Significant associations also remained between (1) Pain<sup>PRS</sup> and lower effectiveness of sertraline; and (2) MD<sup>PRS</sup> and higher effectiveness of amitriptyline and lower effectiveness of venlafaxine. The forest plot depicts the odds ratios (OR) and 95% confidence intervals derived from ordered logistic regressions showing antidepressant effectiveness for MD<sup>PRS</sup>, (chronic) Pain<sup>PRS</sup> and patient-reported chronic pain (from AGDS). These sensitivity analyses adjusted for age, sex and two measures of depression severity: age of depression onset and number of depressive episodes (\**p* < 0.05). See Table 3 for the corresponding descriptive statistics (i.e. samples size, effect size, standard error [SE] and *p*-value) of treatment response association results for each antidepressant with Pain<sup>PRS</sup>, MD<sup>PRS</sup> and patient-reported chronic pain.

between Pain<sup>PRS</sup> and other antidepressants was negative. Given the circular relationship between depression and pain, we performed fully adjusted sensitivity analyses that accounted for MD<sup>PRS</sup> and measures of depression severity (i.e. age of depression onset, number of depressive episodes; interval between age at participation and at depression onset). The association between lower overall effectiveness of antidepressants and Pain<sup>PRS</sup> was robust to these factors, and a similar finding from the stratified analyses was observed.

Our results support the channelling response paradigm to treating depression. Under this paradigm, response heterogeneity is the product of different responsivities that need to be addressed for successful treatment (Malhi et al., 2021). For this subtype, one of such responsivities would be the adequate management and treatment of pain, without which depressive symptom therapies might alone cause a poor response. In a previous study (Roughan et al., 2021), we showed that, when explicitly indicated for chronic pain, duloxetine, venlafaxine and amitriptyline show a positive (but non-significant) association with better treatment response. Consistently, we found MD<sup>PRS</sup> to be associated with a higher amitriptyline response. Altogether, these results suggest that amitriptyline is effective at treating both pain and depressive symptoms, this further supports the CPGs considering it the antidepressant of choice with the highest efficacy (at the drawback of low tolerability) for depressive symptom alleviation. As such, our observations support recently published guidelines suggesting duloxetine and tricyclic antidepressants (TCAs) as preferred antidepressants for depression when pain is present as a prominent symptom (Malhi et al., 2021).

Our study is the first direct assessment of whether polygenic instruments for chronic pain are associated with antidepressant

treatment effectiveness. As such, there are certain limitations to be acknowledged. First, to avoid potential sources of bias that are inherent to genetic studies, analyses were restricted to a subset of unrelated individuals with European ancestry. This approach aims to reduce false-positive associations due to population stratification but limits the generalisability of the findings to other populations. Furthermore, all participants in this study had depression. As such, caution should be taken in generalising the association between chronic pain, depression and their genetic relationship across the general population. All of the studied phenotypes were also obtained through online self-administered instruments and are therefore subject to recall bias. Related to this issue is the interpretability of the antidepressant effectiveness phenotype. For example, amitriptyline is a TCA medication commonly prescribed as a treatment for chronic neuropathic pain (Moore et al., 2015). Most participants reported taking antidepressants for treating depression, as did the vast majority of participants with chronic pain (i.e. 75–98% across antidepressants) (Roughan et al., 2021). As such, those with comorbidities may have considered ‘*treatment effectiveness*’ as a bivariate improvement of both their depression and chronic pain. Finally, we focused only on treatment response with the 10 most commonly prescribed antidepressants in Australia. The extent to which our results may generalise to other antidepressants as well as other pharmacological and non-pharmacological therapies requires further investigation.

The current study’s findings warrant further examination by (1) performing discovery GWAS of comorbid chronic pain and depression for generating PRS in large genotyped populations to assess genetic risk prediction capacity and Generalisability; (2) replication in other DTD cohorts with primary care and genotype data (Fabbri et al., 2020); and (3) replication in a PRS-informed randomised clinical trial integrating both MD and chronic pain polygenic instruments to stratify the placebo and control groups. Further genetic epidemiology studies of treatment response can also focus on patients with chronic pain and depression of non-European ancestry, to collect additional data on medication dosages (including painkillers), the duration and magnitude of functional benefits, drug tolerability and adverse events, other prescribed and self-help therapies, pain-specific questionnaires (Roughan et al., 2021) and other common comorbidities such as sleep and cardiovascular disorders (Fabbri et al., 2020; Shen et al., 2020; Tesarz et al., 2019; van Hecke et al., 2017). Our work demonstrates a strategy for further delineating the heterogeneity across psychiatric and comorbid pain populations to potentially yield other transdiagnostic subtypes, which would pave the way for comparing particular psychotropic medications in pharmacogenomics (Bousman et al., 2019; Dorfman et al., 2020; Kaye et al., 2019; Maciukiewicz et al., 2018; Yamamoto et al., 2019) and neuroimaging trials (Schmaal et al., 2020; Thompson et al., 2020; Wang et al., 2019) specifically targeting identified subtype cohorts.

Since the advent of GWAS and associated methodologies over a decade ago, demonstrating their clinical utility

in complex traits and polygenic disorders (e.g. mental health, chronic diseases) has been challenging. Here we have demonstrated the application of a commonly used genetic analysis method (PRS) to antidepressant treatment response data and showed its utility in the similarly elusive goal of identifying subtypes in psychiatry and pain medicine. We hope this approach can bring a step change in genomic medicine, pain management and multidisciplinary clinical decision-making to deliver improvements in healthcare outcomes and the identification of effective therapeutic targets.

## Acknowledgements

The authors thank their colleagues Richard Parker, Simone Cross, Scott Gordon and Lenore Sullivan for their valuable work coordinating all the administrative and operational aspects of the AGDS project. They also thank the anonymous reviewers for their constructive comments which helped to improve the manuscript. The views expressed are those of the authors and not necessarily those of the affiliated or funding institutions.

## Author Contributions

A.I.C., T.T.N. and M.E.R. designed this study and wrote the first version of the manuscript; A.I.C. performed the analyses with input from M.E.R.; N.G.M., S.E.M., N.R.W., E.M.B. and I.B.H. designed and directed the AGDS data collection efforts; and T.T.N. designed the pain module in the AGDS online survey and conceived the genetic and epidemiological investigation of comorbid pain and depression in this cohort. All authors contributed to the interpretation of the results and provided feedback on the preliminary versions of the manuscript.

## Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: I.B.H. has been Commissioner of Australia’s National Mental Health Commission (2012–2018); Co-director of Health & Policy at the Brain & Mind Centre, University of Sydney; leading community-based and pharmaceutical industry-supported projects (Wyeth, Eli Lilly, Servier, Pfizer, AstraZeneca) focused on the identification and better management of anxiety and depression; a member of the Medical Advisory Panel for Medibank Private until October 2017; a board member of Psychosis Australia Trust; a member of the Veterans Mental Health Clinical Reference group; and Chief Scientific Advisor to and an equity shareholder in Innowell. The remaining authors have nothing to disclose.

## Funding


The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Data collection for AGDS was possible thanks to funding from the Australian National Health & Medical Research Council (NHMRC) to N.G.M. (GNT1086683). A.I.C. is supported by a UQ Research Training Scholarship from The University of Queensland (UQ). M.E.R. thanks the support of NHMRC and the



Australian Research Council (ARC), through a NHMRC-ARC Dementia Research Development Fellowship (GNT1102821).

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## References

- Bair MJ, Robinson RL, Eckert GJ, et al. (2004) Impact of pain on depression treatment response in primary care. *Psychosomatic Medicine* 66: 17–22.
- Bates D, Schultheis BC, Hanes MC, et al. (2019) A comprehensive algorithm for management of neuropathic pain. *Pain Medicine* 20: S2–S12.
- Baune BT, Boyce P, Morris G, et al. (2019) Organising the front line: Is there a rationale for the first-line pharmacotherapy of major depressive disorder? *Australian and New Zealand Journal of Psychiatry* 53: 279–281.
- Bousman CA, Arandjelovic K, Mancuso SG, et al. (2019) Pharmacogenetic tests and depressive symptom remission: A meta-analysis of randomized controlled trials. *Pharmacogenomics* 20: 37–47.
- Brueckle M-S, Thomas ET, Seide SE, et al. (2020) Adverse drug reactions associated with amitriptyline – protocol for a systematic multiple-indication review and meta-analysis. *Systematic Reviews* 9: 59.
- Byrne EM, Kirk KM, Medland SE, et al. (2020) Cohort profile: The Australian Genetics of Depression Study. *BMJ Open* 10: e032580.
- Chang CC, Chow CC, Tellier LC, et al. (2015) Second-generation PLINK: Rising to the challenge of larger and richer datasets. *Gigascience* 4: 7.
- Cipriani A, Furukawa TA, Salanti G, et al. (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *Focus* 16: 420–429.
- Davis KD, Aghaepour N, Ahn AH, et al. (2020) Discovery and validation of biomarkers to aid the development of safe and effective pain therapeutics: Challenges and opportunities. *Nature Reviews. Neurology* 16: 381–400.
- DeVeau-Geiss AM, West SL, Miller WC, et al. (2010) The adverse effects of comorbid pain on depression outcomes in primary care patients: Results from the ARTIST trial. *Pain Medicine* 11: 732–741.
- Dorfman R, London Z, Metias M, et al. (2020) Individualized medication management in Ontario long-term care clinical impact on management of depression, pain, and dementia. *Journal of the American Medical Directors Association* 21: 823.e5–829.e5.
- Fabbri C, Hagenaars SP, John C, et al. (2020) Genetic and clinical characteristics of treatment-resistant depression using primary care records in two UK cohorts. *Molecular Psychiatry*. Epub ahead of print 22 March. DOI: 10.1101/2020.08.24.20178715
- Fishbain DA, Cole B, Lewis JE, et al. (2014) Does pain interfere with antidepressant depression treatment response and remission in patients with depression and pain? An evidence-based structured review. *Pain Medicine* 15: 1522–1539.
- GBD 2017 Disease and Injury Incidence and Prevalence Collaborators (2018) Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the Global Burden of Disease Study 2017. *The Lancet* 392: 1789–1858.
- Gerrits MMJG, van Oppen P, Leone SS, et al. (2014a) Pain, not chronic disease, is associated with the recurrence of depressive and anxiety disorders. *BMC Psychiatry* 358: j3221.
- Gerrits MMJG, van Oppen P, van Marwijk HWJ, et al. (2014b) Pain and the onset of depressive and anxiety disorders. *Pain* 155: 53–59.
- Gold SM, Köhler-Forsberg O, Moss-Morris R, et al. (2020) Comorbid depression in medical diseases. *Nature Reviews. Disease Primers* 6: 69.
- Gueorguieva R, Mallinckrodt C and Krystal JH (2011) Trajectories of depression severity in clinical trials of duloxetine: Insights into antidepressant and placebo responses. *Archives of General Psychiatry* 68: 1227–1237.
- Haibach JP, Beehler GP, Dollar KM, et al. (2014) Moving toward integrated behavioral intervention for treating multimorbidity among chronic pain, depression, and substance-use disorders in primary care. *Medical Care* 52: 322–327.
- IsHak WW, Wen RY, Naghdechi L, et al. (2018) Pain and depression: A systematic review. *Harvard Review of Psychiatry* 26: 352–363.
- Johnston KJA, Adams MJ, Nicholl BI, et al. (2019) Genome-wide association study of multisite chronic pain in UK Biobank. *PLoS Genetics* 15: e1008164.
- Kaye AD, Garcia AJ, Hall OM, et al. (2019) Update on the pharmacogenomics of pain management. *Pharmacogenomics and Personalized Medicine* 12: 125–143.
- Kendrick T, Taylor D and Johnson CF (2019) Which first-line antidepressant? *The British Journal of General Practice: The Journal of the Royal College of General Practitioners* 69: 114–115.
- Lloyd-Jones LR, Zeng J, Sidorenko J, et al. (2019) Improved polygenic prediction by Bayesian multiple regression on summary statistics. *Nature Communications* 10: 5086.
- Maciukiewicz M, Marshe VS, Tiwari AK, et al. (2018) Genome-wide association studies of placebo and duloxetine response in major depressive disorder. *The Pharmacogenomics Journal* 18: 406–412.
- Malhi GS, Bell E, Bassett D, et al. (2021) The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian and New Zealand Journal of Psychiatry* 55: 7–117.
- Means-Christensen AJ, Roy-Byrne PP, Sherbourne CD, et al. (2008) Relationships among pain, anxiety, and depression in primary care. *Depression and Anxiety* 25: 593–600.
- Momen NC, Plana-Ripoll O, Agerbo E, et al. (2020) Association between mental disorders and subsequent medical conditions. *The New England Journal of Medicine* 382: 1721–1731.
- Moore RA, Derry S, Aldington D, et al. (2015) Amitriptyline for neuropathic pain in adults. *Cochrane Database of Systematic Reviews* 2015: CD008242.
- Ni G, Zeng J, Revez JA, et al. (2020) A comprehensive evaluation of polygenic score methods across cohorts in psychiatric disorders. *Medrxiv*.
- Niculescu AB, Le-Niculescu H, Levey DF, et al. (2019) Towards precision medicine for pain: Diagnostic biomarkers and repurposed drugs. *Molecular Psychiatry* 24: 501–522.
- Orhurhu V, Olusunmade M, Akinola Y, et al. (2019) Depression trends in patients with chronic pain: An analysis of the nationwide inpatient sample. *Pain Physician* 22: E487–E494.
- Roughan WH, Campos AI, García-Marín LM, et al. (2021) Comorbid chronic pain and depression: Shared risk factors and differential antidepressant effectiveness. *Frontiers in Psychiatry* 12: 444.
- Schmaal L, Pozzi E, Ho TC, et al. (2020) ENIGMA MDD: Seven years of global neuroimaging studies of major depression through worldwide data sharing. *Translational Psychiatry* 10: 172.
- Shah JL, Scott J, McGorry PD, et al. (2020) Transdiagnostic clinical staging in youth mental health: A first international consensus statement. *World Psychiatry: Official Journal of the World Psychiatric Association* 19: 233–242.
- Shen X, Howard DM, Adams MJ, et al. (2020) A phenome-wide association and Mendelian Randomisation study of polygenic risk for depression in UK Biobank. *Nature Communications* 11: 2301.
- Stubbs B, Vancampfort D, Veronese N, et al. (2017) Depression and pain: Primary data and meta-analysis among 237 952 people across 47 low- and middle-income countries. *Psychological Medicine* 47: 2906–2917.

- Tesarz J, Eich W, Baumeister D, et al. (2019) Widespread pain is a risk factor for cardiovascular mortality: Results from the Framingham Heart Study. *European Heart Journal* 40: 1609–1617.
- Thompson PM, Jahanshad N, Ching CRK, et al. (2020) ENIGMA and global neuroscience: A decade of large-scale studies of the brain in health and disease across more than 40 countries. *Translational Psychiatry* 10: 100.
- Treede R-D, Rief W, Barke A, et al. (2015) A classification of chronic pain for ICD-11. *Pain* 156: 1003–1007.
- Treede R-D, Rief W, Barke A, et al. (2019) Chronic pain as a symptom or a disease. *Pain* 160: 19–27.
- Urits I, Peck J, Orhurhu MS, et al. (2019) Off-label antidepressant use for treatment and management of chronic pain: Evolving understanding and comprehensive review. *Current Pain and Headache Reports* 23: 66.
- van Hecke O, Hocking L, Torrance N, et al. (2017) Chronic pain, depression and cardiovascular disease linked through a shared genetic predisposition: Analysis of a family-based cohort and twin study. *PLoS ONE* 12: e0170653.
- Viana MC, Lim CCW, Pereira FG, et al. (2018) Previous mental disorders and subsequent onset of chronic back or neck pain: Findings from 19 countries. *The Journal of Pain: Official Journal of the American Pain Society* 19: 99–110.
- Wang Y, Bernanke J, Peterson BS, et al. (2019) The association between antidepressant treatment and brain connectivity in two double-blind, placebo-controlled clinical trials: A treatment mechanism study. *The Lancet. Psychiatry* 6: 667–674.
- Wray NR, Lin T, Austin J, et al. (2020) From basic science to clinical application of polygenic risk scores: A primer. *JAMA Psychiatry* 78: 101–109.
- Wray NR, Ripke S, Mattheisen M, et al. (2018) Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature Genetics* 50: 668–681.
- Wu Y, Byrne EM, Zheng Z, et al. (2019) Genome-wide association study of medication-use and associated disease in the UK Biobank. *Nature Communications* 10: 1891.
- Yamamoto PA, Costa ACC, Lauretti GR, et al. (2019) Pharmacogenomics in chronic pain therapy: From disease to treatment and challenges for clinical practice. *Pharmacogenomics* 20: 971–982.