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Clinical Review Article

Pharmacogenetic Implications for Antidepressant Pharmacotherapy in Late-Life Depression: A Systematic Review of the Literature for Response, Pharmacokinetics and Adverse Drug Reactions

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ABSTRACT

Affecting up to 15% of older adults, late-life depression (LLD) is characterized by the occurrence of depressive symptoms after the age of 50–65 years and maybe pathophysiologically distinct from depression in younger adults. Therefore, LLD is challenging to treat, and predictive genetic testing might be essential to improve treatment in this vulnerable population. The current review aims to provide a summary of the literature exploring genetic associations with antidepressant treatment outcomes in late-life. We conducted a systematic search of three integrated electronic databases. We identified 29 articles investigating genetic associations with antidepressant treatment outcomes, pharmacokinetic parameters, and adverse drug reactions in older adults. Given the small number of investigations conducted in older adults, it is difficult to conclude the presence or absence of genetic associations with the outcomes of interest. In

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sum, the most substantial amount of evidence exists for the CYP2D6 *metabolizer status,* SLC6A4 *5-HTTLPR, and* BDNF *rs6265. These findings are consistent in the literature when not restricting to older adults, suggesting that similar treatment recommendations may be provided for older adults regarding genetic variation, such as those outlined for* CYP2D6 *by the Clinical Pharmacogenetics Implementation Consortium. Nonetheless, further studies are required in well-characterized samples, including genome-wide data, to validate if similar treatment adjustments are appropriate in older adults, given that there appear to be significant effects of genetic variation on antidepressant treatment factors.* (Am J Geriatr Psychiatry 2020; 28:609–629)

BACKGROUND

Affecting up to 15% of older adults, late-life depression (LLD) is characterized by depressive symptoms after the age of 50–65 years.[1,2] Notably, LLD is pathophysiologically distinct from depression in young adults, presenting with more medical comorbidities, polypharmacy, cognitive impairment, and cerebrovascular and neurodegenerative changes.[1] As such, the heterogeneity of LLD complicates the response to antidepressant treatment. More than 50% of patients fail to achieve remission and the risk of relapse. Consequently, treatment resistance is associated with progressive cognitive decline and 2–3 times increased risk for dementia.[3,4]

Variability in genes involved in pharmacokinetic (PK) and pharmacodynamic (PD) processes contribute to the observed heterogeneity in antidepressant response.[5] PK genes encode drug-metabolizing enzymes and transporters, most notably including the cytochrome P450 (CYP) family of enzymes, which accounts for the majority of Phase I oxidation of drugs and other xenobiotics making them a significant source of variability in drug response. Particularly, CYP enzymes 2D6 (CYP2D6), and 2C19 (CYP2C19) metabolize 50%–60% of all antidepressants and many antipsychotics.[5] Individuals can be classified into genotype-predicted metabolizer types based on genetic variation in CYP enzyme genes. As such, the resulting classifications include *extensive/normal metabolizers* (EMs) phenotypically presenting with normal CYP enzyme function, *intermediate metabolizers* (IMs) presenting with moderate enzyme function, *poor metabolizers* (PMs) presenting with little or no enzyme function, and *rapid or ultra metabolizers* displaying enhanced enzyme function.[6] Conversely, PD genes encode central or peripheral proteins, which may be the site of action for drug therapy. For antidepressants, polymorphisms in primarily targeted proteins including neurotransmitter transporters, such as the serotonin transporter (SLC6A4) and norepinephrine transporter (SLC6A2), as well as other neurotransmitter-system proteins (e.g., receptors, enzymes) may contribute to variability in treatment response.

Antidepressant treatment in older adults is particularly challenging, given the impact of ageing on PK and PD profiles. Aside from the presence of age-related pathophysiology and increased medical illness burden, physiological changes associated with the ageing process can affect drug metabolism and action in terms of drug absorption, distribution, bioavailability, and clearance.[7,8] In addition to age-related changes (e.g., weight, fat distribution, and renal function), polypharmacy may contribute to the variability observed in PK parameters.[9]

As healthy ageing increasing the presence of vulnerabilities within drug metabolism pathways, such as decreased renal clearance due to declining renal function,[10] pharmacogenetic variation may introduce compounding effects.[11] For example, in the case of decreased renal clearance, older adults who are poor metabolizers may experience a compounded increase in systemic exposure due to the two independent vulnerabilities. For CYP450 enzyme genes, the effects of age-genotype interactions on systemic exposure have been thoroughly reviewed.[11]

Although the genetic effects of the primary antidepressant-metabolizing enzymes (i.e., *CYP2D6* and CYP2C19) on PK parameters are substantial, there may be interactions with age that are not necessarily additive.[11] While PK variation increases with age, the effects of age are not a particular feature of older age

and do not vastly exceed the effects of age in studies, including younger adults.[11] For drugs strongly affected by genetic variation, ageing contributes, on average, a 1.5-fold increase in systemic exposure.[11]

More evidence-based, decision-support tools (e.g., pharmacogenetic tests) are becoming available to provide clinicians with pharmacogenetic information for selecting and adjusting dosages for psychotropic medications.[12] Such tools may be used to genetically guide treatment to establish the right medications or dosage for individuals (i.e., personalized medicine) as an alternative to standard, treatment-as-usual, which typically relies on a "trial-and-error" approach. However, many of these tools are based on investigations that most often do not include sufficient numbers of older adults to examine if genetic effects are comparable across the lifespan.[11] The current review aims to provide an update of the literature exploring genetic associations with antidepressant treatment outcomes, PK profiles and adverse drug reactions (ADRs) in older adults. In addition, we qualitatively evaluate these findings in the context of studies conducted in younger adults to understand if pharmacogenetic effects are age-dependent.

METHODS

We conducted a systematic search of three electronic databases integrated through OVID, including MEDLINE, PsycINFO, and EMBASE, using the search and selection strategy outlined in Supplementary Figure 1 and Table 1. We included studies which were[1] published in a peer-reviewed journal in English,[2] included human participants,[3] included adults ≥50 years of age, and[4] explored associations of genetic variants, whole genes or their gene products (e.g., transcripts, proteins) with antidepressant treatment response, plasma concentration levels of antidepressants and their metabolites, or any treatment-induced side effects. For treatment response and remission, we included definitions as specified by the reviewed articles and did not restrict to specific diagnostic or assessment tools. We excluded nonprimary research, as well as case reports.

Data extraction was conducted independently by VSM, FI, and MM. The authors used a standardized data extraction form to eliminate any discrepancies. Each author was assigned a subset of articles for primary extraction, as well as a subset of articles for secondary extraction to ensure no discrepancies between primary extractors. The third author resolved any disputes in study selection or data extraction. Lastly, to contextualize our findings, we tentatively summarized the levels of evidence for genetic associations in LLD based on the criteria outlined by PharmGKB, based on treatment outcomes, dosage, and pharmacokinetic parameters, as well as, ADRs.[13]

RESULTS

Overall, our search identified 30 articles which examined 20 unique samples (see Tables 1–3, and Supplementary Tables 2–3). A modest proportion (21%) of the studies included analyses of the *Mirtazapine versus Paroxetine Study Group* cohort.[14–19] The articles reviewed most prominently included various antidepressants including citalopram,[20–25] escitalopram,[23,26–28] fluoxetine,[29] mirtazapine,[14–19] nortriptyline,[29–31] paroxetine,[14–19,23,30,32–34] sertraline,[23,29,35] and venlafaxine.[28,36–39] We identified 23 articles that investigated treatment outcomes, including change in depressive symptomatology, response, and remission.[14,16–27,29,30,33–37,40–42] Ten identified articles investigated PK-related parameters, including plasma drug and metabolite concentration levels, as well as daily dosage.[14–16,21,28,30–32,37,43] Finally, eight of the articles identified investigated ADRs, medication discontinuation, treatment changes, and study withdrawal.[14,15,23,37–40,43] Most studies included a majority of individuals of European ancestry, however, one study included individuals of Korean ancestry,[29] and five studies failed to specify the ethnic ancestry of the sample.[25,30,34,37,41] Although we did not identify any genome-wide association studies, we identified two studies that included genome-wide expression data.[25,34]

PK Genes

P-glycoprotein (ABCB1)

P-glycoprotein is a transmembrane efflux pump encoded by the *ABCB1* gene involved in transporting various molecules across the blood-brain-barrier. Variations in *ABCB1* has been implicated in affecting

TABLE 1. Summary Articles Exploring the Association Between Genotypes and Treatment Response/Remission

Authors	Study Design	Age (Years)	Ethnicity Ancestry	Final *N*[a]	Duration (Weeks)	Treatment	Measure/Outcome Definition	Variants Assessed	Results
Candidate Gene									
Pollock et al., 2000	DB-RCT	≥60	-[b]	96	12	NOR (25 mg/d) PAR (20-30 mg/d)	**Response:** ≥50% ↓ HDRS-17	*SLC6A4* (5-HTTLPR)	- Week 12: no association in the whole sample. - PAR-treated S-allele carriers improved slower than L/L carriers ($F_{(12,446)} = 1.95$, $p = 0.0275$), - Week 2: PAR-treated L/L carriers had higher response rates and % Δ in HRSD score (52%; 49.3 ± 10%) than S-allele carriers (0%; 29.6 ± 5%; ($\chi^2 = 20.04$, $p < 0.0001$) - No association in the NOR group
Murphy et al., 2003a	PR	≥65	92% EUR	246	8 weeks	MIR (15-45 mg/d) PAR (20-40 mg/d)	**Response:** ≥50% ↓ HDRS-17 ≥50% ↓ CGI	*APOE* (rs429358, rs7412)	- Week 2: A significant interaction between treatment group and genotype (HDRS, $p = 0.036$; CGI, $p = 0.029$), showed that MIR-treated ε4-carriers had greater improvement but PAR-treated ε4-carriers showed less improvement - After week 2, ε4-carriers showed more improvement on GDS ($p = 0.025$), primarily in the MIR group ($p = 0.021$) but not the PAR group - MIR-treated ε4-carriers were more likely responders at week 2 and 4 ($p \leq 0.05$)
Durham et al., 2004	DB-RCT	≥60	95.4% EUR	206	8 weeks	SRT (50-100 mg/d) PLA	**Response:** ≥50% ↓ HRSD-17, CGI-I ≤ 2	*SLC6A4* (5-HTTLPR)	- SRT-treated L/L carriers showed greater response at weeks 1 and 2 ($p = 0.01$)
Murphy et al., 2004	DB-RCT	≥65	92% EUR	244	8 weeks	MIR (15-45 mg/d) PAR (20-40 mg/d)	Δ HDRS-17 Δ GDS	*SLC6A4* (5-HTTLPR)	- No association, but after adjusting for weight, PAR-treated S-allele carriers had higher GDS scores at week 1 ($F_{(1,210)} = 5.28$, $p = 0.02$) and week 4 ($F_{(1,175)} = 4.11$, $p = 0.04$)
Kim et al., 2006	PR	≥18[c]	100% Korean	241	6	NOR (35-100 mg/d) FLX (20-50 mg/d) SRT (50-100 mg/d)	**Response:** ≥50% ↓ HDRS-17	*SLC6A2* (rs5569)	- In the NRI-treated group, rs5569 was associated with response ($OR = 7.54$ [2.53, 22.49], $p < 0.001$): G/G responded better (83.3%) than G/A and A/A ($p = 0.01$) - G/G responded better to NRIs (83.3%) than SSRIs (58.7%; $OR = 3.52$ [1.39, 8.95], $p = 0.006$)
								SLC6A4 (5-HTTLPR, STin2-VNTR)	- In the NRI-treated group, 5-HTTLPR was associated with response ($OR = 3.73$ [1.32, 10.53], $p = 0.01$): S-allele carriers responded better (76%) than L/S (48%) and L/L (30%; $p = 0.003$) - In the SSRI-treated group, 5-HTTLPR was associated response ($OR = 3.34$ [1.41, 7.91], $p = 0.006$): S/S responded better (71%) that L/S (40%) and L/L (29%; $p = 0.003$). - In the SSRI-treated group, STin2 was associated with response ($OR = 20.11$ [4.27, 94.74], $p < 0.001$): L/L carriers responded better (69%) than other genotypes (9%; $p = 0.01$)
Whyte et al., 2006	PR	≥ 60	-[b]	46	12	VEN XR (37.5-300 mg/d)	Δ HRSD-17	CYP2D6 (*1, *3, *4, *6, *7, *8)	- No association.
Kondo et al., 2007	PR	≥60	100% EUR	236	18 months	Various antidepressants, ECT[b]	**Remission:** MADRS ≤5	*AGTR1* (rs5186)	- Association with time-to-remission ($HR = 0.37$ [0.15, 0.92], $p = 0.03$) - In those with late depression onset (≥ 50 years), C/C carriers reached remission faster ($HR = 0.26$ [0.07, 0.9], $p = 0.04$), with no effect in early onset

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TABLE 1. (*continued*)

Authors	Study Design	Age (Years)	Ethnicity Ancestry	Final *N*[a]	Duration (Weeks)	Treatment	Measure/Outcome Definition	Variants Assessed	Results
Lavretsky et al., 2008	DB-RCT	M = 71.4	87% EUR	15	10	CIT (20-60 mg/d) + PLA CIT + MPH (2.5-20 mg/d)	**Response:** HRSD-24 < 10	*SLC6A4* (5-HTTLPR)	- No association.
								SLC6A3 (VNTR)	- *SLC6A3* 10/10 carriers responded better over time (repeated-measures, $p = 0.01$) - Significant genotype × treatment interaction ($F_{(14,4)} = 8.7$, $p = 0.025$): 10/10 carriers responded better on MPH augmentation ($F_{(4,6)} = 4.6$, $p = 0.049$) showing greater % Δ in HRSD score (84%) compared to non-augmented individuals (50%; $F_{(1,9)} = 11.2$, $p < 0.01$)
Lotrich et al., 2008	PR	≥60	6%−13% AFR	110	12	Cohort 1: PAR (20-30 mg/d) Cohort 2: PAR (variable dosage)	Δ HRSD-17	*SLC6A4* (5-HTTLPR)	- Genotype interaction with early PAR exposure in association with Δ HRSD ($F_{18,59.5} = 1.8$, $p < 0.05$) - Early PAR exposure showed a larger effect in S/S carriers ($F_{(10,31.1)} = 6.3$, $p < 0.0005$) compared to L/S ($F_{(43,18.1)} = 4.6$, $p < 0.0005$) and L/L genotypes ($F_{(33,6.37)} = 4.3$, $p < 0.05$) - PAR concentration was correlated with Δ HRSD after 2 weeks in those with the S-allele ($r = 0.31$, $p < 0.05$)
Alexopoulos et al., 2009	PR	≥60	100% EUR	32	12 weeks	ESC (10 mg/d)	**Remission:** HRSD ≤7	*SLC6A4* (5-HTTLPR, rs25531)	- L/L showed a higher remission rater (89%) than S-allele carriers (44%; $p < 0.04$), and had lower HRSD scores ($t = 2.91$, $df = 25$, $p < 0.001$) - 5-HTTLPR-rs25531 L_A had a higher remission rate than S- and G- allele carriers ($p < 0.02$)
Alexopoulos et al., 2010	PR	≥60	100% EUR	32	12	ESC (10 mg/d)	**Remission:** HDRS ≤7	*BDNF* (rs6265)	- Met (A-allele) carriers had higher remission rate than Val/Val (G/G) carriers (65% vs. 40%) after adjusting for age of onset ($\chi^2 = 4.1$, df = 1, $p < 0.043$)
Sarginson et al., 2010a	DB-RCT	≥65	94% EUR	246	8	MIR (15-45 mg/d) PAR (20-40 mg/d)	**Response:** ≥50% ↓ HDRS-21 **Remission:** HDRS-21 <10	*FKBP5* (rs1360780, rs3800373)	- In the MIR group, rs3800373 A-allele carriers showed faster remission ($p = 0.04$), similar effects were observed for rs1360780 - For rs1360780, compared to non-responders, C/C genotypes were more frequently classified as responders (43% vs. 24%), than C/T (53% vs. 61%) and T/T genotypes (4% vs. 15%, $p = 0.046$) - No effects were observed in the PAR group.
Sarginson et al., 2010b	DB-RCT	≥65	92% EUR	246	8 weeks	MIR (15-45 mg/d) PAR (20-40 mg/d)	**Remission:** HDRS-21 <10	*ABCB1* (rs10245483, rs3213619, rs2214102, rs9282564, rs2235015, rs10276036, rs2229109, rs2235033, rs28381916, rs2235063, rs2235040, rs2032582, rs2032583, rs1045642, rs28381916)	- Prior to correction for multiple testing, in the PAR group, rs2032583 C-allele and rs2235040 A-allele carriers reached remision faster ($p < 0.05$). - There were no significant effects of genotype across time.
Taylor et al., 2011	PR	≥60	100% EUR	229	6 months	SSRIs (109) TCA[14] VEN[12] BUP[23] Other[14] Combination[18] Inadequate trial[17] ECT[22]	**Remission:** MADRS ≤6	*BDNF* rs6265	- No association at 3 months - No differences between genotypes in MADRS score at 6 months, but Met- (A) allele had a higher remission rate (49%) than Val/Val (G/G; 35%; $p = 0.05$) - At MADRS ≤ 3, Met-allele carriers had a higher remission rate (32.9%) than Val/Val (20.3%) only at 6 months ($p = 0.04$) - At MADRS ≤ 9, no association.
								SLC6A4 5-HTTLPR	- No association and no interaction with rs6265 in association with remission.

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TABLE 1. (*continued*)

Authors	Study Design	Age (Years)	Ethnicity Ancestry	Final *N*[a]	Duration (Weeks)	Treatment	Measure/Outcome Definition	Variants Assessed	Results
Zannas et al., 2012	PR	≥60	-[b]	212	12 months	Various, including Li and ECT	**Remission:** MADRS ≤ 6	*SLC6A4* (5-HTTLPR)	- After adjusting for covariates, negative baseline SLEs were associated with worse response in L/L carriers than S-allele carriers ($\chi 2 = 5.84$, $p = 0.02$) - Greater Δ negative stress was associated with lower remission, particularly in S-allele carriers ($\chi 2 = 7.52$, $p = 0.006$)
								COMT (rs4680)	- At 12 months, rs4680 A/A (Met/Met) had a higher remission rate than Val-allele carriers ($\chi 2 = 6.44$, $p = 0.04$)
Jamerson et al., 2013	CS	≥60	100% EUR	104	12	non-SSRIs SSRIs (i.e., PAR, CIT, FLX, ESC, SRT)	**Response:** MADRS 8−15	*BHMT* (rs3733890)	- No association.
								CBS (rs412810, rs1801181, rs4920037, rs234715, rs234783)	- No association.
								FOLR1 (rs2071010)	- No association.
								FOLR2 (rs2298444)	- No association.
								MTHFD1 (rs2236225)	- No association.
								MTHFR (rs1801131)	- In the SSRI-treated group, rs1801131 was associated with remission prior to correction ($p = 0.03$): A/C carriers were 2.5 times more likely to reach remission compared to those with the A/A genotype ($p = 0.01$).
								MTR (rs1805087)	- No association.
								MTRR (rs1801394)	- A/A carriers were 3.2 times more likely to reach remission than G/G carriers (p = 0.002)
								SHMT1 (rs1979277)	- No association.
								TCN2 (rs18011198)	- No association.
Murphy et al., 2013	DB-RCT	≥65	92% EUR	216	8	MIR (15-45 mg/d) PAR (20-40 mg/d)	Δ HRSD-21	*BDNF* (13 SNPs)	- In the PAR group, *BDNF* PC1 (mainly rs988712, rs11030086, rs6265, rs988748) was associated with HRSD Δ ($p < 0.001$; European subsample, $p < 0.001$) with minor-allele homozygotes showing worse response. However, in the MIR group, the effect for PC1 was nominal (p = 0.04).
								CREB1 (9 SNPs)	- In the PAR group, PC1 (mainly rs2253206, rs7569963, rs2551941) was nominally associated with HRSD Δ (p = 0.06; EUR only, p = 0.05), while PC2 was associated (mainly rs2551639, rs4234080, rs2194430; $p = 0.02$; EUR only, $p = 0.004$) - rs2551639 G-allele, rs4234088 C-allele, and rs2194430 G-allele carriers showed greater decrease in HRSD score
								CREBBP (11 SNPs)	- No associations.
								NTRK2 (20 SNPs)	- No associations.

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TABLE 1. (*continued*)

Authors	Study Design	Age (Years)	Ethnicity Ancestry	Final *N*[a]	Duration (Weeks)	Treatment	Measure/Outcome Definition	Variants Assessed	Results
Shiroma et al., 2014	PR	60−75, ≥55 age of onset	100% EUR	221	12	CIT (20-60 mg/d)	**Response:** ≥50% ↓ QIDS-CR_{16} **Remission:** QIDS-CR_{16} ≤5	*SLC6A4* (5-HTTLPR, rs25531, STin2)	- No association with rs25531 and STin2 - Stratifying by age of onset (≥ 56 years), 5-HTTLPR was associated with remission (p = 0.034) and response (p = 0.04): L/L had higher response (80% versus 44.4%; p = 0.05, adjusted p = 0.21), and remission rates (80% versus 43%; p = 0.03, adjusted p = 0.05) - 5-HTTLPR-rs25531 L_A/L_A had a trend higher remission rate (77%) than other genotypes (46%; $p = 0.09$) - 5-HTTLPR-rs25531 L_A allele and STin2 12-allele carriers had higher remission rates (65%) than other combination genotypes (20%; $p = 0.02$)
Seripa et al., 2015	PR	≥45−65[d]	100% EUR	234	6 months	ESC (10 mg/d) SRT (50 mg/d) PAR (20 mg/d) CIT (20 mg/d)	**Response:** ≥50% ↓ HDRS-21	*SLC6A4* (rs4795541, rs140701, rs3813034)	- *SLC6A4* rs4795541 (5-HTTLPR) S-allele carriers had a higher response rate than other genotypes (43.6% versus 32.1%, $p = 0.02$) - Under a dominant inheritance pattern, rs4795541 S-allele was associated with response ($OR = 1.83$ [1.04, 3.22], p = 0.04) with a dose effect ($OR = 1.53$ [1.03, 2.26], p = 0.03), as well as after adjusting for covariates ($OR = 2.17$ [1.14, 4.13], p = 0.02; dose effect ($OR = 1.74$ [1.12, 2.69], p = 0.01) - For Δ HDRS-21, rs4795541 was associated under a free ($p = 0.03$) and dominant ($p = 0.02$) model of inheritance - No associations with rs140701, rs3813034
Marshe et al., 2017	PR	≥ 60	88.9% EUR	350	12	VEN XR (37.5-300 mg/d)	**Remission:** MADRS ≤ 10	*HTR1A* (rs6295)	- No association.
								HTR1B (rs6296, rs130058, rs11568817)	- No association.
								HTR2A (rs9567746, rs2274639, rs6311)	- rs6311 associated with % Δ MADRS prior to correction for multiple testing ($p = 0.047$; EUR only, $p = 0.044$)
								HTR2C (rs6318, rs10521432, rs1801412, rs3813929, rs17260600, rs518147)	- No association.
								SLC6A2 (rs2242446, rs5569)	- rs2242446 C/C carriers had higher remission rate (73.1%) than C/T (51.8%) and T/T carriers (47.3%; OR = 1.66 [1.13, 2.42], $p = 0.009$) - rs2242446 was associated with change in MADRS score (partial eta squared = 0.03, $p = 0.006$; EUR only, $\eta^2 = 0.028$ $p = 0.013$), with C/C carriers reaching remission faster (Mantel-Cox $\chi^2 = 9.47$, $p = 0.009$; EUR only, $\chi^2 = 7.84$, $p = 0.02$)
								SLC6A4 (5-HTTLPR, rs25531, STin2-VNTR)	- No association.
								TPH1 (rs1800532)	- No association.
								TPH2 (rs11178998, rs11178997, rs4570625)	- No association.

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TABLE 1. (*continued*)

Authors	Study Design	Age (Years)	Ethnicity Ancestry	Final *N*[a]	Duration (Weeks)	Treatment	Measure/Outcome Definition	Variants Assessed	Results
Scutt et al., 2018	PR	≥80	89% EUR	19	4	CIT (20 mg/d)	**Remission:** GDS ≤ 11	*HTR1A* (rs6295)	- The final model for Δ GDS score included only rs6295, explaining 32% of variance ($p = 0.005$) - C/C responded better than G-allele carriers ($p = 0.02$) - At week 4, C/C had higher remission rates (71%) than C/G (0%) and G/G (50%; $p = 0.03$) - C/G were 1.79 times more likely to not remit versus C/C who were 1.9 times more likely remit
Genome-wide Eyre et al., 2016	DB-RCT	Remitters: M = 67.2 Non-Remitters:: 73.5 (9.3)	-[b]	35	16	CIT + PLA (20-60 mg) MPH + PLA (5-40 mg) CIT + MPH	**Remission:** HDRS-24 ≤ 6 **Early remission:** HDRS-24 ≤ 6 by week 4	Expression: genome-wide	- At baseline, 18 genes had higher expression in the early remitters versus non-remitter group ($p < 0.05$, fold-change > 2): HLA-DRB5, ALAS2 (PID:1230376), SELENBP1, CA1, AHSP, LOC100131164, SLC4A1, EPB42, C16orf35, FAM46C, HBD, MYL4, SNCA, SLC6A10P, ALAS2 (PID:4180768), RBM38, GMPR, RBM38 - There was no association between remission status and CA1/SNCA expression levels (relevant to antidepressant response) - 3 genes had higher expression in all remitters: HLA-DRB5 (FC = 6.53, $p = 0.02$), (SELENBP1; FC = 2.02, $p = 0.04$), LOC388588 (FC = 2.39, $p = 0.03$)
Eyre et al., 2017	PR, DB-RCT	VIL: 71.5 (7.2) PAR: 71.5 (7.7)	-[b]	56	16	VIL (10-40 mg/d) PAR (10-30 mg/d)	HDRS-24	Expression gene set 1: canonical proinflammatory gene transcripts (e. g., IL-1B, IL-6, IL-8, TNF) Expression gene set 2: 31 canonical innate antiviral transcripts (e. g., OAS1-3, MX1-2)	- Change in composite expression score of pro-inflammatory genes showed an association with HRSD score ($\beta = 0.14 \pm 0.06$ change in log2 RNA expression, $p = 0.04$), but no association with composite expression score of interferon-related genes (p = 0.80)

Abbreviations: 5-HTTLPR: serotonin-transporter-linked polymorphic region; ABCB1: ATP Binding Cassette Subfamily B Member 1; AFR: African-ancestry; AHSP: Alpha Hemoglobin Stabilizing Protein; APOE: apolipoprotein E; AGTR1: Angiotensin II Receptor Type 1; ALAS2: erythroid ALA-synthase; BDNF: brain-derived neurotrophic factor; BHMT: Betaine-Homocysteine S-Methyltransferase;BUP: bupropion; C16orf35, NPR3 Like, GATOR1 Complex Subunit; CA1: Carbonic Anhydrase 1; CBS: cystathionine beta-synthase; CGI: Clinical Global Impression Scale; CIT: citalopram; COMT: catechol-O-methyltransferase; CREB1: CAMP Responsive Element Binding Protein 1; CREBBP: CREB Binding Protein; CS: cross-sectional; CYP2D6: Cytochrome P450 2D6; DB-RCT: double-blind randomized controlled trial; EPB42: Erythrocyte Membrane Protein Band 4.2; ECT: electroconvulsive therapy; ESC: escitalopram; EUR: European-ancestry; FAM46C: Terminal Nucleotidyltransferase 5C; FKBP5: FK506 Binding Protein 5; FOLR1: Folate Receptor 1; FOLR2: Folate Receptor 2; FLX: fluoxetine; GDS: Geriatric Depression Rating Scale; GLM: Generalized linear model; GMPR: Guanosine Monophosphate Reductase; HBD: Hemoglobin subunit delta; HLA-DRB5: Major Histocompatibility Complex, Class II, DR Beta 5; HRSD: Hamilton Rating Scale for Depression; HTR1A: serotonin receptor 1A; HTR1B: serotonin receptor 1B; HTR2A: serotonin receptor 2A; HTR2C: serotonin receptor 2C; IL-1B: Interleukin 1 Beta; IL-6: Interleukin 6; IL-8: interleukin 8; Li: Lithium; MADRS: Montgomery-Asberg Depression Rating Scale; MIR: mirtazapine; MPH: methylphenidate; MTHFD1: Methylenetetrahydrofolate Dehydrogenase 1; MTHFR: methylenetetrahydrofolate reductase; MTR: methionine synthase; MTRR: Methionine synthase reductase; MX1-2: MX Dynamin Like GTPase; MYL4: Myosin Light Chain 4; NOR: nortriptyline; NRI: norepinephrine reuptake inhibitor; NTRK2: Neurotrophic Receptor Tyrosine Kinase 2; OAS1-3: 2′-5′-oligoadenylate synthetase 1; OR: odds ratio; PAR: paroxetine; PC: principal component; PLA: placebo; PR: prospective; QIDS-CR: Quick Inventory of Depressive Symptomatology - Clinician Rated; RBM38: RNA Binding Motif Protein 38; RNA: ribonucleic acid; SHMT1: Serine Hydroxymethyltransferase 1; SLC4A1: Anion Exchanger-1; SLC6A2: norepinephrine transporter; SLC6A3: dopamine transporter; SLC6A4: serotonin transporter; SLC6A10P: Solute Carrier Family 6 Member 10, Pseudogene; SELENBP1: Selenium Binding Protein 1; SLE: stressful life event; SNCA: alpha-synuclein; SRT; sertraline; SSRI: selective serotonin-reuptake inhibitor; STin2: Serotonin Transporter Intronic VNTR Enhancer; TCA: tricyclic antidepressant; TCN2: transcobalamin; TNF: tumor necrosis factor; TPH1: Tryptophan Hydroxylase 1; TPH2: Tryptophan Hydroxylase 1; VEN: venlafaxine; VIL: vilazodone; VNTR: variable number tandem repeat.

[a] The final sample size for which statistics are reported.

[b] Ethnic-ancestry of sample was not clearly specified in the methods.

[c] Only 77% of the sample included older adults; however, authors confirmed no statistical differences in genotype distributions between samples with early- and late- onset depression (age ≥60 years).

[d] The lowest of age of onset for inclusion was 45.

TABLE 2. Summary Articles Exploring the Association Between Genotypes and Plasma Drug/Metabolite Levels

Authors	Study Design	Age (Years)	Ethnicity Ancestry	Final N[a]	Duration (Weeks)	Treatment	Variants Assessed	Results
Pollock et al., 2000	DB-RCT	≥60	-[b]	96	12	NOR (25 mg/d) PAR (20-30 mg/d)	*SLC6A4* (5-HTTLPR)	- No association.
Murphy et al., 2001	PR	≥60	89% EUR	36	3	NOR (25-50 mg/d)	CYP2D6 (*1, *2, *10, *3, *4A, *5)	- Non-EMs had higher NOR concentration levels ($p < 0.02$) and concentration levels per unit dose ($t = 4.9$, $df = 34$, $p < 0.0001$) than EMs, but lower doses ($t = 3.4$, $df = 34$, $p < 0.002$). - The number of non-WT alleles was correlated with NOR concentration ($\rho = 0.46$, $p < 0.005$), dose ($\rho = -0.58$, $p < .001$) and concentration per unit dose ($\rho = 0.73$, $p < .0001$).
Murphy et al., 2003a	PR	≥65	92% EUR	246	8	MIR (15-45 mg/d) PAR (20-40 mg/d)	*APOE* (rs429358, rs7412)	- Mean PAR concentration levels were higher ε4-carriers ($M = 88.82 \pm 9.22$) than non-carriers ($M = 69.31 \pm 6.29$, $p = 0.012$)
Murphy et al., 2003b	DB-RCT	≥65	94% EUR	241	8	MIR (15-45 mg/d) PAR (20-40 mg/d)	*CYP2D6* (*1, *2, *3, *4A, *4D, *5, *6A, *6B, *9, *10B, *41, *1 × 2, *2 × 2)	- No associations with final dose, compliance or week 4 plasma levels.
Murphy et al., 2004	DB-RCT	≥65	92% EUR	244	8	MIR (15-45 mg/d) PAR (20-40 mg/d)	*SLC6A4* (5-HTTLPR)	- PAR-treated S/S had a lower final daily dose ($M = 23.19 \pm 11.26$) than L/S (30.74 ± 8.37, $F_{(1,221)} = 7.09$, $p = 0.008$) and L/L ($M = 32.08 \pm 8.62$, $F_{(1,221)} = 8.63$, $p = 0.004$) - PAR-treated S/S-carriers had lower plasma levels at day 28 ($M = 51.03 \pm 34.24$) than L/S ($M = 84.47 \pm 57.47$, $F_{(1,169)} = 4.30$, $p = 0.04$) and L/L carriers ($M = 72.55 \pm 47.41$, $F_{(1,169)} = 7.25$, $p = 0.008$) - PAR-treated S/S-carriers showed decreased dosing compliance than S/L ($F_{(1,221)} = 23.06$, $p = 0.001$) and L/L carriers ($F_{(1,221)} = 19.12$, $p = 0.001$) - MIR-treated L/L-carriers had lower final daily dosages ($M = 28.65 \pm 11.99$) compared L/S ($M = 30.23 \pm 10.51$, $F_{(1,221)} = 4.19$, $p = 0.04$) and S/S carriers ($M = 35.95 \pm 10.56$, $F_{(1,221)} = 7.17$, $p = 0.008$), but there were no differences in dosing compliance or plasma levels
Feng et al., 2006	PR	≥70	91% EUR	171	26	PAR (10-40 mg/d)	*CYP2D6* (*1, *5, *2, *4, *10, *17)	- *CYP2D6* metabolizer status improved PK model fit ($p < 0.005$) and estimated drug volume to be largest in UMs and smallest in PMs (UMs > EMs > IMs > PMs)
Whyte et al., 2006	PR	≥ 60	-[b]	46	12	VEN XR (37.5-300 mg/d)	CYP2D6 (*1, *3, *4, *6, *7, *8)	- *4-allele carriers had higher VEN ($M = 2.26 \pm 2.80$ vs. $M = 0.69 \pm 0.43$, $t = 3.26$, $df = 44$, $p = 0.002$) and ODV ($M = 1.74 \pm 1.19$ vs. $M = 2.52 \pm 1.27$, $t = 2.35$, $df = 44$, $p = 0.02$) concentration per unit dose than WT - The number of non-WT alleles showed a positive correlation with concentration per unit dose of VEN (Spearman's $\rho = 0.44$, $p = 0.002$) and ODV (Spearman's $\rho = 0.36$, $p = 0.013$)
Bijl et al., 2008	PR	≥ 55	100% EUR	1198	45 days	TCAs (68.3% AMI) SSRIs (46.8% PAR) MIR (34.3%)	*CYP2D6* (*1, *4)	- No association with mean dose. - TCA-treated PMs had lower mean doses than EMs on the 3rd and 4th prescriptions ($p = 0.03$), whereas SSRI-treated PMs only showed lower doses on the third prescription ($p = 0.02$) - TCA-treated PMs were more likely to switch medications ($OR = 5.77$ [1.59, 21.03], $p = 0.01$), but showed no difference in drug ratio or dose compared to EMs
Lavretsky et al., 2008	DB-RCT	$M = 71.4$	87% EUR	15	10	CIT (20-60 mg/d) + PLA CIT + MPH (2.5-20 mg/d)	*SLC6A4* 5-HTTLPR	- No associations with plasma levels or dose.
							SLC6A3 VNTR	- No associations with plasma levels or dose.

(*continued on next page*)

TABLE 2. (*continued*)

Authors	Study Design	Age (Years)	Ethnicity Ancestry	Final N[a]	Duration (Weeks)	Treatment	Variants Assessed	Results
Waade et al., 2014	RR	*16–95*[c]	-[b]	796	-	ESC (2.5–120 mg/d) VEN (8.75–900 mg/d)	*CYP2C19* (*2, *3,*4) *CYP2D6* (*3, *4, *5, *6)	- Among PMs, individuals >65 years had 1.4-fold non-significantly higher mean ESC concentration-dose ratio compared to <40 years ($p = 0.1$); however, in other metabolizer groups, a similar ratio was significant ($p < 0.02$) - No significant differences in above-recommended ESC serum concentrations across age-groups in PMs - Compared to younger individuals (<40 years), PMs >65 years showed an 8-fold higher VEN concentration-dose ratio ($M = 2.4$ [1.6, 3.7] vs. 18.8 [9.4, 37.6] nmol/L/mg/day, $p < 0.001$) - Older individuals showed 1.5-fold higher VEN+ODV concentration-dose ratios of in older individuals as compared to younger EMs and IMs ($p < 0.01$) - In VEN-treated PMs, all individuals >65 years ($n = 3$) had above-recommended serum concentrations compared to those <40 years (25%) and those aged 40–65 years (40%)

Abbreviations: 5-HTTLPR: serotonin-transporter-linked polymorphic region; AMI: amitriptyline; APOE: apolipoprotein E; CIT: citalopram; CYP2D6: Cytochrome P450 2D6; DB-RCT: double-blind randomized controlled trial; EM: extensive metabolizer; ESC: escitalopram; EUR: European-ancestry; FLX: fluoxetine; IM: intermediate metabolizer; MIR: mirtazapine; MPH: methylphenidate; NOR: nortriptyline; ODV: o-desmethylvenlafaxine; OR: odds ratio; PAR: paroxetine; PLA: placebo; PM: poor metabolizer; PR: prospective; RR: retrospective; SLC6A3: dopamine transporter; SLC6A4: serotonin transporter; SSRI: selective serotonin-reuptake inhibitor; TCA: tricyclic antidepressant; UM: ultra-rapid metabolizer; VEN: venlafaxine; VIL: vilazodone; VNTR: variable number tandem repeat.

[a] The final sample size for which statistics are reported.

[b] Not clearly specified in the methods.

[c] Only 16% (n = 127) of individuals were aged >65 years.

transporter activity and expression, which may regulate the concentration of some antidepressants in the brain.[18] We identified one study investigating *ABCB1* gene variants in older adults (see Table 1).[18] Within *ABCB1*, rs2032583 C-allele and rs2235040 A-allele achieved remission with paroxetine faster than carriers of alternative alleles. There was no impact of *ABCB1* genotypes on trajectories of depressive symptoms.[18]

CYP2C19

Amongst the CYP450 metabolizing liver enzymes, CYP2C19 is a major metabolizer of several antidepressants, including citalopram, escitalopram, and several tricyclics. We identified one study which investigated the effects of CYP2C19 variation on antidepressant plasma levels.[28] *CYP2C19* PMs in older than 65 years of age have been shown to have 1.4-fold nonsignificantly higher mean escitalopram concentration-dose ratios compared to individuals less than 40 years. However, amongst other metabolizer groups, a similar degree of difference in the concentration-dose ratio was found to be significant between older and younger adults ($p < 0.02$). Despite higher concentration-dose ratios, there were no differences in the proportion of individuals with above-recommended escitalopram serum concentrations across age-groups in PMs.

CYP2D6

We identified five studies investigating the effects of *CYP2D6* variation on our outcomes of interest,[15,31,32,37,43] see Table 2. There is no evidence for the association of *CYP2D6* metabolizer status with changes in depressive symptoms after treatment in older adults.[37] However, there is limited evidence that *CYP2D6* metabolizer status may affect daily dosage.[31,43] In the mirtazapine- and paroxetine-treated cohort, there were no associations with metabolizer status and daily dosages.[15] While one study found that non-EMs (i.e., IMs, PMs) had lower final daily nortriptyline doses than EMs,[31] another showed that there were no differences between genotypes in tricyclic antidepressant dose.[43] However, when considering the number of previously-failed antidepressant treatments, PMs treated with tricyclic antidepressants had lower doses than EMs on the third and fourth

TABLE 3. Summary Articles Exploring the Associations Between Genotypes and Adverse Events

Authors	Study design	Age (years)	Ethnicity ancestry	Final N[a]	Duration (weeks)	Treatment	Variants Assessed	Results
Murphy et al., 2003b	DB-RCT	≥65	94% EUR	241	8	MIR (15-45 mg/d) PAR (20-40 mg/d)	*CYP2D6* *1, *2, *3, *4A, *4D, *5, *6A, *6B, *9, *10B, *41, *1 × 2, *2 × 2	- No associated with severity of ADRs, discontinuations, final dose, compliance or week 4 plasma levels
							HTR2A rs6313	- PAR-treated C/C-carriers had more discontinuations due to ADRs than T/C and T/T (46% vs. 16%) over time ($\chi^2 = 12.8$, $df = 1$, $p = 0.001$) and across all time points ($p = 0.025$ to 0.009), as well as more severe side effects ($F_{(1,179)} = 4.61$, $p = 0.03$)
Murphy et al., 2004	DB-RCT	≥ 65	92% EUR	244	8	MIR (15-45 mg/d) PAR (20-40 mg/d)	HTR2A rs6313	- In the PAR-treated group, rs6313 ($HR = 3.03$, $\chi^2 = 9.14$, $p = 0.003$) was associated with discontinuations due to ADRs
							SLC6A4 (5-HTTLPR)	- Overall, S/S carriers showed more severe ADRs than L/L carriers ($F_{(1,201)} = 5.52$, $p = 0.02$), particularly gastrointestinal issues, fatigue, agitation, sweating, and dizziness - PAR-treated S/L carriers were more likely to discontinue treatment than L/L carriers ($p < 0.05$) - In the PAR-treated group, 5-HTTLPR ($HR = 2.62$, $\chi^2 = 6.69$, $p = 0.01$) was associated with discontinuations due to ADRs - MIR-treated L/L carriers had more severe ADRs across time ($F_{(1,201)} = 5.18$, $p = 0.02$) particularly drowsiness, dizziness, and anxiety
Whyte et al., 2006	PR	≥ 60	-[b]	46	12	VEN (37.5-300 mg/d)	CYP2D6 (*1, *3, *4, *6, *7, *8)	- No association with UKU score at week 4 or Δ UKU, before or after controlling for plasma levels - *4-allele carriers showed nominally higher side effects related to skin, sexual function, and breast tissue (Wilcoxon Exact, $p = 0.08$) - No associations with the onset of new hypertension, orthostatic hypotension, or increased QTc interval - No associations with study withdrawal
Bijl et al., 2008	PR	≥ 55	100% EUR	1198	45 days	TCAs (68.3% AMI) SSRIs (46.8% PAR) MIR (34.3%)	*CYP2D6* (*1, *4)	- TCA-treated PMs were more likely to switch medications than EMs ($OR = 5.77$ [1.59, 21.03], $p = 0.01$) - No association with medication discontinuation.
Taylor et al., 2011	PR	≥ 60	100% EUR	229	6 months	SSRI (109) TCA[14] VEN[12] BUP[23] Other[71]	*BDNF* (rs6265)	- No association with change in treatment or treatment selection
Garfield et al., 2014	PR	≥ 60	100% EUR	69	12	VEN (37.5-150 mg/d)	*HTR1B* (rs11568817)	- rs11568817 G-allele carriers showed a greater decrease in P1NP levels ($\Delta M = -4.9 \pm 13.0$, $p = 0.04$) compared to non-carriers ($\Delta M = 1.6 \pm 18.4$, $p = 0.30$) - No associations with β-CTX levels.
							SLC6A4 (5-HTTLPR, rs25531)	- 5-HTTLPR-rs25531 L_A-allele carriers showed a greater decrease in P1NP ($\Delta M = -4.1 \pm 15.7$, $p = 0.02$) than non-carriers ($\Delta M = 0.2 \pm 19.8$, $p = 0.74$) - No associations with β-CTX levels.
Seripa et al., 2015	PR	≥65	100% EUR	234	6 months	ESC (10 mg/d) SRT (50 mg/d) PAR (20 mg/d) CIT (20 mg/d)	*SLC6A4* (5-HTTLPR, rs140701, rs3813034	- There were no differences between genotypes in terms of side effects or drop-outs due to ADRs.
Rawson et al., 2017	PR	≥ 60	91.7% EUR	168	12	VEN (37.5-300 mg/d)	*SLC6A4* (5-HTTLPR, rs25531) *HTR1B* (rs11568817)	- For β-CTX, rs11568817 T/T carriers showed no change in levels while G-allele carriers showed an increase at the end of treatment ($M = 0.08 \pm 0.31$ pg/mL, $p = 0.013$) - For P1NP, rs11568817 T/T carriers showed a greater decrease in levels ($\Delta M = -0.09 \pm 0.24$ μg/L, $p = 0.018$) compared to G-allele carriers ($\Delta M = -0.04 \pm 0.23$ μg/L, $p = 0.07$) - 5-HTTLPR-rs25531 L_A-allele carriers showed an increase in β-CTX ($\Delta M = 0.06 \pm 0.31$ pg/mL, $p = 0.034$) and decrease in P1NP ($\Delta M = -0.07 \pm 0.21$ μg/L, $p = 0.001$) levels, while non-carriers showed no change

Abbreviations: 5-HTTLPR: serotonin-transporter-linked polymorphic region; ADR: adverse drug reaction; AMI: amitriptyline; β-CTX: β-isomerized C-terminal telopeptides; BUP: bupropion; CIT: citalopram; CYP2D6: Cytochrome P450 2D6; DBRCT: double-blind randomized controlled trial; EM: extensive metabolizer; ESC: escitalopram; EUR: European-ancestry; FLX: fluoxetine; HTR1B: serotonin receptor 1B; HTR2A: serotonin receptor 2A; MIR: mirtazapine; NOR: nortriptyline; OR: odds ratio; P1NP: total procollagen type 1 N-terminal propeptide; PAR: paroxetine; PM: poor metabolizer; PR: prospective; SLC6A4: serotonin transporter; SSRI: selective serotonin-reuptake inhibitor; TCA: tricyclic antidepressant; VEN: venlafaxine.

[a] The final sample size for which statistics are reported.

[b] Not clearly specified in the methods.

prescriptions, as well as lower doses on the third prescription when treated with selective serotonin reuptake inhibitors (SSRIs).[31,43]

There appears to be modest evidence for the association between CYP2D6 metabolizer status and plasma drug or metabolite concentration levels in older adults on antidepressant monotherapy.[31,32,37] Compared to EMs, non-EMs show higher mean nortriptyline[31] and venlafaxine concentration levels, as well as lower venlafaxine metabolite levels (i.e., o-desmethylvenlafaxine).[37] In terms of statistical PK modelling, which is the exploration of the statistical relationship between drug plasma levels, time and biological parameters, the inclusion of *CYP2D6* metabolizer status not only improved model fit for estimated plasma concentration but also confirmed that plasma volumes are the smallest in PMs.[32] However, one study failed to observe any associations between *CYP2D6* metabolizer status and either mirtazapine or paroxetine plasma levels.[15]

In addition to the effects of CYP2D6 metabolizer status on plasma levels, there appears to be an interaction effect with increasing age. Compared to younger individuals (<40 years), *CYP2D6* PMs show an eightfold higher venlafaxine concentration-dose ratio.[28] Similarly, older (>65 years) EMs and IMs show a 1.5-fold higher venlafaxine and o-desmethylvenlafaxine concentration-dose ratio.[28] While all older venlafaxine-treated PMs were found to have above-recommended serum concentrations, only 25% and 40% of those older than 40 years and those aged 40−65 years had above-recommended serum concentrations, respectively.[28] Therefore, the CYP2D6 metabolizer status mediates the age-related effects on venlafaxine exposure.

However, there is little evidence to suggest that CYP2D6 metabolizer status is associated with ADRs or medication discontinuation.[44] PMs were more likely to switch medications than EMs when treated with tricyclic antidepressants, but not SSRIs.[43] There were no differences between PMs and EMs in terms of medication discontinuation[43] or the severity of ADRs.[15,37] However, non-EMs showed nominally higher ADRs relating to the skin, sexual function, and breast tissue.[37]

PD Genes

Brain-derived neurotrophic factor gene

Three reviewed studies explored variants in the brain-derived neurotrophic factor gene (*BDNF*), which has been implicated in neurotransmitter signalling pathways, neurogenesis, and synaptic plasticity.[45] The *BDNF* rs6265 variant (Val66Met) is a functional polymorphism, including the G-allele (Val) which results in higher BDNF expression as compared to the A-allele (Met), which can impact neuronal development and plasticity.[46] In a cohort of older adults treated with escitalopram, rs6265 Val/Val homozygotes showed significantly lower rates of remission (40%) than Met carriers (65%); however, these results were not replicated in a larger cohort treated with various antidepressants, see Table 1.[27,40] When principal components were investigated, the genetic component composed of mainly *BDNF* rs988712, rs11030086, rs6265, and rs988748 was associated with changes in depressive severity following paroxetine, but not mirtazapine treatment.[17]

Cardiovascular-related pathway genes

The angiotensin II receptor type 1 (*AGTR1*) is an essential regulator of blood pressure within the cardiovascular system.[47] When stratifying by the age of major depressive disorder (MDD) onset (≥50 years), individuals with the *AGTR1* rs5186 C/C genotype have been shown to reach remission 2.7 times faster than those with either the A/C or A/A genotypes; however, no effect was observed in those with onset of depression prior 50 years.[20] Another cardiovascular gene is the apolipoprotein E (*APOE*) gene, which encodes a low-density lipoprotein involved in cholesterol transport. The *APOE* gene contributes to the strongest-known genetic risk for late-onset Alzheimer's disease.[48] In *APOE*, the most studied polymorphism is indicated by the combination of genotypes at rs429358 and rs7412 which results in a tri-allelic polymorphism (i.e., ε2, ε3, and ε4), of which ε4-allele carriers are at 2−3 times increased risk for Alzheimer's disease compared to ε3 carriers.[48] In the mirtazapine- and paroxetine-treated cohort, after 2 weeks of treatment, mirtazapine-treated ε4-carriers showed a greater improvement, but paroxetine-treated ε4-carriers showed less improvement.[14] In addition, mirtazapine-treated ε4-allele carriers were more likely to be responders.[14]

Catechol-o-methyltransferase

Catechol-o-methyltransferase (*COMT*) is a commonly-investigated catalyst in the metabolic pathway

of catecholamine neurotransmitters, including norepinephrine and dopamine.[49] The *COMT* rs4680 (Val158-Met) variant is a functional polymorphism in which the A-allele (Met) results in lower expression levels of *COMT* as compared to the G-allele (Val). In a cohort treated with various antidepressants, nonremitters showed an under-representation of rs4680 A/A (Met/Met) genotypes, suggesting that higher expression of *COMT* may be associated with nonremission.[41]

FK506 binding protein 5

The FK506 binding protein 5 (FKBP5) protein is a trafficking chaperone involved in regulating the glucocorticoid receptor, thereby playing a crucial role within the hypothalamic-adrenal-pituitary axis.[50] Only one study has investigated the association of *FKBP5* variants in older adults with LLD. While no associations were observed in paroxetine-treated individuals, mirtazapine-treated older adults with the rs1360780 C/C genotype were significantly more likely to be responders (43% versus 24%), than C/T (53% versus 61%) and T/T genotypes (4% versus 15%).[19]

Folate pathway genes

One study investigated variants in 10 genes of the folate-metabolism system, including methylenetetrahydrofolate reductase (*MTHFR*), methionine synthase (*MTR*), methionine synthase reductase (*MTRR*), betaine homocysteine methyltransferase (*BHMT*), folate receptor 1 (*FOLR1*), folate receptor 2 (*FOLR2*), methylenetetrahydrofolate dehydrogenase 1 (*MTHFD1*), serine hydroxymethyltransferase 1 (*SHMT1*), cystathionine-beta-synthase (CBS), and transcobalamin II (TCN2). Individuals with the *MTRR* rs1801394 A/A genotype were 3.2 times significantly more likely to reach remission versus those with the G/G genotype. In individuals taking SSRIs, *MTHFR* rs1801131 was associated with remission before correction for multiple testing, with carriers of the A/C genotype being 2.5 times more likely to reach remission compared to those with the A/A genotype.[42]

Serotonin receptor and tryptophan hydroxylase genes

Various serotonin receptors, particularly HTR1A, HTR1B, HTR2A, and HTR2B, have been implicated not only in the etiology of depression but also with antidepressant response.[51,52] Our search identified six studies investigating variants across serotonin receptor genes, including *HTR1A, HTR1B, HTR2A*, and *HTR2C*.[15,16,22,36,38,39] While in a small citalopram-treated cohort, *HTR1A* rs6295 C/C homozygotes showed a higher remission rate than G-allele carriers,[22] in a larger cohort treated with venlafaxine, no associations were observed.[36] One study showed an association of *HTR2A* rs6311 and remission, but not *HTR1B, HTR2C* or tryptophan hydroxylases, which are involved in the metabolic pathway of serotonin.[36]

Overall, there is modest evidence that serotonergic receptors are associated with side effects in older adults.[15,16,38,39] For example, *HTR2A* rs6313 was significantly associated with discontinuations due to ADRs in individuals treated with paroxetine,[16] with C/C genotypes showing more severe ADRs and discontinuations compared to T-allele carriers; however, no such association were observed in mirtazapine-treated individuals.[15] In venlafaxine-treated cohorts, the *HTR1B* rs11568817 has been explored with bone-related side effects[38,39] including reduced bone formation and increased bone resorption as measured by levels of procollagen type I N-propeptide (P1NP) and C-terminal cross-linking telopeptide of type 1 collagen (β-CTX), respectively. While both cohorts showed a significant association of rs11568817 with bone formation marker levels, one study found that the G-allele was associated with a greater decrease in bone formation[38] while the other study showed the opposite association of the T-allele.[39] For bone resorption, G-allele carriers showed increased β-CTX levels post-treatment,[39] while a previous study showed no association.[38]

Norepinephrine transporter

The norepinephrine transporter (*SLC6A2*) is a direct target of many antidepressants, including norepinephrine reuptake inhibitors (NRIs) such as bupropion and tricyclics such as nortriptyline, and dual serotonin-norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine. We identified two studies investigating variants in *SLC6A2*.[29,36] In a Korean cohort treated with nortriptyline, fluoxetine, and sertraline, *SLC6A2* rs5569 was associated with response in those treated with NRIs but not SSRIs. Specifically, G/G carriers showing a higher response rate (83.3%)

compared to G/A and A/A genotypes.[29] Individuals carrying the G/G genotype demonstrated significantly higher response rates (83.3%) to NRI treatment compared to SSRI treatment (58.7%). In another cohort treated with venlafaxine, no associations were observed with rs5569.[36] However, individuals with the rs2242446 C/C genotype showed higher remission rates (73.1%) than those with C/T (51.8%) or T/T genotypes (47.3%). In addition, rs2242446 was associated with a change in depressive severity and time-to remission.[36]

Dopamine transporter

Several antidepressants have known interactions with the dopamine transporter (*SLC6A3*), such as bupropion. Only one study has investigated associations between *SLC6A3* and treatment response.[21] In a cohort treated with citalopram and methylphenidate augmentation, those with SLC6A3 40-bp variable number tandem repeat (VNTR) 10/10 genotype displayed a greater decline in depressive severity over time and responded better to methylphenidate augmentation.[21] However, the study reported no evidence of the *SLC6A3* VNTR affecting daily dosage or plasma levels for citalopram or methylphenidate.[21]

Neurotrophic pathway genes

Neurotrophic receptor tyrosine kinase 2 (NTRK2) binds BDNF and is a key regulator of the mitogen-activated protein kinases pathway, which has been extensively implicated in neuroplasticity and depression.[53] As a result of this binding, there is the phosphorylation of the transcription factor cAMP-responsive element-binding protein 1 (CREB-1). CREB-1 requires the co-activating transcriptional factor CREB binding protein (CREBBP). No associations of *NTRK2* or *CREBBP* gene variants and treatment outcomes have been observed in individuals treated with mirtazapine or paroxetine.[17] However, a primary genetic principal component from *CREB1,* including substantial contributions from rs2253206, rs7569963, and rs2551941, showed a trend toward association with change in depressive symptomatology in Europeans, while the second principal component (mainly rs2551639, rs4234080, rs2194430) showed a significant effect.[17] Individuals carrying *CREB1* rs2551639 G-allele, rs4234088 C-allele, and rs2194430 G-allele showed a more considerable improvement in depressive symptomatology.[17]

Serotonin transporter

The serotonin transporter (SLC6A4) regulates serotonergic neurotransmission, which is a direct target for most antidepressants, particularly SSRIs (e.g., citalopram).[54] We identified 13 studies investigating the association between *SLC6A4* variants and treatment outcomes,[16,23,24,26,29,30,33,35,36,41] PK parameters,[16,21,30] and ADRs.[16,23,38,39] 5-HTTLPR is a polymorphic region in the *SLC6A4* promoter consisting of short (S) and long (L) repeats.[55] The 5-HTTLPR L-allele produces a higher expression of the *SLC6A4* gene compared to the S-allele and has been generally associated with the risk of depression, particularly modulated by stressful life events.[56–58] In combination with rs25531 (A and G alleles), 5-HTTLPR-rs25531 L_A genotypes are associated with higher expression, while S and G alleles are associated with lower expression.[59]

We identified seven studies investigating the 5-HTTLPR and rs25531, which provide mixed evidence for association.[16,21,26,29,30,35,36] The majority of studies have shown that the L/L genotype is associated with better treatment outcomes in individuals treated with SSRIs, including change in depressive symptoms, response, and remission.[16,26,30,35] However, in a Korean cohort, in both NRI- and SSRI-treated individuals, the opposite was found showing S-allele carriers having significantly higher response rates (71%–76%) compared to L/S (40%–48%) and L/L (29%–30%) genotypes.[29] This was supported in a cohort treated with various antidepressants in which responders were more likely to carry the 5-HTTLPR S-allele (44% versus 32%) after adjusting for covariates.[23] Two other studies failed to observe any association.[21,36] The effects of the 5-HTTLPR on treatment outcome may be mediated by several factors, including the presence of early drug exposure (i.e., within the first 2 weeks), negative life stress, and age of depression onset.[24,33,41] Specifically, in S-allele carriers, lower early drug exposure (i.e., at 2 weeks), a higher number of stressful life events, and a later age of onset (≥56 years) may be associated with a smaller change in depressive symptomatology and worse treatment response.[24,33,41]

There is mixed evidence for the association of 5-HTTLPR with dosage and plasma levels. While the

S/S genotype has been associated with a lower daily dose of paroxetine, conversely, the L/L genotype has been associated with a lower dose of mirtazapine.[16] Another study failed to show any association in individuals treated with citalopram and methylphenidate.[21] For plasma concentration levels, while one study showed that those with the S/S genotype had lower plasma paroxetine levels after 4 weeks compared to L/L and S/L genotypes,[16] no such associations have been observed in those treated with mirtazapine or nortriptyline.[16,30]

The *SLC6A4* 5-HTTLPR is also the most frequently investigated gene in association with antidepressant side effects in older adults.[16,23,38,39] While one study observed that paroxetine-treated individuals with the S/S genotype and mirtazapine-treated individuals with the L/L genotype reported more severe ADRs, another SSRI study failed to show an association.[23] For bone-related side effects, carriers of the combined 5-HTTLPR-rs25531 high-functionality allele (L_A) showed a greater decrease in bone formation markers (i.e., P1NP) compared to noncarriers.[38,39] While one study showed that that high-functionality allele might also increase bone resorption markers (i.e., β-CTX),[39] another failed to show an association.[38] In terms of study discontinuation due to ADRs, in paroxetine-treated individuals, the 5-HTTLPR was significantly associated with discontinuation due to ADRs, with S/L carriers being more likely to discontinue.[15] However, in another cohort treated with SSRIs, no associations were observed between 5-HTTLPR or other *SLC6A4* variants (rs140701, rs3813034) with study withdrawal due to ADRs.[23]

The *SLC6A4* second intron STin2 polymorphism is a VNTR region located in intron 2 consisting of three alleles (9,10, or 12 repeats). In a Korean cohort, while STin2 showed no association with response in NRI-treated individuals, carriers of the 12-repeat allele showed a higher response rate (69%) compared to other genotypes (9%) in the SSRI-treated subgroup.[29] However, two studies in European cohorts failed to show the main effects of STin2 on treatment outcomes.[24,36] In the Korean cohort, individuals carrying STin2 12/12 and 5-HTTLPR S/S genotypes showed higher response rates to SSRIs (77.4%) compared to other combination genotypes (0−54.3%).[29] Similar effects were observed in a European cohort treated with citalopram, with those carrying the 5-HTTLPR-rs25532 L_A allele and the STin2 12 allele showing higher remission (65%) compared to other combination genotypes (20%).[24]

Genome-Wide Associations

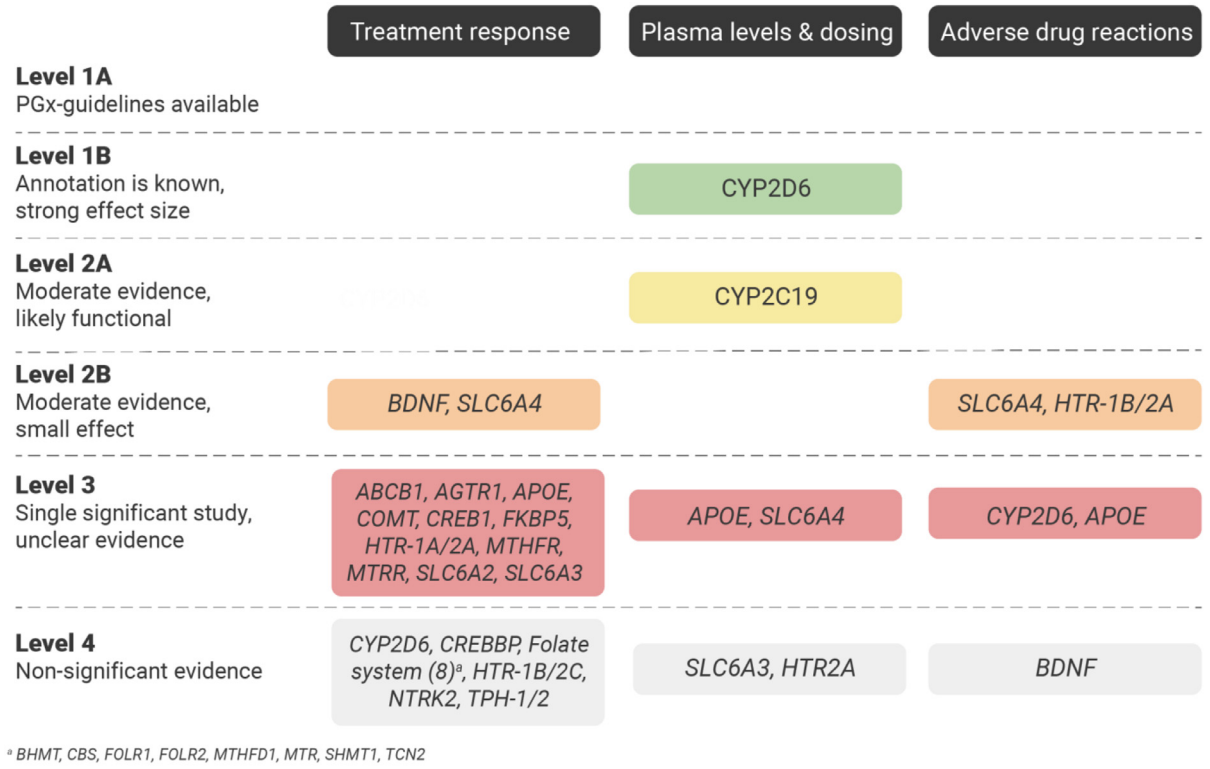
To date, there have been no genome-wide association studies conducted in older adults for antidepressant treatment outcomes. However, we identified two transcriptome studies that investigated associations with treatment outcomes.[25,34] In a hypothesis-free study, 18 genes showed higher expression in early remitters (before week 4) from a cohort treated with citalopram and methylphenidate augmentation, including the major histocompatibility complex class II DR beta 5 (*HLA-DRB5*), the selenium-binding protein (*SELENBP1*), and LOC388588.[25] A hypothesis-driven study of proinflammatory and innate antiviral gene pathways in a cohort treated with vilazodone or paroxetine, a composite score for proinflammatory gene expression was positively associated with a change in depressive symptomatology; however, there was no association with type-I interferon-related gene expression.[34]

DISCUSSION

In this review, we have summarized the pharmacogenetic studies of antidepressants in older adults and clinical levels of evidence (see Fig. 1) Based on PharmGKB levels of evidence,[13] CYP2D6 metabolizer status shows the strongest level of evidence with dosage and PK parameters (Level 2A), but not treatment response in older adults. Two studies showed that individuals with reduced or null function alleles showed lower doses than EMs but higher plasma levels,[31,43] which is consistent with findings in younger adults. The *Clinical Pharmacogenetics Implementation Consortium* provides dosing recommendations based on *CYP2D6* and *CYP2C19* genotypes for tricyclic and SSRI antidepressants in adults.[60,61] Further studies are required to validate if similar treatment adjustments may be appropriate in older adults.

The largest amount of evidence exists for the *SLC6A4* 5-HTTLPR, showing that there is a modest association (Level 1B) with symptom improvement. Individuals with the L/L homozygous genotype tend to respond to antidepressant treatment better than S-allele carriers, which is consistent with the literature

FIGURE 1. Levels of evidence for gene associations with treatment response, pharmacokinetic parameters (PK) and adverse drug reactions (ADRs) in older adults with depression as defined by PharmGKB. ***Note.*** **Genetic analyses were not conducted assuming that these genes are directly involved in drug metabolism, but to assess their indirect influence on plasma levels by way of the level of medication adherence, side effects, and response.**



in all adults.[62] While *BDNF* rs6265 shows a modest level of association (Level 2B), in older adults, carriers of the Met (A) allele showed better remission, suggesting that lower expression of BDNF may be beneficial for treatment outcomes in older adults.[27] These findings are inconsistent with a meta-analysis of studies in all adults in which individuals with the Val/Met respond better than those with either then Val/Val and Met/Met (odds ratio: 1.26 [1.07, 1.48]).[63]

Limitations of the Literature

During our review, we identified several limitations which impact our ability to synthesize evidence across studies (e.g., conduct a meta-analysis), as well as to evaluate the quality of evidence. We encountered issues related to the quality of phenotyping, definition of LLD, population stratification, the inclusion of covariates, and statistical considerations. Of note, all the identified studies were retrospective, and none assessed the utility of using pharmacogenetic information to guide treatment in older adults.

The main limitation of this review is related to the issue of defining clinical response or remission, which is a primary challenge in psychiatry that can severely affect the quality of genetic association studies. Across the studies reviewed, several measures of depressive severity were used including the Montgomery-Åsberg Depression Rating Scale (MADRS), the 17-, 21- or 24-item Hamilton Rating Scale for Depression (HRSD), Clinical Global Impressions Scale, Geriatric Depression Scale and the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated ($QIDS\text{-}CR_{16}$).[64–68] While response was consistently defined as a higher than or equal to 50% reduction in depressive severity by the end of

treatment, various definitions of remission were used regardless of the questionnaire, with only a minority of studies adhering to the generally-accepted thresholds for remission on the MADRS and HRSD (MADRS <10, HRSD ≤7).[69,70] Although there is a debate surround which thresholds are optimal for defining remission,[71,72] the variable definitions of phenotypes across studies ultimately impact the commensurability and the potential for replication.

Another limitation of the included studies is the lack of investigation of the age of MDD onset as a mediator. Without a specified age of onset, it is unclear whether these studies reflect associations in individuals with first-onset MDD in late-life or only older adults with MDD which may have been present from an earlier point in their life. Of the studies reviewed, two studies used later-age of onset as an exclusion criteria,[23,24] whereas other studies investigated age-of-onset as a covariate[20,26,27,29,36,40,42] or did not specify it as a variable of interest.[14–19,21,22,25,30–35,37–39,41,43] In addition, the studies reviewed use several age cutoffs to define LLD, with ages ranging from 45 to 65 (see Tables 1–3). While age-of-onset for MDD may not affect current biological processes regulating drug plasma concentration levels or the presence of ADRs, it may have an impact on treatment outcomes, such as response.[73] Therefore, a consensus is required to define LLD (e.g., ≥55 years) and studies should specifically investigate the moderating effects of age-of-onset.

Aside from the age of onset, the number and length of depressive episodes may be considered another limitation. Although a large cohort study showed a lack of difference in treatment response between individuals having one, one-to-three or more than three episodes,[74] a review of randomized control trials in older adults also showed evidence that a higher rate of response for individuals at their first episode of illness.[75]

Population stratification can exist when genetic studies are conducted in samples of mixed ethnic ancestry leading spurious associations due to systematic differences between regional populations (see Supplementary Table 2 for ancestry-specific minor allele frequencies). Currently, the literature suggests that some pharmacogenetic evidence may be ethnicity-specific, such as the strong association of *BDNF* rs6265 in individuals of Asian-Pacific ancestry[63] and the ethnicity-dependent association of *SLC6A4* 5-HTTLPR with escitalopram efficacy.[76] Some of the reviewed studies failed to specify the ethnicity/ancestry of participants or failed to adequately describe the steps taken to control for the potential effects of ancestry. Therefore, the lack of clear information regarding the ethnicity/ancestry of individuals, including within a sample and the lack of appropriate correction, may lead to the inability to replicate findings.

Polypharmacy, which is the use of concomitant medications, is a primary pharmacological concern given the increased risk for drug-drug interactions which may affect antidepressant treatment outcomes and result in ADRs.[2,77] Note that concomitant medications can mask genetic variation in CYP enzymes due to phenoconversion (i.e., transient conversion of EMs into IMs or PMs through enzyme inhibition or induction).[78,79] None of the reviewed studies have taken into consideration the potential effects of polypharmacy in older adults. While several studies have listed certain medications as study exclusion criteria (e.g., steroids),[27] others have not explicitly considered other medications that may impact response to antidepressants or PK parameters. One study cited that in a sample of 36 older adults, 121 different medications were taken concurrently, with an average of 8.6 medications per individual.[31] Future studies should take into consideration the potential effects of co-prescribed medications which may affect outcomes.[61]

Future Directions

Surprisingly, we did not identify any studies investigating associations between CYP2D6 metabolizer status and ADRs or other CYP enzymes which have been implicated in modulating antidepressant plasma levels. As such, further research is required for other CYP enzymes which may be involved in antidepressant response. Of note, given the importance of antidepressant metabolism, future studies should explore the impact of various metabolic and PK parameters which may confound associations. In addition, despite the current emphasis on genome-wide and hypothesis-generating studies, it striking that we were only able to identify two whole-transcriptome studies conducted in depressed older adults. Of note, there are currently no antidepressant genome-wide

studies in older adults. As such, there is a missed opportunity to leverage promising advances in the field using genome-wide data and polygenic risk scoring (i.e., models including multiple genetic variants). Additionally, as medications are often metabolized by more than one enzyme, the reported results explain only a limited amount of variance. Therefore, we suggest that future PK studies should investigate the effects of other CYP enzymes, including nonprimary metabolizing enzymes.

Given the progression and advances in psychiatric genetics, future studies in older adults should consider reporting methods and results in adherence to the basic standards outlined in genetic epidemiology. Several studies included in this review failed to clearly report various aspects of study design, ethnic distribution, covariate use and exploration, and sample selection. The *STrengthening the REporting of Genetic Association studies* initiative has outlined a checklist for reporting including information required for the successful replication of results which is often hindered by inadequate reporting of results.[80] Of note, most studies failed to report pre- and post-hoc power calculations, therefore it is unclear whether the reported results are derived from sufficiently-powered studies. Particularly for genetic studies, adequate reporting of control for the effects of ancestry or studies should be conducted in ethnically homogenous samples where possible (e.g., conducting subgroup analyses). Lastly, more prospective, carefully-planned investigations are required to assess the impact of genetic variation on treatment outcomes in diverse cohorts of older adults.

CONCLUSIONS

In summary, given the small number of studies and relatively small sample sizes, it is challenging to draw general conclusions regarding the presence or absence of genetic associations with treatment outcomes, PK and PD factors, and ADRs. However, the largest amount of evidence exists for the *CYP2D6* metabolizer status, *SLC6A4* 5-HTTLPR, and to a lesser extent, *BDNF* rs6265. These findings are consistent with the literature when not restricting to older adults. As such, similar treatment recommendations may be suggested for older adults regarding genetic variation for *CYP2D6*, such as those outlined by *Clinical Pharmacogenetics Implementation Consortium*, whenever genotype information is available. In line with recommendations recently published by the *International Society of Psychiatric Genetics* (https://ispg.net/genetic-testing-statement/), pharmacogenetic testing should also be considered for individuals with LLD who have failed one antidepressant treatment trial or have experienced a history of intolerable side effects. Further carefully-designed pharmacogenetic studies in adults with LLD should be conducted while adjusting for clinical heterogeneity, such as polypharmacy and including genome-wide data. Such samples will allow researchers to make new discoveries and validate if similar treatment adjustments are appropriate in older adults, given that there appear to be significant effects of genetic variation on antidepressant treatment outcomes.

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SUPPLEMENTARY MATERIALS

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