Review

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Pharmacogenomics

Pharmacogenetic guidelines and decision support tools for depression treatment: application to late-life

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Late-life depression (LLD) is a major depressive disorder that affects someone after the age of 60 years. LLD is frequently associated with inadequate response and remission from antidepressants, in addition to polypharmacy. Pharmacogenetics offers a promising approach to improve clinical outcomes in LLD via new discoveries determining the genetic basis of response rates and side effects, as well as the development of tailored pharmacogenetic-based decision support tools. This invited review evaluates the LLD pharmacogenetic evidence base and the extent to which this was incorporated into existing commercial decision support tools and clinical pharmacogenetic guidelines.

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Over 4% of adults aged 65 or older have been diagnosed with late-life depression (LLD), a major depressive disorder (MDD) that affects someone after the age of 60 years [1–4]. Many LLD patients are often inadequately treated pharmacologically with lower than recommended dosages [5–7]. Existing antidepressant therapies have the modest efficacy in LLD. A recent meta-analysis of trials found a response rate of 48% and a remission rate of 33.7% [8] Clearly, there is a need for improved treatment outcomes with antidepressants.

The clinical presentation of LLD is often different from MDD presenting in adults, and this is important to consider in the context of treatment innovations. Elderly adults diagnosed with LLD often have no family history of depression [9]. When compared with younger patients with depression, LLD patients typically have more medical and neurologic co-morbidities and display more cognitive impairment [10]. Polypharmacy is also a major issue to manage in the clinical setting with LLD [11,12]. Two-thirds of adults over the age of 65 use one or more prescription drugs daily [12]. An estimated 35% of seniors experience adverse drug events, nearly half of these are preventable, and 10–17% of hospitalizations of older patients are directly related to adverse drug reactions [13,14]. Polypharmacy issues are also shown to increase risk for negative health outcomes such as higher healthcare costs, drug interactions, medication nonadherence, decreased functional status and geriatric syndromes [11].

Future Medicine

There are unique pharmacokinetic (PK) and pharmacodynamic profiles to consider with late-life physiology relevant to pharmacological treatments of LLD [15]. For example, studies have noted a reduction in serotonin receptors with aging, which could influence the relationship of serotonin gene polymorphisms with treatment response [16]. Furthermore, there is higher and more variable antidepressant concentrations in older adults, which could influence the relationship of genetically predicted CYP450 metabolizer status with antidepressant safety outcomes [17]. Potential reasons for this variability are discussed in more detail, below.

Pharmacogenetics offers a promising approach to remedy treatment inadequacies (i.e., poor response, remission and increased likelihood of polypharmacy) and improve clinical outcomes in LLD via discovery and confirmation of gene–drug interactions that could be used to develop decision support tools (DSTs) and clinical guidelines [18]. To date, however, pharmacogenetic discovery efforts, tool development and guidelines have focused on MDD presenting in adults, without a clear indication of whether they are applicable to LLD. To address this gap in knowledge, via this invited review, we reviewed the LLD pharmacogenetic evidence base, then evaluated the extent to which this evidence was captured or incorporated by current commercial DSTs and clinical pharmacogenetic guidelines available for the treatment of MDD presenting in adults.

Methods

This paper is a narrative and invited expert review. The literature search for included papers involved searching Embase, PsycINFO, Ovid Medline, ScienceDirector, Google Scholar, ClinicalTrials.Gov, the Cochrane Central Register of Clinical Trials and other gray data sources. These databases were searched up to May 2018. To optimize sensitivity in searching, we used the following basic terms: late-life depression, polypharmacy, geriatric depression, pharmacogenetics, pharmacogenomics, discovery, depression, clinical tools and guidelines. For included tables, two independent reviewers (DD Chang and HA Eyre) used a custom data extraction template to summarize the selected articles. Where possible, we also sought key data that were missing from the original reports through correspondence with the investigators.

The unique phenotype of LLD is instructive for novel therapeutic development

When considering antidepressant pharmacology and pharmacogenetics in LLD, it is important to first understand the unique pathophysiology, pharmacokinetics and pharmacodynamics of LLD. These types of insights are important to consider in pharmacogenetic research, where the inclusion of both phenotypic and genetic factors is key [19].

The unique pathophysiology of LLD

The pathophysiology of LLD is different from MDD presenting in adults in various ways [20,21]. Amyloid and tau protein aggregation may represent a pathophysiological cascade which, along with vascular compromise, may predispose individuals to LLD, and increase the risk of dementia [21]. White matter hyperintensities (WMH; vascular dysfunction markers noted on brain MRI) are very common in LLD, but rare in MDD presenting in adults [22]. The disconnection hypothesis suggests that ischemia and WMH may disrupt neural connections among regions modulating mood and cognition, a process proposed to be driven by widespread cerebral WMHs that cause focal damage to tracts and circuits [23]. Thus, the WMH more commonly seen in LLD could adversely affect the tract connectivity by causing 'disconnection' of brain regions.

A recent review by Lavretsky outlined the importance of understanding antidepressant treatment response based upon the unique biological mechanisms of LLD, as well as leveraging this knowledge for the development of new therapeutic approaches. For example, the response of LLD to selective serotonin reuptake inhibitor antidepressants can be hindered by the presence of cerebrovascular disease and executive dysfunction [24–26].

The unique pharmacokinetics of late-life

The aging process is accompanied by a decline in the function of numerous organs and systems, affecting PK processes to different extents and making more variable the interindividual response to the same drug and dosage [27].

Absorption

The most significant change in absorption associated with aging is a reduction in first pass metabolism due to alternations in liver structure and function [27]. Hypochlorhydria is more common in older adults due to gastric mucosal atrophy and other medications (e.g., antiulcer medications), hence leading to reduced absorption of weakly

basic drugs. An emerging literature also suggests that microbiota are also different in aged populations and could affect absorption of medications [28,29].

Distribution

Aging is associated with increased fat/muscle ratio, decreased bodyweight and total body water, along with a reduction in blood albumin level, all of which play a role in drug distribution [15]. In addition, blood–brain barrier permeability increases with age [30] and P-glycoprotein (i.e., a drug efflux transporter) in particular has been shown to be decreased in older versus younger adults [31]. Importantly, some of the most frequently used antidepressants (citalopram, escitalopram, paroxetine, sertraline, venlafaxine, desvenlafaxine, reboxetine, doxepin, amitriptyline and trimipramine) are substrates for P-glycoprotein [32,33] and as such older adults may have increased brain exposure to these drugs and be at greater risk for neurological adverse drug reactions [27]. While the role of P-glycoprotein, encoded by the *ABCB1* gene, has been explored in MDD presenting in adults, there are no data in LLD [34].

Metabolism & elimination

At a macroscopic level in the liver, the altered drug metabolic rate in the aged organ is explained by a general reduction in the liver mass with reduced blood flow meaning decreased delivery of drug molecules to the organ [35].

At a molecular level, the CYP450 isozymes CYP1A, CYP2C9, CYP2C19, CYP2E1 and CYP3A4 undergo a decrease in enzymatic activity, while the activity of the CYP2D6 isozyme is not influenced by age [36–39]. More broadly, Phase I metabolism is reduced while Phase II metabolism appears to be unaltered [27].

Drug molecules are eliminated mainly in urine and bile, and impaired elimination has potentially toxic consequences. Therefore, renal function testing, via glomerular filtration rate is clinically salient [40].

Boyce *et al.* [41] conducted a large systematic review to explore the effects of aging on antidepressant clearance. This study showed reduced clearance in aging for amitriptyline, doxepin, imipramine, nortriptyline, citalopram, escitalopram, sertraline, desvenlafaxine, venlafaxine, bupropion and trazodone. The study compared the available pharmacology evidence with US FDA package inserts and found there was a major lack of information in the package inserts, such as noting age-related clearance changes and drug–drug interactions. Furthermore, in late-life, a decreased rate of drug elimination, caused by impairment of both hepatic and renal function, has been noted [15].

The unique pharmacodynamics of late-life

There are a number of pharmacodynamic changes that occur in late-life and are pertinent to the use of psychotropic medications, however, this is a significantly understudied area and an area where pharmacogenetics is helpful. For a thorough review, see [42]. In particular, there are greater sensitivities to anticholinergic and benzodiazepine effects [27]. The use of antipsychotic medications is associated with greater neuroleptic sensitivity (e.g., extrapyramidal reactions) in patients with Lewy body dementia, as well as greater risk of cerebrovascular events in patients with vascular or mixed dementia [43].

Antidepressant pharmacogenetic studies in LLD

Current discovery efforts have mainly focused on elucidating the pharmacodynamics and pharmacokinetics of genetic loci implicated in LLD such as 5-HTTLPR, DAT1, MDR1 and BDNF [44]. There are relatively few studies conducted in this area as compared with the MDD presenting in the adult literature. The following section reviews the latest pharmacogenetic trials in LLD.

Selective serotonin reuptake inhibitors

The gene encoding for the serotonin transporter (*SLC6A4*) contains a length polymorphism in its promoter region known as 5-HTTLPR, which appears to be relevant to selective serotonin reuptake inhibitor (SSRI) treatment efficacy and side effects [45,46]. This region can contain either long or short repeats denoted as either a long (*L*) or short (*S*) allele, respectively. The *S* allele is associated with decreased serotonin transporter and uptake [47,48]. An early study found that depressed elderly individuals homozygous for the long allele (*LL*), displayed a more pronounced acute response than those heterozygous or homozygous for the *S* allele to the SSRI paroxetine [49]. The plasma concentration of paroxetine after dosage was also observed to be influenced by polymorphisms in the serotonin transporter promoter region and correlated with a change in Hamilton depression rating scale outcomes over a 12-week period [50]. These findings are underscored by another study that found individuals carrying the *S* allele experienced greater adverse effects from paroxetine treatment [51] Subsequently, another study found that

depressed elderly with the *LL* genotype displayed an increased response to sertraline treatment relative to individuals heterozygous or homozygous for the short allele [52].

Adverse events have also been associated with the 5-HTTLPR short allele. One study found that paroxetine-treated *S* allele carriers in depressed elderly experienced greater incidence of gastrointestinal discomfort, sweating and dizziness [51]. One recent 12-week randomized control trial (RCT) investigated how polymorphisms in the promoter regions of the serotonin transporter and receptor impacted adverse events associated with treatment by another SSRI, escitalopram, in elderly depressed adults [53]. The study found that certain allele combinations in the serotonin transporter or receptors (i.e., 1A or 2A) were more strongly associated with adverse events such as dry mouth, decreased sexual desire and increased sleep duration [53]. Interesting, this same study did not observe a significant association between escitalopram concentrations and side effect profile. The importance of *LL* genotype has also been observed in a meta-analysis study [54] that found Caucasians carrying the *LL* genotype showed increasing probability of treatment response versus *S* allele carriers as age of onset increases ($p = 0.0069$). Further details of the pharmacogenomic discovery trials of SSRIs in LLD can be seen in Table 1.

Serotonin noradrenaline reuptake inhibitors

While there have been a number of studies on how genetic variants in depressed young adults affect SNRI response (see for review [60]), to date, there has been only one study on how genetic variation affects SNRI response in LLD [57]. This clinical trial evaluated the response of 350 adults with MDD aged 60 years or older to venlafaxine and how it related to functional variations in their serotonin (*SLC6A4*) and norepinephrine transporter (*SLC6A2*) genotype. Out of 22 polymorphisms across eight genes, the study found that the rs2242446/*T-182C* variant in the *SLC6A2* gene was associated with significantly higher rates of remission as well as shorter time to remission with venlafaxine treatment. Effects were most favorable for the C/C genotype, intermediate for the C/T genotype and lowest for T/T genotype carriers. In contrast, genetic variations in *SLC6A4* did not significantly affect remission rates [57]. Interestingly, a pilot study in MDD presenting in adults found similar results, noting also that history of child abuse appears relevant to antidepressant efficacy, such that susceptibility to the impact of abuse may be influenced by the *SLC6A4* rs2242446 polymorphism [60].

Comparative studies

In patients with LLD, one study found that 36% of LLD patients treated with either the tricyclic antidepressant (TCA) nortriptyline or SNRI venlafaxine, both of which are metabolized by CYP2D6, displayed *CYP2D6* phenoconversion (i.e., genotype-predicted metabolism of the drug differed from the actual observed metabolism of the drug) [58]. Understanding how the rate at which an antidepressant medication is metabolized is of particular importance in the geriatric population given the high prevalence of polypharmacy and the reliance, many practitioners have on therapeutic drug monitoring in managing the elderly. In fact, phenoconversion is typically attributed to other medications in the patient's therapeutic regimen [61] and underscores how genotype, careful therapeutic monitoring and a clear understanding of additional risk factors, including medication metabolic pathways in patients on more than one medication, are important details to account for in LLD.

Similarly, there have been broader studies conducted to identify genomic predictors of remission. One recent study looked at the genomic predictors of treatment remission in elderly patients with depression and identified three genes (*HLA-DRB5*, *SELENBP1*, *LOC388588*) whose expression was significantly associated with antidepressant remission [59]. The treatments involved included either the norepinephrine–dopamine reuptake inhibitor, methylphenidate, with the SSRI citalopram or each treatment alone, although the study did not control for age, gender or treatment group. In another study conducted by the same group, a variable number, tandem-repeat polymorphism of the dopamine-transporter gene, was associated with stronger response in elderly depressed treated with methylphenidate combined with citalopram as compared with citalopram alone [62]. This finding supports the notion that specific genetic polymorphisms may improve SSRI treatment when coupled with a dopamine transporter antagonist compared with SSRI treatment alone. See Table 1 for further details.

Clinical pharmacogenetic guidelines for antidepressants

The Clinical Pharmacogenetics Implementation Consortium [63–66] and Dutch Pharmacogenetics Working Group [67] have developed dosing guidelines for serotonin selective reuptake inhibitors and TCAs for MDD based exclusively on *CYP2D6* and *CYP2C19* genetic variation.

Table 1. Pharmacogenetic discovery trials exploring antidepressants in late-life depression.

Study (year)	Study design	Sample size	Sample characteristics	Eligibility	Pharmacological details	Findings	Ref.
Pollock *et al.* (2000)	– 12-week, double blind, RCT – Two arms: nortriptyline vs paroxetine – Assessment points: weekly plasma measurements – Efficacy measure: HDRS-17 – Other measures: genotype of serotonin transporter gene promoter region (5-HTTLPR) analyzed for long, *l* and short, *s* variants	N = 95	– Nortriptyline (n = 45) vs paroxetine (n = 51) – Age (mean): 72.0 ± 7.9 – No significant difference between groups in gender, race – Genotype results: 35 *l*//*l*, 40 *s*/*l*, 20 *s*/*s*	Inclusion: – Age ≥60 years – Diagnosis of MDD (DSM-IV criteria) – HDRS score ≥15 – MMSE score ≥18 Exclusion: – History of psychosis, bipolar or schizoaffective disorder – History of alcohol or substance abuse	Paroxetine: – 20 mg initial dose – Increased to 30 mg after 5 weeks if HDRS >15 still or if less than 50% decrease in HDRS-17 score Nortriptyline: – 25 mg initial dose – Adjusted weekly until plasma concentrations 50–150 ng/ml – No significant difference in mean weekly plasma levels of each treatment	Primary outcomes – Treatment with paroxetine resulted in more rapid reductions of HDRS scores in patients with *ll* genotype compared with *s* carrier genotype (*s*/*l and s*/*s*) – By end of 2nd week, 52% of those with *l*//*l* genotype had a 50% reduction in HDRS score compared with none in the *s* carrier genotype group ($\chi^2 = 20.04$; $p < 0.0001$)	[49]
Lotrich *et al.* (2008)	– 12-week study combining two RCT cohorts [55,56] – Cohort 1 [55] – Cohort 2 [56] – Assessment points: plasma concentrations for paroxetine at week 2 or 3, HDRS-17 scores at baseline and 12 weeks – Efficacy measure: HDRS-17 – Other measures: genotype of serotonin transporter promoter gene region (5-HTTLPR) for *l* and *s* allele	N = 110 HDRS >15 DSM-IV criteria for MDD Paroxetine plasma levels obtained weeks 1–3	Cohort 1: – n = 47 (*l*//*l* allele = 19, *s* allele = 28) – Age (mean): 72 ± 7.8 – Gender (% females): 78.7% Cohort 2: – n = 63 (*l*//*l* allele = 21, *s* allele = 42) – Age (mean): 78 ± 5.5 – Gender (% females): 63.5%	Inclusion: – Age ≥60 years – Diagnosis of MDD (DSM-IV criteria) – HDRS score ≥15 – MMSE score ≥18 Exclusion: – History of psychosis, bipolar or schizoaffective disorder – History of alcohol or substance abuse	Cohort 1: – Paroxetine, 20 mg starting, increased to 30 mg after 5 weeks if HDRS >15 still or if less than 50% decrease in HDRS-17 score Cohort 2: – Open-label paroxetine treatment	Primary outcomes – Interaction between early paroxetine concentration and 5-HTTLPR genotype ($F_{18,59.5} = 1.8$, $p < 0.05$) – Early paroxetine exposure (week 2) was correlated with significant improvement in HDRS-17 scores for patients carrying the *s* allele ($r = 0.31$, $p < 0.05$) – Early paroxetine exposure not correlated for improvement in HDRS-17 scores for patients carrying *l*//*l* allele ($r = 0.12$; $p = 0.45$)	[50]
Murphy *et al.* (2004)	– Double-blinded, multicenter, 8-week RCT – Two arms: mirtazapine vs paroxetine – Assessment points: baseline, weeks 1, 2, 3, 4, 6, 8 – Efficacy measures: HDRS-17, GDS – Other measures: plasma drug concentrations at 4 weeks, 5-HTTLPR genotyping	N = 246	Mirtazapine (n = 124) vs paroxetine (n = 122): – Age ≥65 years – Sex (females): 54 vs 61 – *l*//*l* genotype (32%), *s*/*l* genotype (45.5%), *s*/*s* genotype (22.5%)	Inclusion: – Age ≥65 years – HDRS ≥18 – Diagnosis of MDD (DSM-IV criteria) – HDRS score ≥15 Exclusion: – Unstable medical illness – Principle psychiatric diagnosis other than depression – ECT within 6 months History of alcohol or substance abuse	Mirtazapine: – Starting dose of 15 mg/day, increased to 30 mg/day after day 14 with option to increase to 45 mg/day Paroxetine: – Starting dose of 20 mg/day increased to 30 mg/day after day 14 with option to increase to 40 mg/day	– Patients carrying the S allele showed impaired antidepressant response compared with *LL* genotype based off GDS scales at week 1 ($F_{1,210} = 5.28$; $p = 0.02$) and week 4 ($F_{1,175} = 4.11$; $p = 0.04$) – 5-HTTPLR polymorphisms have significant effects on discontinuations – Paroxetine-treated patients showed significant association with carrying the *s* allele and probability of discontinuation due to adverse events at weeks 2, 3, 4, 6, 7 (Cox regression analyses; $p < 0.05$ for all) – In contrast, mirtazapine-treated patients showed significant association with carrying *l* allele and discontinuation due to adverse events at weeks 2, 3, 4, 6, 7 (Cox regression analyses; $p < 0.05$ for all)	[51]

CGI: Clinical Global Improvement; DSM-IV: Diagnostic and Statistical Manual 4; ECT: Electroconvulsive therapy; EM: Extensive metabolized; GDS: Geriatric depression scale; HARS: Hamilton anxiety rating scale; HDRS: Hamilton depression rating scale; IM: Intermediate metabolizer; MADRS: Montgomery Åsberg Depression Rating Scale; MDD: Major depressive disorder; MMSE: Mini-mental state examination; OR: Odds ratio; PM: Poor metabolizer; RCT: Randomized control trial; RR: Relative risk; TAU: Treatment as usual; TCA: Tricyclic antidepressant; TDM: Therapeutic drug monitoring; UKU: Udvalg fur Kliniske Undersøgelser rating scale.

Table 1. Pharmacogenetic discovery trials exploring antidepressants in late-life depression (cont.).

Study (year)	Study design	Sample size	Sample characteristics	Eligibility	Pharmacological details	Findings	Ref.
Garfield *et al.* (2014)	– Double blind, 12-week RCT – Two arms: escitalopram vs placebo – Assessment points: side effects assessed at weeks 1, 2, 3, 4, 6, 8, 10, 12 – Efficacy measures: UKU side effect rating scale – Other measures: plasma samples for escitalopram measured at weeks 2, 8, 12 and genotyping serotonin receptor polymorphisms	N = 177	Escitalopram (n = 85) vs placebo (n = 92) – Age (mean): 71.1 vs 72.2 (p = 0.56) – Sex (% male): 28.3 vs 37% (p = 0.22) – Baseline HDRS (mean): 11.8 vs 12.3 (p = 0.98) – Baseline HARS (means): 22.9 vs 23.1 (p = 0.92)	Inclusion: – Age ≥60 years – Principal diagnosis of generalized anxiety disorder – HDRS score ≥17 Exclusion: – Lifetime psychosis or bipolar disorder, dementia – Medical instability – Exogenous steroid use – Antidepressant or anxiolytic coprescription	Escitalopram: – Starting dose 10 mg/day, increased to 20 mg after 4 weeks if tolerated or needed – Placebo control arm Side effects: – 17 side effects evaluated Genotyping: – Genetic polymorphisms assessed in promoters of the serotonin transporter (5-HTTLPR) and 1A (HTR1A) and 2A receptors (HTR2A)	Primary outcomes – Four significant side effects were associated with escitalopram treatments: increased duration of sleep, dry mouth, diarrhea, diminished sexual desire – Genetic variation in serotonin transporter 5-HTTLPR associated with dry mouth and diminished sexual desire – Genetic variation in HTR1A receptor was associated most strongly with diarrhea side effect – Genetic variation in HTR2A receptor was associated most strongly with diminished sexual desire	[53]
Marshe *et al.* (2017)	– 12-week, open-label trial – Treatment: venlafaxine – Assessment points: baseline, weeks 1, 2, 4, 6, 8, 10, 12 – Efficacy measure: remission defined as MADRS ≤10 – Other measures: genotypes of polymorphisms in eight genes: *SLC6A2, SLC6A4, HTR1A, HTR1B, HTR2A, HTR2C, TPH1, TPH2*	N = 350	Remitters (n = 179) vs nonremitters (n = 171) – Age (mean): 69.9 vs 67.3 – Sex (% females): 71.5 vs 55.6% – Baseline MADRS: 24.8 vs 28.4 – Venlafaxine dosage: 206.8 vs 278.3	Inclusion: – Age ≥60 years – Diagnosis of MDD (DSM-IV criteria) – MADRS score ≥15 Exclusion: – Patients with dementia (DSM-IV criteria) – MMSE score of <24	Treatment – Venlafaxine, starting with 37.5 mg/day and titrated up to a maximum of 300 mg/day over approximately 12 weeks Gene profiling: – A total of 17 SNPS across the eight genes were analyzed: *SLC6A4* (5-HTTLPR, VNTR, rs25531), *SLC6A2* (rs2242446, rs5569), *HTR1A* (rs6295), *HTR1B* (rs6296, rs130058, rs11568817), *HTR2A* (rs9567746, rs2274639, rs6311), *HTR2C* (rs6318, rs10521432, rs1801412, rs3813929, rs17260600, rs518147), *TPH1* (rs1800532) (19), *TPH2* (rs11178998, rs11178997, rs4570625)	Primary outcomes – The functional variant rs224246 in the norepinephrine transporter gene (*SLC6A2*) was associated with remission (OR = 1.66; 95% CI: 1.13–2.42) – Of those with the functional variant rs224246, more patients carrying C/C genotype remitted (71%) than those with the C/T genotype (51.8%) or T/T genotype (47.3%) – No significant associations with the serotonin transporter gene (*SLCA6A4*) (p > 0.05)	[57]

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Table 1. Pharmacogenetic discovery trials exploring antidepressants in late-life depression (cont.).

Study (year)	Study design	Sample size	Sample characteristics	Eligibility	Pharmacological details	Findings	Ref.
Berm *et al.* (2016a)	– 12-week, double-blind, RCT – Two arms: nortriptyline vs venlafaxine – Assessment points: baseline, 12 weeks for antidepressant response, blood samples for TDM assessed at 3, 5, 12 weeks – Efficacy measure: HDRS-17, MADRS – Other measures: genotypes of *CYP2D6 *3* and **4* alleles, predicted metabolic and measured metabolic phenotype, number of phenoconversion occurrences	N = 81	Nortriptyline (n = 41) vs venlafaxine (n = 40) – Age (mean): 71.6 vs 72.8 (p = 0.48) – Sex (% females): 27 vs 32% (p = 0.286) – Baseline HDRS-17 (mean): 25.0 vs 23.8 (p = 0.309) Baseline MADRS (mean): 32.9 vs 32.9 (p = 0.998)	Inclusion: – Age ≥60 years – Diagnosis of MDD (DSM-IV criteria) – MADRS score ≥20 Exclusion: – Patients with dementia (DSM-IV criteria) – MMSE score of <15 – Patients refractory to prior treatments for depression with either a TCA or venlafaxine	Genotype/predicted phenotype: – Patients classified as either EM if no dysfunctional alleles, IM if possessing a **3* or **4* allele or PM if two dysfunctional alleles Measured phenotype: – Serum ratios between *CYP2D6* metabolites (OH-nortriptyline and O-desmethylvenlafaxine) to original drug – Categorized as PM (0–0.5), IM (0.5–1.5) or EM (1.5–10) Phenoconversion: – Defined as a discrepancy between predicted and measured phenotype Treatment: – Nortriptyline patients: TAU and TDM – Venlafaxine patients: TAU	Primary outcomes: – No phenoconversion observed from PM to EM – Only observed phenoconversions occurred between IM to EM – PMs had a greater risk of nonresponse compared with non-PMs measured on HAM-D (RR: 1.56; 95% CI: 1.03–2.37) – Most phenoconversions for nortriptyline users were from EM-genotyped to IM-phenotype (28%) – Most phenoconversions for venlafaxine users were from IM-genotyped to EM-phenotype (77% or 34 out of 44) – Men had a higher risk of phenoconversion toward increased enzymatic activity (RR: 2.40; 95% CI: 1.14–5.07) Other outcomes: – Phenoconversion toward less enzyme activity was associated with gender or age	[58]
Eyre *et al.* (2016a)	– 16-week, double blind, placebo-controlled RCT – Three arms: methylphenidate + citalopram, citalopram + placebo or methylphenidate + placebo – Assessment points: baseline, 16 weeks – Efficacy measure: remission (HDRS-24 ≤6) vs nonremission, MADRS, HAM-A – Other measures: genome-wide transcriptional profiles on peripheral blood leukocytes at baseline and 16 weeks – Trial registration: NCT00602290	N = 35	Remitters (n = 24) vs nonremitters (n = 11) – Age (mean): 67.2 vs 73.5 (p = 0.05) – Sex (% females): 68.6 vs 31.5% (p = 0.3) – Baseline HDRS-24 (mean): 18.2 vs 20.3 (p = 0.11) – Baseline MADRS (mean): 17.0 vs 20.1 (p = 0.07)	Inclusion: – Diagnosis of unipolar MDD (DSM-IV TR criteria) – HDRS-24 score ≥16 – MMSE score ≥26 Exclusion: – History of another psychiatric disorder – Severe, acute or unstable medical illness – Suicidal or violent behavior within the last year – CNS diseases	Methylphenidate – Starting dose of 5 mg/day up to 40 mg/day until patients achieve CGI score 1 or 2 – After day 28, dose was kept same till end of trial Citalopram: – Starting dose of 20 mg/day, up to 60 mg/day if inadequate response Gene profiling: – Gene expression was analyzed by sampling peripheral blood leukocytes at baseline and 16 weeks	Primary outcomes – Three genes identified (*HLA-DRB5, SELENBP1, LOC388588*) whose expression was significantly associated with antidepressant remission (fold change ≥2; p ≤ 0.05) – Two genes associated with early remission, defined as remission by week 4 (*CA1*, fold change 2.54; p = 0.03 and *SNCA-α-synuclein* gene, fold change 2.1; p = 0.03)	[59]

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CYP2D6 metabolizes most antidepressant and is not influenced by age [37] but it is susceptible to phenoconversion in patients taking multiple medications [60]. *CYP2C19*, however, is responsible for demethylating TCAs into their active form and has been shown to have decreased enzymatic activity with age [15], suggesting *CYP2C19* guidelines should, but currently do not, account for age-related changes.

Efficacy of pharmacogenetic-based DSTs in MDD presenting in adults & LLD

Pharmacogenetic-based DSTs are designed to help clinicians select medications that will optimize treatment efficacy based on a patient's genotype [18]. In addition to providing the clinician information that will assist in determining medication and dosage, they may offer clinical interpretation, caution on drug–drug interactions and predicted patient phenotype [19]. However, no pharmacogenetic-based DST accounts for clinical and/or psychosocial factors [68] that have been shown to be robust predictors of treatment response [69]. Furthermore, selected genes and gene variants vary considerably from tool to tool, although what is consistent across all antidepressant pharmacogenetic tools is a focus on PK genes, specifically *CYP2D6* and *CYP2C19* [19]. The focus on *CYP2D6* and *CYP2C19* is primarily a result of expert groups such as the CPIC and the Clinical Pharmacogenetics Implementation Consortium, as outlined previously. Despite these guidelines, a majority of tools also include other PK and/or pharmacodynamics genes in their testing panels with varying degrees of evidence [19]. These gene panels are then subjected to the tool's decision algorithm, which in turn produces an interpretative report. Interpretative reports vary in the depth of content but at minimum include a snapshot of the patient's pharmacogenetic status along with recommendations and/or considerations aimed at optimizing efficacy and/or reducing adverse events associated with antidepressant therapy.

Efficacy studies of pharmacogenetic-based DSTs in depression have focused on their use only in MDD presenting in adults and as such, there has been a paucity of studies focused on LLD [70,71]. To date, four DSTs have been subjected to evaluation via an RCT: CNSDose, Genesight, NeuroIDgentix and Neuropharmagen [72–75], all of which focused on MDD presenting in adults populations (see Table 2 for reviews of this trials). However, a study by Elliott *et al.* [12] used a prospective, open-label, RCT design to explore the role of a YouScript DST on polypharmacy in home-care elderly patients aged over 50 years. In this study, 110 patients were randomized and the intervention group involved a pharmacist reviewing drug–drug, drug–gene and cumulative drug and/or gene interactions using the YouScript DST to provide drug therapy recommendations to clinicians. The mean number of rehospitalizations per patient in the tested versus untested group was 0.33 versus 0.70 at 60 days following enrollment ($p = 0.007$). The mean number of emergency department (ED) visits per patient in the tested versus untested group was 0.39 versus 0.66 at 60 days ($p = 0.045$). Of the total 124 drug therapy recommendations passed on to clinicians, 96 (77%) were followed. These results suggest that pharmacogenetic-based DSTs may reduce polypharmacy-related hospitalizations in elderly depressed patients but it remains unclear whether these DSTs will improve efficacy in LLD.

Cost–effectiveness of pharmacogenetic-based DSTs in LLD

To our knowledge, two studies have examined the cost–effectiveness of a pharmacogenetic-based DST in LLD [76,77]. In the most recent study by Mayhew *et al.*, a subanalysis of geriatric participants from a larger pharmacogenomics trial showed that the use of the GeneSight DST in older adults with MDD resulted in medications savings of over $5000 per patient per year [76]. In a study by Berm *et al.*, routine CYPD26 genotyping for depressed geriatric patients on 12 weeks of nortriptyline was modeled for its cost–effectiveness and they found that it would only be cost-effective if genotyping costs were lowered below 40 € at an assumed 200 € per genotyping test based on the 2014 price set by the Dutch Healthcare Authority [77].

We are also aware of one ongoing study designed to evaluating the cost–effectiveness of implementing genetic screening in depressed geriatric patients. The CYSCE trial (Cytochrome P450-2D6 Screening Among Elderly Using Antidepressants) is a prospective RCT based in The Netherlands that will determine the CYPD26 genotype of patients over age 60 years with MDD and start their treatment with either TCA nortriptyline or SNRI venlafaxine [78]. Patients that are either poor, intermediate or ultra-rapid metabolizers based on *CYPD26* genotype are randomized to either a control or intervention group where dosing advice is followed per the Royal Dutch Pharmacist Association pharmacogenetic guidelines [67]. This trial has been completed, but results are pending.

Table 2. Characteristics of prospective, randomized controlled trials evaluating the clinical outcomes of pharmacogenetic-guided prescribing in major depressive disorder presenting in adults.

Study (year)	Study design	Sample size	Sample characteristics	Eligibility	Target genes and report format	Findings	Ref.
Winner *et al.* (2013)	– 10-week prospective, double-blind RCT – Two arms: PGx-guided vs unguided – Assessment points: double-blinded: baseline, 4, 6 and 10 weeks – Efficacy measure: HDRS-17 improvement, response and remission; QIDSC-16 and PHQ-9 – Other measures: FIBSERS – Trial registration: NCT01261364	51	Guided (n = 25) vs unguided (n = 24) – Age (mean): 51 vs 48 (ns) – Sex (% males): 32 vs 8% (p = 0.04) – Ethnicity (% Caucasian): 96 vs 100% (ns) – Baseline HDRS (mean): 21.6 vs 21.1 (ns)	Inclusion: – Diagnosis of MDD or DDNOS – HDRS-17 score ≥14 Exclusion: – Other active psychiatric diagnosis – Substance use disorder	– Target genes: *CYP2D6, CYP2C19, CYP1A2, SLC6A4, HTR2A* – Report format: bins medications into either a green ('use as directed'), yellow ('use with caution') or red ('use with increased caution and with more frequent monitoring') category based on genotype results	Efficacy: – Greater than double the likelihood of response (GeneSight = 36%; TAU = 20.8%; OR: 2.14; 95% CI: 0.59–7.69) and remission (GeneSight = 20%; TAU = 8.3%; OR: 2.75; 95% CI: 0.48–15.80) in the GeneSight group measured by HDRS-17 at week 10 – Mean percent improvement in depressive symptoms on HAMD-17 was higher for the GeneSight group over treatment as usual (30.8 vs 20.7%; p = 0.28) – Not statistically significant improvement in PHQ-9 (Genesight = 35.4 vs TAU = 21.3%; F = 1.84; p = 0.18) or QIDSC-16 scores (Genesight = 27.6 vs TAU = 22.1%) Other outcomes: – Drug switching: all subjects in guided group on a red bin medication were changed over during the study period, by comparison 50% of TAU subjects were switched or dose adjusted (X^2 = 5.09; p = 0.02) – Prescribing: no difference in the mean number of psychotropics prescribed between groups at the end of the study period (Genesight = 1.9 vs TAU = 1.7; p = 0.27) – Mental health visits: no difference in the number of visits between groups at the end of the study (X^2 = 6.86; df = 11; p = 0.81)	[72]

ADR: Adverse drug reaction; CGI-S: Clinical global impression-severity; DDNOS: Depressive disorder not otherwise specified; DSM-5: Diagnostic and statistical manual of mental disorders, 5th edition; ECT: Electroconvulsive therapy; FIBSERS: Frequency, intensity, and burden of side effects ratings; GDS: Geriatric depression scale; HAM-A: Hamilton rating scale for anxiety; HAMD-17: Hamilton rating scale for depression, 17 item; HARS: Hamilton anxiety rating scale; HDRS: Hamilton depression rating scale; HDRS-17: 17-item Hamilton rating scale for depression; MADRS: Montgomery Åsberg depression rating scale; MDD: Major depressive disorder; ns: Non-significant; OR: Odds ratio; QIDSC-16: Quick inventory of depression symptomatology scales, 16-item; PGI-I: Patient global impression of improvement; PGx: Pharmacogenetics; PHQ-9: Patient health questionnaire, 9 item; RCT: Randomized control trial; SATMED-Q: Treatment satisfaction with medicines questionnaire; SDI: Sheehan disability inventory; TAU: Treatment as usual.

Table 2. Characteristics of prospective, randomized controlled trials evaluating the clinical outcomes of pharmacogenetic-guided prescribing in major depressive disorder presenting in adults (cont.).

Study (year)	Study design	Sample size	Sample characteristics	Eligibility	Target genes and report format	Findings	Ref.
Singh (2015)	– 12-week prospective double blind RCT – Two arms: PGx-guided vs unguided – Assessment points: double-blinded: baseline, 4, 8 and 12 weeks. – Efficacy measure: HDRS-17 remission – Other measures: intolerability events and number of sick days taken off work or studies due to depression – Trial registration: ACTRN12613001135707	148	Guided (n = 74) vs unguided (n = 74): – Age (mean): 44 vs 44 (ns) – Sex (% males): 42 vs 39% (ns) – Ethnicity (% Caucasian): 100 vs 100% (ns) – Baseline HDRS (mean): 24.81 vs 24.66 (ns)	Inclusion: – Age ≥18 years – Primary diagnosis of MDD by DSM-5 criteria assessed by semistructured psychiatrist interview – HDRS-17 score ≥18 – Caucasian subjects Exclusion: – Other active psychiatric diagnosis – Substance use disorder – Pregnancy or breastfeeding – Hepatic or renal impairment – Coprescription of known *CYP2D6, CYP2C19 or ABCB1* inducers/inhibitors – Regular grapefruit drinkers – Current smoker	– Target genes: *ABCB1, ABCC1, CYP2C19, CYP2D6* and *UGT1A1* – Report format: bins medications into either a mid-range, high-range or low-range dose category based on genotype results	Efficacy: – Subjects receiving genetically guided prescribing had a 2.52-fold greater chance of remission (95% CI: 1.71–3.73, z = 4.66, $p < 0.0001$) Other outcomes: – Intolerability events: The unguided group were 1.13-times more likely to have medication tolerability problems (95% CI: 1.01–1.25, z = 2.208, p = 0.0272) requiring either dose reduction or cessation – Sick days: The genetically guided group had significantly less risk of taking sick leave (4 vs 15%, p = 0.0272) and significantly less duration of sick leave when such was needed (4.3 vs 7.7 days, p = 0.014)	[73]
Pérez *et al.* (2017)	– 12-week, multicenter, prospective, double-blind RCT – Two arms: PGx-guided vs unguided – Assessment points: single –blinded: baseline, 6 and 12 weeks. double-blinded: 4, 8 and 12 weeks – Efficacy measure: PGI-I improvement – Other measures: HDRS-17, FIBSERS, SDI, SATMED-Q – Trial registration: NCT02529462	316	Guided (n = 155) vs unguided (n = 161): – Age (mean): 52 vs 51 (ns) – Sex (% male): 36 vs 37% (ns) – Ethnicity (% Caucasian) 94 vs 91% (ns) – Baseline HDRS (mean): 19.5 vs 19.0 (ns)	Inclusion: – Age ≥18 years – Primary diagnosis of MDD by DSM-5 criteria assessed by semistructured psychiatrist interview – CGI-S ≥4 Exclusion: – Primary psychiatric diagnosis other than MDD – Pregnant or breastfeeding – Use of quinidine, cinacalcet and/or terbinafine	– Target genes: *A BCB1, AKT1, BDNF, CACNG2, CES1, COMT, CRHR1, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, DDIT4, DRD3, EPHX1, FCHSD1, GRIK2, GRIK4, HLA-A, HTR1A, HTR2A, HTR2C, LPHN3, NEFM, OPRM1, RGS4, RPTOR, SLC6A4, UGT2B15* – Report format: uses color-coding system to highlight gene–drug interactions related to ADRs (red), drug metabolism variations (yellow) or likelihood of response (green). Provides drug-specific treatment recommendations per the US FDA-approved drug labeling, PGx guidelines and selected clinical studies	Efficacy: – A higher proportion of responders (PGI-I ≤2) was observed at 12 weeks in the guided group (47.8 vs 36.1%, p = 0.0476, OR: 1.62 [95% CI: 1.00–2.61]) – Participants in the guided group showed a higher reduction in HDRS at 6 weeks (p = 0.0364) but not 12 weeks (p = 0.0771) – Patients who had received 1–3 previous treatments (n = 173) had significant reductions in PGI-I at 12 weeks and HDRS scores at 6 and 12 weeks Other outcomes: – Medication tolerability: of the participants reporting side effects at baseline via FIBSER score (n = 177), the likelihood of reaching a score <3 was higher among guided participants at 6 weeks (66.7 vs 50.0%, p = 0.0294, OR: 2.00 [95% CI: 1.07–3.75]), and was maintained at 12 weeks (68.5 vs 51.4%, p = 0.0260, 2.06 [95% CI: 1.09–3.89])	[74]

ADR: Adverse drug reaction; CGI-S: Clinical global impression-severity; DDNOS: Depressive disorder not otherwise specified; DSM-5: Diagnostic and statistical manual of mental disorders, 5th edition; ECT: Electroconvulsive therapy; FIBSERS: Frequency, intensity, and burden of side effects ratings; GDS: Geriatric depression scale; HAM-A: Hamilton rating scale for anxiety; HAMD-17: Hamilton rating scale for depression, 17 item; HARS: Hamilton anxiety rating scale; HDRS: Hamilton depression rating scale; HDRS-17: 17-item Hamilton rating scale for depression; MADRS: Montgomery Åsberg depression rating scale; MDD: Major depressive disorder; ns: Non-significant; OR: Odds ratio; QIDSC-16: Quick inventory of depression symptomatology scales, 16-item; PGI-I: Patient global impression of improvement; PGx: Pharmacogenetics; PHQ-9: Patient health questionnaire, 9 item; RCT: Randomized control trial; SATMED-Q: Treatment satisfaction with medicines questionnaire; SDI: Sheehan disability inventory; TAU: Treatment as usual.

Table 2. Characteristics of prospective, randomized controlled trials evaluating the clinical outcomes of pharmacogenetic-guided prescribing in major depressive disorder presenting in adults (cont.).

Study (year)	Study design	Sample size	Sample characteristics	Eligibility	Target genes and report format	Findings	Ref.
Bradley *et al.* (2018)	– 12 week multicenter RCT – Two arms: PGx-guided vs Treatment as usual: – Assessment points: double-blinded: Baseline, 4, 8 and 12 weeks – Efficacy measure: HAM-A and HDRS-17 ratings – Trial registration: NCT02878928	685	PGx-guided (n = 352) vs TAU (n = 333) – Age (mean): 47.8 ± 14.5 vs 47.3 ± 51 (ns) – Sex (% male): 27 vs 28% (ns) – Ethnicity (% Caucasian) 63 vs 63% (ns) Baseline HDRS (mean): 20 ± 5.8 vs 20 ± 5.8 (ns)	Inclusion: – Age ≥19 years – Primary diagnosis of MDD by DSM-5 criteria Exclusion: – Concurrent diagnosis of bipolar disorder, schizophrenia, personality disorder, traumatic brain injury, significant risk of suicide, chronic kidney disease, pregnancy or abnormal liver function	– Target genes: *CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, SLC6A4, COMT, HTR2A, MTHFR* – Report format: the PGx report classifies medications based on either 'Used as Directed' or 'Use with Caution/Increased monitoring.' Reasons for caution are provided as well as recommendations for clinical management	Efficacy: – Patients under PGx guidance displayed a significantly higher response (p = 0.001; OR: 4.72 [1.93–11.52]) and remission rate (p = 0.02; OR: 3.54 [1.27–9.88]) – Patients with PGx-guided treatment also showed reduced HAM-A ratings at weeks 8 (p = 0.02) and 12 (p = 0.02)	[75]

ADR: Adverse drug reaction; CGI-S: Clinical global impression-severity; DDNOS: Depressive disorder not otherwise specified; DSM-5: Diagnostic and statistical manual of mental disorders, 5th edition; ECT: Electroconvulsive therapy; FIBSERS: Frequency, intensity, and burden of side effects ratings; GDS: Geriatric depression scale; HAM-A: Hamilton rating scale for anxiety; HAMD-17: Hamilton rating scale for depression, 17 item; HARS: Hamilton anxiety rating scale; HDRS: Hamilton depression rating scale; HDRS-17: 17-item Hamilton rating scale for depression; MADRS: Montgomery Åsberg depression rating scale; MDD: Major depressive disorder; ns: Non-significant; OR: Odds ratio; QIDSC-16: Quick inventory of depression symptomatology scales, 16-item; PGI-I: Patient global impression of improvement; PGx: Pharmacogenetics; PHQ-9: Patient health questionnaire, 9 item; RCT: Randomized control trial; SATMED-Q: Treatment satisfaction with medicines questionnaire; SDI: Sheehan disability inventory; TAU: Treatment as usual.

Conclusion & future perspective

Pharmacological treatment of LLD is characterized by inadequate response, remission, significant side effects and a higher likelihood of polypharmacy. Furthermore, there are unique phenotypic factors in LLD which are not currently factored into antidepressant treatment algorithms. Thus, as the prevalence of LLD increases with life expectancies [10], there is an impetus for novel innovations to optimize antidepressant treatment outcomes in LLD. There is an increasing interest in pharmacogenetics in LLD and promising findings.

Currently available pharmacogenetic-based guidelines and tools are relevant to the treatment of LLD, but the evidence supporting their use is limited. As such, more discovery-based research is required and evaluations of existing DSTs in LLD settings are warranted in order to bring pharmacogenetic evidence in LLD into alignment with MDD presenting in adults.

We suggest that it is key to accounting for polypharmacy and predicting potential phenoconversion through better characterization of drug–drug–gene interactions. Looking beyond metabolism is also important, via examination of phenotypic markers related to drug absorption, distribution and excretion processes. Life-span pharmacogenetic studies to understand age effects on pharmacogenetic factors, such as birth cohorts, as well as cross-sectional studies that cover wide age range will be useful. Sex and gender differences in psychiatry are increasingly recognized as an

Executive summary

Unique clinical scenario of late-life depression

- The clinical scenario of late-life depression (LLD) is often different to major depressive disorder (MDD) presenting in adults. It is characterized by more co-morbidities and cognitive impairment, polypharmacy, greater adverse drug events, decreased functional status and risk of suicide.

The unique phenotype of LLD is instructive for novel therapeutic development

- The pathophysiology of LLD is unique to MDD presenting in adults in various ways, including due to amyloid and tau protein aggregation, increased white matter hyperintensities and damage to tracts and circuits causing disconnection of brain regions. This is an important consideration in pharmacogenetic research.
- The aging process is accompanied by a decline in the function of numerous organs and systems, affecting pharmacokinetic processes (e.g., absorption, distribution, metabolism and excretion) to different extents and making more variable the interindividual response to medications. Therefore, such phenotypic factors should be incorporated into pharmacogenetic decision support tools (DSTs).
- There are presumably a number of pharmacodynamic changes that occur in late-life and are pertinent to the use of psychotropic medications; however, this is a significantly understudied area.

Antidepressant pharmacogenetic studies in LLD

- Current discovery efforts have mainly focused on elucidating the pharmacodynamics and pharmacokinetics of genetic loci implicated in LLD such as *SLC6A4, DAT1, ABCB1* and *BDNF*.

Clinical pharmacogenetic guidelines for antidepressants

- *CYP2D6* metabolizes most antidepressant and is not influenced by age, but it is susceptible to phenoconversion in patients taking multiple medications. *CYP2C19*, however, is responsible for demethylating tricyclic antidepressants into their active form and has been shown to have decreased enzymatic activity with age, suggesting *CYP2C19* dosing guidelines should account for age-related changes.

Efficacy of pharmacogenetic-based DSTs in MDD presenting in adults & LLD

- Pharmacogenetic-based DSTs are designed to help clinicians select medications that will optimize treatment efficacy based on a patient's genotype.
- Efficacy studies of pharmacogenetic-based DSTs in depression have focused on their use primarily in MDD presenting in adults and as such, there has been a paucity of studies focused on depression in older adults.

Cost–effectiveness of pharmacogenetic-based DSTs in LLD

- There are early promising data from two studies examining the cost–effectiveness of pharmacogenetic-based DSTs in LLD.

Conclusion & future perspectives

- Pharmacogenetic-based guidelines and tools are relevant to the treatment of LLD, but the evidence supporting their use in treating LLD is limited.
- More discovery-based research is required and evaluations of existing pharmacogenetic-based DSTs in LLD settings are warranted in order to bring pharmacogenetic evidence in LLD into alignment with MDD presenting in adults.
- Unique factors relevant to LLD need to be considered in the development of pharmacogenentic-based DSTs for LLD, including pathophysiological factors, phenotypic factors relevant to pharmacokinetics, diverse ethnicities and factors such as suicidal ideation.

area for further exploration, and therefore are an important consideration in pharmacogenetics for LLD. Evidence suggests differences in prevalence, symptomatology, risk factors, influencing factors, course of illness, pathophysiology and optimal treatment based on sex and/or gender [79]. More research is needed on gender differences in illness behavior, coping, help-seeking and compliance, as well as on sex-specific aspects of psychopharmacology, hormonal therapies or gender-sensitive psychotherapy [79]. The increasingly racial and ethnic diversity of the aging population, particularly in the USA [80], should be taken into account in tool development, given the ethnic variability seen in treatment response [81]. Finally, because major depression in older adults often follows a relapsing chronic course, research into the development and application of pharmacogenetic DSTs to the long-term maintenance treatment of older adults is of great clinical relevance.

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