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Pharmacogenetic Decision Support Tools: A New Paradigm for Late-Life Depression?

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Abstract

Clinicians still employ a “trial-and-error” approach to optimizing treatment regimens for late-life depression (LLD). With LLD affecting a significant and growing segment of the population, and with only about half of older adults responsive to antidepressant therapy, there is an urgent need for a better treatment paradigm. Pharmacogenetic decision support tools (DSTs), which are emerging technologies that aim to provide clinically actionable information based on a patient’s genetic profile, offer a promising solution. Dozens of DSTs have entered the market in the past fifteen years, but with varying level of empirical evidence to support their value. In this clinical review, we provide a critical analysis of the peer-reviewed literature on DSTs for major depression management. We then discuss clinical considerations for the use of these tools in treating LLD, including issues related to test interpretation, timing, and patient perspectives. There are no primary clinical trials in LLD cohorts. However, in adult populations, newer generation DSTs show promise for the treatment of major depression. Further independent and head-to-head clinical trials are required to further validate this field.

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Keywords

depression; geriatric; pharmacogenomic; decision support tool; genetic testing; late-life depression; precision medicine

Introduction

The pathophysiology of late-life depression (LLD) differs from that of major depressive disorder (MDD) in adult populations (1). LLD has been linked with aberrant activity of the hypothalamic-pituitary-adrenocortical (HPA) and neuroimmune systems, amyloid and tau pathology, and neurological abnormalities such as executive dysfunction which predict poor response to antidepressants (2–5). Physical ailments associated with advanced age such as vascular disorders are also significant risk factors for LLD (6). When compared to depressed adults, LLD patients often have no family history of depression, increased incidence of dementia, and increased presence of white matter hyperintensities detected by magnetic resonance imaging (MRI) which is associated with poorer response to pharmacological treatments (7). LLD patients are susceptible to side effects from antidepressants, given that many have comorbid conditions, and studies have reported that nearly 6% of naïve antidepressant users experience a side effect within the first 30 days of treatment initiation (8; 9). Common side effects include cardiovascular (e.g. hypotension), gastrointestinal (e.g. nausea, vomiting), and anticholinergic complications which may incite cognitive impairment (10).

For moderate to severe LLD, clinicians employ a “trial-and-error” approach to optimize treatment regimens with antidepressants. In LLD, a recent meta-analysis of trials found only a response rate of 48% and a remission rate of 33.7% from treatment (11). With poor recovery rates from antidepressants, and the LLD population expected to double by 2050, the development and availability of effective interventions to treat LLD will be an increasingly important public health issue (12; 13).

An emerging and promising approach to aid in the treatment of depression lies in the field of “precision medicine,” which uses genetic, lifestyle, and environmental information to guide treatment (14; 15). Pharmacogenetics is one tool of precision medicine which utilizes an individual’s genetic make-up to guide medication prescription via the use of DSTs (16–18). A growing evidence-base suggests that individual genetics influences the treatment response to antidepressants (19). Yet enthusiasm for DST use has been tempered by findings from three large independent genome-wide pharmacogenetic studies (the Genome-Based Therapeutic Drugs for Depression [GENDEP] project, the Munich Antidepressant Response Signature [MARS] project, and the Sequenced Treatment Alternatives to Relieve Depression [STAR*D] study) that failed to find a reliable predictor of antidepressant treatment outcomes (20). Although more recently, pharmacogenetic evidence compiled by the Pharmacogenomics Knowledgebase (PharmGKB) and efforts by the Clinical Pharmacogenetics Implementation Consortium (CPIC) has led to the development of pharmacogenetic-informed antidepressant guidelines (21; 22). These guidelines have

prompted clinicians to consider use of DSTs in the context of adult MDD (23; 24). However, there is a paucity of literature examining the role of these tools in older adult populations.

In this clinical review, we provide a critical review of the peer-reviewed literature on pharmacogenetic DSTs for major depression management and discuss the biological and clinical considerations for the use of these tools in treating LLD.

Review of Pharmacogenetic Decision Support Tools for Major Depression Management

The arrival of Roche's Amplichip in 2004 signaled the introduction of first generation DSTs —tools that provide liver-only genotype and phenotype information without providing clinical interpretation. By contrast, second generation DSTs analyze both liver and brain genetics, and provide clinical interpretation. This may include information related to drug selection and dosage, as well as warnings of drug-drug interactions (25; 26). There are currently 28 pharmacogenetic DSTs relevant to major depression management, and 18 of these tools are available in the US (see table 1).

Several industry-sponsored studies have evaluated the clinical utility and economic benefits of DSTs in a psychiatric context via prospective study design (see supplementary table). Initial results provide modest evidence for DST clinical utility and end-user support. Only 3 DSTs have been subjected to randomized controlled trials (i.e., CNSDose, Baycrest Biotechnology; Genesight, AssureRx; Neuropharmaogen, AB Biotics) (27–29) (see table 2). Genesight and CNSDose studies have been reviewed in prior systematic reviews (27; 29; 30). The Genesight group conducted a randomized, double-blind, 10-week prospective study and reported a non-statistically significant trend toward improved outcomes (31). The CNSDose group conducted a randomized, double-blind, 12-week prospective study and reported a 2.5-fold increase in remission rates in the CNSDose group ($P<0.0001$) (16). The Neuropharmagen group conducted a randomized, double-blind, 12-week prospective study and reported a higher proportion of responders at 12 weeks in the guided group vs. unguided group ($P=0.0476$) (32). The three RCTs were all industry-sponsored, hence independent replication and head-to-head trials are needed. These studies primarily focused on the utility of DSTs in adult depression; no clinical trial has primarily evaluated a DST for LLD.

Attitudes Toward Pharmacogenetic Decision Support Tools for Major Depression Management

Recent surveys have found that 80% of clinicians surveyed believe pharmacogenetic testing will become standard in psychiatry (33), and that patients who received DST guided treatment report more positive perceptions of care (34). Another recent survey found that while up to 98% of physicians surveyed agreed that drug response may be influenced by genetic variation, only 13% indicated they had ordered a DST within the last half year (35). Currently, there are no estimates of the prevalence of DST use specifically for depression. However, a recent survey of 300 psychiatrists found that about 7% had ordered a DST to guide treatment (36). Anecdotally, practitioners at non-academic settings may be more likely

to use DSTs than physicians at university hospitals who may have more conservative approaches to adopting technologies due to the lack of rigorous peer-reviewed research supporting such practices (37). There are some exceptions, such as St. Jude Children's Research Hospital in Memphis affiliated with the University of Tennessee that has integrated DSTs into their electronic health records systems to guide gene-based clinical decisions on tricyclic antidepressants and selective serotonin reuptake inhibitors (SSRIs) (37; 38).

Clinical and Biological Considerations for Pharmacogenetic Decision Support Tool use in Late-Life Depression

As the use and availability of DSTs continues to increase, and their evidence-base continues to evolve, it will be more important for clinicians to understand when and how to apply DSTs to guide LLD management. Reviews of the clinical use of these tools have previously focused on adult MDD (23).

Are pharmacogenetic DSTs applicable to LLD?

The recognition of LLD as a distinct psychiatric condition separate from adult depression has important clinical implications for the use of DSTs, given that no trials have been conducted in late-life cohorts. For instance, plasma levels for certain tricyclic antidepressants (TCAs) and SSRIs are known to be influenced by polymorphisms in cytochrome P450 enzyme genes implicated in adult depression (21; 39). However, this correlation deviates for LLD. This has been demonstrated in studies on gene-drug interactions between the CYP2D6 gene and the TCA nortriptyline as well as the CYP2C19 gene and the SSRI citalopram, where the same extent of variation seen in adult depression did not apply in LLD (40–42).

Patient age can impact both the pharmacodynamics and pharmacokinetics of drugs (43). For example, age has been shown to reduce 2C19 but not 2D6 activity in subjects older than 50 years of age (44). Pharmacodynamic genes encode proteins that mediate the action of the drug (e.g., receptors, signaling), whereas pharmacokinetic genes encode proteins involved in the absorption, distribution, metabolism, or elimination of the drug. Thus, recommendations provided for adult patients may not have the same clinical utility for LLD patients.

Are DSTs pre-emptive or reactive tools?

There is not yet a consensus on the best clinical timing to utilize DSTs. Providers may use DSTs before initiating pharmacotherapy to improve the odds of successful treatment. Some DST manufacturers have evidence to support pre-emptive use via clinical trials (29). Alternately, providers may use DSTs only after treatment failure. This is because patients who fail one or more lines of treatment and develop treatment resistance may be more likely to harbor genetic mutations and thus are more likely to benefit from pharmacogenomics approaches (45).

For now, the timing of DST use largely depends on individual provider and patient preference, and medical necessity criteria (46). For example, the Centers for Medicare & Medicaid Services (CMS) has issued a Local Coverage Determination (LCD) for

Genesight's combinatorial depression test which requires that a psychiatrist must be considering changing medication for a patient with major depressive disorder suffering from refractory moderate to severe depression. It also requires a patient to have suffered at least one prior psychiatric medication failure (47). In the future, if the clinical efficacy and cost utility of DSTs can be robustly established and accepted by clinical practice guidelines, pre-emptive use will likely be most appropriate as it will reduce the risk of initial treatment failure.

Can DST results be easily interpreted and integrated into my practice?

All DST manufactures attempt to report pharmacogenetic results in a clinician-friendly manner, but end-user knowledge varies widely. Accurate interpretation of DST reports may be challenging for psychiatrists without training in pharmacogenetics. Physicians may vary in terms of competency for selection and dosing in the context of potentially confounding environmental and lifestyle factors (48), and many providers lack access to geneticists or genetic counsellors (36). Complicating this issue further is the lack of standardization in reporting pharmacogenetic results. The Centers for Disease Control and Prevention as well as the Clinical Pharmacogenetics Implementation Consortium have recently published recommendations aimed at increasing standardization of pharmacogenetic test result reporting (49; 50). However, the extent to which these recommendations will be followed by DST manufacturers is unclear.

Some DST manufactures offer expert consultation, but the quality of these services has not been independently evaluated. In the absence of formal consulting services, several resources are available to assist clinicians with interpretation and implementation of pharmacogenetic information. For example, Implementing Genomics in Practice (IGNITE), from the National Institutes of Health (NIH), provides an online toolbox with guidelines, best practices, and clinical examples for providers (51). Yet this and other resources are not specific to psychiatry, or to unique clinical populations such as LLD. Thus, the ease of interpreting and integrating DST results into practice may still depend on a clinician's personal knowledge and access to consultants.

Do patients want DSTs, and do they promote shared decision-making?

DSTs provide an opportunity to increase the potential benefits of shared decision-making, a process that emphasizes the importance of both patients and clinicians in making treatment decisions. Recently, shared decision-making has received significant attention as a promising strategy to improve clinical outcomes in depression (52). Given that LLD patients often have multiple medications and are less involved in their care (53; 54), the presence of DST results may encourage shared decision-making.

Do DSTs work for patients prescribed multiple medications?

Depressed patients, particularly patients with LLD, are often prescribed multiple medications (55). Patients taking multiple medications may also be more likely to harbor genetic variations. For instance, frequently hospitalized (defined by at least 3 admissions during the past 2 years) older adults with a prescribed drug regimen of at least five

medications have been shown to have a higher frequency of pharmacogenetic polymorphisms compared to older adults who were not frequently hospitalized (55; 56).

Many DSTs relevant to psychiatry provide genetic information related to medications commonly used in other fields of medicine (e.g., cardiology, oncology). Most DSTs also provide a list of drug-gene interactions based on a patients' genetic profile, although clinicians are given the task of identifying potential drug-drug interactions based on which medications patients are taking (57). Few tests clearly flag possible drug-drug interactions that could affect decisions to modify drug regimens or dosing. Future DSTs may provide added benefit by combining potential drug-gene interactions with the known drug-drug interactions of the medications patients are already taking at the time of genetic testing.

Conclusion

LLD is a growing public health problem due to the increased prevalence of depression and aging of the general population. However, as an improved understanding of the genetic component of LLD emerges from ongoing clinical and basic scientific research, it may be that pharmacogenetic DSTs will become a mainstream tool in improving treatment outcomes. For now, the clinical use of DSTs has remained minimal due to the lack of evidence from high-quality clinical trials and low awareness of the existing evidence-base.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1

Clinical and Research Recommendations for the use of Pharmacogenetic Decision Support Tools in the Treatment of Late-Life Depression

- There is limited evidence supporting the use of DSTs for major depressive disorder (MDD) in adult populations and there is no primary research data in older adults.
- There is a need for prospective clinical trials specifically in LLD cohorts, as well as for independent replication of industry-sponsored research and head-to-head trials for MDD.
- Pharmacogenetic DSTs are not the standard of care for LLD treatment, but have theoretical and anecdotal support.
- Physicians should cautiously consider the use of DSTs for LLD treatment, and be aware that DSTs are a heterogeneous group of products with a rapidly evolving evidence-base.

Highlights

- This clinical review is the first to provide a critical analysis of the peer-reviewed literature on pharmacogenetic support tools (DSTs) for late-life depression management.
- There is limited evidence supporting the use of DSTs for major depressive disorder (MDD) in adult populations and there is no primary research data in older adults.
- There is a need for prospective clinical trials specifically in LLD cohorts, as well as for independent replication of industry-sponsored research and head-to-head trials for MDD.
- Pharmacogenetic DSTs are not the standard of care for LLD treatment, but have theoretical and anecdotal support.
- Physicians should cautiously consider the use of DSTs for LLD treatment, and be aware that DSTs are a heterogeneous group of products with a rapidly evolving evidence-base.

Table 1

Pharmacogenetic decision-support tools for major depression in the US

Name	Company	Genes Evaluated	Clinical Evidence
CNSDose	Baycrest Biotechonology	ABCB1, ABCC1, CYP2C19, CYP2D6, UGT1A1	(17; 59)
Genecept	Geomind	CYP2C19, CYP2D6, CYP3A4, ANK3, CACNA1C, COMT, DRD2, HTR2C, MTHFR, SLC6A4	(60; 61)
Genesight	Assurex Health	CYP1A2, CYP2C19, CYP2D6, UGT1A4 *, UGT2B15 *, HLA-A *, HLA-B *, HTR2A, SLC6A4	(24; 62–66)
IGL Psychiatry	International Genetics Laboratories	CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, MTHFR, SLC6A4, SULT4A1	N/A
Mental Health DNA Insight	Pathway Genomics	CYP2D6, CYP2C19, CYP3A4, CYP2B6, SLC6A4	N/A
Millennium PGT	Millennium Health	CYP2B6, CYP2C19, CYP2D6, CYP3A5, UGT2B15, VKORC1, COMT, MTHFR, OPRM1	N/A
MyPGt	MyGENETX	ANKK1/DRD2, COMT, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, OPRM1, SLCO1B1	N/A
Personalized Medicine Panel	AlphaGenomix	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2D6, CYP3A, ADR2A, APOE, COMT, DRD2, F2, F5, DPYD, G6PD, MTHFR, OPRM1, SLC6A4, SLCO1B1, SULT4A1, TPMT, UGT1A1, UGT2B15, VKORC1	N/A
Personalized Medicine Test	Advance Genomic Solutions	APOE, COMT, CYP1A2, CYP2B6, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, HTR2A, HTR2C, MTHFR, OPRM1, SLCO1B1, UGT2B7, VKORC1	N/A
PRIMER	PGXL Laboratories	CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4, NAT2, VKORC1, COMT, F2, F5, HLA-B, MTHFR, OPRM1, SLC6A4, SLCO1B1	N/A
PGxPredict	Transgenomic	ABCB1, CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, VKORC1, F2, F5, MTHFR	N/A
PGxOne	Admera Health	CYP1A2, CYP2C19, CYP2C9, CYP2D6, DYPD, TPMT, UGT1A1, VKORC1, F5, G6PD, HLA-B, IFNL3	N/A
Pharm D	DNA Stat	CYP2C19, CYP2C9, CYP2D6, CYP3A4, CYP3A5, VKORC1, F2, F5, MTHFR	N/A
Proove Drug Metabolism	Proove Biosciences	CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, UGT2B7, VKORC1	N/A
PsychPanel	GeneAlign	N/A	N/A
RenaissanceRX	RenaissanceRX	CYP1A2, CYP2C19, CYP2C9, CYP2D6, UGT1A1, UGT2B7, VKORC1, MTHFR, OPRM1	N/A
Rxight	MD Labs	ADRA2A, ANKK1, COMT, CYP2B6, CYP CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, DPYD, GRIK4, HTR2C, MTHFR, OPRM1, SLCO1B1, TPMT, UGT2B15, VKORC1	N/A
YouScript	Genelex	CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, ADRA2A, COMT, GRIK4, HTR2A, HTR2C, MTHFR, SLC6A4	(55)

* These genes were not included in clinical studies evaluating the Genesight panel.

Table 2

Randomized Controlled Trials Assessing Pharmacogenetic Decision Support Tools for Major Depression

Reference	Year	Study design	Sample size	Sponsorship	Sample characteristics	Eligibility	Target genes and report format (if applicable)	Findings
[1]	2015	• 12-week prospective double blind RCT. Assay guided prescribing vs treatment as usual • Remission rates assessed with baseline and 4 weekly HDRS by independent blinded rater • Intolerability events, where patient needed to reduce the dose or stop their antidepressant, were recorded • Number of sick days taken off work or studies due to depression were recorded	148	CNSDose, Australia	Guided vs unguided • Mean baseline HDRS: 24.81 vs 24.66 (NS) • Mean duration of MDE 8.51 vs 8.59 months (NS) • Mean number of MDD episodes 2.22 vs 2.18 (NS) • Proportion male 42% vs 39% (NS) • Mean age (years) 44.2 vs 44.3 (NS) • Proportion employed 91% vs 89% (NS)	Inclusion: • Age ≥18 years • Male and female • Primary diagnosis of MDD by DSM-5 criteria assessed by semi-structured psychiatrist interview • HDRS score ≥18 • Caucasian subjects Exclusion: • Other active psychiatric diagnosis • Substance use disorder • Pregnancy or breastfeeding • Hepatic or renal impairment • Co-prescription of known CYP2D6, CYP2C19 or ABCB1 inducers/ inhibitors • Regular grapefruit drinkers • Current smoker	Target genes: ABCB1, ABCC1, CYP2C19, CYP2D6 and UGT1A1 Medications: Sertraline, escitalopram, paroxetine, fluoxetine, fluvoxamine, reboxetine, venlafaxine, desvenlafaxine, duloxetine, mirtazapine, agomelantine, clomipramine, nortriptyline, amitriptylline Report format: Pharmacogenetic interpretive report indicated if the patient's genotype suggested mid-range, high-range or low-range doses were needed.	Outcome 1: Efficacy, by remission (HDRS ≤ 7) • Subjects receiving genetically guided prescribing had a 2.52-fold greater chance of remission (95% confidence interval [CI]=1.71–3.73, z=4.66, p<0.0001). • The number needed to genotype (NNG)=3 (95% CI=1.7–3.5) to produce an additional remission. Outcome 2: 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. Outcome 3: Sick days • The genetically guided group had significantly less risk of taking sick leave (4% versus 15%, p=0.0272) and significantly less duration of sick leave when such was needed (4.3 days versus 7.7 days, p=0.014).
[3]	2013	• 10-week prospective, double-blind RCT. Assay guided prescribing vs treatment as usual (TAU)	51	GeneSight, USA	TAU vs Guided, values as mean ± SD • Randomization scheme did not balance for	Inclusion: • Diagnosis of MDD or DDNOS	Target genes: CYP2D6, CYP2C19, CYP1A2, SLC6A4, HTR2A. Medications:	Outcome 1: Utilisation of GeneSight • The likelihood of clinicians switching, augmenting or dose-adjusting medication regimens during the trial period was the

Reference	Year	Study design	Sample size	Sponsorship	Sample characteristics	Eligibility	Target genes and report format (if applicable)	Findings
		• Clinicians of patients randomised to the assay guided prescribing arm were provided with the report at first clinic visit (week 2 of study) • Study subjects and raters were blinded to the treatment arm for the duration of the study • In both arms, antidepressant adjustment started from the first clinic visit (week 2 of study) • Assessment data was collected at baseline and 4, 6 and 10 weeks and included the HAMD-17, the FIBSERS, the QIDS-CR and QIDS-SR and the PHQ-9.			age, gender and ethnicity • Mean number of psychiatric medications at baseline 2.7 ± 1.2 vs. 2.9 ± 1.2 (NS) • Mean number of previous psychiatric medication trials 4.5 vs 4.3 (NS) • Mean age 47.8 ± 13.9 vs 50.6 ± 14.6 (NS) • Proportion female 92% vs 69% (p=0.04) • Proportion non-Hispanic white 100% vs 96% (NS)	• HAMD-17 score ≥ 14 Exclusion: • Other active psychiatric diagnosis • Substance use disorder	SSRIs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline; SNRIs: desvenlafaxine, duloxetine and venlafaxine; TCAs: amitriptyline, clomipramine, desipramine, doxepin, imipramine and nortriptyline; MAOi: selegiline; Atypical antidepressants: bupropion, trazodone and mirtazapine; Typical antipsychotics: chlorpromazine, fluphenazine, haloperidol, perphenazine, thioridazine and thiothixene; Atypical antipsychotics: aripiprazole, clozapine, iloperidone, olanzapine, quetiapine, risperione and ziprasidone. Report format: The interpretive report categorized each of the 26 psychotropic medications into either a green (‘use as directed’), yellow (‘use with caution’) or red category (‘use with increased caution and with more frequent monitoring’) phenotype.	same in both groups (Genesight=53% vs TAU=58%; X^2=0.19; p=0.66) • All GeneSight subjects 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) • 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) • No difference in the number of mental health visits between groups at the end of the study (X^2=6.86; df=11; p=0.81) Outcome 2: 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 HAMD-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%)
[7]	2016	• 3-month prospective, naturalist, double-blind RCT • Assay guided prescribing vs treatment as usual • Evaluated at baseline, 6 and 12 weeks and with telephone interviews at 4, 8, and 12 weeks by	316	Neuropharmagen, Spain	Sample Characteristics not clear from abstract but authors have noted: • The study cohort displayed a large diversity in terms of duration of disease, number of previous treatments, depression severity and	Inclusion and Exclusion criteria Inclusion: • Adult patients Diagnosis of MDD	Target Genes, medications and report format are not specified in the abstract.	Outcome 1: Efficacy • Participants in the guided group showed a higher reduction in HDRS at 6 weeks (p=0.0364), but not at 12 weeks. • Patients with baseline HDRS ≥14 (n=254), and in those who had received 1 to 3 previous treatments (n=190) had significant reductions in PGI-I at 12 weeks and HDRS at 6 and 12 weeks.

Reference	Year	Study design	Sample size	Sponsorship	Sample characteristics	Eligibility	Target genes and report format (if applicable)	Findings
		PGI-I, 17-HDRS, FIBSERS, SDI, SATMED-Q.			psychiatric comorbidities.			• 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]). No statistical significance in the rate of sustained response was observed at week 4 or 8. Outcome 2: Tolerance • Of the participants reporting side-effects at baseline via FIBSER score, 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]).

Abbreviations:
CPGx Combinatorial pharmacogenomic test, trade name of Assurex Health Inc.
CGI-S Clinical Global Impressions – Severity of Illness
CGI-I Clinical Global Impressions – Improvement
DDNOS Depressive disorder not otherwise specified
DSM Diagnostic and Statistical Manual of Mental Disorders
FIBSERS Frequency, Intensity, and Burden of Side Effects Rating Scale
HAMD-17 17-item Hamilton Rating Scale for Depression
HDRS 17-item Hamilton Depression Rating Scale
ICD International Statistical Classification of Diseases and Related Health Problems
MDD Major Depressive Disorder
NS Not statistically significant (p>0.05)
PDC Proportion of days covered
PGI-I Patient Global Impression of Improvement scale
PHQ-9 9-item Patient Health Questionnaire
QIDS-C16 16-item Quick Inventory of Depression Symptomatology Scales – Clinician Rated
QIDS-CR 16-item Quick Inventory of Depression Symptomatology Scales – Clinician Rated
QIDS-SR 16-item Quick Inventory of Depression Symptomatology Scales – Subject Rated
Q-LES-Q-SF Quality of Life Enjoyment and Satisfaction Questionnaire Short Form
SAS Zung Self-Rated Anxiety Scale
SATMED-Q Treatment Satisfaction with Medicines Questionnaire
SD Standard deviation
SDI Sheehan Disability Inventory
TAU Treatment as usual
UKU Udvalg for Kliniske Undersogelser Side Effect Rating Scale

Table References:

[1] Singh, A.B., *Improved Antidepressant Remission in Major Depression via a Pharmacokinetic Pathway Polygene Pharmacogenetic Report.* Clin Psychopharmacol Neurosci, 2015. **13**(2): p. 150–6.

[3] Winner, J.G., et al., *A prospective, randomized, double-blind study assessing the clinical impact of integrated pharmacogenomic testing for major depressive disorder.* Discov Med, 2013. **16**(89): p. 219–27.

[7] Pérez, V., et al. *Effectiveness of pharmacogenetic information in the treatment of major depressive disorder: results from the AB-GEN randomized clinical trial. in 29th ECNP Congress.* 2016. Vienna.