The extent of treatment response and preference heterogeneity in major depressive disorder: implications for population-level resource allocation

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Supplemental Information and References

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Background

- Major depressive disorder (MDD) affects ~21 million US adults annually, 8.3% of the adult population.[1]
- Despite a wide range of available treatments, health outcomes remain suboptimal, with less than half of US adults receiving antidepressants achieving remission.[2]
- Payers often design coverage and utilization management (UM) around population-average outcomes, and Health Economics Methods Advisory (HEMA) guidance recommends using "average preferences" for population-level resource allocation decisions.[3] However, this may lead to suboptimal health outcomes, as treatment effects and patient preferences can be heterogeneous.

Study Objectives:

To characterize the nature and extent of heterogeneity of (1) treatment effects and (2) patient preferences for treatment across individuals and subgroups with MDD.

Methods

- Two targeted literature reviews were performed: one to identify evidence of heterogeneous treatment effects in MDD, and another to identify evidence of heterogeneous patient preferences in MDD.

Selection Criteria

Heterogeneity of Treatment Response:

- Included studies reported antidepressant outcomes stratified by patient characteristics, with effect magnitudes and statistical significance, published ≥2010 that also included US patients. Studies were excluded if they were: pediatric-only (<18 years), single-arm, or non-English studies.

Heterogeneity of Patient Preference:

- Included studies reported quantitative or qualitative MDD treatment preferences with subgroup heterogeneity testing or stratification, published ≥2010 that also included US patients. Studies were excluded if they were: non-MDD-specific, provider/caregiver preferences only, pediatric-only (<18 years), or non-English studies.

Search Strategy

- Targeted literature searches were performed on PubMed and Google Scholar databases between October 29, 2025 and November 28, 2025, supplemented with forward/backward citation searching of key publications.
- Study eligibility was assessed in two stages: titles/abstracts were screened against predefined criteria, followed by full-text review to select articles for inclusion. Source quality was evaluated qualitatively by the study team.

Evidence Synthesis

- Data was extracted from the final set of included studies on study characteristics, design, data years and sources, treatments evaluated, outcome measures, specific subgroups/patient types identified, and estimates of heterogeneity.

Heterogeneity of Treatment Response:

- Evidence was categorized by heterogeneity signal credibility using Sun et al. (2010) criteria for assessing subgroup effects based on methodological standards established since 1992: signals were deemed more credible when effect modifiers were pre-specified (not post-hoc), tested via formal interaction tests (not within-group comparisons), and adjusted for multiple comparisons to minimize chance findings.[4] Evidence was labeled as "strong-to-moderate" when meeting those criteria with clinically meaningful effect modification, and "weak/tentative" when exploratory, unadjusted for multiple tests, statistically non-significant, or lacking clear modifier interactions.

Heterogeneity of Patient Preference:

- Evidence was categorized by the number of available studies reporting: (1) key preference differences in treatment attributes (e.g., efficacy, treatment delivery, adverse events) across subgroups, if the preferences were supported by multiple studies, or (2) other preference differences across subgroups, if they were supported by only one study.

Results

Heterogeneity of Treatment Response

- Of 182 publications evaluated, 23 studies (18 RCTs, 3 RWD, 2 meta-analyses) met inclusion criteria, examining primarily antidepressant monotherapy and some combination/augmentation strategies, with outcomes focused on symptom severity (18/23, 78.3%) and response/remission (10/23, 47.8%); see Supplement Figure 1, Supplement Table 1.

Strong-to-Moderate Signals

- **Inflammation Markers**: Patients with higher inflammation (elevated CRP,[5] IL-17,[6] PDGF[7]) responded better to bupropion-containing combinations, while those with lower inflammation responded better to selective serotonin reuptake inhibitor (SSRI) monotherapy (Figure 1, Supplement Table 2).
- **Metabolic Factors**: Higher-risk metabolic profiles (adiponectin level,[8] BMI[9,10]) favored bupropion combinations, while lower-risk profiles favored venlafaxine-based treatments.
- **Neurophysiological Characteristics**: Brain imaging predicted differential treatment responses. Patients who received treatment favorable to individual cerebral blood perfusion profile[11] observed greater remission rates than those receiving non-targeted treatment. Neural connectivity patterns[12-14] varied by antidepressant, with stronger reward circuit connectivity (NACC-rACC) favoring bupropion over sertraline, while weaker reward pathway connectivity and certain brain region activity patterns favored sertraline.
- **Clinical Features**: Augmentation outperformed bupropion in treatment-resistant patients with hypomanic symptoms.[15] High neuroticism and strong cognitive control favored sertraline.[16] SSRIs benefited severe MDD without anxiety but underperformed with comorbid anxiety.[17] Escitalopram underperformed versus psychotherapy in patients with psychomotor activation or reassurance-seeking.[18]

Weak-to-Tentative Signals

- Demographics (age and sex),[19-21] medical history,[20,22-24] certain comorbidities (i.e., irritable bowel syndrome),[25] and certain MDD features (core emotional score,[15] trauma,[26] and cognitive control[27]) showed tentative differentiation of treatment effect. These patterns suggested potential treatment effect modification but remained as "hypothesis-generating factors", given observational designs and lack of pre-specified hypotheses (Supplement Table 3).

Figure 1. Heterogeneity in Antidepressant Treatment Response Across MDD Patient Characteristics

		ARI	BUP	CIT	ESC	SER	FLU	VEN	BUP+ ESC	VEN+ MIR
Inflammatory	CRP (higher vs, lower)				S/R				S/R	
	IL-17 (higher vs. lower)								S	
	PDGF (higher vs. lower)								S	
Metabolic	Adiponectin (higher vs. lower)								S	S
	BMI (higher vs. lower)				R			R	R	R
Neurological	CBP Profile (more favorable vs. less favorable)					R				
	Neural Connectivity - Alpha Band (higher vs. lower)					S				
	Neural Connectivity - Beta Band (higher vs. lower)					S				
	Neural Connectivity - Gamma Band (higher vs. lower)					S				
	Functional Connectivity - NAAC-rACC (higher vs. lower)	S				S				
Clinical	Cognitive Control (higher vs. lower)					S/R				
	Neuroticism (higher vs. lower)					S				
	Hypomanic Symptoms	R	R							
	Anxiety (higher vs. lower)				S/R					
	Psychomotor Activation (higher vs. lower)				R					
	Need for Medical Reassurance (higher vs. lower)				R					

Abbreviations: ARI -- Aripiprazole; BMI – Body mass index; BUP -- Bupropion; BUP+ESC -- Bupropion + Escitalopram; CBP – Cerebral blood perfusion; CIT -- Citalopram; CRP – C-reactive protein; ESC -- Escitalopram; FLU -- Fluoxetine; IL-17 – Interleukin 17; MIR -- Mirtazapine; NAAC-rACC -- The rostral anterior cingulate cortex (rACC) and the nucleus accumbens (NAAC) reward circuits in the brain; PDGF – Platelet-derived growth factor; SER -- Sertraline; VEN -- Venlafaxine; VEN+MIR -- Venlafaxine + Mirtazapine

Legend for Figure 1	
Comparisons:	
	Significant positive relationship between the variable and treatment outcome
	Significant negative relationship between the variable and treatment outcome
	Mixed findings across multiple studies
Treatment Outcome:	
S	Change in depression severity
R	Remission

Heterogeneity of Patient Preference

- Of 110 publications evaluated, 19 studies (10 DCEs, 2 qualitative, 7 other quantitative/reviews) met inclusion criteria, examining pharmacological treatments, psychotherapy, and self-care interventions across attributes including treatment efficacy, modality, adverse events, and cost (Supplement Figure 2, Supplement Table 4).

Key Preferences

- **Treatment Effects**: Preferences for treatment efficacy varied by age,[28,29] sex,[28,29] depression severity,[29,30] education,[29,30] income,[30] and current treatment type.[31] Younger patients prioritized faster symptom relief, men prioritized effect magnitude and accepted more adverse events, and women prioritized speed of benefit. Patients with severe depression were willing to tolerate adverse events for greater efficacy (Figure 2, Supplement Table 5).
- **Treatment Delivery**: Preferences for how treatment is delivered varied substantially by age,[28,32-36] sex,[34,36-38] education,[30,32,33] depression severity,[30,34,39-42] race,[36-38,43,44] income,[30,43] and relapse history.[45] Older patients favored structured, high-touch formats, while younger patients preferred individual or digital interventions. Education influenced access preferences, and severity affected acceptance of medication and stigma concerns, with additional variation documented for subgroups based on race/ethnicity, income, and relapse history (Figure 2, Supplement Table 5).
- **Adverse Events**: Willingness to tolerate adverse events varied by age,[28,29,31] sex,[29] education,[29] depression severity,[29,39] and relapse history.[45] Younger patients and women prioritized minimizing adverse events, while men accepted higher risk for greater efficacy. Depression severity influenced which adverse events were deemed most concerning, and higher education correlated with lower adverse event risk tolerance (Figure 2, Supplement Table 5).

Other Preferences

- Single studies identified heterogeneity in preferences for out-of-pocket costs,[46] medication purchase convenience (online vs. pharmacy),[45] visit frequency/intensity,[32] and willingness to make lifestyle changes[35] across patients differing in severity, relapse history, age, and education (Supplement Table 6).

Figure 2. Studies Reporting Heterogeneity in Patient Preferences for MDD Treatment Attributes

Discussion

- ***Treatment response in MDD was heterogeneous***, varying across inflammatory biomarkers, metabolic characteristics, neurophysiology, clinical features, and demographics, with relative treatment benefits differing by 1.3-fold to 15-fold across patient subgroups.
  - Many key modifiers of treatment response, (e.g., inflammatory biomarkers, clinical characteristics), are visible to providers and patients but not captured in payers' claims data.
- ***Patient preferences across attributes varied substantially*** by age, sex, depression severity, education, and care setting.
- From both welfarist (patient-centered) and extra-welfarist (payer) perspectives, accommodating this heterogeneity through open formularies and shared decision-making is essential, aligning with quality care principles[47,48] while also improving treatment adherence, outcomes, and costs.[49-51]

Conclusions

There is substantial treatment response and preference heterogeneity across patient subgroups. Population-level resource allocation decisions that ignore the variation in these patient-level factors will result in wasted resources and poorer health outcomes.

Disclosures

This study was sponsored by Johnson & Johnson. JS and NZ are employees of FTI Consulting. CN is an employee of and holds stock in Johnson & Johnson.