Patient Preference and Adherence

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ORIGINAL RESEARCH

Treatment-Related Factors for Medication Non-Adherence Among Patients with Major Depressive Disorder: An Explanatory Sequential Mixed-Methods Study

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Purpose: This study aimed to examine treatment-related factors influencing antidepressant non-adherence among patients with Major depressive disorder in Pakistan.

Methods: An explanatory sequential mixed-methods cross-sectional design was employed. The study first conducted questionnaire-based quantitative research to assess non-adherence and its treatment-related predictors. This was followed by semi-structured interviews with a purposively selected subset of participants who were poorly adherent to explore their contextual experiences. Quantitative and qualitative findings were integrated using narrative synthesis and joint displays.

Results: A total of 2,513 participants with recurrent major depressive disorder (MDD) were surveyed. Among them, 812 (32.3%) were classified as poorly adherent, 719 (28.6%) as moderately adherent, and 982 (39.1%) as highly adherent, based on the UMGLS-4. High ADR burden, low DAI-10 scores, unemployment, low income, and age above 55 years were significantly associated with non-adherence ($p < 0.05$). Participants with high ADR burden were 1.42 times more likely to be non-adherent (AOR = 1.42, $p < 0.001$). Qualitative findings from 17 interviews supported and expanded these associations, revealing how sedation, weight gain, cultural interpretations of medication as "hot", lack of treatment timelines, and poor pharmacy support discouraged routine antidepressant use.

Conclusion: A combination of physiological, cognitive, and systemic treatment-related barriers drives antidepressant non-adherence among Pakistani MDD patients. Addressing these factors through culturally sensitive ADR counselling, consistent follow-up, and pharmacist-led support may improve adherence and treatment outcomes in low-resource mental health settings.

Keywords: medication non-adherence, major depressive disorder, antidepressants, adverse drug reactions, mixed-methods study

Introduction

Major Depressive Disorder (MDD) is a common and disabling mental health condition impacting approximately 300 million individuals around the globe.[1] Despite the availability of antidepressant medications, achieving and maintaining patient adherence to these treatments remains a critical challenge.[2,3] Poor medication adherence in MDD is common and has dire consequences: studies indicate that roughly half of patients do not take their antidepressants as prescribed.[4,5] This non-adherence is a chief contributor to suboptimal outcomes, including symptom relapse, persistent depression, recurrent episodes, and increased risk of hospitalisation and mortality.[6]

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Medication Non-Adherence (MNA) is a complex problem with various treatment-related barriers. Negative perceptions and treatment experiences play a significant role on the patient side.[7,8] Many patients discontinue antidepressants due to adverse drug reactions (ADRs), concerns about long-term dependency, and doubts about the medication's effectiveness.[9] Such negative beliefs about antidepressant therapy can erode a patient's motivation to continue treatment. Additionally, practical issues like the delay in antidepressants' therapeutic onset and the financial cost of medication can further diminish adherence.[10,11] On the healthcare provider and system side, system-level barriers are also influential. Inadequate patient education and counselling about depression and its treatment[12] lack of clear guidance or follow-up from health professionals,[13] and limited involvement of patients in treatment decisions[14] have all been identified as factors undermining adherence.[15,16] These challenges underscore the need to address both individual and treatment-system factors to improve adherence.

While antidepressant non-adherence is a worldwide concern, it poses particular challenges in low- and middle-income regions such as South Asia.[17] Among these countries, Pakistan faces a substantial burden of depression: recent estimates indicate that about 4.8 million Pakistanis suffer from MDD.[18] Despite this high burden, relatively few studies have investigated medication adherence in Pakistani MDD patients. For example, a study from Pakistan found that about one-third of MDD patients were non-adherent to antidepressants. Key reasons included perceived lack of effectiveness and issues with the treatment regimen.[19] There is a clear knowledge gap regarding the specific treatment-related factors, such as ADRs and insufficient counselling for managing these ADRs, that hinder medication adherence among Pakistani patients with MDD. Most local research to date has been purely quantitative[19–22] or purely qualitative,[23–25] with no study integrating both approaches for a deeper understanding in the MDD context. To address this gap, the present study employs an explanatory sequential mixed-methods design to investigate treatment-related factors for medication non-adherence among patients with MDD in Pakistan. Therefore, this study aims to identify and understand the treatment-related determinants of antidepressant non-adherence in MDD patients within the Pakistani healthcare context. The specific objectives are: a) to determine the prevalence of medication non-adherence in a sample of Pakistani MDD patients, b) to examine how non-adherence correlates with treatment-related factors, c) to explore the experiences and perceptions of MDD patients regarding antidepressant treatment, explaining how side effects, medication beliefs, and healthcare support influence adherence to medication. And d) to merge and interpret the quantitative and qualitative findings to explain how and why treatment-related factors affect antidepressant adherence.

Methodology

Study Design and Mixed-Methods Rationale

The present study was designed as an explanatory sequential mixed-methods study. This sequence was selected to first quantify the magnitude and predictors of non-adherence and then use qualitative inquiry to explain the mechanisms behind the observed statistical associations.

Study Settings and Population

The quantitative phase of this study was conducted as part of a multi-centre cross-sectional survey aimed at generating a broad, representative view of antidepressant adherence patterns across Pakistan. Data were collected from three districts: Lahore, Rawalpindi, and Quetta, between January 2024 and April 2025.

Phase I – Quantitative Component

Data Collection and Sample Size

Eligibility Criteria

Inclusion criteria included age ≥18 years, a clinician-confirmed diagnosis of recurrent MDD using DSM-5 criteria,[26] and at least six weeks of antidepressant therapy. Patients with bipolar disorder, psychosis, or cognitive impairment interfering with consent or who do not understand, read or write Urdu were excluded.

Recruitment and Procedure

Eligible patients were approached during clinic hours and completed a structured questionnaire. Participants were recruited through non-probability consecutive sampling from outpatient psychiatry clinics. During the data-collection

period, 2,645 patients attended the outpatient psychiatry clinics and were screened for eligibility. Of these, 2,610 met eligibility criteria, and 2,513 completed the questionnaire battery and were included in the final analysis (response rate among eligible patients: 96.3%).

Clinician Case Identification and Diagnostic Coding

At each participating outpatient psychiatry clinic, the treating psychiatrist/physician identified potential cases during routine consultations based on DSM-5 criteria for recurrent MDD. Diagnostic codes were not used; diagnosis was confirmed clinically using DSM-5.

Sample Size Calculation

The target sample for this multi-centre cross-sectional survey was calculated with the single-population-proportion formula,[27] assuming a 95% confidence level ($Z = 1.96$), a 3% absolute precision ($d = 0.03$), and an expected non-adherence prevalence of 50% (the most conservative estimate), yielding 1,067 participants. Anticipating clustering across five clinics and a design effect of 2.0, the figure was doubled to 2,134. A further 15% buffer for dropouts set the final recruitment ceiling at 2,500.

Measures

Medication adherence level was assessed using the Urdu version of the Morisky, Green, and Levine 4-Item Medication Adherence Scale (UMGLS-4), which was cross-culturally adapted and psychometrically validated for Urdu-speaking patients with Major Depressive Disorder in Pakistan (Cronbach's α = 0.829).[28,29] The four items measure unintentional and intentional non-adherence (eg., forgetfulness, stopping when feeling better or worse), with yes/no responses scored to yield three adherence levels: high (0), moderate (1–2), or low (3–4).

Patients' attitudes towards antidepressant medication were captured using the Urdu-translated 10-item Drug Attitude Inventory (UDAI-10).[30] The UDAI-10 yields scores ranging from –10 to +10, with higher scores indicating more positive attitudes and likely better adherence. Internal consistency for the Urdu version was acceptable (Cronbach's α = 0.70). For classification purposes, total DAI-10 scores were categorised as: adherent (≥6), moderately adherent (1 to 5), and non-adherent (≤0), consistent with prior adherence studies.[31]

The ADRs were assessed using the Urdu-translated version of the Antidepressant Side-Effect Checklist (UASEC)[32] previously validated and submitted for publication elsewhere. The UASEC is a 21-item self-report tool that evaluates the presence and severity of common antidepressant side effects. Participants rated each symptom as absent, mild, moderate, or severe. Symptom-specific burden scores were calculated (Mild = 1, Moderate = 2, Severe = 3), and a total burden score was obtained by summing scores across all symptoms (possible range 0–63). Additionally, a mean symptom severity score (0–3; Mean ± SD) was computed for each side effect to assess its average impact. The combined use of DAI-10, UMGLS-4, and UASEC enabled a multidimensional assessment of adherence by capturing four interlinked domains. This approach enhances explanatory depth and supports a nuanced interpretation of adherence behaviour. The final form of the data collection set is available as Supplementary Figure 1.

Variables

The primary outcome for regression analyses was medication non-adherence, operationalised as poor adherence on the UMGLS-4. Independent variables encompassed a wide range of demographic factors (age, gender, education, income), clinical characteristics (duration of MDD, presence of comorbidities), psychological predictors (beliefs and attitudes captured by DAI-10), and physiological burden (measured via UASEC). This comprehensive variable framework enabled a multidimensional understanding of how structural, cognitive, behavioural, and somatic factors collectively influence antidepressant adherence.

Statistical Analysis

Descriptive statistics (means, standard deviations, frequencies, and percentages) were used to summarise participant demographics, clinical characteristics, adherence scores, and ADR profiles. UDAI-10 and UMGLS-4 adherence levels were categorised and analysed accordingly. UASEC responses use four built-in categories (absent, mild, moderate,

severe). For analyses requiring simplification, symptoms were also coded as present (mild/moderate/severe) versus absent.

Group differences in adherence were assessed using Kruskal–Wallis and Mann–Whitney *U*-tests. Correlations among UMGLS-4, DAI-10, and ADR burden were examined using Pearson's correlation coefficients. Bivariate logistic regression was used to explore the associations between non-adherence (a binary outcome) and demographic, clinical, and attitudinal predictors. Non-adherence (UMGLS-4 poor adherence = 1; high/moderate = 0) was used as the dependent variable in bivariate and multivariable logistic regression. ADR burden was analysed as a continuous predictor (per 1-point increase). A multivariable logistic regression model retained variables significant at $p < 0.10$. Model fit and performance were evaluated using Nagelkerke R^2 and Variance Inflation Factors (VIFs) to assess multicollinearity. A p-value < 0.05 was considered statistically significant. All analyses were conducted using R version 4.4.1.

Phase II – Qualitative Component

Sampling

The qualitative phase employed a purposive sampling strategy. The qualitative phase was conducted in Healing House, Rawalpindi. The participants were selected from the quantitative sample who were classified as non-adherent (poor adherent) based on their DAI-10 and UMGLS-4 scores. Participants were chosen to reflect variation in age, gender, income, occupational status, duration of MDD, and ADR burden, allowing for diverse perspectives within the non-adherent population. Interviews continued until thematic saturation was reached, indicating that no new themes emerged from subsequent interviews.

Development of a Semi-Structured Interview Guide

A semi-structured interview guide was developed using a prior literature review, an expert panel, and insights from Phase I. The guide focused on treatment-related factors, such as side effect experiences, treatment decisions, and barriers to adherence. It was developed in English and then translated into Urdu using the forward-backward method to ensure validity.[33] The English and Urdu versions of the interview guide are available as Supplementary Figures 2 and 3, respectively.

Interview Procedure

To minimise social desirability bias, all interviews were conducted in Urdu by the principal investigator (S.R)., who was not involved in participants' clinical care. Interviews were held in a private outpatient consultation room at the study site. Participants were encouraged to speak openly. Interviews were audio-recorded with written informed consent and transcribed verbatim in Urdu by S.R. and A.N., with cross-verification by F.K. and A.K. Transcripts were anonymised and assigned ID codes. English translations were checked for accuracy and cultural nuance by the research team. All files were stored securely with access restricted to the study team.

Thematic Analysis

Qualitative data were analysed using reflexive thematic analysis following Braun and Clarke (2006).[34] An inductive-dominant approach was used, while findings from the quantitative phase sensitised the analysis to treatment-related issues. Coding was conducted manually using printed transcripts. An initial codebook was developed by S.R. and independently reviewed by F.K. and A.K. to enhance credibility. Themes were iteratively refined through discussion and constant comparison across transcripts. The original Urdu quotations from the thematic analysis and the deviant case analysis are provided in Supplementary Tables 1 and 2, respectively.

Mixed-Methods Integration

An explanatory sequential approach was used, in which quantitative results were analysed first to (i) estimate prevalence and (ii) identify statistically supported treatment-related predictors of poor adherence; interview sampling and qualitative prompts were then guided by these findings. The joint display was subsequently developed using a structured "following-a-thread" procedure.[35] First, key quantitative predictors were listed and the corresponding effect estimates and directions were extracted. Second, qualitative codes/themes were mapped to each quantitative predictor by identifying interview segments that directly explained the same construct (explanatory) or introduced mechanisms not captured in the survey

(expansion). Third, the joint display rows were populated independently by two authors, disagreements were discussed, and a consensus was reached. Finally, each row was classified as convergent, expansion, or discordant (strands conflicted), and these classifications were used to structure the integrated results.

The qualitative phase was conducted after the quantitative phase because the study aimed to first estimate prevalence and identify statistically supported predictors in a large multi-centre sample, and then explain the mechanisms and lived experiences underlying those patterns in a targeted subgroup. Conducting qualitative work second also enabled purposeful sampling from verified non-adherent participants and ensured the interviews directly addressed the most policy- and clinically-relevant quantitative findings.

Ethical Considerations

This study strictly followed the ethical principles outlined in the Declaration of Helsinki.[36] Ethical approval was obtained from the Advanced Studies and Research Board (ASRB) of the University of Peshawar, Pakistan (Approval No. ASRB PhD/5th 2023). This study received ethical approval from the Institutional Review Board (IRB) of Shaikh Zayed Medical Complex, Lahore (Reference No. 02-TERC/NHRC-SZH/Ext-SC/465), and written permissions were obtained from all clinical settings, including Healing House, Rawalpindi (Ref No. 004), and Sandeman Provincial Hospital, Quetta. Moreover, permission to use validated scales was secured from the original developers. All participants were briefed about the study and provided written informed consent before their participation. The informed consent process also included consent for the publication of anonymized responses and direct quotes. We assured anonymity, voluntary participation, and the option to withdraw at any point without consequence.

Results

Phase-I Quantitative Findings

Patients' Demographic and Clinical Characteristics

A total of 2513 participants were included in the study. The majority were aged 26–40 (42.5%) and were male (54.9%). Most participants were married (59.9%) and employed (32.7%), while 27.1% were housewives. A large proportion had completed higher secondary (33.4%) or bachelor's education (25.3%). Over half had a monthly income between 20,000–40,000 PKR (53.3%). Tobacco use was reported by 38.7% in varying frequencies. All participants had recurrent MDD, with 56.7% experiencing symptoms for less than one year. Comorbidities were present in 49.4%, including diabetes (25.0%) and hypertension (21.4%). The demographic and clinical characteristics of the participants are summarised in Table 1.

Table 1 Demographic and Clinical Characteristics of the Participants

Category	Sub-Category	n (%)
Age groups (Years)	18-25	420 (16.7)
	26-40	1068 (42.5)
	41-55	768 (30.6)
	>55	257 (10.2)
Sex	Male	1380 (54.9)
	Female	1133 (45.1)
Marital Status	Single	652 (25.9)
	Married	1506 (59.9)
	Divorced	245 (9.8)
	Widow	110 (4.4)

(*Continued*)

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Table 1 (Continued).

Category	Sub-Category	n (%)
Occupation	Employed	821 (32.7)
	Unemployed	538 (21.4)
	Housewife	682 (27.1)
	Student	356 (14.2)
	Retired	116 (4.6)
Qualification	Matriculation	559 (22.2)
	Higher Secondary	840 (33.4)
	Bachelors	637 (25.3)
	Masters and higher	477 (19.0)
Monthly Income (Pkr)	<20,000	426 (16.9)
	20,000–40,000	1340 (53.3)
	Above 40,000	747 (29.7)
Tobacco use	Never	1540 (61.3)
	Occasionally	470 (18.7)
	Often	337 (13.4)
	Regularly	166 (6.6)
Self-report Alcohol use	No	2513 (100.0)
	Yes	0 (0.0)
Type of MDD	First Episode	0 (0.0)
	Recurrent	2513 (100.0)
Duration of MDD	<1 year	1425 (56.7)
	1-2 years	561 (22.3)
	2-3 years	269 (10.7)
	>3 years	258 (10.3)
Comorbidities	No	1272 (50.6)
	Diabetes Mellitus T2	628 (25.0)
	Hypertension	538 (21.4)
	Other	75 (3.0)

Adherence Levels (UMGLS-4)

A total of 982 (39.1%) participants showed high adherence, 719 (28.6%) had moderate adherence, and 812 (32.3%) reported poor adherence. Adherence levels are summarised in Table 2.

Participants' Attitude Towards Antidepressants

Based on DAI-10 scoring, 1214 (48.3%) were adherent, 1040 (41.4%) moderately adherent, and 259 (10.3%) non-adherent; mean DAI-10 score was 3.99 (±3.40). Most participants endorsed perceived benefit (n=2138, 85.1%) agreed that the good effects outweigh the bad) and treatment necessity (n=2261, 89.9%) believed medication prevents a breakdown). Autonomy was also frequently endorsed (n=1873, 74.5%) reported taking medication by their own free choice). Regarding experienced effects, 2241 (89.2%) reported feeling more relaxed on treatment, whereas 1169 (46.5%) reported feeling tired or sluggish. Concerns were common: 1225 (48.7%) felt it was "unnatural" to be controlled by medication, and 2130 (84.7%) reported taking medication only when feeling unwell. Overall findings are presented in Table 3 and Figure 1.

Table 2 Medication Adherence Using UMGLS-4

	UMGLS-4		
Items	**High n (%)**	**Moderate n (%)**	**Poor n (%)**
Do you ever forget to take your medicine?	982 (39.1)	719 (28.6)	812 (32.3)
Are you careless at times about taking your medicine?	965 (38.4)	730 (29.0)	818 (32.6)
When you feel better do you sometime stop taking your medicine?	943 (37.5)	740 (29.4)	830 (33.0)
Sometimes if you feel worse when you take the medicine, do you stop taking it?	950 (37.8)	725 (28.8)	838 (33.3)
Overall	982 (39.1)	719 (28.6)	812 (32.3)

Table 3 Attitude Towards Antidepressants

DAI-10 Item	**True n (%)**	**False n (%)**
For me, the good things about medications outweigh the bad.	2138 (85.1)	375 (14.9)
I feel strange "doped up" on medications.	769 (30.6)	1744 (69.4)
I take medications of my own free choice.	1873 (74.5)	640 (25.5)
Medications make me feel more relaxed.	2241 (89.2)	272 (10.8)
Medications make me feel tired and sluggish.	1169 (46.5)	1344 (53.5)
I take medications only when I feel ill.	2130 (84.7)	383 (15.2)
I feel more normal on medications.	2226 (88.6)	287 (11.4)
It is unnatural for my mind and body to be controlled by medications.	1225 (48.7)	1288 (51.3)
My thoughts are clearer on medications.	2103 (83.7)	410 (16.3)
Taking medications will prevent me from having a breakdown.	2261 (89.9)	252 (10.1)
DAI-10 summary/scoring outputs	**Value**	
DAI-10 adherence level (based on total score)		
Adherent	1214 (48.3)	
Moderately adherent	1040 (41.4)	
Non-adherent	259 (10.3)	
DAI-10 total score (Mean ± SD)	**3.99 ± 3.40**	

Frequency and Burden of Antidepressant Side Effects

The most frequent side effects by any severity were dry mouth (74.3%), sweating (53.8%), headache (43.1%), increased appetite (42.5%), and weight gain (41.1%). For the most common severity category, dry mouth was most frequently reported as moderate (851, 33.9%), whereas sweating was most frequently reported as mild (1054, 41.9%). For other common effects, headache was most often mild (774, 30.8%) and weight gain was most often mild (622, 24.8%). The overall mean ADR burden score was 0.38 (±0.63), with a total summed burden score of 21,392, as described in Table 4 and Figure 2.

Scale Inter-Correlations

Significant positive correlations were observed between DAI-10 and UMGLS-4 ($r = 0.43$, $p < 0.01$). ADR burden was negatively correlated with DAI-10 ($r = –0.35$, $p < 0.01$) and UMGLS-4 ($r = –0.38$, $p < 0.01$) (Table 5).

Factors Associated with Non-Adherence

In bivariate analysis, higher odds of non-adherence were associated with age above 55 years (OR = 1.68, 95% CI: 1.27–2.21, $p < 0.001$), unemployment (OR = 1.36, $p = 0.018$), housewife status (OR = 1.31, $p = 0.045$), and retirement (OR = 1.54, $p = 0.038$). Lower income levels, including <20,000 PKR (OR = 1.91, $p < 0.001$), showed increased odds. A one-point decrease in DAI-10 score (OR = 1.22, $p < 0.001$) and a one-point increase in ADR burden (OR = 1.45, $p < 0.001$) were also significant predictors. These findings are summarised in Table 6.

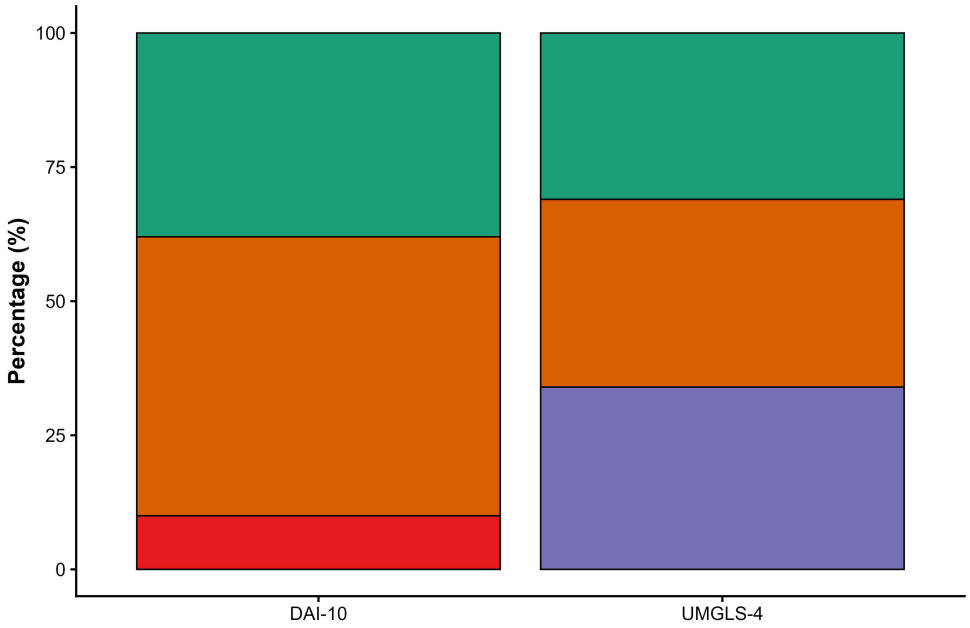

Figure 1 Adherence Level Distribution across UMGLS-4 and DAI-10. The stacked bar colours show adherence levels: green = adherent, Orange = moderately adherent, purple = poor adherence, and red = non-adherent.

In the adjusted model, age above 55 years (AOR = 1.65, 95% CI: 1.20–2.27, $p = 0.002$), unemployment (AOR = 1.43, $p = 0.004$), and income below 20,000 PKR (AOR = 1.79, $p < 0.001$) were significantly associated with increased odds of non-adherence. Each one-point decrease in DAI-10 score (AOR = 1.20, $p < 0.001$) and one-point increase in ADR burden (AOR = 1.42, $p < 0.001$) also predicted non-adherence. Duration of MDD beyond three years was not statistically significant ($p = 0.08$), as described in Table 7 and Figure 3.

Although model diagnostics indicated acceptable fit and predictive strength, the explained variance was modest (Nagelkerke $R^2 = 0.27$), suggesting that additional unmeasured factors may contribute to non-adherence. The AUC value

Table 4 ADR Burden Using UASEC

Side Effect	Absent n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Burden Score n	Mean Severity (Mean ± SD)
Dry mouth	645 (25.7)	744 (29.6)	851 (33.9)	273 (10.9)	3244	1.3 ± 0.97
Insomnia	1610 (64.1)	591 (23.5)	220 (8.8)	92 (3.7)	1415	0.52 ± 0.8
Drowsiness	1677 (66.7)	629 (25.0)	162 (6.4)	45 (1.8)	1046	0.43 ± 0.69
Blurred vision	1924 (76.5)	448 (17.8)	99 (3.9)	42 (1.7)	768	0.31 ± 0.63
Headache	1430 (56.9)	774 (30.8)	234 (9.3)	75 (3.0)	1537	0.58 ± 0.78
Constipation	2024 (80.5)	407 (16.2)	82 (3.3)	–	571	0.23 ± 0.49
Diarrhea	2306 (91.7)	162 (6.4)	45 (1.8)	–	252	0.1 ± 0.36
Increased appetite	1446 (57.5)	580 (23.1)	416 (16.6)	71 (2.8)	1866	0.65 ± 0.85
Decreased appetite	1965 (78.2)	380 (15.1)	121 (4.8)	47 (1.9)	700	0.3 ± 0.65
Nausea and vomiting	2007 (79.9)	393 (15.6)	113 (4.5)	0 (0.0)	619	0.25 ± 0.52
Problem with urination	2100 (83.6)	311 (12.4)	56 (2.2)	46 (1.8)	613	0.22 ± 0.57
Problem with sexual function	2303 (91.6)	142 (5.7)	46 (1.8)	22 (0.9)	326	0.12 ± 0.44
Palpitation	1745 (69.4)	679 (27.0)	75 (3.0)	14 (0.6)	965	0.35 ± 0.57
Feeling light-headed	2022 (80.4)	389 (15.5)	71 (2.8)	31 (1.2)	667	0.25 ± 0.56

(*Continued*)

Table 4 (Continued).

Side Effect	Absent n (%)	Mild n (%)	Moderate n (%)	Severe n (%)	Burden Score n	Mean Severity (Mean ± SD)
Room spinning sensation	2210 (87.9)	202 (8.0)	51 (2.0)	50 (2.0)	605	0.18 ± 0.55
Sweating	1161 (46.2)	1054 (41.9)	231 (9.2)	67 (2.7)	1820	0.68 ± 0.75
Increased body temp	2273 (90.4)	155 (6.2)	62 (2.5)	23 (0.9)	423	0.14 ± 0.47
Tremor	1628 (64.8)	611 (24.3)	174 (6.9)	100 (4.0)	1229	0.5 ± 0.79
Disorientation	2102 (83.7)	318 (12.6)	93 (3.7)	-	504	0.2 ± 0.48
Yawning	2317 (92.2)	145 (5.8)	30 (1.2)	21 (0.8)	288	0.1 ± 0.41
Weight gain	1481 (58.9)	622 (24.8)	333 (13.2)	77 (3.1)	1934	0.6 ± 0.83
Total Burden					21392	
Mean + S. D					8.5 ± 0.3	0.38 ± 0.63

of 0.80 reflects good discrimination; however, model performance may differ in other settings or populations. Furthermore, the cross-sectional nature of the data limits the ability to draw causal inferences.

Phase-II Qualitative Findings

The qualitative sample included 17 participants. Most were aged 46–60 (8, 47.1%) and 31–45 (6, 35.3%). Nine (52.9%) were male and eight (47.1%) were female. Thirteen (76.5%) were married, 11.8% were single, and the remainder were divorced or widowed. Occupations varied, with housewives comprising 29.4%, followed by informal laborers (23.5%)

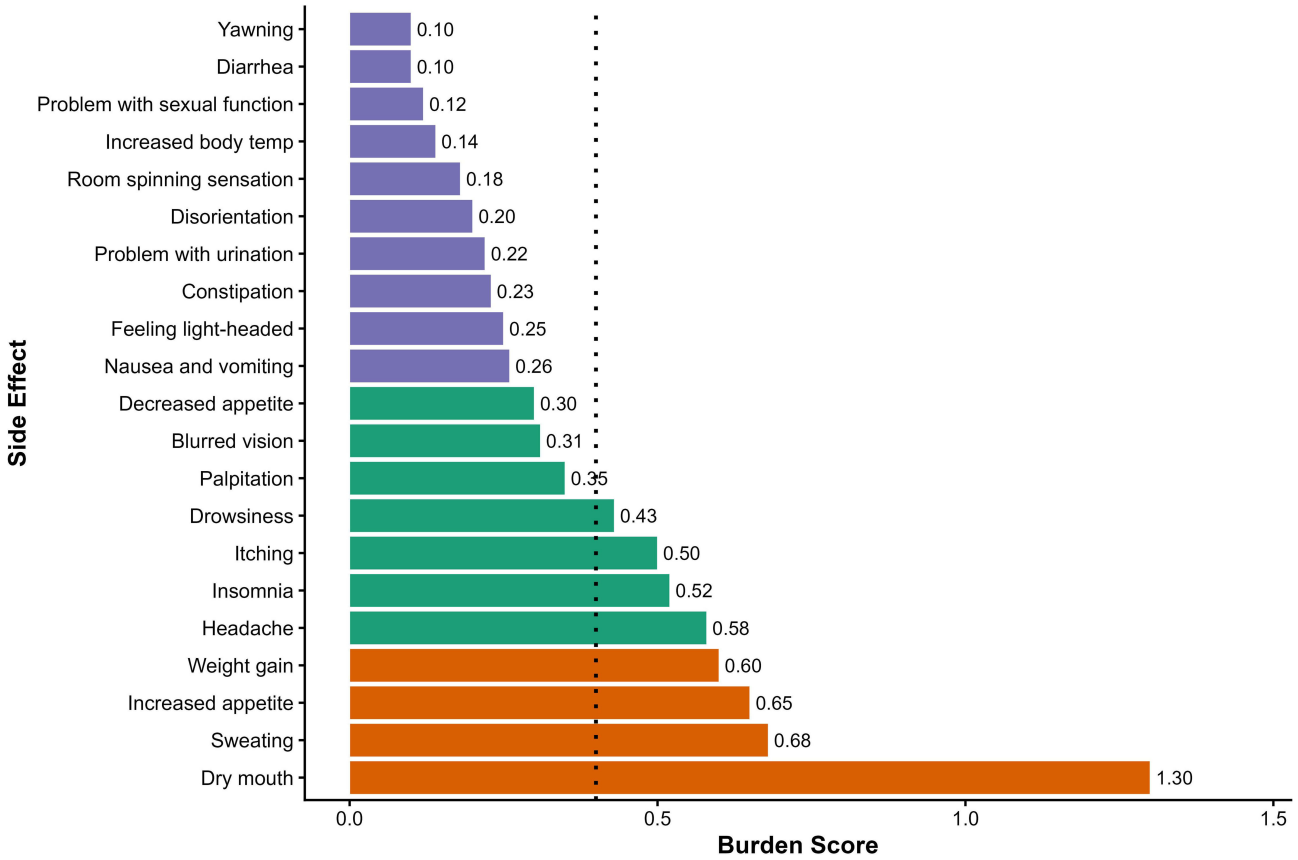

Figure 2 ADR burden categorized by mean severity. Burden level: Orange = High burden; Green = Moderate burden; Purple = Low burden.

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Table 5 Correlations Among Adherence, Attitude, and ADR Burden Scores

Measure	DAI-10	UMGLS-4	ADR Burden
DAI-10	1	0.43*	–0.35*
UMGLS-4		1	–0.38*
ADR Burden Score			1

Note: Pearson correlation coefficients, *$p < 0.01$.

Table 6 Unadjusted (Bivariate) Logistic Regression of Factors Associated with Medication Non-Adherence

Predictor Variable	OR (95% CI)	*p*-value
Age 26–40 vs. 18–25	0.92 (0.71–1.20)	0.53
Age 41–55 vs. 18–25	1.28 (1.00–1.65)	0.051
Age >55 vs. 18–25	1.68 (1.27–2.21)	**<0.001**
Female vs. Male	1.14 (0.94–1.38)	0.18
Unemployed vs. Employed	1.36 (1.05–1.77)	**0.018**
Housewife vs. Employed	1.31 (1.01–1.70)	**0.045**
Student vs. Employed	1.09 (0.80–1.48)	0.58
Retired vs. Employed	1.54 (1.02–2.34)	**0.038**
Income <20,000 PKR vs. >40,000	1.91 (1.45–2.52)	**<0.001**
Income 20,000–40,000 PKR vs. >40,000	1.32 (1.05–1.66)	**0.016**
DAI-10 score (per 1-point decrease)	1.22 (1.14–1.30)	**<0.001**
ADR burden (per 1-point increase)	1.45 (1.30–1.62)	**<0.001**
Duration of MDD >3 years vs. <1 year	1.26 (0.98–1.62)	0.074
Diabetes Mellitus vs. No comorbidity	1.13 (0.91–1.40)	0.27
Hypertension vs. No comorbidity	1.17 (0.94–1.46)	0.15

Note: Reference categories: Age (18–25), Gender (Male), Employment (Employed), Income (>40,000 PKR), Duration of MDD (<1 year), No comorbidity. Bold p-values indicate statistical significance at $p < 0.05$.

Table 7 Adjusted Multivariable Logistic Regression Model

Predictor Variable	β	SE	AOR	95% CI for AOR	*p*-value	VIF
Age >55 vs. 18–25	0.5	0.16	1.65	1.20–2.27	0.002	1.4
Unemployed vs. Employed	0.36	0.13	1.43	1.12–1.81	0.004	1.3
Income <20,000 vs. >40,000	0.58	0.15	1.79	1.34–2.38	<0.001	1.5
DAI-10 score (per 1-point decrease)	0.18	0.03	1.2	1.13–1.28	<0.001	1.6
ADR burden score (per 1-point increase)	0.35	0.06	1.42	1.26–1.60	<0.001	1.5
Duration of MDD >3 years vs. <1 year	0.23	0.14	1.26	0.97–1.65	0.08	1.2

Note: β: logistic regression coefficient (log odds); AOR: adjusted odds ratio; CI: confidence interval; VIF: variance inflation factor. Reference categories: Age (18–25), Gender (Male), Employment (Employed), Income (>40,000 PKR), Duration of MDD (<1 year), No comorbidity. Nagelkerke $R^2 = 0.27$; AUC = 0.80.

and formally employed individuals (17.6%). The majority (12, 70.6%) reported a monthly income below 20,000 PKR. The duration of MDD was reported as 1–3 years in 10 (58.8%) cases and more than 3 years in 4 (23.5%) cases. The Summary of participants' characteristics is described in Table 8, and detailed individual characteristics of participants are provided in Supplementary Table 3.

Thematic Analyses

Theme 1: Medication Side Effects and Physiological Concerns

Participants described how the physical effects of medication, particularly dry mouth, drowsiness, and weight gain, disrupted daily life and contributed to irregular or discontinued use.

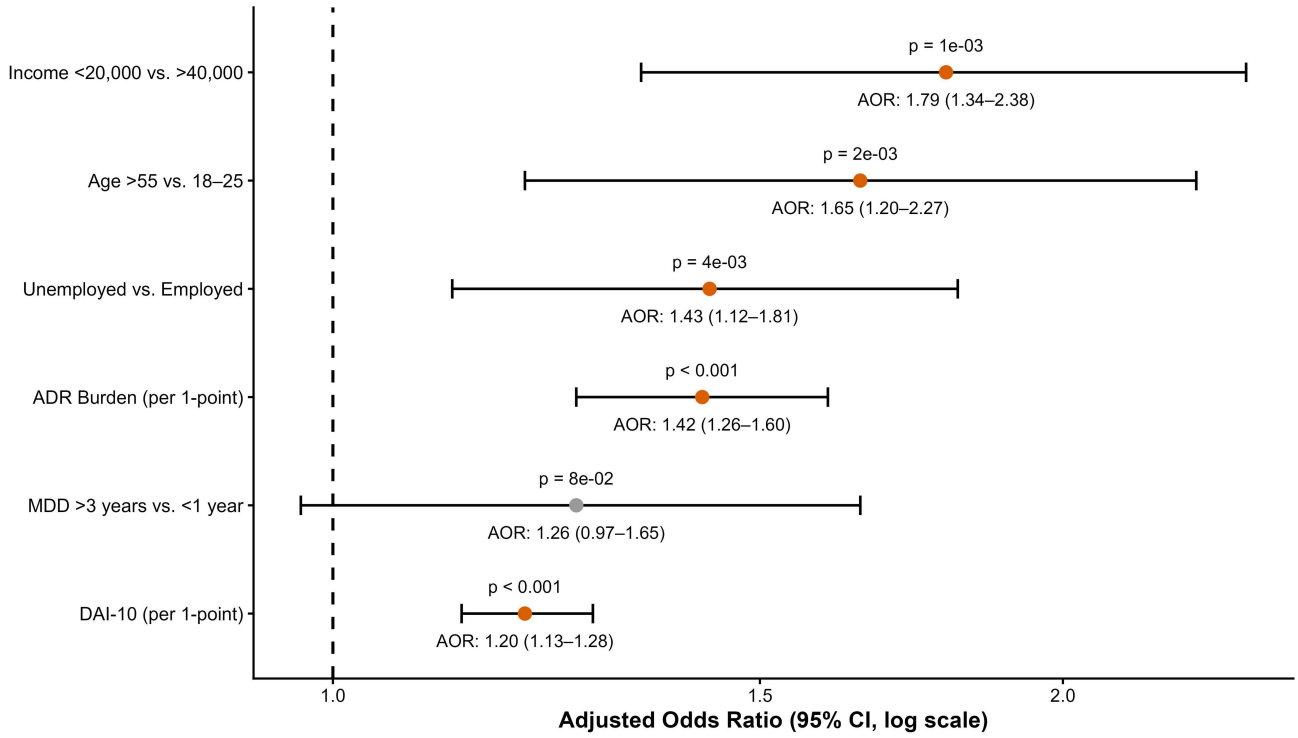

Figure 3 Adjusted odds ratios (AORs) with 95% confidence intervals for factors independently associated with medication non-adherence.

As soon as I take the medicine my mouth goes dry like sand and I keep drinking water but it still feels sticky- (QP-09) ……. (Quote 1)

I started taking it a few months ago and now I sleep like ten to twelve hours a day and even then I feel heavy in the head- (QP-08) ……. (Quote 2)

These medicines make you fat slowly I didn't even realize until my sister said your face has become round and I saw myself in the mirror - (QP-03) ……. (Quote 3)

Table 8 Summary of Demographic and Clinical Characteristics (n = 17)

Category	Sub-Category	n (%)
Age Group (Years)	18–30	3 (17.6)
	31–45	6 (35.3)
	46–60	8 (47.1)
Gender	Male	9 (52.9)
	Female	8 (47.1)
Marital Status	Married	13 (76.5)
	Single	2 (11.8)
	Divorced	1 (5.9)
	Widow	1 (5.9)

(*Continued*)

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Table 8 (Continued).

Category	Sub-Category	n (%)
Occupation	Housewife	5 (29.4)
	Employed (formal)	3 (17.6)
	Informal labor	4 (23.5)
	Retired	1 (5.9)
	Unemployed/Jobless	2 (11.8)
	Self-employed (home)	2 (11.8)
Monthly Income (PKR)	<20,000	12 (70.6)
	20,000–40,000	4 (23.5)
	>40,000	1 (5.9)
Duration of MDD	<1 year	3 (17.6)
	1–2 years	5 (29.4)
	2–3 years	5 (29.4)
	>3 years	4 (23.5)

Concerns were also raised about the perceived long-term harm of antidepressants on vital organs, especially when used continuously over time.

> I've heard these tablets damage the liver and I don't trust taking them every single day for years I feel like it will harm me slowly - (QP-10) ……. (Quote 4)

> I used to manage housework easily now I get tired even after folding clothes like my body is not the same since starting the treatment - (QP-06) ……. (Quote 5)

> Instead of getting better I feel my health is declining there's weakness and no energy in my body after taking these pills regularly - (QP-14) ……. (Quote 6)

Culturally embedded interpretations of antidepressants as "hot" medicines further complicated adherence, framing side effects as harmful imbalances in the body. The attribution of side effects to heatiness led to avoidance behaviors, including dose-skipping or self-initiated breaks in medication.

> This medicine has garam taseer I feel heat rising in my chest and I even got mouth ulcers after taking it for a week straight - (QP-12) ……. (Quote 7)

> It makes my whole body feel heated up I sweat more than before and sometimes I feel agitated for no reason - (QP) ……. (Quote 8)

> My mother-in-law told me this is hot medicine and that's why I get headaches and body heat after taking it- (QP-05) ……. (Quote 9)

Theme 2: Unsafe or Unsupervised Medication Practices

Few participants described unsupervised changes to their medication routines, including doubling doses during emotional distress. These self-directed actions reflected a lack of professional guidance and contributed to poor adherence.

> One day I felt very low and thought one tablet is not enough so I took another one without telling anyone because I just wanted the pain to stop - (QP-11) ……. (Quote 10)

> Sometimes when the sadness gets unbearable I take the tablet twice a day even if the doctor said once I don't follow that exactly - (QP-07) ……. (Quote 11)

Some participants reported developing tolerance over time. When medication effects diminished, rather than consulting a clinician, they either increased the dose independently or stopped altogether.

> At first I felt better but after a few weeks the effect went away so I thought maybe I should take two instead of one without asking the doctor - (QP-02) ……. (Quote 12)

> I was taking it regularly but one day it stopped helping me sleep and I got scared it's not working so I just left it completely on my own - (QP-08) ……. (Quote 13)

The absence of clear information regarding treatment duration further contributed to disengagement. Participants expressed confusion and frustration about how long they were expected to continue medication.

> No one ever told me how long I have to take this I thought it's just for a few weeks but it's been months now so I gave up - (QP-13) ……. (Quote 14)

> When I asked the doctor how long I'll need this he just said take it and come back later but he never explained anything and that's why I stopped going - (QP-17) … (Quote 15)

Theme 3: Health Beliefs and Alternative Explanations

Participants shared beliefs and interpretations that influenced their treatment behaviors. For some, symptom relief prompted a switch to non-medical practices rooted in faith or tradition. Others showed emotional disengagement and lacked intention to recover, which contributed to irregular medication use.

> I stopped taking the tablets when I started feeling okay and now I just read wazifas and drink herbal tea daily it gives me peace - (QP-05) ……. (Quote 16)

> When I felt better I thought these medicines were not needed anymore so I switched to desi totkay like ashwagandha and tulsi water someone told me about it - (QP-16) ……. (Quote 17)

> I take the pills when I remember but honestly I don't think anything can really change now this is just how life is - (QP-04) ……. (Quote 18)

> I don't feel like I want to get better anymore I just go on with the day and I forget about the medicine most of the time - (QP-15) ……. (Quote 19)

Theme 4: Health System Limitations Affecting Adherence

Participants described health-system barriers that directly affected adherence, particularly medication/brand switching at dispensing, lack of consistent counselling at the pharmacy counter, and disruptions in follow-up care. These system gaps created confusion, reduced trust, and contributed to missed doses or temporary discontinuation.

> Every time I go they give a different brand one time it's a red box next time blue I don't know if it's the same medicine or not and I get confused - (QP-14) ……. (Quote 20)

> I asked the dispenser why the medicine looked different this time he said it's the same but I felt dizzy after that so I skipped it for a few days - (QP-02) ……. (Quote 21)

A few participants expressed deeper emotional disengagement from the recovery process itself. This passive stance toward illness and treatment reflected low expectations of improvement, contributing to irregular medication use.

> I went to the clinic twice then the doctor changed and the new one didn't know my history so I just stopped going because it felt like starting over - (QP-13) ……. (Quote 22)

> There's no proper schedule they tell me to come after fifteen days but when I go the doctor is not there and then I stop for weeks - (QP-12) ……. (Quote 23)

Participants highlighted gaps in medication counselling at the point of dispensing, noting that limited or absent guidance from pharmacists or dispenser contributed to confusion and inconsistent medication use.

> I just get the medicine slip and collect it no one explains how or when to take it and I'm too shy to ask in the crowded counter - (QP-05) ……. (Quote 24)

> There's no pharmacist at my clinic it's just the dispenser he only gives the tablets and I don't think he knows about side effects or dose adjustments - (QP-06) ……. (Quote 25)

Theme 5: Decision-Making Burden Around Medication Use

One participant also described internal conflict about whether to take their medication. They hesitated and overthought their decision. This often led to delays or skipped doses. The uncertainty reflected the burden of daily decision-making. It showed how a lack of confidence or guidance affected regular treatment use.

> Sometimes I sit with the tablet in my hand and think should I take it now or wait or maybe skip it because what if it makes me feel worse and then I don't take it at all - *(QP-11)* ……. (Quote 26)

Deviant Cases

Although all participants had suboptimal adherence overall, a few demonstrated patterns where common barriers like side effects or system issues did not fully disrupt medication use. For example, some participants continued their treatment despite discomfort from ADRs.

> Even though I get a bitter taste and dizziness I've never missed a dose because I know what it's like when I stop and I don't want to go back there - (QP-01) ……. (Quote 27)

> My hands tremble sometimes but I still take the medicine because I've seen worse days without it and this is still manageable - (QP-17) ……. (Quote 28)

One participant highlighted how simple guidance from a dispenser helped continue treatment.

> There was one day I felt weak and confused and the dispenser explained that it's normal at the beginning and that helped me continue instead of stopping - (QP-07) ……. (Quote 29)

Others described religious beliefs that encouraged regular intake.

> I believe medicine and dua go together so I take my pills after praying and I feel like both are part of healing - *(QP-11)* ……. (Quote 30)

A few showed better engagement by consulting doctors before changing doses.

> Sometimes I feel the dose is too much but I confirm with my doctor before making changes I don't stop it on my own - *(QP-09)* ……. (Quote 31)

In instances, some participants accepted long-term treatment early on and planned accordingly.

> From the first visit the doctor explained it will take months and that helped me stay regular I was ready for it mentally - (QP-16) ……. (Quote 32)

> He told me this is not a painkiller but a treatment and I understood so I keep taking it even when I feel better - (QP-02) ……. (Quote 33)

One participant interpreted brand switching as thoughtful care, not confusion.

> They told me this new brand would be lighter on my stomach and it actually was so I felt they care not just giving random pills - *(QP-13)* ……. (Quote 34)

Integrated Findings

The quantitative predictors and qualitative themes were merged using a joint display matrix. Each row was developed by linking one statistically supported quantitative association to the most relevant qualitative theme(s) and representative quote(s), after which the inferred mechanism was stated. Rows were classified as convergence, expansion, or discordance to make the logic of integration explicit.

Integrated analysis demonstrated clear convergence between quantitative and qualitative findings, showing that higher ADR burden, lower DAI-10 scores, low income, unemployment, and age >55 years were consistently associated with greater odds of antidepressant non-adherence, and these patterns were strongly echoed in participant narratives. Interviews explained the quantitative relationships by describing how dry mouth, sedation, weight gain, and fears of long-term organ harm undermined daily dosing; how perceptions of antidepressants as "unnatural", ineffective, or unnecessary after symptom improvement aligned with poorer attitudinal profiles captured by DAI-10; and how financial strain, irregular work demands, and transport/refill costs disrupted follow-up and continuity. The integrated findings also captured divergence and nuance not fully visible in survey measures: despite the overall ADR–non-adherence gradient, some participants reported sustaining treatment despite distressing side effects due to fear of relapse and prior experience of deterioration; and although some demographic variables were weak/non-significant quantitatively, interviews highlighted practical barriers (eg, childcare demands and discomfort seeking advice at crowded pharmacies) that may moderate adherence in daily life Finally, qualitative expansion added culturally and cognitively grounded mechanisms that extend the quantitative model, including culturally embedded interpretations of medicines as garam taseer ("hot") that reframed side effects as harmful imbalances and triggered dose-skipping even when symptoms were reported as mild, confusion and distrust arising from brand switching at dispensing, unclear treatment timelines that contributed to disengagement, and a day-to-day decisional burden ("hesitation" and overthinking) that plausibly explains fluctuation in adherence behaviours. Overall, the integrated evidence indicates that non-adherence in this population is driven by an interlinked side-effect–belief–resource–system mechanism, and the mixed-methods results are summarised in Table 9.

Discussion

This explanatory sequential mixed-methods study examined treatment-related factors influencing medication non-adherence among patients diagnosed with MDD. Over one-third (32.3%) were classified as poorly adherent based on the UMGLS-4 scale. Quantitative findings highlighted statistically significant associations between non-adherence and high ADR burden, negative attitudes towards medication, low income, unemployment, and older age. These patterns were further elaborated and contextualised through qualitative narratives. The principal findings indicate that medication non-adherence among MDD patients is driven by an interlinked mechanism involving ADRs, particularly side effects like dry mouth, sedation, and weight gain, negative cognitive and emotional beliefs about antidepressants, and lack of professional counselling. This study identified high ADR burden, lower DAI-10 scores, income below 20,000 PKR, and unemployment as significant predictors of medication non-adherence. These quantitative associations were reinforced by qualitative accounts describing confusion about treatment regimens, culturally embedded interpretations of medication as "hot" or harmful, and reliance on alternative medicine. Despite the diversity of narratives, a convergent mechanism emerged, demonstrating how treatment-related burdens undermine long-term adherence in this population.

Our findings align with a large body of international literature confirming that treatment-related factors such as ADRs, negative beliefs about antidepressants, and socio-economic constraints are central drivers of non-adherence among patients with MDD. For instance, the strong association we observed between ADR burden and non-adherence (AOR 1.42, $p < 0.001$) mirrors the results of Marasine et al (2020), who reported that 82% of patients experienced ADRs and nearly one in eight discontinued treatment due to them.[37] A likely explanation is that patients perceive these side effects as intrusive to daily life or as signs that the medication is harmful rather than helpful.[38–40] This interpretation is supported by Vilhelmsson et al (2012), whose qualitative study showed that even mild ADRs were perceived through personal and cultural lenses (eg., "heat in the body"), intensifying non-adherence behavior.[41]

Similarly, our finding that each one-point drop in DAI-10 score increased the odds of non-adherence by 20% (AOR 1.20, $p < 0.001$) reflects the conclusions of a meta-analysis of 94 studies by Foot et al (2016), who demonstrated

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Table 9 Mechanistic Integration of Quantitative and Qualitative Results

Integration Type	Factor/Theme	Quant Source (Table/Variable)	Key Quantitative Result	Qual Source (Theme/Quotes)	Key Qualitative Evidence	Integrated Mechanism (Passive Voice)
Convergence	ADR burden	Table 7: ADR burden score (continuous)	Higher ADR burden was associated with higher odds of non-adherence (AOR = 1.42, $p < 0.001$).	Theme 1; Quotes 1–3, 7–9	Side effects disrupted routine use; "garam taseer/heatiness" framed adverse effects and avoidance.	Tolerability was reduced and side effects were culturally framed as harmful; dose skipping/ discontinuation was triggered.
Convergence	Medication beliefs (DAI-10)	Table 7: DAI-10 score (per 1-point decrease)	Lower DAI-10 scores were associated with higher odds of non-adherence (AOR = 1.20 per 1-point decrease, $p < 0.001$).	Theme 3; Quotes 4–6, 18–19	Medicines were described as unnatural/ harmful or unnecessary after improvement; hopelessness reduced motivation.	Negative beliefs were reinforced, adverse effects were interpreted as proof of harm, and irregular use/early stopping was promoted.
Convergence	Socioeconomic constraints (income)	Table 7: Income <20,000 PKR	Income <20,000 PKR was associated with higher odds of non-adherence (AOR = 1.79, $p < 0.001$).	Theme 4B; Quotes 23 (and any cost quote you already have)	Follow-up gaps and access barriers were described; missed visits/refills occurred due to practical constraints.	Treatment continuity was interrupted by access/ cost barriers; intermittent supply and missed follow-up were produced.
Convergence	Employment status	Table 7: Unemployed vs employed	Unemployment was associated with higher odds of non-adherence (AOR = 1.43, $p = 0.004$).	Theme 4B/Theme 3 (as relevant)	Work/instability and disengagement were described as affecting consistency and follow-up.	Routine adherence was destabilized and follow-up was reduced, contributing to non-adherence.
Convergence	Older age	Table 7: Age >55 vs 18–25	Age >55 years was associated with higher odds of non-adherence (AOR = 1.65, $p = 0.002$).	Not strongly captured in quotes (if none)	Age-related barriers were not explicitly prominent in the qualitative sample.	Quant association was observed; qualitative explanation was limited due to sample focus and should be noted as a gap.
Expansion	Theme 4A: Brand switching/ dispensing confusion	Not measured	—	Theme 4A; Quotes 20–21	Pill/box changes were described as confusing and were linked to distrust and temporary stopping.	Confusion and distrust were generated at dispensing; short-term discontinuation was precipitated.
Expansion	Theme 4C: Lack of counselling/ pharmacist support	Not measured	—	Theme 4C; Quotes 24–26	Limited counselling at dispensing and decisional uncertainty were described.	An informational void was created; uncertainty about dosing/duration increased and missed/ delayed doses were promoted.
Expansion	Religious/ traditional substitution vs complementarity	Not measured	—	Theme 3; Quotes 16–17, 30	Wazifa/herbal substitutes were described; faith also supported adherence in some cases.	Pharmacotherapy was competed with when substitutes were adopted; adherence was supported when practices were framed as complementary.
Discordance (deviant cases)	Persistence despite ADRs	Table 7: ADR burden predicts non-adherence	ADR burden generally increased odds of non-adherence.	Deviant cases; Quotes 27–28	Some participants continued medication despite ADRs due to relapse fear.	ADR impact was overridden when perceived necessity was high; adherence was sustained in a minority.

that patients' beliefs about medication necessity versus concerns significantly predicted adherence across chronic illnesses.[42] Patients may internalize stigma or mistrust, especially in settings where antidepressants are viewed as addictive or unnatural, which has been well-documented in both Western[43,44] and Middle Eastern contexts.[45,46]

In socioeconomic terms, our participants with a monthly income under 20,000 PKR were nearly twice as likely to be non-adherent, consistent with Piette et al (2011), who found a 21% prevalence of cost-related non-adherence among low-income patients in the U.S.[47] The mechanism likely involves direct and indirect costs that standard surveys may not capture.[48] Moreover, non-adherence was observed to be higher in older adults, in contrast with some literature reporting better adherence in older populations[49] possibly because, in low-resource settings like Pakistan the older adults face cognitive barriers, lack of family support, or language barriers that limit flexibility in daily medication use.[50]

Lastly, we found that many participants discontinued or skipped medications due to unclear treatment timelines or a lack of pharmacist explanation. This aligns with study showing the difference between guideline and treatment guidelines received by patients.[51] Patients may remain uncertain about why they are taking medication, for how long, or whether improvement is expected without routine counseling and shared decision-making.

This study underscores the importance of a clinically grounded, multifactorial approach to improving antidepressant adherence. ADRs consistently disrupted routine medication-taking, highlighting the need for regular side-effect monitoring and timely regimen adjustments within clinical practice. Beyond prescribing, clinicians must attend to patients' embodied experiences and treatment beliefs, often framing ADRs as harmful or intolerable. Incorporating brief, structured discussions around ADR management and adherence challenges into follow-up visits can help sustain long-term use. At the service level, empowering pharmacists and dispensers with basic adherence counselling skills and checklists could bridge the communication gap observed in this study, particularly in low-resource public clinics.[52,53] Clinically, pharmacists and dispensers have a clear role in providing ongoing medication support, a strategy that improves adherence in low-resource settings.[54] With mobile phone access widespread, digital nudges such as SMS-based refill reminders have shown promising results in other chronic conditions such as hypertension, stroke and diabetes.[55–57]

A key strength of this study is the explanatory sequential mixed-methods design, which quantified treatment-related predictors of non-adherence and then explained these associations through qualitative interviews. This integration improved interpretability by linking statistical patterns with patient narratives. However, limitations persist, mainly beyond methodological control. Self-reported adherence measures risk recall and social desirability biases. More objective measures, like pharmacy refill data or electronic monitoring, were infeasible due to healthcare constraints in Pakistan.[58] The cross-sectional design limits causal inference, offering only a snapshot of fluctuating adherence behaviors.[59] Furthermore, lacking caregiver or healthcare provider perspectives restricts exploring adherence dynamics from all viewpoints. Future research should pursue longitudinal designs tracking adherence trajectories over time to capture fluctuations and causal relationships. Given resource constraints, pharmacist-led adherence counselling sessions and mobile health reminders should be experimentally evaluated in the MDD context. Expanding research to incorporate caregiver and healthcare provider insights is recommended to understand adherence dynamics within the broader therapeutic ecosystem.

Conclusion

This mixed-methods study highlights how treatment-related factors significantly contribute to antidepressant non-adherence among patients with MDD in Pakistan. Qualitative insights reinforced quantitative findings, revealing cultural beliefs, misinformation, and weak healthcare communication as key barriers. Despite a high ADR burden, a minority remained adherent due to prior illness experience or trust in providers. These findings underscore the urgent need for culturally sensitive adherence support, patient education, and pharmacist-led interventions to improve treatment continuity and outcomes for depression in low-resource settings.

Data Sharing Statement

The dataset is available from Dr. Fazli Khuda (co-corresponding author) upon reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

References

1. World Health Organization. Depressive disorder (depression). 2023. Available from: https://www.who.int/news-room/fact-sheets/detail/depression. Accessed May 16, 2025.
2. Lassen RH, Gonçalves W, Gherman B, et al. Medication non-adherence in depression: a systematic review and metanalysis. *Trends Psychiatry Psychother*. 2024. doi:10.47626/2237-6089-2023-0680
3. Jayasree A, Shanmuganathan P, Ramamurthy P, Alwar MC. Types of medication non-adherence & approaches to enhance medication adherence in mental health disorders: a narrative review. *Indian J Psychol Med*. 2024;46(6):503–510. doi:10.1177/02537176241233745
4. Freccero C, Sundquist K, Sundquist J, Ji J. Primary adherence to antidepressant prescriptions in primary health care: a population-based study in Sweden. *Scand J Prim Health Care*. 2016;34(1):83–88. doi:10.3109/02813432.2015.1132884
5. Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. *Med Care*. 2006;44(4):300–303. doi:10.1097/01.mlr.0000204287.82701.9b
6. Semahegn A, Torpey K, Manu A, Assefa N, Tesfaye G, Ankomah A. Psychotropic medication non-adherence and its associated factors among patients with major psychiatric disorders: a systematic review and meta-analysis. *Syst Rev*. 2020;9(1):17. doi:10.1186/s13643-020-1274-3
7. Meißner C, Meyrose A-K, Nestoriuc Y. What helps and what hinders antidepressant discontinuation? Qualitative analysis of patients' experiences and expectations. *Br J Gen Pract*. 2024;74(744):e466–e474. doi:10.3399/BJGP.2023.0020
8. Mahmood R, Wallace V, Wiles N, Kessler D, Button KS, Fairchild G. The lived experience of withdrawal from selective serotonin reuptake inhibitor (SSRI) antidepressants: a qualitative interview study. *Health Expect*. 2024;27(1):e13966. doi:10.1111/hex.13966
9. Pannu A, Goyal RK. From evidence to practice: a comprehensive analysis of side effects in synthetic anti-depressant therapy. *Curr Drug Saf*. 2024. doi:10.2174/0115748863301630240417071353
10. Hempenius M, Rijken S, Groenwold RHH, et al. Primary nonadherence to drugs prescribed by general practitioners: a Dutch database study. *Br J Clin Pharmacol*. 2023;89(1):268–278. doi:10.1111/bcp.15472
11. Lam WY, Fresco P. Medication adherence measures: an overview. *Biomed Res Int*. 2015;2015(2015):217047. doi:10.1155/2015/217047
12. Mishra A, Kishor MR, Ramesh M. Randomized controlled trial to assess medication adherence and health-related quality of life through a collaborative pharmacist-psychiatrist approach to patient education in patients with depression in India. *Front Psychiatry*. 2025;16:1499893. doi:10.3389/fpsyt.2025.1499893
13. Abrahams AB, Beckenstrom AC, Browning M, et al. Exploring the incidence of inadequate response to antidepressants in the primary care of depression. *Eur Neuropsychopharmacol*. 2024;83:61–70. doi:10.1016/j.euroneuro.2024.04.005
14. Megnin-Viggars O, O'Donoghue K, Pilling S, Chew-Graham C. Experience of choice of treatment for adults with depression: a systematic review and meta-synthesis of qualitative research. *J Ment Health*. 2024;1–18. doi:10.1080/09638237.2024.2390369
15. Niarchou E, Roberts L, Naughton BD. What is the impact of antidepressant side effects on medication adherence among adult patients diagnosed with depressive disorder: a systematic review. *J Psychopharmacol*. 2024;38(2):127–136. doi:10.1177/02698811231224171
16. Baryakova TH, Pogostin BH, Langer R, McHugh KJ. Overcoming barriers to patient adherence: the case for developing innovative drug delivery systems. *Nat Rev Drug Discov*. 2023;22(5):387–409. doi:10.1038/s41573-023-00670-0
17. Kazdin AE, Wu C-S, Hwang I, et al. Antidepressant use in low- middle- and high-income countries: a world mental health surveys report. *Psychol Med*. 2023;53(4):1583–1591. doi:10.1017/S0033291721003160
18. GBD. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Psychiatry*. 2022;9(2):137–150. doi:10.1016/S2215-0366(21)00395-3.
19. Rajper AB, Dars JA, Iqbal F, et al. Factors leading to Non-Compliance to Antidepressants Among Patients with Major Depressive Disorder: A Cohort Study from Pakistan. *PJMHS*. 2022;16(1):441. doi:10.53350/pjmhs22161441
20. Amir M, Rickles N, Feroz Z, Beg AE. Determination of factors effecting medication adherence in depressed patients receiving antidepressants in Pakistan. *RADS J Pharm Pharmaceut Sci*. 2020;8(1):1–6. doi:10.37962/jpps.v8i1.396
21. Taj F, Tanwir M, Aly Z, et al. Factors associated with non-adherence among psychiatric patients at a tertiary care hospital, Karachi, Pakistan: a questionnaire based cross-sectional study. *J Pak Med Assoc*. 2008;58(8):432–436.

22. Akhunzada WA, Rahman RU, Dogar IA, Maqsood N. Depression and drug non- adherence. *The Profess Med J*. 2010;17(02):340–346. doi:10.29309/TPMJ/2010.17.02.2448
23. Wright J, Mazumdar P, Barua D, et al. Integrating depression care within NCD provision in Bangladesh and Pakistan: a qualitative study. *Int J Mental Health Syst*. 2020;14(1):63. doi:10.1186/s13033-020-00399-y
24. Ahsan Q, Saleem J, Ishaq M, et al. Determinant factors and coping strategies for depression among pregnant women: an intervention-based qualitative study in Lahore, Pakistan. *BMC Psychiatry*. 2024;24(1):829. doi:10.1186/s12888-024-06280-3
25. Naeem F, Ayub M, Kingdon D, Gobbi M. Views of depressed patients in pakistan concerning their illness, its causes, and treatments. *Qual Health Res*. 2012;22(8):1083–1093. doi:10.1177/1049732312450212
26. Ma F. Diagnostic and statistical manual of mental disorders-5 (DSM-5). In: Gu D, Dupre ME, editors. *Encyclopedia of Gerontology and Population Aging*. Cham: Springer International Publishing; 2021:1414–1425. doi:10.1007/978-3-030-22009-9_419
27. Wang X, Ji X. Sample size estimation in clinical research: from randomized controlled trials to observational studies. *Chest*. 2020;158(1):S12–S20. doi:10.1016/j.chest.2020.03.010
28. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. *Med Care*. 1986;24 (1):67–74. doi:10.1097/00005650-198601000-00007
29. Riaz S, Khuda F, Malik NS, et al. Cross-cultural adaptation and psychometric evaluation of the Urdu version of the Morisky, Greene, and Levine medication adherence scale (MGLS-4) for major depressive disorder patients. *PLoS One*. 2025;20(4):e0320258. doi:10.1371/journal.pone.0320258
30. Saleem F, Hassali MA, Shafie AA, Awad AG, Bashir S. Association between knowledge and drug adherence in patients with hypertension in Quetta, Pakistan. *Trop J Pharm Res*. 2011;10(2). doi:10.4314/tjpr.v10i2.66552
31. Nielsen RE, Lindström E, Nielsen J, Levander S. DAI-10 is as good as DAI-30 in schizophrenia. *Eur Neuropsychopharmacol*. 2012;22 (10):747–750. doi:10.1016/j.euroneuro.2012.02.008
32. Uher R, Farmer A, Henigsberg N, et al. Adverse reactions to antidepressants. *Br J Psychiatry*. 2009;195(3):202–210. doi:10.1192/bjp.bp.108.061960
33. Chen H, Boore JR. Translation and back-translation in qualitative nursing research: methodological review. *J Clin Nurs*. 2010;19(1–2):234–239. doi:10.1111/j.1365-2702.2009.02896.x
34. Clarke V, Braun V. Thematic analysis. *J Positive Psychology*. 2017;12(3):297–298. doi:10.1080/17439760.2016.1262613
35. O'Cathain A, Murphy E, Nicholl J. The quality of mixed methods studies in health services research. *J Health Serv Res Policy*. 2008;13(2):92–98. doi:10.1258/jhsrp.2007.007074
36. Goodyear MDE, Krleza-Jeric K, Lemmens T. The Declaration of Helsinki. *BMJ*. 2007;335(7621):624–625. doi:10.1136/bmj.39339.610000.BE
37. Marasine NR, Sankhi S, Lamichhane R, Marasini NR, Dangi NB. Self-reported antidepressant drug side effects, medication adherence, and its associated factors among patients diagnosed with depression at the psychiatric hospital of Nepal. *Depress Res Treat*. 2020;2020:7024275. doi:10.1155/2020/7024275
38. Aikens JE, Nease DE, Klinkman MS. Explaining patients' beliefs about the necessity and harmfulness of antidepressants. *Ann Fam Med*. 2008;6 (1):23–29. doi:10.1370/afm.759
39. Cartwright C, Gibson K, Read J, Cowan O, Dehar T. Long-term antidepressant use: patient perspectives of benefits and adverse effects. *Patient Prefer Adher*. 2016;10:1401–1407. doi:10.2147/PPA.S110632
40. Gibson K, Cartwright C, Read J. Patient-centered perspectives on antidepressant use: a narrative review. *Int J Ment Health*. 2014;43(1):81–99. doi:10.2753/IMH0020-7411430105
41. Vilhelmsson A, Svensson T, Meeuwisse A, Carlsten A. Experiences from consumer reports on psychiatric adverse drug reactions with antidepressant medication: a qualitative study of reports to a consumer association. *BMC Pharmacol Toxicol*. 2012;13(1):19. doi:10.1186/2050-6511-13-19
42. Foot H, La Caze A, Gujral G, Cottrell N. The necessity–concerns framework predicts adherence to medication in multiple illness conditions: a meta-analysis. *Patient Educ Couns*. 2016;99(5):706–717. doi:10.1016/j.pec.2015.11.004
43. Wiles N, Taylor A, Turner N, et al. Management of treatment-resistant depression in primary care: a mixed-methods study. *Br J Gen Pract*. 2018;68 (675):e673–e681. doi:10.3399/bjgp18X699053
44. Fortney JC, Pyne JM, Edlund MJ, et al. Reasons for antidepressant nonadherence among veterans treated in primary care clinics. *J Clin Psychiatry*. 2011;72(6):827–834. doi:10.4088/JCP.09m05528blu
45. Yassen AO, Mahmud NM, Bilal AD, Abd Wahab MS. Antidepressant adherence among outpatients with major depressive disorder. *Pharmacia*. 2024;71(1):1–10. doi:10.3897/pharmacia.71.e123345
46. Alomar AO, Khushaim RH, Al-Ghanem SK, et al. Relationship between depression and medication adherence among chronic disease patients in the Middle East. *Cureus*. 2024. doi:10.7759/cureus.69418
47. Piette JD, Beard B, Rosland R, McHorney CA. Beliefs that influence cost-related medication non-adherence among the "haves" and "have nots" with chronic diseases. *Patient Prefer Adher*. 2011;5:389–396. doi:10.2147/PPA.S23111
48. Zemedikun DT, Kigozi J, Wynne-Jones G, et al. Methodological considerations in the assessment of direct and indirect costs of back pain: a systematic scoping review. *PLoS One*. 2021;16(5):e0251406. doi:10.1371/journal.pone.0251406
49. Jamal I, Ali AM, Gul E, et al. Patient characteristics and adherence to antidepressant medication treatment at psychiatric outpatient department of Mardan medical complex, Pakistan. *J Saidu Med Coll Swat*. 2024;14(1):24–29. doi:10.52206/jsmc.2024.14.1.778
50. Saqlain M, Riaz A, Malik MN, et al. *Medication Adherence and Its Association with Health Literacy and Performance in Activities of Daily Livings Among Elderly Hypertensive Patients in Islamabad*; 2019; Pakistan.
51. Day E, Shah R, Taylor RW, et al. A retrospective examination of care pathways in individuals with treatment-resistant depression. *BJPsych Open*. 2021;7(3):e101. doi:10.1192/bjo.2021.59
52. Haq UU, Ellahi S, Khan Z, Mansoor A. Impact of pharmacist-led interventions on medication adherence in patients with chronic psychiatric disorders. *Pak J Health Sci*. 2025;11–17. http://www.thejas.com.pk/index.php/pjhs/article/view/2923.
53. Chatha ZF, Rashid U, Olsen S, et al. Pharmacist-led counselling intervention to improve antiretroviral drug adherence in Pakistan: a randomized controlled trial. *BMC Infect Dis*. 2020;20(1):874. doi:10.1186/s12879-020-05571-w
54. Haq NU, Riaz S, Nasim A. Pharmacy without pharmacist: body without soul. *Arch Pharm Pract*. 2017;8(2):84. doi:10.4103/2045-080X.204492

55. Siddiqui M, Islam MYU, Mufti BAI, et al. Assessing acceptability of hypertensive/diabetic patients towards mobile health based behavioral interventions in Pakistan: a pilot study. *Int J Med Inform*. 2015;84(11):950–955. doi:10.1016/j.ijmedinf.2015.08.009
56. Kamal AK, Shaikh Q, Pasha O, et al. A randomized controlled behavioral intervention trial to improve medication adherence in adult stroke patients with prescription tailored short messaging service (SMS)-SMS4Stroke study. *BMC Neurol*. 2015;15(1):212. doi:10.1186/s12883-015-0471-5
57. Hashmi NR, Khan SA. Interventional study to improve diabetic guidelines adherence using mobile health (m-Health) technology in Lahore, Pakistan. *BMJ Open*. 2018;8(5):e020094. doi:10.1136/bmjopen-2017-020094.
58. Naqvi AA, Hassali MA, Aftab MT, Nadir MN. A qualitative study investigating perceived barriers to medication adherence in chronic illness patients of Karachi, Pakistan. *J Pak Med Assoc*. 2019;69(2):216–223.
59. Wang X, Cheng Z. Cross-sectional studies: strengths, weaknesses, and recommendations. *Chest*. 2020;158(1):S65–S71. doi:10.1016/j.chest.2020.03.012