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Individualized psychological intervention for medication adherence in outpatients with depression

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In China's mental healthcare system, a critical shortage of professionals limits the implementation of guideline-recommended shared decision-making, leading to high rates of antidepressant non-adherence. This study tested whether a brief, theory-based psychological intervention could improve early medication adherence within existing resource constraints. We conducted a parallel-group, assessor-blinded randomized controlled trial at a tertiary hospital in Guangdong. Eighty outpatients with major depressive disorder were randomized to receive either a 12-week personalized intervention or treatment as usual. The personalized intervention, delivered in eight 30-min sessions, integrated a predictive risk algorithm with stage-matched behavioral techniques to target key adherence determinants. The primary outcomes were medication adherence (MMAS-8) and depressive symptoms (SDS). Among the 60 study completers, the intervention group achieved significantly higher medication adherence at 12 weeks than the control group (between-group difference: 1.09 points), representing an 18% relative improvement. Depressive symptoms decreased substantially in both groups, with no between-group difference. The intervention also led to a significant increase in patient autonomy. This theory-guided protocol effectively improved antidepressant adherence without accelerating short-term symptom reduction. This scalable approach shows promise for bridging the treatment gap in routine psychiatric care in China without requiring additional specialist resources.

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Introduction

Depression represents a paramount global public health challenge, ranking as the single largest contributor to disability worldwide and affecting over 260 million people annually (GBD 2017 Disease and Injury Incidence and Prevalence Collaborators, 2018; Kazdin and Rabbitt, 2013). By 2021, it was already declared the leading cause of disability globally, imposing substantial personal suffering and immense economic costs on societies (World Health Organization, 2011; World Health Organization, 2025).

The China Mental Health Survey (CMHS) confirms a steadily increasing trend in depression rates, reporting a 12-month prevalence of 3.6% and a lifetime prevalence of 6.8% among adults (Huang et al., 2019). This solidifies depression's status as a critical national public health priority.

The optimal treatment pathway, however, is increasingly contested within global discourse. International guidelines, such as those from the National Institute for Health and Care Excellence (National Institute for Health and Care Excellence, 2022), recommend prioritizing lower-risk interventions like psychotherapy as first-line treatment for mild-to-moderate depression. This is supported by emerging perspectives, such as the analytical rumination hypothesis (Hollon et al., 2021), which posits depression as an evolutionary adaptation and suggests cognitive-behavioral interventions targeting its proposed function may hold long-term advantages over symptom-targeting antidepressants.

China's ambulatory mental health services, however, operate within a unique and complex socio-medical context characterized by a fundamental contradiction. On one hand, national guidelines adeptly reflect a nuanced, patient-centered approach. The Chinese Guidelines for the Prevention and Treatment of Depressive Disorders (Li and Wang, 2025) advocates for a stepped-care model, recommending psychosocial interventions for mild cases and emphasizing shared decision-making for moderate cases, where treatment choice is based on availability and patient preference. For severe cases, it recommends active pharmacotherapy, often combined with psychotherapy. Crucially, its management principles stress open communication, psychoeducation to reduce stigma, and building a trusting therapeutic alliance—all hallmarks of respecting patient autonomy.

On the other hand, the system is strained by a severe scarcity of resources. China faces a massive mental health treatment gap, exacerbated by a critical shortage of specialized manpower. China faces a massive mental health treatment gap, exacerbated by a critical shortage of specialized manpower, with only 3.5 psychiatrists and ~60 psychiatric beds per 100,000 people (National Health Commission of the People's Republic of China, 2023). The practical implementation of ideal, labor-intensive SDM and psychotherapy is profoundly challenged. This resource constraint makes pharmacological treatment a necessary and widespread option for many patients. Even so, guidelines still urge clinicians to collaboratively determine the treatment plan with patients.

It is within this tension—between ideal patient-centric guidelines and resource-limited reality—that the crisis of medication non-adherence becomes a critical focal point. The 2022 National Depression Bluebook identifies poor medication adherence as the foremost factor contributing to relapse. Studies reported non-adherence rates to antidepressants ranging from 30 to 97%, which is notably higher compared to other psychotropic medications such as antipsychotics and mood stabilizers (Mert et al., 2015). Poor adherence contributes to treatment failure, relapse, progression to chronic depression, higher healthcare utilization, and diminished health-related quality of life (Chong et al., 2011; Alekhya et al., 2015).

Multiple factors contribute to antidepressant non-adherence, including doubts about medication efficacy, fear of dependency, complex treatment regimens, side effects (e.g., sexual dysfunction), financial burden, inadequate patient–provider communication, and societal stigma surrounding mental illness (Jaffray et al., 2014; van Geffen et al., 2011; Milosavljevic et al., 2018). Studies have shown that treatment satisfaction is closely linked to medication adherence, particularly among individuals with chronic illnesses (Barbosa et al., 2012; Aljumah et al., 2014). Patients who perceive their treatment as effective and consistent with their expectations are more likely to adhere. Factors influencing treatment satisfaction include perceived effectiveness, side effect profile, convenience of dosage form, dosing frequency, and patients' positive beliefs about the treatment, all of which ultimately affect adherence (Bharmal et al., 2009).

Therefore, while the international "efficacy-versus-risk" debate is relevant, it cannot be simply transplanted to China and does not negate the urgent need for adherence interventions. Here, improving adherence is not about paternalistically 'forcing patients to take pills,' but rather represents a pragmatic and ethical imperative to empower patients within a constrained system. The goal is to enable them to complete a co-determined treatment course through transparency and structured support, thereby navigating the interplay between global evidence, local constraints, and individual autonomy.

Our research group previously developed the Psychiatric Medication Adherence Prediction Scale, validated its reliability and validity among individuals with depression, established cutoff scores, and refined the predictive tool. Subsequently, we explored the relationship between early-stage depression characteristics and acute-phase medication adherence, using this foundation to construct a medication adherence prediction model for outpatient depression patients. This model predicts future medication adherence during acute treatment based on patients' early-stage characteristics. Additionally, we investigated the developmental trajectories and influencing factors of acute-phase medication non-adherence among outpatient depression patients. Building upon the research team's prior findings, this study further advanced personalized psychological interventions targeting medication adherence in depression patients.

Building upon our previous development of a Psychiatric Medication Adherence Prediction Scale and related foundational studies, this research aims to develop and evaluate a personalized psychological intervention to enhance medication–adherence in outpatients with depression. The intervention integrates a predictive model to identify at-risk patients and applies a dynamic framework informed by the Health Belief Model (HBM) and Self-Determination Theory to provide tailored support. This approach not only addresses practical barriers but also targets the core psychological determinants of adherence.

Literature review

Conceptual definitions

Medication adherence. Medication adherence is defined as the extent to which a patient's behavior corresponds with agreed recommendations from a healthcare provider (World Health Organization, 2003). Operationally, this encompasses the degree to which patients take their medication as prescribed, including dosage, frequency, and duration. Non-adherent behaviors include outright refusal to take medication, premature discontinuation, and incorrect dosing (taking the wrong dose or taking it at the wrong time).

Acute phase. According to the Chinese Guidelines for the Prevention and Treatment of Depressive Disorders, the full-course management of depression comprises four distinct phases: acute, consolidation, maintenance, and termination, spanning a total period from 7 months to 4 years. The acute phase constitutes the initial stage of treatment. Its primary objective is to achieve symptomatic control and restore the patient's functional capacity to pre-illness levels, aiming for clinical remission (Li and Wang, 2025).

Theoretical foundations: from behavioral correction to patient empowerment. The conceptual understanding of medication adherence has evolved significantly, shifting from a paternalistic model of "compliance" toward a collaborative framework of "adherence" grounded in patient empowerment and shared decision-making. This theoretical progression provides the essential foundation for the present intervention.

Several theoretical models offer valuable insights into the determinants of health behavior. Among the most influential are the Health Belief Model (HBM; Rosenstock, 1974), the Theory of Planned Behavior (TPB; Ajzen, 1991), Self-Determination Theory (SDT; Deci and Ryan, 2000), and the Transtheoretical Model (TTM; Prochaska and DiClemente, 1983). Each contributes to a multifaceted understanding of adherence.

The HBM posits that health behaviors are determined by an individual's perceived threats and benefits. Key constructs include perceived susceptibility, severity, benefits, barriers, self-efficacy, and cues to action. This means a patient is more likely to take their medication if they feel susceptible to depression, believe it is severe, and see the benefits of treatment as outweighing barriers like side effects or stigma. Thus, non-adherence can be reframed not as a failure to obey, but as a rational choice based on the patient's personal calculus.

The Transtheoretical Model (TTM), or Stages of Change model, is particularly critical for designing personalized interventions. TTM conceptualizes behavior change as a dynamic, non-linear process through which individuals progress through distinct stages: precontemplation, contemplation, preparation, action, and maintenance. The core implication is that an intervention effective for a patient in precontemplation (unaware or unwilling to change) will be fundamentally different from one tailored for a patient in preparation (intending to act). This "stage-matched" approach is the cornerstone of providing truly individualized support, moving beyond generic advice to "take your medication."

Synthesis and Perspective: Therefore, the theoretical lens adopted in this study is that effective adherence intervention is not about coercing behavior but about facilitating informed choice and providing empowerment. It involves using HBM-based assessments to understand a patient's unique perceptual barriers and benefits and then applying TTM to provide the stage-appropriate tools and support to empower them to successfully execute their treatment plan.

Current landscape of adherence interventions: limitations and insights. A wide array of interventions has been developed to improve medication adherence in depression, which can be broadly categorized as follows:

Educational interventions. Aim to improve knowledge about depression and medication. While necessary, they are often insufficient, as knowledge alone rarely changes deep-seated behaviors or beliefs.

Behavioral interventions. Employ reminders (e.g., SMS, pillboxes) to cue the correct behavior. These address the barrier of "forgetfulness" but fail to engage with the motivational and cognitive barriers underlying intentional non-adherence.

Psychosocial interventions. Include strategies like Motivational Interviewing (MI) and Cognitive-Behavioral Therapy (CBT). These are among the most effective approaches, as they target underlying beliefs and motivations (Interian et al., 2010).

Technology-based interventions. Leverage mobile health applications (apps) and digital platforms to deliver reminders, education, and monitoring. Systematic reviews indicate that such mobile technologies can show positive effects on adherence rates.

Despite this variety, existing interventions are constrained by three critical limitations that hinder their effectiveness and scalability, particularly in the Chinese context:

Lack of a coherent theoretical foundation. Many interventions are pragmatic but atheoretical. Without being explicitly guided by models like TTM, they cannot achieve true stage-matched personalization, applying identical strategies to patients at vastly different stages of readiness.

Neglect of individual heterogeneity. The predominant "one-size-fits-all" model fails to account for differences in patients' readiness to change, their specific beliefs (HBM dimensions), and their unique life contexts.

Resource inaccessibility. The most effective strategies (e.g., MI, CBT) are highly resource-intensive, requiring extensive, trained specialist time that is profoundly scarce in China's mental healthcare system, thus creating a significant implementation gap (Emmelkamp, 2025).

This review underscores an urgent need for a novel intervention that is simultaneously theory-driven, personalized, and deliverable within the constraints of routine clinical care.

The conceptual framework and innovation of the present study. Directly responding to this triple mandate for theoretical coherence, individualization, and practicality, this study proposes a novel, two-phase personalized psychological intervention program, grounded in the integrated application of the HBM and the TTM.

Conceptual framework. The intervention begins with a Predictive Phase, utilizing a pre-developed adherence predictive scale to identify patients at high risk for non-adherence and to diagnose their specific perceptual barriers based on HBM dimensions (e.g., low perceived necessity, high perceived barriers from family, low self-efficacy). This diagnostic assessment directly informs a Process-Based Phase, where the patient's identified stage on the TTM continuum dictates the specific, stage-matched interventional strategy delivered over the subsequent weeks (e.g., consciousness-raising for precontemplation, stimulus control for action).

Innovations of this study are multifold:

Theoretical integration innovation. By explicitly integrating HBM and TTM to first diagnose the root cause of non-adherence and then prescribe a tailored strategy, this study advances beyond descriptive theory toward an operationalized support mechanism.

Intervention model innovation. The "Predictive + Processual" two-stage model allows for early identification of at-risk patients

before non-adherence occurs and provides a continuous support pathway that adapts to the patient's evolving journey.

Practical value innovation. The protocol is designed for high feasibility and scalability within the Chinese healthcare system by being structured for delivery by physicians and nurses within standard workflows, thereby maximizing impact without requiring an expansion of specialist resources.

Method
Study design. We conducted a two-arm, parallel-group, assessor-blinded, randomized controlled trial (RCT). This trial was designed to evaluate the efficacy of a personalized, theory-based psychological intervention compared to treatment-as-usual (TAU) on medication adherence in outpatients with depression. The intervention was delivered over a 12-week period, comprising an initial predictive phase (Weeks 0–4) and a subsequent Process-Based Phase (Weeks 5–12). The trial was conducted at the Department of Psychiatry and Psychology of a tertiary general hospital in Guangdong Province, China.

Participants. Participants were recruited via convenience sampling from first-visit outpatients at the study site. All participants were receiving routine multidisciplinary psychiatric care. After randomization, participants were included in only one study arm (intervention or TAU). Researchers collecting outcome assessments were blinded to the participants' group allocation.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of Southern Medical University (Approval Nan Yi Lun Shen 2021 No.011). Prior to enrollment, all participants (and their parents or legal guardians, where applicable) received a comprehensive explanation of the study and provided written informed consent.

To ensure confidentiality, all participant data were de-identified and stored under a unique code, with access restricted to the principal investigators. The authors declare no potential conflicts of interest concerning the research, authorship, and/or publication of this article.

Eligibility criteria. Inclusion criteria were: (1) Outpatients with a clinician-confirmed diagnosis of a depressive episode according to DSM-5 criteria; (2) A score of ≥53 on the Self-Rating Depression Scale (SDS); (3) Minimum education level of primary school; (4) Access to a telephone for follow-up purposes.

Exclusion criteria were: (1) Presence of organic brain diseases; (2) Current psychotic symptoms; (3) Diagnosis of organic depressive disorders; (4) Severe comorbid somatic diseases that could interfere with participation; (5) Substance abuse or dependence; (6) A history of severe drug allergy.

Eligibility was confirmed by a study psychiatrist based on medical record review and clinical assessment.

Randomization and blinding. Eligible participants were randomly allocated (1:1) to the intervention or TAU control group after the completion of all baseline assessments (T1).

An independent statistician generated the randomization schedule (block sizes of 4 and 6), prepared by an independent statistician. Allocation was stratified by sex to ensure balance between groups. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes. These envelopes were stored in a locked location and were opened sequentially by a research coordinator only after a participant's baseline data had been collected.

Due to the nature of the psychological intervention, participants and the intervention providers could not be blinded to group assignment. However, outcome assessors, the data management team, and the trial statistician were blinded to group allocation for the duration of the study. Participants were instructed not to reveal their assignment to assessors.

Interventions
Experimental intervention (personalized, theory-based psychological intervention). The experimental intervention was a 12-week, multi-component program grounded in behavioral change theories. It was delivered across eight individualized, 30-min sessions. The intervention was structured in two phases:

Predictive phase (weeks 0–4): The baseline PSPMA assessment guided the application of tailored strategies across five key domains: Autonomy Enhancement, Perceived Necessity, Medication Beliefs, Family Support, and Self-Efficacy. This included psychoeducation, MI, and collaborative problem-solving.

Process-based phase (weeks 5–12): Intervention strategies were dynamically adapted weekly based on the participant's assessed Stage of Change (Precontemplation, Contemplation, Preparation, Action, Maintenance). Focus shifted from building motivation in early stages to reinforcing behavior and preventing relapse in later stages. The intervention was delivered by trained psychological research staff under the supervision of a licensed clinical psychologist.

Control intervention (treatment-as-usual—TAU). Participants allocated to the TAU group received standard outpatient care, which included regular psychiatric consultations, medication management, and general advice. They did not receive the structured, theory-based psychological intervention provided to the experimental group.

Outcome measures. Assessments were conducted at baseline (T1), week 2 (T2), week 4 (T3), week 8 (T4), and week 12 (T5) as detailed in Table 1. Data were collected through on-site paper-based questionnaires, telephone follow-ups, and electronic medical record reviews.

Primary outcome. The primary outcomes of this study were assessed using two validated instruments to capture changes in depressive symptomatology and medication adherence behavior:

Self-Rating Depression Scale (SDS): The SDS is a widely used 20-item self-report measure that assesses the affective, cognitive, and somatic dimensions of depression. Each item is scored on a 4-point Likert scale. The total score ranges from 20 to 80, with higher scores indicating more severe depressive symptoms. This scale was selected as a primary endpoint to directly evaluate the intervention's impact on the core clinical manifestation of depression.

Morisky Medication Adherence Scale (MMAS): The MMAS is an 8-item self-report questionnaire designed to measure adherence behaviors and attitudes toward psychotropic medications. The MMAS was chosen as a co-primary outcome because improving adherence is the central objective of the proposed intervention.

Secondary outcomes. Secondary outcomes were employed to explore the intervention's effects on underlying mechanisms and predictive factors related to adherence:

Table 1 Measurement tools and assessment schedule.

	Predictive Phase		Process-Based Phase		
	T1 (Baseline)	T2 (Week 2)	T3 (Week 4)	T4 (Week 8)	T5 (Week 12)
Sociodemographic Data	√				
Clinical Data Related to Diseases, etc.	√				
Primary Outcome					
MMAS		√	√	√	√
SDS	√				√
Secondary Outcomes					
PSPMA	√	√			
SEAMS	√				√

MMAS Morisky Medication Adherence Scale, *SDS* Self-Rating Depression Scale, *PSPMA* Predictive Scale for Psychotropic Medication Adherence, *SEAMS* Self-efficacy for Appropriate Medication Use Scale.

Predictive scale for psychotropic medication adherence (PSPMA): This scale was used to identify patients at high risk of non-adherence at baseline and to monitor changes in predictive risk factors (e.g., beliefs about medication, perceived self-efficacy) throughout the study period.

Self-efficacy for Appropriate Medication Use Scale (SEAMS): The SEAMS is a 13-item instrument that assesses a patient's confidence in their ability to manage medication use under various challenging situations. Responses are scored on a 3-point scale, and higher total scores reflect greater medication self-efficacy. This measure was included to evaluate whether the intervention effectively enhanced this critical psychological mechanism, which is theorized to mediate long-term adherence behavior.

Sample size. The sample size was determined a priori for the marginal model (GEE) analysis of the primary continuous outcome. The sample size calculation was based on the Zhang–Ahn formula for marginal models. Key assumptions included a medium effect size (Cohen's $d = 0.50$) at 12 weeks, an exchangeable working correlation structure with an intra-class correlation coefficient (ICC) of $\rho = 0.20$, and three repeated measurements (baseline, 6-week, and 12-week). With $\alpha = 0.05$ (two-sided) and power $= 0.80$, a total of 66 participants (33 per group) were required. Accounting for an estimated 20% attrition over 12 weeks, we aimed to recruit 80 participants (40 per group).

Statistical analysis. Analyses were performed using SPSS 28 (IBM Corp.). Two-tailed α was set at 0.05; Bonferroni–Holm correction was applied when multiple contrasts were tested.

Continuous repeated measures. Medication adherence (MMAS-8), depressive symptoms (SDS), self-efficacy (SEAMS), and PSPMA sub-scores were analyzed with generalized estimating equations (GEE, unstructured correlation, robust SEs). The model included the fixed effects of Group, Time (as a categorical factor), and their Group × Time interaction. Effect sizes are Cohen's d from model-implied marginal means. Simple contrasts used the Bonferroni–Holm adjustment.

Ordinal outcomes. Stage of Change and Medication Effectiveness Rating were analyzed with ordinal GEE (logit link, unstructured correlation); proportional-odds assumptions were met (Brant test $p \geq 0.08$).

Robustness. All models were re-estimated with AR(1) correlation, and after excluding two participants who switched to mania, significance and effect magnitudes were unchanged. VIF < 1.9 excluded multicollinearity.

Result

Participant flow and attrition analysis. A total of 80 eligible patients with acute-phase major depressive disorder were recruited from a tertiary hospital in Guangdong, China, and randomly allocated to the intervention ($n = 40$) or control ($n = 40$) group. Twenty participants (25%) dropped out before study completion and were excluded from the per-protocol analysis, yielding a final analysis sample of 60 participants. The attrition rate did not differ significantly between groups ($\chi^2 = 0.00$, $p = 1.00$). Loss to follow-up was the most common reason for dropout ($n = 14$), followed by switching to psychotherapy ($n = 4$), self-discontinuation of medication ($n = 3$), transition to a manic episode ($n = 2$), and physician-advised discontinuation ($n = 1$).

Baseline sociodemographic and clinical characteristics. Baseline sociodemographic and clinical characteristics for the 60 participants who completed the study are presented in Table 2. The sample had a mean age of 21.88 years (±5.53) and was predominantly female (78.3%). The intervention and control groups were well-balanced at baseline, with no statistically significant differences in any demographic variables, including age, sex, ethnicity, residence, or education (all $p > 0.05$). Clinical characteristics, such as depression severity, family history of mood disorders, and treatment preferences, were also comparable between groups (all $p > 0.05$), confirming the success of the randomization process.

Primary outcomes

Medication adherence (MMAS-8). Generalized estimating equations revealed a significant group × time interaction (Wald $\chi^2 = 17.30$, p = 0.001) with substantial main effects for both time (Wald $\chi^2 = 95.94$, $p < 0.001$) and group (Wald $\chi^2 = 23.19$, $p < 0.001$). Detailed GEE results are provided in Table 3. Analysis of simple effects with Bonferroni-Holm correction demonstrated comparable baseline scores between groups (T2 difference $= -0.63$, $p = 1.00$). Full details of between-group comparisons at all time points are available in Table 4. The intervention group showed a characteristic pattern: an initial decline at T2 ($\beta = -1.73$, $p < 0.001$) followed by progressive improvement. By endpoint (T5), the intervention group achieved significantly higher adherence (mean $= 7.02$, SE $= 0.64$) compared to controls (mean $= 5.93$, SE $= 1.06$), with a between-group difference of 1.09 points (95% CI 0.38–1.80, $p < 0.001$; Cohen's $d = 0.38$). This represents an 18.4% relative improvement in adherence.

Within-group analyses revealed sustained improvement exclusively in the intervention group (T5 vs T2: +2.83 points, $p < 0.001$), while control participants showed minimal change (+1.10 points, $p = 0.076$). Sensitivity analysis using an

Table 2 Comparison of sociodemographic and disease-related data between the two groups.

Characteristic	Category	Intervention (n = 30)		Control (n = 30)		χ^2	P value
		n	%	n	%		
Sex	Male	3	10.00	10	33.30	4.81	0.03
	Female	27	90.00	20	66.70		
Age (years)	0–18	7	23.30	15	50.00	4.97	0.08
	19–30	20	66.70	14	46.70		
	31–40	3	10.00	1	3.30		
Ethnicity	Han	28	93.30	30	100.00	2.07	0.15
	Minority	2	6.70	0	0.00		
Residence	Rural	4	13.30	5	16.70	0.39	0.94
	Small town/county	10	33.30	8	26.70		
	Medium-sized city	8	26.70	8	26.70		
	Large city	8	26.70	9	30.00		
Birth order	Only child	12	40.00	6	20.00	5.31	0.26
	Eldest	11	36.70	10	33.30		
	Second	4	13.30	11	36.70		
	Third	1	3.30	1	3.30		
	Fourth	2	6.70	2	6.70		
Economic status	Good	5	16.70	10	33.30	2.27	0.32
	Fair	22	73.30	18	60.00		
	Poor	3	10.00	2	8.30		
Employment status	Unemployed	19	63.30	19	63.30	0.00	1.00
	Employed	11	36.70	11	36.70		
Education level	Below senior high	2	6.70	1	3.30	5.50	0.23
	Senior high	8	26.70	12	40.00		
	College diploma	10	33.30	5	16.70		
	Bachelor	8	26.70	12	40.00		
	Master	2	6.70	0	0.00		
Marital status	Never married	28	93.30	28	93.30	1.33	0.51
	Married	1	3.30	2	6.70		
	Divorced	1	3.30	0	0.00		
Severity of depression	Mild	1	3.30	3	10.00	1.50	0.47
	Moderate	11	36.70	8	26.70		
	Severe	18	60.00	19	63.30		
Family history of mental disorders	Absent	25	83.30	27	90.00	0.58	0.45
	Present	5	16.70	3	10.00		
Treatment preference	Psychotherapy only	2	6.70	2	6.70	0.23	0.97
	Pharmacotherapy only	9	30.00	9	30.00		
	Combined	17	56.70	16	53.30		
	Self-adjustment	2	6.70	3	10.00		
Pharmacotherapy preference	Western medicine	14	46.70	13	43.30	0.24	0.89
	Traditional Chinese medicine	2	6.70	3	10.00		
	Combined Chinese & Western	14	46.70	14	46.70		

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 3 GEE analysis of medication adherence.

Parameter	B	Std. Error	95% CI	Wald χ^2	p-value
Intercept (Control at Tm5)	5.925	0.194	5.545 to 6.305	932.18	<0.001
Time (Ref: Tm5)				95.935	<0.001
Tm2	−1.1	0.367	−1.819 to −0.381	8.985	0.003
Tm3	−0.392	0.373	−1.123 to 0.339	1.103	0.294
Tm4	−0.158	0.213	−0.575 to 0.258	0.555	0.456
Group [Intervention vs. Control]	1.092	0.227	0.647 to 1.536	23.185	<0.001
Time × Group Interaction				17.295	0.001
Tm2 × Intervention	−1.725	0.471	−2.648 to −0.802	13.418	<0.001
Tm3 × Intervention	−0.683	0.439	−1.543 to 0.177	2.426	0.119
Tm4 × Intervention	−0.408	0.291	−0.979 to 0.162	1.967	0.161

The Model used an unstructured working correlation matrix. The significant interaction for Tm2 × Intervention indicates lower adherence in the intervention group at that specific early time point. Scale Parameter = 1.786.

Table 4 Simple effects analysis of medication adherence: between-group and within-group comparisons based on GEE.

Comparison Type	Comparison	Time Point	Mean Difference	Standard Error	95% Confidence Interval	p Value	Cohen's d
Between-Group(Intervention - Control)	Intervention vs. Control	T2	−0.63	0.42	(−1.94, 0.68)	1.00	−0.12
		T3	0.41	0.418	(−0.90, 1.72)	1.00	0.08
		T4	0.68	0.24	(−0.07, 1.43)	0.13	0.23
		T5	1.09	0.227	(0.38, 1.80)	<0.001	0.38
Within-Group (vs. Baseline T2)	Intervention Group	T3	1.75	0.2	(1.13, 2.37)	<0.001	0.70
		T4	2.26	0.232	(1.53, 2.98)	<0.001	0.78
		T5	2.83	0.295	(1.90, 3.75)	<0.001	0.76
	Control Group	T3	0.71	0.25	(−0.07, 1.49)	0.13	0.23
		T4	0.94	0.258	(0.13, 1.75)	0.01	0.29
		T5	1.10	0.367	(−0.05, 2.25)	0.08	0.24

Mean differences are based on estimated marginal means from the GEE model. For between-group comparisons, the mean difference is calculated as (Intervention—Control). For within-group comparisons, the mean difference is (Follow-up—Baseline T2). P-values are adjusted using the Bonferroni method. Cohen's d is provided as a measure of effect size. The significance level was set at $\alpha = 0.05$.

Table 5 GEE analysis of depressive symptoms (SDS Score).

Parameter	B	Std. Error	95% CI	Wald χ^2	p-value
Intercept (Control at T5)	66.967	1.602	63.83 to 70.11	1748.003	<0.001
Time [T1 vs. T5]	7.167	1.347	4.53 to 9.81	28.321	<0.001
Group [Intervention vs. Control]	0.767	2.068	−3.29 to 4.82	0.137	0.711
Time × Group	0.4	1.608	−2.75 to 3.55	0.062	0.803

The Model used an unstructured working correlation matrix. A positive B for Time indicates higher scores at T1 (i.e., symptom reduction over time). Scale Parameter = 75.419.

Table 6 GEE Analysis of SEAMS.

Parameter	B	Std. Error	95% CI	Wald χ^2	p-value
Intercept (Control at T5)	28.733	0.733	27.30 to 30.17	1536.846	<0.001
Time [T1 vs. T5]	−2.233	1.009	−4.21 to −0.26	4.904	0.027
Group [Intervention vs. Control]	0.133	1.268	−2.35 to 2.62	0.011	0.916
Time × Group	0.6	1.337	−2.02 to 3.22	0.201	0.654

The Model used an unstructured working correlation matrix. A negative B for Time indicates an increase in self-efficacy over time. Scale Parameter = 30.467.

autoregressive correlation structure confirmed the robustness of these findings, yielding a nearly identical group × time interaction (Wald $\chi^2 = 17.30$, $p = 0.001$).

Self-Rating Depression Scale (SDS). Table 5 displays the marginal mean SDS scores across five waves. Both groups demonstrated substantial symptom improvement over time, as evidenced by a strong main effect of time (Wald $\chi^2 = 84.0$, $p < 0.001$), with an average reduction of 7.17 points from T1 to T5 (95% CI: 4.53–9.81). However, neither the main effect of group (Wald $\chi^2 = 0.22$, $p = 0.64$) nor the group × time interaction (Wald $\chi^2 = 0.06$, $p = 0.80$) reached significance. The between-group difference at study endpoint was minimal (0.77 points, 95% CI: −3.29 to 4.82, $p = 0.71$) and substantially below the established minimal clinically important difference of 5 points. Multiple imputation analysis addressing potential missing data confirmed these null findings (group × time interaction: Wald $\chi^2 = 0.06$, $p = 0.80$).

Secondary outcomes
Self-efficacy for Appropriate Medication Use Scale (SEAMS). Table 6 shows that a small but significant main effect of time was observed (Wald $\chi^2 = 8.40$, $p = 0.004$), with self-efficacy scores

increasing by an average of 2.23 points in both groups combined (95% CI: −4.21 to −0.26, $p = 0.027$). Neither the main effect of group nor the group × time interaction was significant ($p = 0.65$), indicating similar improvement in both groups.

Predictive Scale for Psychotropic Medication Adherence (PSPMA). Analysis of the PSPMA dimensions revealed distinct patterns over time and between groups (Table 7). Significant improvements over time were observed in three of the five dimensions after Bonferroni-Holm correction: patient autonomy (mean increase = 0.32 points), perceived necessity (0.24 points), and drug acceptance (0.45 points). Medication self-efficacy and family support remained stable across the study period.

Regarding group differences, the intervention group demonstrated significantly higher patient autonomy than the control group (mean difference = 0.55 points, $p = 0.001$). Conversely, the control group reported higher levels of family support (mean difference = −0.40, $p = 0.031$). No significant group differences were found for the other three dimensions.

Finally, the Time × Group interaction for Medication Self-Efficacy showed a non-significant trend (Wald $\chi^2 = 3.54$, $p = 0.060$), suggesting a potential differential change between groups. All other interaction terms were non-significant.

Table 7 GEE analysis of the PSPMA dimensions.

Dimension	Effect	Wald χ^2	p-value	B [95% CI]
Medication Self-Efficacy	Time	0.166	0.684	0.141 [−0.104, 0.386]
	Group	2.18	0.14	0.400 [0.095, 0.705]
	Time × Group	3.537	0.06	−0.359 [−0.733, 0.015]
Patient Autonomy	Time	5.447	0.02	0.318 [0.070, 0.567]
	Group	11.649	0.001	0.548 [0.280, 0.817]
	Time × Group	1.484	0.223	−0.218 [−0.570, 0.133]
Perceived Necessity	Time	5.602	0.018	0.237 [0.017, 0.457]
	Group	0.123	0.726	−0.077 [−0.362, 0.208]
	Time × Group	0.127	0.722	0.062 [−0.279, 0.403]
Drug Acceptance	Time	7.673	0.006	0.450 [0.173, 0.727]
	Group	0.108	0.742	−0.138 [−0.556, 0.280]
	Time × Group	0.445	0.505	0.175 [−0.339, 0.688]
Family Support	Time	0.01	0.921	−0.125 [−0.249, 0.000]
	Group	4.645	0.031	−0.401 [−0.660, −0.141]
	Time × Group	2.163	0.141	0.267 [−0.089, 0.624]

NS not significant ($p \geq 0.05$). B represents the effect of Time (Tyc1 vs. Tyc2), Group (Intervention vs. Control), or their interaction. All models used an unstructured working correlation matrix. Model intercepts are not shown.

Table 8 GEE (Ordinal Logistic) Analysis of Behavioral Stage of Change.

Parameter	B	Std. Error	95% CI	Wald χ^2	p-value
Time [T3 vs. T5]	−1.573	0.961	−3.455 to 0.310	2.681	0.102
Group [Intervention vs. Control]	−1.09	1.206	−3.453 to 1.274	0.816	0.366
Time × Group Interaction	0.792	1.235	−1.628 to 3.212	0.412	0.521

The model included threshold parameters (not shown). A negative B for Time indicates a lower odds of being in a higher stage at T3 versus T5 (reference). The overall model test for Time was significant ($p = 0.037$).

Table 9 GEE (ordinal logistic) analysis of medication effectiveness rating.

Parameter	B	Std. Error	95% CI	Wald χ^2	p-value
Time [T1 vs. T4]	−2.777	0.383	−3.527 to −2.027	52.689	<0.001
Time [T2 vs. T4]	−1.353	0.4	−2.138 to −0.569	11.429	0.001
Time [T3 vs. T4]	−0.352	0.384	−1.105 to 0.401	0.839	0.36
Group [Intervention vs. Control]	0.347	0.458	−0.551 to 1.245	0.572	0.449
Time × Group Interaction				1.879	0.598

The model included threshold parameters (not shown). A negative B for Time indicates a lower odds of a higher effectiveness rating at the earlier time point versus T4 (reference).

Ordinal outcomes

Behavioral stage of change. Analysis of the Behavioral Stage of Change, assessed at the end of the predictive (T3) and process-based (T5) phases, showed a significant main effect of time (Wald $\chi^2 = 4.339$, $p = 0.037$). The negative coefficient at T3 ($B = -1.573$) indicates that participants progressed to more advanced stages of change by the end of the study (T5). There was no significant main effect of group (Wald $\chi^2 = 0.836$, $p = 0.361$) and no significant time-by-group interaction (Wald $\chi^2 = 0.412$, $p = 0.521$), indicating that this progression was comparable between the intervention and control groups (Table 8).
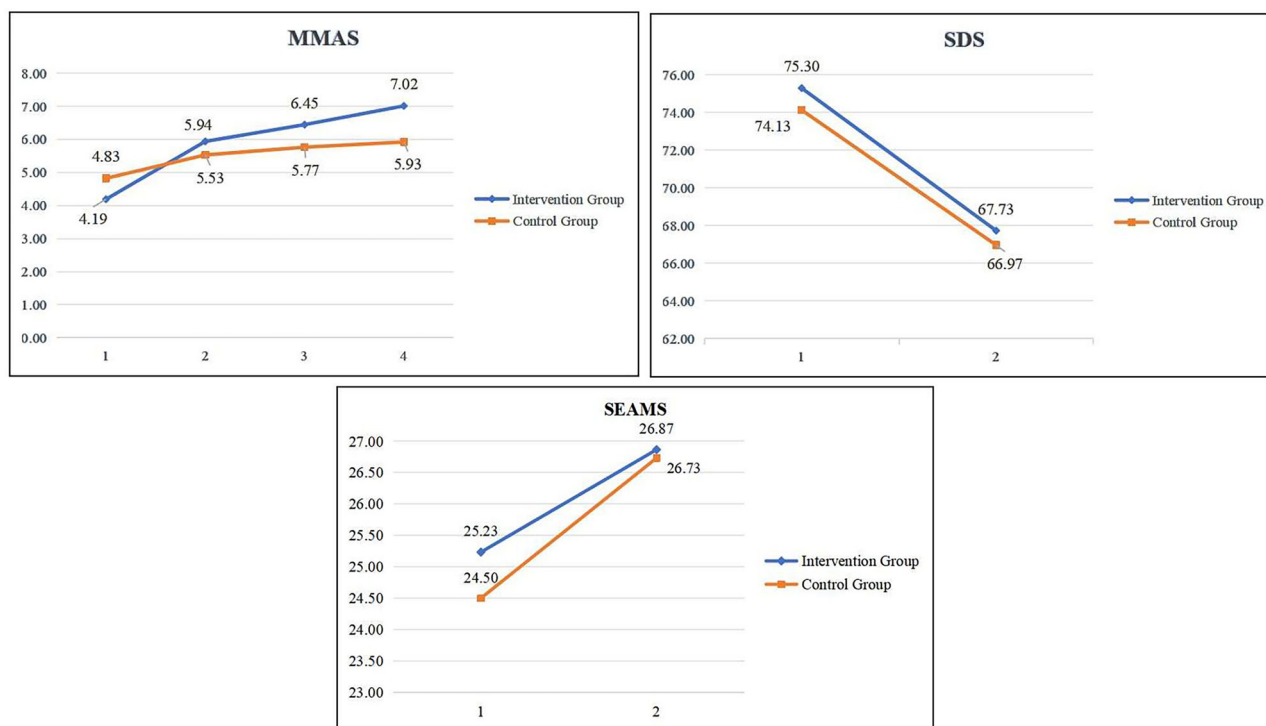
Medication effectiveness rating. Analysis of the Medication Effectiveness Rating across four time points (T1-T4) revealed a highly significant main effect of time (Wald $\chi^2 = 88.463$, $p < 0.001$). Post-hoc comparisons indicated that ratings were significantly lower at both T1 ($B = -2.78$, $p < 0.001$) and T2 ($B = -1.35$, $p = 0.001$) compared to T4, but not at T3 ($B = -0.35$, $p = 0.360$). Neither the main effect of group nor the time-by-group interaction was significant (both $p > 0.05$), demonstrating a uniform positive trajectory in both groups (Table 9).

Figure 1 illustrates the trajectories of primary and secondary outcomes across the five measurement points. Panel A (MMAS-8) shows a divergent course between groups after T2, with the intervention group demonstrating a steady upward trajectory while the control group plateaued after T3. This visual separation corroborates the significant group × time interaction observed in the GEE model. In contrast, Panels B (SDS) and C (SEAMS) display nearly superimposable trajectories for both groups, with parallel declines in depressive symptoms and concurrent increases in self-efficacy, consistent with the non-significant group effects for these outcomes.

Discussion

Principal findings and interpretation. Our personalized, theory-based intervention significantly improved medication adherence, as measured by the Morisky Medication Adherence Scale-8 (MMAS-8), demonstrating a moderate and sustained effect size (Cohen's $d = 0.38$) over the 12-week trial. Sensitivity analyses confirmed the robustness of this finding. The intervention group achieved a mean score increase of 2.83 points from baseline to endpoint (T5), substantially surpassing the 1.10-point

Fig. 1 Trajectory Diagram.

improvement in the TAU control group, underscoring the specific efficacy of our approach.

It is important to contextualize our study's 25% attrition rate. Dropout during acute-phase depression treatment is a common challenge; reported rates typically range from 20 to 40% in clinical trials and can be even higher in observational studies (Demyttenaere, 2003). Our attrition rate, which did not differ significantly between groups, falls within this expected range and is consistent with the practical difficulties of maintaining engagement in this patient population.

The adherence trajectory within the intervention group offered further insight into the mechanism of change. We observed an initial decline at T2, a pattern congruent with the TTM's postulate that individuals often experience ambivalence and temporary setbacks when progressing from contemplation to action. This was followed by a significant and steady rise in adherence through T5, indicating that the intervention's components (e.g., skill-building, autonomy support) effectively facilitated progression through the stages of change to foster durable behavior.

The magnitude of our effect size places the intervention at the higher end of the spectrum reported in the adherence literature. For instance, the effect surpasses that of a technology-based strategy using a smartphone app (Krell et al., 2004) and appears more robust than the often modest effects highlighted in recent systematic reviews (Kengne et al., 2024). This enhanced efficacy is likely attributable to our theory-driven, multifaceted design. It integrates several evidence-based behavior change techniques—such as "action planning" and "instruction on how to perform the behavior," which are associated with success (Teo et al., 2024)—within a structured, stage-matched framework. This synergy creates a tailored approach to overcoming individual barriers, proving more potent than single-component strategies.

Null effect on depressive symptoms. A key finding of this study is the clear dissociation between improved medication adherence

and short-term depressive symptom reduction. Despite the intervention's significant effect on adherence, it did not accelerate symptom improvement compared to the control group over 12 weeks. The between-group difference at endpoint was negligible (0.77 points on the SDS) and well below the minimal clinically important difference, a conclusion robust to sensitivity analysis.

This dissociation suggests that the psychological mechanisms driving medication-taking behavior are distinct from the neurobiological processes governing antidepressant response. The primary benefit of enhanced adherence may thus lie in long-term outcomes, such as relapse prevention and sustained recovery, rather than in accelerating initial symptom resolution.

Our null finding regarding symptoms contrasts with some literature. For instance, a systematic review by Marasine et al. (2025) reported that some integrated care models improved both adherence and depression severity. This contrast underscores that improving adherence, while achievable, is not invariably sufficient for symptom remission, highlighting the multifaceted nature of treatment response.

Several interrelated factors may explain the lack of symptomatic benefit. First, methodological considerations may have played a role; the self-rated SDS, assessed at a single endpoint, may lack the sensitivity to capture nuanced symptom dynamics. More substantially, clinical and pharmacological complexities are likely pivotal. Symptoms can follow non-linear trajectories influenced by unmanaged side effects, psychosocial stressors, or developing pharmacological tolerance. Furthermore, adherence alone cannot overcome inherent pharmacotherapeutic limitations, such as treatment-resistant profiles in a portion of the cohort. Finally, a conceptual limitation of our intervention is that it primarily targeted behavioral adherence, potentially without sufficiently addressing deeper perceptual barriers, such as persistent negative beliefs about medication, which can undermine its perceived efficacy and thus its symptomatic benefit.

Mechanisms of change: autonomy vs. self-efficacy. The intervention successfully enhanced patient autonomy, fostering a greater sense of personal control and self-determination in medication management. This empowerment, addressing a crucial psychological need in depression, appears to be a key mechanism through which the intervention improved adherence.

In contrast, the intervention did not yield a significant additional improvement in general medication self-efficacy compared to standard care. This clear dissociation confirms that autonomy and general self-efficacy are distinct constructs and indicates that our intervention specifically and effectively targeted the former. The non-significant finding for self-efficacy could be due to the SEAMS scale's potential insensitivity to the context-specific self-efficacy our intervention cultivated, or a ceiling effect created by the general self-efficacy support inherent in standard care.

Therefore, the intervention's success in improving adherence primarily through enhancing autonomy, rather than general self-efficacy, positions patient autonomy as a particularly critical mechanism of change for individuals with Major Depressive Disorder. This finding aligns with theories of intrinsic motivation, which emphasize that personal control over treatment decisions can be a more powerful driver of behavior than general confidence beliefs (Luo et al., 2023; Liu et al., 2018).

The unexpected role of social and family support. A counterintuitive finding was that the control group reported significantly higher levels of family support than the intervention group. While this could point to an unmeasured baseline imbalance, a more compelling interpretation relates to the intervention's core mechanism.

We hypothesize that by actively fostering patient autonomy and self-management skills, the intervention may have reduced patients' perceived need for external familial support. Patients in the intervention group, feeling empowered to manage their own treatment, might have become less reliant on family reminders. Conversely, the control group, lacking this targeted empowerment, may have remained more dependent on family members for practical and emotional support, leading to their higher reported levels of perceived support.

Theoretical and mechanistic insights. The intervention's success in improving medication adherence, despite its null effect on depressive symptoms, underscores the critical role of its theoretical underpinnings, particularly the TTM, in guiding its mechanism of action.

The TTM provides a powerful lens through which to interpret the observed adherence trajectory. The characteristic early dip in adherence at T2 is not indicative of failure but rather exemplifies the early-stage resistance and ambivalence theorized by the TTM as individuals commit to behavior change. This initial setback likely represents a critical transition point as patients grappled with the cognitive and emotional demands of moving from contemplation to action.

Subsequently, the significant and steady rise in adherence from T3 to T5 demonstrates the intervention's efficacy in facilitating progression through the stages of change. Through continued, stage-matched support—which may have ranged from resolving ambivalence in earlier stages to reinforcing new habits in later stages—the intervention helped patients consolidate medication-taking into a stable behavior. This pattern underscores that short-term fluctuations are an expected part of the change process, highlighting the importance of sustained, theory-driven support over a one-size-fits-all approach for achieving long-term adherence.

Conclusion

This RCT establishes that a structured, theory-based intervention can significantly improve medication adherence in outpatients with acute-phase major depressive disorder by successfully enhancing patient autonomy. The core finding—a clear dissociation between improved adherence and accelerated short-term symptom relief—challenges the assumption that modifying adherence behavior will directly and immediately translate into symptomatic benefit. It underscores that adherence is a valid, independent treatment target governed by distinct psychological mechanisms.

These insights carry significant clinical implications. They provide a robust evidence base for integrating theory-driven, personalized adherence support into standard depression care, moving beyond a one-size-fits-all approach. The intervention demonstrates that empowering patients in their treatment journey is a viable and effective strategy, even within the constraints of routine clinical practice.

Study limitations, including the single-center design and 12-week follow-up, point to clear priorities for future research. Subsequent investigations should employ longer-term trials to determine if the achieved adherence gains translate into the ultimate goal of sustained recovery and relapse prevention. Further exploration is also warranted to bridge the identified gap between adherence and symptom change, and to refine the intervention's components for different patient subpopulations. This work paves the way for a new generation of adherence strategies that are not only effective but also precisely targeted to the psychological needs of individuals with depression.

Data availability

The datasets generated and analyzed in this study involve sensitive personal information and are therefore not publicly accessible. Researchers who wish to access the data may submit a formal request, which will be considered following approval by the relevant ethics committee.

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Author contributions

Wanying Cheng revised the paper and participated in the writing and editing process, and led the additional work required, which encompassed a comprehensive re-analysis of the entire dataset and a substantial rewrite of the "Results and Discussion" sections. Xiayida Maimaiti completed the design of the questionnaire, data collection, and thesis writing. Jiubo Zhao provided theoretical guidance and experimental design, reviewed a draft of the thesis, and provided valuable revisions. All authors read and approved the final manuscript and agreed to take responsibility for all aspects of the work.

Funding

Competing interests

The authors declare no competing interests.

Ethical approval

Ethical approval for this study was obtained from the Ethics Committee of Southern Medical University (Approval Nan Yi Lun Shen 2021 No.011) on July 14, 2021. All research procedures were performed in accordance with the ethical standards of the Declaration of Helsinki. The approved protocol encompassed the recruitment of outpatients with depression, the delivery of the personalized psychological intervention and treatment-as-usual, and the collection and analysis of all outcome measures.

Informed consent

Written informed consent was obtained from all participants and, for participants under the age of 18, from their parents or legal guardians. The consent process was conducted by the principal investigator and trained research coordinators prior to any study procedures (between August 2023 and February 2024). Participants and their guardians were comprehensively informed about the study's aims, procedures, potential risks and benefits, confidentiality safeguards, and their right to withdraw without penalty. The consent covered participation in the study, the use of their anonymized data for research purposes, and the publication of aggregated findings.

Additional information

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