Supplementary Materials

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Title: Application of medication therapy management-based "in-hospital assessment - home-based intervention" pharmaceutical care in patients with depression

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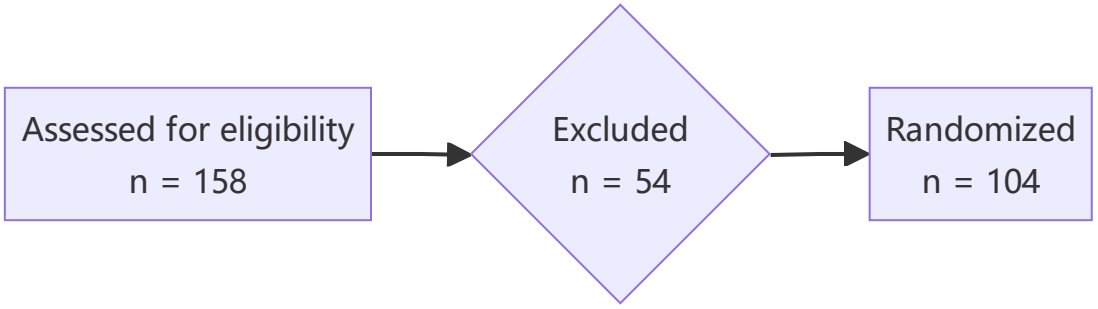
Supplementary Figure 1: CONSORT 2010 Flow Diagram

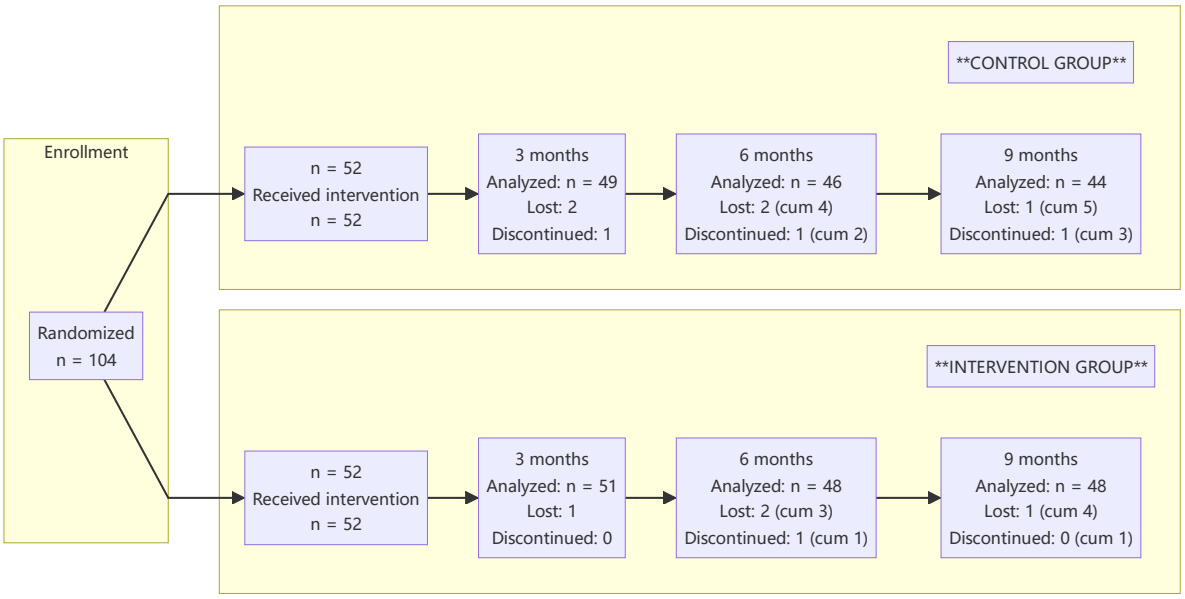
A. Screening and Enrollment



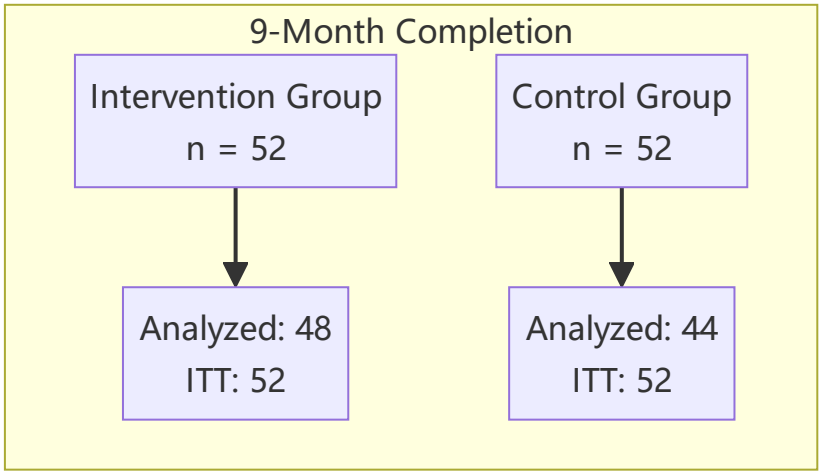
Reasons for exclusion (n = 54):

Category	Reason	n
Not meeting inclusion criteria (n = 32)	HAMD-17 < 17	14
	Age < 18 or > 65	6
	Not on stable-dose monotherapy	8
	Other	4
Declined to participate (n = 15)	Unable to commit to 9-month follow-up	9
	Unwilling to sign informed consent	6
Other reasons (n = 7)	Living outside catchment area	4
	Enrolled in competing study	3

B. Group Allocation and Longitudinal Follow-up



C. Final Disposition



Summary of Attrition

Time Point	Intervention Group (n = 52)	Control Group (n = 52)
Randomized	52	52
3-month: Analyzed / Lost / Discontinued	51 / 1 / 0	49 / 2 / 1
6-month: Analyzed / Lost / Discontinued	48 / 2 (cum 3) / 1 (cum 1)	46 / 2 (cum 4) / 1 (cum 2)
9-month: Analyzed / Lost / Discontinued	48 / 1 (cum 4) / 0 (cum 1)	44 / 1 (cum 5) / 1 (cum 3)

Time Point	Intervention Group (n = 52)	Control Group (n = 52)
ITT population	52	52

Overall attrition rate: 7.7% (8/104) — below the pre-specified 10% threshold.

Primary reasons for attrition:

Reason	Intervention (n)	Control (n)	Total (n)
Moved away	3	0	3
Unable to contact	1	2	3
Withdrew consent	0	2	2
Patient request to discontinue	1	1	2
Non-compliance with study procedures	0	1	1
Hospitalized for severe adverse event	0	1	1
Any missing data	**4**	**8**	**12**

> The 3 excluded criteria sub-nodes in panel A have been simplified into a table for clarity. The side-by-side layout in panel B allows direct comparison of attrition across groups. ITT = intention-to-treat; cum = cumulative.

Supplementary Table 1: Extent and Pattern of Missing Data

1. Overview of Missing Data

Time Point	Intervention (n = 52)	Control (n = 52)	Overall (N = 104)
Baseline	0 (0.0%)	0 (0.0%)	0 (0.0%)
3 months	1 (1.9%)	3 (5.8%)	4 (3.8%)
6 months	4 (7.7%)	6 (11.5%)	10 (9.6%)
9 months	4 (7.7%)	8 (15.4%)	12 (11.5%)

2. Pattern of Missing Data by Variable Category

2.1 Primary Outcomes

Variable	3 months	6 months	9 months
Medication possession rate (MPR)	3.8%	9.6%	11.5%

Variable	3 months	6 months	9 months
Dose omission rate	3.8%	9.6%	11.5%
Self-initiated dose reduction rate	3.8%	9.6%	11.5%
HAMD-17 score	3.8%	9.6%	11.5%

2.2 Secondary Outcomes

Variable	3 months	6 months	9 months
Clinical response / remission / relapse	3.8%	9.6%	11.5%
Healthcare resource utilization	1.9%	5.8%	7.7%
Quality of life (SF-36, WHOQOL-BREF)	3.8%	9.6%	11.5%
Remote pharmacist consultation frequency	0.0%	1.9%	1.9%
Patient satisfaction	—	—	11.5%
Adverse drug reaction reporting	3.8%	9.6%	11.5%

3. Missing Data Mechanism Assessment

Method	Result
Little's MCAR test	$\chi^2 = 15.32$, df = 12, P = 0.224
Logistic regression: missing vs. baseline characteristics	No significant predictor (all P > 0.10)
Completers vs. non-completers baseline comparison	No significant differences (all P > 0.05)

4. Handling of Missing Data in the Analysis

Analysis Set	Definition	N (Intervention / Control)
ITT (primary)	All randomized; LOCF for continuous outcomes; non-completers = non-responders for binary outcomes	52 / 52
Per-protocol (sensitivity)	Completed 9-month follow-up without major protocol deviations	48 / 44
Completer analysis	Complete data at all time points	48 / 44

Additional sensitivity analyses using multiple imputation (MI) with 20 imputed datasets under MAR assumption yielded consistent results (all effect directions and significance levels unchanged).

Supplementary Appendix 1: Sample Structured Follow-up Script

> **Note:** This script was used by research pharmacists during scheduled telephone follow-ups with intervention-group participants. Calls were scheduled at Month 1, Month 2, Month 3, Month 4, Month 6, and Month 8 post-discharge (in addition to in-person assessments at 3, 6, and 9 months).

Call timing: Approx. 15–20 minutes

Phase 1: Opening & Rapport Building (2 min)

> "Hello, may I speak with [Patient Name]? This is [Pharmacist Name], the clinical pharmacist from Rugao Hospital of Traditional Chinese Medicine. Thank you for taking my call today."

> "How are you feeling this week? I'm calling to check in on how you're doing with your medication and to see if you have any questions since your last visit."

Phase 2: Medication Adherence Assessment (5 min)

> "Since our last call on [Date], have you been taking your [antidepressant name + dose] every day as prescribed?"

- ☐ Yes, as prescribed → *Skip to follow-up questions*
- ☐ No / Sometimes → *Proceed to adherence barriers*

If non-adherent:

> "I understand it can be challenging to take medication every day. Can you tell me a little about what has made it difficult?"

Probing questions (check all that apply):

- ☐ Forgot to take the medication
- ☐ Experienced side effects (e.g., nausea, dry mouth, dizziness, sleep problems)
- ☐ Felt better and thought medication was no longer needed
- ☐ Felt the medication was not helping
- ☐ Concerns about long-term effects or dependence
- ☐ Difficulty refilling prescription / cost concerns
- ☐ Family or social stigma
- ☐ Other: _____

> "How many doses have you missed in the past week? In the past month?"

> "Have you changed your dose on your own at any time since our last call?"

Phase 3: Side Effect Screening (4 min)

> "I'd like to check on any possible side effects you may be experiencing. Please tell me if you've had any of the following since your last visit:"

Side Effect	None (0)	Mild (1)	Moderate (2)	Severe (3)	Since when?
Nausea / vomiting	□	□	□	□	___
Dry mouth	□	□	□	□	___
Constipation	□	□	□	□	___
Dizziness / lightheadedness	□	□	□	□	___
Headache	□	□	□	□	___
Sleep disturbance (insomnia/somnolence)	□	□	□	□	___
Sexual dysfunction	□	□	□	□	___
Weight gain / appetite change	□	□	□	□	___
Fatigue / sedation	□	□	□	□	___
Blurred vision	□	□	□	□	___
Other: ___	□	□	□	□	___

If any severe (3) side effects:

> "I'm concerned about the symptoms you're describing. I recommend that we discuss this with your treating physician. Would you like me to arrange an earlier appointment?"

Phase 4: Symptom Monitoring (3 min)

> "Compared to before you started treatment, how would you describe your mood this week?"

- [ ] Much better
- [ ] Somewhat better
- [ ] About the same
- [ ] Somewhat worse
- [ ] Much worse

> "Have you experienced any of the following in the past 2 weeks?"

- [ ] Persistent sadness or low mood
- [ ] Loss of interest or pleasure in activities
- [ ] Significant change in appetite
- [ ] Difficulty sleeping or sleeping too much
- [ ] Fatigue or loss of energy

- [ ] Feelings of worthlessness or guilt
- [ ] Difficulty concentrating
- [ ] Thoughts of death or self-harm → **URGENT: Activate Emergency Protocol**

If any thoughts of self-harm:

> "Thank you for telling me. This is very important. I'm going to connect you with our crisis support team right now. Please stay on the line."

→ **Activate Emergency Protocol:** Immediate referral to on-call psychiatrist; if patient cannot be reached, contact emergency contacts and/or local emergency services.

Phase 5: Lifestyle & Coping (2 min)

> "In addition to medication, have you been able to:"

- [ ] Maintain regular daily routine
- [ ] Engage in physical activity (e.g., walking)
- [ ] Eat regular meals
- [ ] Connect with family or friends
- [ ] Engage in hobbies or activities you enjoy
- [ ] Practice relaxation or mindfulness

> "Is there anything else affecting your health or well-being that you'd like to share?"

Phase 6: Education & Plan (3 min)

Individualized education (select based on patient needs):

> "Let me share a few important points about your medication..."

Key messages:

1. **Consistency is key:** Antidepressants work best when taken at the same time every day. Consider linking it to a daily habit (e.g., brushing teeth, having breakfast).
2. **Don't stop abruptly:** Even if you feel better, stopping medication suddenly can cause withdrawal symptoms and increase the risk of relapse.
3. **Time to effect:** Remember that antidepressants may take 2–4 weeks to show full benefit. Patience is important.
4. **Side effect management strategies:**
    - Nausea → Take with food; usually resolves within 1–2 weeks
    - Dry mouth → Sip water regularly, use sugar-free gum
    - Constipation → Increase fiber intake, stay hydrated
    - Sleep disturbance → Take medication in the morning (if activating) or at bedtime (if sedating)

> "Shall we set a specific time each day for taking your medication?"

> "What questions do you have about your treatment plan?"

Phase 7: Closing (1 min)

> "Thank you for taking the time to speak with me today. Your next follow-up call is scheduled for [Date]. You can also reach our pharmacy team at [Phone Number] during office hours if you have any concerns before then."

> "Please remember to bring your medication bottles to your next appointment at the hospital. Take care, and have a good [day/evening]."

Post-Call Actions (Pharmacist)

Action	Completed
Update Medication Review Template	□
Update medication adherence tracking log	□
Report any severe adverse events to PI within 24 hours	□
Schedule next follow-up call	□
Flag any urgent issues for physician review	□
If emergency protocol activated: Confirm handoff to crisis team	□

Adherence Support Interventions (Pharmacist Decision Guide)

Identified Barrier	Suggested Intervention
Forgot to take medication	Pillbox organizer; smartphone alarm; family reminder system
Side effect concerns	Symptom management counseling; schedule physician review for dose adjustment
Feeling better → stopped	Psychoeducation on relapse prevention; review treatment goals
Perceived lack of efficacy	Validate concerns; remind of onset timeline; schedule physician review
Cost concerns	Assess insurance coverage; discuss generic alternatives with physician
Stigma / family opposition	Provide family education materials; offer joint counseling session
Complex regimen	Simplify schedule; use blister packaging

Supplementary Appendix 2: Patient Education Manual (Excerpt)

> **Note:** This manual was provided to all participants in the intervention group at enrollment. It was designed for patients with a range of health literacy levels. A Chinese-language version was used in the study; this is the English translation.

Understanding Your Depression Treatment: A Guide for Patients and Families

Section 1: Understanding Depression

What is depression?
Depression is more than just feeling sad or "blue." It is a medical condition that affects how you think, feel, and function. Common symptoms include:

- Persistent sadness or low mood
- Loss of interest in activities you once enjoyed
- Changes in appetite or weight
- Sleep difficulties (too much or too little)
- Fatigue or low energy
- Difficulty concentrating or making decisions
- Feelings of worthlessness or guilt
- Thoughts of death or self-harm

Good news: Depression is treatable. With the right care, most people recover and return to their normal lives.

Section 2: Understanding Your Medication

How do antidepressants work?
Antidepressants help balance natural brain chemicals (neurotransmitters) that affect mood. They do not work immediately — most people begin to feel better after **2–4 weeks** of regular use, with full benefits often seen after **6–8 weeks**.

Common types of antidepressants used in this study:

Type	Examples	How They Work
SSRI (Selective Serotonin Reuptake Inhibitor)	Sertraline, Escitalopram, Fluoxetine	Increases serotonin levels
SNRI (Serotonin-Norepinephrine Reuptake Inhibitor)	Venlafaxine, Duloxetine	Increases serotonin and norepinephrine

Type	Examples	How They Work
NaSSA (Noradrenergic and Specific Serotonergic Antidepressant)	Mirtazapine	Increases norepinephrine and serotonin

Important rules for taking your medication:

1. ✅ **Take it every day** at the same time
2. ✅ **Do not skip doses** — even when you feel better
3. ✅ **Do not stop abruptly** — this can cause withdrawal symptoms and raise the risk of depression returning
4. ✅ **Do not change the dose** without talking to your doctor
5. ✅ **Keep enough supply** — refill your prescription before you run out

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Section 3: Managing Side Effects

Many side effects are **temporary** and improve within 1–2 weeks. If side effects are bothering you, please call your pharmacist — do not stop your medication.

Side Effect	How to Manage
Nausea	Take medication with food; avoid greasy foods
Dry mouth	Sip water frequently; use sugar-free gum or candy
Constipation	Drink more water; eat high-fiber foods (fruits, vegetables, whole grains); gentle exercise
Drowsiness / Fatigue	Take medication at bedtime; avoid driving if feeling sleepy
Insomnia / Restlessness	Take medication in the morning; avoid caffeine in the evening
Dizziness	Stand up slowly; avoid sudden movements
Weight gain	Maintain a balanced diet; regular physical activity (e.g., 30-min walk daily)
Sexual difficulties	Talk to your doctor — dose adjustment or switching medications may help

📞 **Contact your pharmacist if:**

- Side effects are severe or do not improve after 2 weeks
- You have thoughts of harming yourself
- You develop a rash, swelling, or difficulty breathing (rare — may be allergic reaction)

Section 4: Relapse Prevention

What is relapse?
Relapse means that symptoms of depression return after a period of improvement.

Tips to prevent relapse:

1. **Continue medication as prescribed** — Even after you feel fully recovered, continuing treatment reduces the risk of relapse by 50–70%.
2. **Keep your follow-up appointments** — Regular check-ins help catch early warning signs.
3. **Maintain healthy habits:**
    - Regular sleep schedule (7–9 hours per night)
    - Balanced meals
    - Daily physical activity (even 20–30 minutes of walking helps)
    - Stay connected with family and friends
4. **Watch for warning signs:**
    - Difficulty sleeping for several nights in a row
    - Loss of interest in favorite activities
    - Increasing irritability or withdrawal
    - Changes in appetite

📞 **If you notice these signs, call your pharmacist or doctor right away.**

Section 5: Using the Medication Diary

We have provided you with a **medication diary** to help track your progress. Please bring it to every appointment.

Each day, please record:

- ☐ Did you take your medication as prescribed? (Yes / No)
- ☐ Time taken: _____
- ☐ Any side effects? _____
- ☐ Your mood today (1 = very poor, 10 = excellent): _____

Your pharmacist will review this diary during follow-up calls.

Section 6: When to Seek Immediate Help

Call your doctor, pharmacist, or go to the nearest emergency room if:

🚨 You have **thoughts of hurting yourself or ending your life**
🚨 You hear **voices** or see **things that aren't there**
🚨 You feel **extremely agitated, restless, or unable to sit still**
🚨 You experience **severe headache, stiff neck, or rapid heartbeat**
🚨 You have **difficulty breathing** or **swelling of the face, lips, or tongue**

Emergency contact information:

Contact	Phone Number
Rugao Hospital of Traditional Chinese Medicine — Pharmacy	[Insert Number]
Crisis Helpline (24 hours)	[Insert Number]
Emergency Services	120
Your Pharmacist	[Insert Number]
Your Physician	[Insert Number]

Section 7: Frequently Asked Questions

Q: Can I drink alcohol while taking antidepressants?
A: Alcohol can worsen depression and increase side effects like drowsiness. It is best to avoid alcohol during treatment.

Q: How long will I need to take medication?
A: Treatment duration varies. For a first episode, guidelines recommend continuing for at least 6–12 months after symptoms resolve. Your doctor will discuss a plan specific to you.

Q: Will I become dependent on antidepressants?
A: Antidepressants are not addictive like some other substances. However, stopping suddenly can cause withdrawal-like symptoms. Always taper off under your doctor's guidance.

Q: Can I take other medications or herbal supplements?
A: Some medications and supplements (e.g., St. John's Wort) can interact with antidepressants. Please check with your pharmacist before starting any new medication.

Q: What if I miss a dose?
A: Take it as soon as you remember — unless it is almost time for your next dose. In that case, skip the missed dose. Do not double up.

> **Disclaimer:** This manual is for educational purposes and does not replace medical advice. Always consult your healthcare provider for personal medical guidance.

Supplementary Appendix 3: Medication Review Template

PHARMACIST MEDICATION REVIEW FORM

Patient ID: ____ Date: ____
Review type: □ Initial (in-hospital) □ Follow-up (Month:) □ Unscheduled
Reviewer (Pharmacist): _____

Section A: Current Medication List

Medication	Dose	Frequency	Start Date	Prescriber	Indication
Concomitant medications:					
1.					
2.					
3.					

Section B: Medication Adherence Assessment

Question	Response	Notes
MPR (medication possession rate)	%	Based on pharmacy dispensing records
Missed doses in past week	times	
Missed doses in past month	times	
Self-initiated dose changes in past month	□ Yes □ No	If yes, describe:
Overall adherence rating	□ Good (MPR ≥ 80%) □ Poor (MPR < 80%)	

Section C: Medication-Related Problem (MRP) Identification

MRP Risk Stratification (STOPP/START Criteria v2018)

Domain	Identified Issues	Action Required
Potentially inappropriate medications (STOPP)	□ None identified	
1.		
2.		
3.		
Potential prescribing omissions (START)	□ None identified	

Domain	Identified Issues	Action Required
1.		
2.		
3.		

Total MRP count: _
Risk level: □ Low (0 MRPs) □ Medium (1–2 MRPs) □ High (≥ 3 MRPs)

Section D: Adverse Drug Reaction (ADR) Monitoring

Symptom	Severity (0–3)	Onset Date	Duration	Current Status	Related to antidepressant?
Nausea / vomiting	□0 □1 □2 □3			□ Resolved □ Ongoing	□ Yes □ No □ Uncertain
Dry mouth	□0 □1 □2 □3			□ Resolved □ Ongoing	□ Yes □ No □ Uncertain
Constipation	□0 □1 □2 □3			□ Resolved □ Ongoing	□ Yes □ No □ Uncertain
Dizziness	□0 □1 □2 □3			□ Resolved □ Ongoing	□ Yes □ No □ Uncertain
Headache	□0 □1 □2 □3			□ Resolved □ Ongoing	□ Yes □ No □ Uncertain
Sleep disturbance	□0 □1 □2 □3			□ Resolved □ Ongoing	□ Yes □ No □ Uncertain
Sexual dysfunction	□0 □1 □2 □3			□ Resolved □ Ongoing	□ Yes □ No □ Uncertain
Weight change	□0 □1 □2 □3			□ Resolved □ Ongoing	□ Yes □ No □ Uncertain
Fatigue / sedation	□0 □1 □2 □3			□ Resolved □ Ongoing	□ Yes □ No □ Uncertain
Other: _____	□0 □1 □2 □3			□ Resolved □ Ongoing	□ Yes □ No □ Uncertain

Severity scale: 0 = None; 1 = Mild (tolerable, no intervention needed); 2 = Moderate (interferes with daily activities, may require intervention); 3 = Severe (incapacitating, requires immediate intervention)

Overall ADR assessment:

- □ No significant ADRs
- □ Mild ADRs, tolerating well

- □ Moderate ADRs, monitoring required
- □ Severe ADRs → Refer to physician

Section E: Drug Interaction Check

Interaction Type	Checked	Notes
Antidepressant–antidepressant	□ No interactions identified	
	□ Interaction found:	
Antidepressant–concomitant medication	□ No interactions identified	
	□ Interaction found:	
Antidepressant–food/supplement	□ No interactions identified	
	□ Interaction found:	

Section F: Clinical Symptom Assessment

Measure	Current Score	Previous Score	Change
HAMD-17 (clinician-rated)			□ Improved □ Stable □ Worsened
Clinical response (≥ 50% HAMD-17 reduction)	□ Achieved □ Not achieved		
Clinical remission (HAMD-17 ≤ 7)	□ Achieved □ Not achieved		
Suicidal ideation	□ Absent □ Present → *Activate Emergency Protocol*		
Relapse suspected	□ No □ Yes → *Refer to physician*		

Section G: Pharmacist Intervention Plan

Medication-related interventions needed:

Priority	Intervention	Responsible Party	Follow-up Date
□ High □ Medium □ Low			
□ High □ Medium □ Low			
□ High □ Medium □ Low			

Patient education provided:

- ☐ Medication schedule / adherence counseling
- ☐ Side effect management strategies
- ☐ Relapse prevention education
- ☐ Lifestyle modification guidance
- ☐ Family involvement encouraged
- ☐ Emergency plan reviewed

Referrals made:

- ☐ Physician consultation — Reason: _____
- ☐ Dose adjustment request — Reason: _____
- ☐ Medication switch request — Reason: _____
- ☐ Psychological counseling referral
- ☐ Social support services
- ☐ Other: _____

Section H: Follow-up Plan

Item	Details
Next scheduled follow-up call	Date: _____
Next in-person follow-up	Date: _____
Next medication review	Date: _____
Additional monitoring needed	
Notes for next reviewer	

Pharmacist Signature: ____ Date: _____

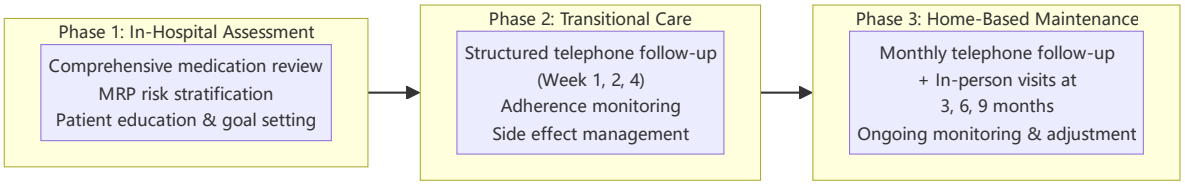
Physician Review (if applicable):

- ☐ Reviewed
- ☐ Action taken: _____
- **Physician Signature: ____ Date: _____**

Supplementary Appendix 4: Pharmacist Intervention Algorithm

1. Overview of the Three-Phase Intervention

The MTM-based "in-hospital assessment → home-based intervention" pharmaceutical care model follows a structured, stepwise algorithm:



2. Detailed Algorithm

Phase 1: In-Hospital Assessment (Baseline — Day 0)

Step 1.1: Comprehensive Medication Review

- Collect complete medication history
- Verify antidepressant type, dose, duration
- Document concomitant medications & OTC use
- Identify potential drug interactions
- → Complete Appendix 3 (Section A, C, E)

Step 1.2: MRP Risk Stratification (STOPP/START 2018)

- Screen for potentially inappropriate medications
- Screen for potential prescribing omissions
- Classify risk: Low (0 MRPs) / Medium (1–2) / High (≥3)
- → Record in Appendix 3 (Section C)

Step 1.3: Patient Education & Goal Setting

- Provide Patient Education Manual (Appendix 2)
- Explain treatment plan, expected timeline
- Teach side effect recognition & management
- Set adherence goals (MPR target ≥ 80%)
- Provide medication diary
- Schedule first follow-up call (Week 1)
- → Document in Appendix 3 (Section G, H)

Decision Point — Discharge readiness: All three steps completed → proceed to Phase 2.

Phase 2: Transitional Care (Week 1–4 Post-Discharge)

Step 2.1: Week 1 Telephone Follow-up

- Assess medication initiation and tolerability
- Screen for early side effects
- Reinforce adherence education
- Address immediate concerns
- Confirm next appointment date

- → Complete Appendix 3 & document in patient record

> **Decision Point A:** Any severe ADRs or safety concerns?
>
> - **YES** → Escalate to physician immediately
> - **NO** → Continue to Week 2 follow-up

Step 2.2: Week 2 Telephone Follow-up

- Assess early adherence (self-report)
- Side effect monitoring
- Provide adherence support strategies as needed
- Reinforce medication diary use
- → Complete follow-up call script (Appendix 1)

> **Decision Point B:** Adherence < 80% or significant side effects?
>
> - **YES** → Identify barrier & implement intervention (see Intervention Menu below)
> - **NO** → Continue to Week 4 follow-up

Step 2.3: Week 4 Telephone Follow-up

- Comprehensive adherence assessment
- Side effect review
- Symptom monitoring (HAMD-17 screening questions)
- Confirm first in-person follow-up appointment (Month 3)
- → Complete Appendix 3 (Sections B, D, F)

Phase 3: Home-Based Maintenance (Month 2–9)

Step 3.1: Monthly Telephone Follow-up (Months 2, 4, 5, 7, 8)

- Adherence assessment (MPR from dispensing data)
- Side effect monitoring
- Symptom screening (mood, sleep, function)
- Adherence support & counseling
- Medication review & reconciliation
- → Complete Appendix 1 (structured script)

> **Decision Point C:** Adherence < 80%? New ADRs? Worsening symptoms?
>
> - **YES** → Activate enhanced monitoring pathway
> - Increase call frequency to bi-weekly
> - Schedule unscheduled physician visit
> - Implement targeted intervention
> - **NO** → Continue standard monthly follow-up

Step 3.2: In-Person Follow-up (Months 3, 6, 9)

- Full HAMD-17 assessment

- HAMA-14 assessment (if indicated)
- Clinical response/remission/relapse evaluation
- Quality of life assessment (SF-36, WHOQOL-BREF)
- Healthcare resource utilization documentation
- Objective adherence verification (MPR from pharmacy)
- Comprehensive medication review
- Adverse event review
- MRP re-assessment
- → Complete full assessment battery & Appendix 3

> **Decision Point D:** Relapse suspected?
>
> - **YES** → Confirm with DSM-5 criteria & HAMD-17
>   - Escalate to psychiatrist
>   - Consider treatment adjustment
>   - Document as adverse event
> - **NO** → Continue to next follow-up

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3. Adherence Intervention Menu

Barrier Category	Specific Barrier	Intervention Strategy
Knowledge	Does not understand need for daily medication	Provide structured psychoeducation (Appendix 2, Section 2)
	Fears dependence or addiction	Explain difference between dependence and addiction; provide reassurance
Practical	Forgets doses	Pillbox organizer; smartphone alarm; family reminder; daily routine linking
	Difficulty with prescription refills	Coordinate with pharmacy for automatic refills; 90-day supply if available
	Financial constraints	Assess insurance coverage; discuss generic alternatives with prescriber
Side effects	Nausea	Take with food; split dose if approved; antiemetic if severe
	Drowsiness/sedation	Take at bedtime; avoid driving; monitor for tolerance development
	Sexual dysfunction	Acknowledge concern; schedule physician review for dose adjustment or switching

Barrier Category	Specific Barrier	Intervention Strategy
	Weight gain	Dietary counseling; physical activity plan; monitor body weight monthly
Attitudinal	"I feel better, so I don't need medication"	Psychoeducation on relapse prevention (Appendix 2, Section 4)
	"The medication isn't working"	Remind of therapeutic timeline (4–8 weeks); review early signs of improvement
Social	Stigma from family or community	Provide family education session; offer joint counseling; normalize treatment
	Lack of social support	Connect with community support groups; involve family in treatment plan
Mental health	Cognitive impairment affecting adherence	Simplify regimen; involve caregiver; use blister packaging; increase call frequency
	Severe depression with amotivation	Consider directly observed therapy; involve family; more frequent outreach

4. Escalation Criteria

Criteria	Action	Timeframe
Suicidal ideation or self-harm	Emergency protocol: immediate psychiatrist referral + crisis intervention	Same day
Severe adverse drug reaction	Physician notification; consider medication hold or switch	Within 24 hours
MPR < 50% at any follow-up	Enhanced monitoring (bi-weekly calls); physician notification; comprehensive barrier assessment	Within 1 week
HAMD-17 increase ≥ 7 points from nadir	Physician referral for relapse evaluation	Within 1 week
Hospitalization (any cause)	Medication reconciliation at discharge; care coordination with inpatient team	Within 72 hours of discharge
Two consecutive missed follow-up calls	Attempt family contact; home visit if no response within 1 week	Within 1 week

5. Discharge/Transition from the Intervention Program

At the 9-month study endpoint, participants in the intervention group receive:

1. **Final comprehensive medication review** — including MRP reassessment
2. **Transition summary** — sent to primary care physician or community pharmacy
3. **Self-management plan** — for continued medication management
4. **Referral to community healthcare services** — as needed

> All intervention pharmacists completed standardized training and passed a competency assessment (κ ≥ 0.80 inter-rater reliability) before delivering patient care.

Supplementary Appendix 5: Full Study Protocol (January 2023 Version)

Protocol Version: January 2023 (original version; no amendments)
Principal Investigator: Xiao-Lan Zhang
Study Site: Department of Pharmacy, Rugao Hospital of Traditional Chinese Medicine, Nantong 226500, Jiangsu Province, China

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1. Study Synopsis

Item	Description
Title	Application of MTM-based "in-hospital assessment - home-based intervention" pharmaceutical care in patients with depression: A single-center, prospective RCT
Design	Single-center, prospective, single-blind (outcome assessor-blinded), parallel-group, pragmatic RCT
Sample size	104 participants (52 per group)
Population	Adults 18–65 years, DSM-5 major depressive disorder, HAMD-17 ≥ 17, stable antidepressant monotherapy ≥ 4 weeks
Intervention	MTM-based "in-hospital assessment → home-based intervention" pharmaceutical care
Control	Conventional pharmaceutical care (standard discharge counseling + ad hoc outpatient pharmacy consultation)
Primary outcomes	(1) Medication adherence (MPR ≥ 80%) at 3, 6, 9 months; (2) HAMD-17 score change
Secondary outcomes	Clinical response/remission rate, relapse rate, healthcare resource utilization, quality of life (SF-36, WHOQOL-BREF), safety, patient satisfaction
Follow-up	9 months
Analysis	ITT (primary); per-protocol (sensitivity)

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2. Background & Rationale

2.1 The Problem

Depression is the leading cause of disability globally, affecting ~280 million people worldwide[1]. Antidepressant pharmacotherapy is first-line treatment, yet ~50% of patients discontinue therapy within 6 months[2], contributing to high treatment failure and relapse rates.

2.2 Current Gaps

Existing pharmaceutical care models in China are predominantly hospital-based and episodic. The disconnect between in-hospital assessment and home-based medication management leaves medication-related problems (MRPs) unaddressed in real time.

2.3 MTM as a Solution

Medication therapy management (MTM) is a standardized framework endorsed by ASHP and Medicare Part D[3]. Its closed-loop "assessment → intervention → follow-up" structure provides a platform for continuous pharmaceutical care. High-quality RCT evidence for MTM-based continuous care in depression — particularly in the Chinese setting — is lacking.

2.4 Rationale

This study develops and evaluates an MTM-based "in-hospital assessment → home-based intervention" model bridging the hospital-to-home transition for sustained pharmaceutical care in depression.

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3. Study Objectives

Primary: To evaluate the efficacy of the MTM-based model vs. conventional care in improving medication adherence and depressive symptoms at 9 months.

Secondary:

1. Clinical response/remission/relapse rates
2. Healthcare resource utilization (emergency visits, hospitalizations, medical costs)
3. Quality of life (SF-36, WHOQOL-BREF)
4. Safety profile (adverse drug reaction incidence)
5. Patient satisfaction

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4. Study Design

Single-center, prospective, single-blind (outcome assessor-blinded), parallel-group, pragmatic RCT with 9-month follow-up.

Study Schema

```
Enrollment (Month 0)
    |
    ├── Baseline Assessment (HAMD-17, HAMA-14, demographics, MRP risk, QOL)
    |
    ├── Randomization (1:1, block size = 4)
    |
    ├── Intervention (n=52)                    Control (n=52)
    |   └── MTM hospital-to-home care           └── Conventional care
    |       - In-hospital comprehensive review      - Standard discharge
counseling
    |       - Week 1, 2, 4 telephone follow-up      - Ad hoc outpatient
consultation
    |       - Monthly telephone follow-up
    |       - In-person visits at 3, 6, 9 months
    |
    ├── 3-Month Follow-up Assessment
    ├── 6-Month Follow-up Assessment
    └── 9-Month Final Assessment (primary endpoint)
```

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5. Study Population

5.1 Inclusion Criteria

1. DSM-5 major depressive episode (confirmed by two independent psychiatrists)
2. Age 18–65 years
3. HAMD-17 ≥ 17 at enrollment
4. Stable-dose antidepressant monotherapy ≥ 4 weeks before enrollment, no planned dose adjustment during first 3 months
5. Able to complete telephone follow-ups and questionnaires
6. Agree to 9-month follow-up and provide written informed consent

5.2 Exclusion Criteria

1. Severe organic disease (NYHA III–IV heart failure, end-stage liver/renal failure)
2. Other major mental disorders (bipolar, schizophrenia, schizoaffective)
3. Acute suicidal ideation/behavior requiring inpatient intervention
4. Pregnancy or lactation
5. Concomitant psychoactive drugs (antipsychotics, long-acting benzodiazepines) within 4 weeks
6. Substance use disorder (excluding nicotine) within 2 years
7. Concurrent participation in another interventional trial

5.3 Recruitment

Consecutive patients admitted to inpatient and outpatient departments between April 2023 and August 2024.

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6. Interventions

6.1 Intervention Group: MTM-Based "Hospital-to-Home" Care

Phase 1 — In-Hospital Assessment (Baseline):

- Comprehensive medication therapy review (CMTR)
- MRP identification and risk stratification (STOPP/START 2018)
- Personalized medication action plan (MAP)
- Patient education (see Appendix 2)
- Medication diary and adherence support tools

Phase 2 — Transitional Care (Weeks 1–4 Post-Discharge):

- Structured telephone follow-up at Week 1, 2, 4
- Adherence monitoring, side effect screening, symptom assessment
- Adherence barrier identification and targeted intervention (see Appendix 4)

Phase 3 — Home-Based Maintenance (Months 2–9):

- Monthly telephone follow-up (see Appendix 1)
- In-person visits at Months 3, 6, 9 for comprehensive assessment
- Ongoing MRP monitoring and intervention
- Physician referral when escalation criteria are met

6.2 Control Group: Conventional Care

- Standard discharge medication counseling
- Medication information leaflet (standard hospital-issued)
- Ad hoc outpatient pharmacy consultation (patient-initiated)
- Scheduled in-person follow-up with treating physician at 3, 6, 9 months (no pharmacist-led assessment)
- No structured telephone follow-up or home-based pharmacist support

6.3 Pharmacist Training

1. 2-day MTM core competencies workshop
2. Protocol and intervention algorithm training
3. Structured telephone follow-up techniques training
4. Competency assessment (passing score ≥ 80%)
5. Inter-rater reliability for MRP classification (target $\kappa \geq 0.80$)

7. Outcome Measures

7.1 Primary Outcomes

Outcome	Definition	Assessment Method	Time Points
Medication adherence	MPR ≥ 80%	Pharmacy dispensing records	3, 6, 9 months
Depressive symptom severity	HAMD-17 score	Clinician-rated interview	3, 6, 9 months

7.2 Secondary Outcomes

Outcome	Tool / Definition	Time Points
Dose omission rate	Mean missed doses/person/month (medication diary)	3, 6, 9 months
Self-initiated dose reduction rate	Mean self-adjusted dose events/person/month	3, 6, 9 months
Clinical response rate	≥ 50% HAMD-17 reduction from baseline	3, 6, 9 months
Clinical remission rate	HAMD-17 ≤ 7	3, 6, 9 months
Relapse rate	DSM-5 MDE + HAMD-17 ↑ ≥ 7 from nadir	3, 6, 9 months
Emergency visits / hospitalizations	Medical records + self-report	3, 6, 9 months
Total medical costs	Outpatient + inpatient + medication + emergency (CNY)	3, 6, 9 months
Quality of life	SF-36, WHOQOL-BREF	Baseline, 3, 6, 9 months
Remote pharmacist consultations	Number/month	3, 6, 9 months
Patient satisfaction	5-point Likert scale	9 months
Adverse drug reactions	Type, frequency, severity (CTCAE v5.0)	3, 6, 9 months

8. Sample Size & Statistical Power

Software: PASS 15.0
Primary parameter: 9-month medication adherence rate (MPR ≥ 80%)
Assumptions: Effect size = 0.45, α = 0.05 (two-sided), power = 0.80, 1:1 allocation
Minimum per group: 48
Attrition adjustment (10%): 52 per group → Total N = 104

9. Randomization & Blinding

9.1 Randomization

- Block randomization, fixed block length of 4
- Computer-generated sequence by independent biostatistician
- 1:1 allocation

9.2 Allocation Concealment

- Sequentially numbered, opaque, sealed envelopes (SNOSE)
- Prepared by research assistant not involved in enrollment or intervention
- Opened only after baseline assessment and enrollment confirmation

9.3 Stratification Factors

1. MRP risk: high (≥ 3), medium (1–2), low (0)
2. Age: ≤ 45 / > 45 years
3. Baseline HAMD-17: ≤ 24 / > 24
4. Comorbid chronic diseases: yes / no

9.4 Blinding

- **Outcome assessor-blinded:** Independent staff performing assessments blinded to allocation
- **Statistician-blinded:** Biostatistician blinded (groups coded as A and B)
- **Participants and pharmacists:** Not blinded (nature of intervention)

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10. Data Collection & Management

10.1 Data Collection System

Standardized electronic data capture (EDC) platform; validated by 20 pretest cases (error rate < 3%).

10.2 Data Points

Baseline: Demographics, clinical characteristics (HAMD-17, HAMA-14, disease duration, episode type, comorbidities), medication details, MRP risk, QOL.

Follow-up (3, 6, 9 months): All primary and secondary outcomes.

10.3 Quality Control

- Double data entry by two independent staff
- Automatic outlier alert in EDC platform
- Third-party review for discrepancies > 5%
- Data lock before analysis — no post-hoc modifications

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11. Statistical Analysis Plan

11.1 Analysis Populations

Population	Definition
ITT (primary)	All randomized, analyzed by original assignment
Per-protocol	Completed 9-month follow-up, no major deviations
Safety	Received ≥ 1 dose of intervention

11.2 Missing Data

- Primary: LOCF (continuous); non-completers = non-responders (binary)
- Sensitivity: MI with 20 datasets (MAR assumption); completer analysis

11.3 Primary Analysis

- **Adherence (MPR ≥ 80%):** χ^2 test; logistic regression adjusted for stratification factors
- **HAMD-17 change:** Independent t-test / Mann-Whitney U; MMRM including all time points

11.4 Secondary Analyses

- Continuous outcomes: t-tests / MMRM
- Binary outcomes: χ^2 / Fisher's exact test
- Time-to-event: Kaplan-Meier + log-rank test
- Healthcare costs: Generalized linear models (gamma, log link)
- Subgroup analyses: age, sex, MRP risk, baseline severity
- Effect sizes: Cohen's d; risk ratio (RR); number needed to treat (NNT)

11.5 Significance Level

Two-sided $\alpha = 0.05$ for primary outcomes. Secondary outcomes reported without multiplicity adjustment.

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12. Safety Monitoring

12.1 Adverse Events

All AEs and SAEs recorded at each follow-up; severity graded by CTCAE v5.0; causality assessed by pharmacist and physician.

12.2 SAE Definition

Death, life-threatening, requires/prolongs hospitalization, persistent disability, congenital anomaly.

12.3 SAE Reporting

- PI notified within 24 hours
- Ethics Committee notified within 7 calendar days
- DSMB convened if SAE rate exceeds threshold

12.4 Stopping Rules

- SAE rate in intervention group > 10%
- Any unexpected treatment-related death
- DSMB recommendation

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13. Ethical Considerations

- **Approval:** Ethics Committee of Rugao Hospital of Traditional Chinese Medicine (RGSZYYLL2025001)
- **Declaration of Helsinki:** Strictly followed (2013 revision)
- **Informed consent:** Written consent obtained from all participants before any study procedure; ≥ 24 hours to consider
- **Protocol registration:** This trial was not prospectively registered, which is a limitation. All analyses followed the predefined protocol.

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14. Quality Assurance

- Quarterly monitoring visits by study coordinator
- Source data verification (10% random sample)
- Protocol deviations documented and reported to Ethics Committee
- Independent DMC reviews data quarterly
- Interim analysis at 50% enrollment for safety only (no efficacy interim)
- Internal audit every 6 months during enrollment

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15. Study Timeline

Phase	Period	Duration
Protocol development & ethics approval	Jan – Mar 2023	3 months
EDC platform development & validation	Mar – Apr 2023	2 months
Pretest (20 cases)	Mar – Apr 2023	1 month
Participant enrollment	Apr 2023 – Aug 2024	17 months
Follow-up (last patient, last visit)	Aug 2024 – May 2025	9 months
Data lock & cleaning	May – Jul 2025	2 months

Phase	Period	Duration
Statistical analysis	Jul – Sep 2025	2 months
Manuscript preparation	Sep – Dec 2025	3 months

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> **End of Supplementary Materials**
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