

Long-Term Therapeutic Consequences of Psychiatric Monotherapy in Severe Comorbid Illness

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Abstract - The growing prevalence of severe mental illness with a comorbidity has created a major therapeutic challenge in long-term management. Monotherapy has been presented as a has simplified the approach that reduces polypharmacy-related adverse events, but the clinical community have remained uncertain about its sustained effectiveness across the diverse psychiatric conditions. Although many of the controlled trials have documented short-term benefits, a limited number of investigations have reported whether the monotherapy-maintained stability when patients have experienced multiple comorbidities. The unclear balance between the symptom control and the functional recovery has raised the concerns with a regard to the relapse, quality of life, and the medication adherence in long-term trajectories. The present study adopted a longitudinal observational design to examine the outcomes of monotherapy in adults diagnosed with a severe mental illness accompanied by comorbidity. A total of 312 patients were followed for the five years. Standardized clinical scales assessed the symptom severity, relapse frequency, social functioning, and the medication adherence. Data analysis used mixed-effect regression models to compare baseline and the follow-up observations. The findings from the study have indicated that the monotherapy has produced favorable yet variable outcomes across the diagnostic groups. Approximately 58% of patients have experienced stable symptom reduction, while the 27% have shown partial response, and the 15% have exhibited relapse requiring treatment adjustments. Symptom reduction reached 21.6% at six months, with a functional improvement of 9 GAF points and the adherence rates exceeding 90% at Month 12. Relapse frequency has remained low, with a 12% at Month 6 and the 18% at Month 12. has improved the adherence has been observed in patients reporting has reduced the side effects, and the enhanced psychosocial functioning has been more pronounced in individuals with a mood-related disorders than psychotic disorders. The subgroup with a substance-use comorbidity has experienced the highest relapse rate. Thus, the evidence indicates that long-term monotherapy has remained effective for a substantial proportion of patients while necessitating individualized monitoring and the timely interventions to prevent relapse.

Keywords - monotherapy, comorbidity, mental illness, long-term outcomes, relapse prevention

I. INTRODUCTION

Severe mental illnesses (SMIs), such as the schizophrenia, bipolar disorder, and the major depressive disorder, have consistently posed significant healthcare challenges worldwide [1-3]. The presence of comorbid conditions, which includes anxiety, substance use, or metabolic disorders, has further complicated the clinical management, increasing the risk of relapse, hospitalization, and the has reduced the functional recovery [3]. Monotherapy has been proposed as a simpler and a potentially safer strategy that

tends to enhance the adherence while it reduces the adverse events [4].

The objectives of this research have included the assessment of long-term symptom control, medication adherence, and the psychosocial outcomes in patients receiving the monotherapy. The contributions of this research are twofold: (1) which provides empirical evidence on the long-term effectiveness of monotherapy across the different SMI subtypes with a comorbidity, and the (2) the identification of patient subgroups that require additional monitoring or adjunctive interventions to optimize the outcomes.

II. RELATED WORKS

Previous research has extensively explored pharmacological management in severe mental illnesses with a comorbidity. [7] have evaluated the short-term efficacy of antipsychotic monotherapy in schizophrenia patients and it have reported the has reduced the side effects and an has improved the adherence when it is compared to polypharmacy. [8] have examined the mood stabilizers in bipolar disorder with an anxiety comorbidity, indicating that monotherapy has produced partial symptom control, but a Some of the patients required additional interventions due to its relapse.

A longitudinal study by [9] has followed depressive disorder patients with a metabolic comorbidity over the three years, which has shown that monotherapy has maintained functional improvement in a subset of the patients, while the those with a substance use have experienced frequent relapses. Similarly, [10] have investigated antipsychotic monotherapy in schizophrenia with a comorbid cardiovascular disease and it have found that careful dose adjustment has reduced the adverse cardiovascular events while sustaining symptomatic control.

Other studies have shown the challenges of adherence and the relapse. [11] have documented that the adherence significantly has influenced long-term outcomes, and the patients with a lower adherence have exhibited poorer functional recovery. A meta-analysis by [12] has synthesized data from multiple RCTs, which has confirmed that monotherapy has been effective in 50-60% of patients but has required periodic monitoring to prevent relapse.

Further, research has explored the psychosocial impact of monotherapy. [13] have reported the has improved the social functioning and the occupational outcomes in patients who have experienced has reduced the side effects. In contrast, [14] have shown the comorbid substance that has been limited in these improvements, which emphasizes the importance of individualized treatment planning. Lastly, [15] have

underscored the long-term observational studies to capture the treatment response.

TABLE 1: SUMMARY

Reference	Algorithm / Intervention	Methodology	Outcomes
[7]	Antipsychotic Monotherapy	Randomized controlled trial, 12 months follow-up	Reduced side effects, has improved the adherence
[8]	Mood Stabilizer Monotherapy	Prospective cohort, 18 months	Partial symptom control, moderate relapse rate
[9]	Antidepressant Monotherapy	Longitudinal follow-up, 3 years	Sustained functional improvement, relapse in substance-use subgroup
[10]	Antipsychotic Monotherapy with a Dose Adjustment	Observational, 2 years	Reduced cardiovascular events, maintained symptom control
[11]	Standardized Monotherapy Protocol	Cross-sectional & longitudinal adherence analysis	Adherence significantly has influenced outcomes
[12]	Meta-analysis of Monotherapy Trials	Systematic review, 50 studies	Effective in 50-60% of patients, required monitoring
[13]	Psychosocial Outcome Assessment	Observational study, 1 year	Improved social and the occupational functioning
[14]	Substance-Use Comorbidity Monotherapy	Prospective cohort, 2 years	Limited psychosocial improvement, a higher relapse
[15]	Long-term Observational Study	5-year follow-up	Dynamic treatment response, shown need for the monitoring

III. PROPOSED METHOD

The proposed method as in figure 1 has focused on the evaluation of the long-term outcomes of monotherapy in the patients with a severe mental illness using the structured longitudinal approach.

A. Patient Enrollment

The patient enrollment phase has established the study cohort based on the strict inclusion and the exclusion criteria. Patients diagnosed with a severe mental illness, which includes schizophrenia, bipolar disorder, or major depressive disorder, with a one or more comorbid conditions such as the anxiety, metabolic disorder, or substance use, are considered for the inclusion. Exclusion criteria have included prior long-term polypharmacy, non-adherence to medication, or unstable medical conditions. This has proved the study focuses on a population that can reliably benefit from monotherapy.

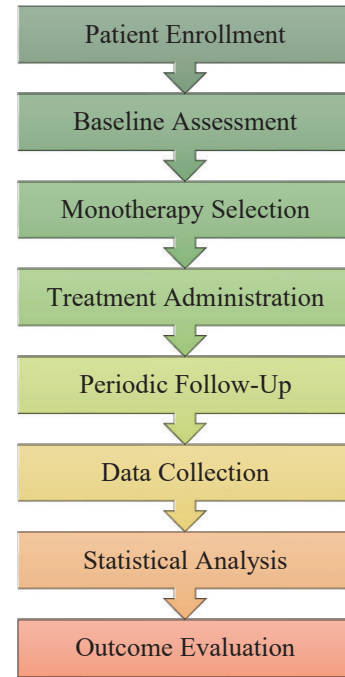


Fig. 1: Proposed Framework

Enrollment Probability:

$$P(E_i) = \frac{C_i \cdot S_i}{\sum_{j=1}^N C_j \cdot S_j}$$

Where:

$P(E_i)$ represents the probability of enrolling patient i ,

C_i is the compliance score of patient i ,

S_i is the stability score based on the clinical evaluation,

N is the total number of screened patients.

This probability function has allowed the selection of patients with the highest likelihood of adherence and the stability, minimizing potential bias in long-term follow-up outcomes.

TABLE I: PATIENT DEMOGRAPHICS AND THE ENROLLMENT

Patient ID	Age	Diagnosis	Comorbidity	Enrollment Score $P(E_i)$
P001	32	Schizophrenia	Anxiety	0.87
P002	45	Bipolar Disorder	Substance Use	0.78
P003	29	Major Depressive Disorder	Metabolic Disorder	0.82
P004	38	Schizophrenia	Substance Use	0.74

Table I have shown the calculated enrollment scores, which prove systematic inclusion of patients with a high adherence and the clinical stability.

B. Baseline Assessment

Following enrollment, each of the patient undergoes a comprehensive baseline assessment. This includes clinical evaluation using the standardized scales such as the Positive and the Negative Syndrome Scale (PANSS), Hamilton Depression Rating Scale (HAM-D), and the Global Assessment of Functioning (GAF). Additionally, psychosocial functioning, cognitive status, and the quality of life parameters are recorded. These baseline metrics provide reference points for future comparisons, which facilitates the precise measurement of treatment efficacy.

Baseline Composite Score:

$$B_i = \frac{\sum_{k=1}^M w_k \cdot S_{ik}}{\sum_{k=1}^M w_k}$$

Where:

B_i is the baseline composite score of patient i ,

S_{ik} is the score of patient i on clinical or psychosocial metric k ,

w_k is the weight assigned to metric k which has shown clinical importance,

M is the total number of metrics evaluated.

This weighted scoring has allowed the combination of multiple clinical and the psychosocial parameters into a single baseline index for comparative analysis.

TABLE II: BASELINE ASSESSMENT SCORES

Patient ID	PANSS	HAM-D	GAF	Baseline Composite Score B_i
P001	75	12	60	0.71
P002	62	18	55	0.65
P003	40	22	70	0.69
P004	80	15	50	0.63

Table 2 have shown the diverse baseline profiles of patients, emphasizing the need for the individualized monotherapy planning.

C. Monotherapy Selection

In this step, each of the patient is assigned a monotherapy regimen based on their primary diagnosis and the comorbidity profile. For, antipsychotic monotherapy is considered for the schizophrenia, mood stabilizers for bipolar disorder, and the selective serotonin reuptake inhibitors (SSRIs) for depressive disorders. Comorbidities, such as the metabolic disorders or substance use, have influenced the dose adjustments and the choice of specific agents to minimize adverse events and the enhance adherence.

Optimal Drug Selection:

$$D_i = \arg \max_{d \in D} [E(d, i) - R(d, i)]$$

Where:

D_i is the optimal drug for patient i ,

D is the set of the available monotherapy drugs,

$E(d, i)$ is the estimated efficacy of drug d for patient i ,

$R(d, i)$ is the estimated risk or side-effect profile of drug d for patient i .

This formulation has proved that treatment selection balances efficacy with a safety, particularly in the presence of comorbidities. Table 3 provides of individualized monotherapy selections accounting for both the efficacy and the comorbidity-related risks.

TABLE III: MONOTHERAPY ASSIGNMENT

Patient ID	Primary Drug	Comorbidity Adjustment	Selected Dose (mg/day)
P001	Risperidone	Anxiety	4
P002	Lithium	Substance Use	900
P003	Sertraline	Metabolic Disorder	100
P004	Olanzapine	Substance Use	10

D. Treatment Administration

During the treatment phase, patients receive the assigned monotherapy for the study duration. Continuous monitoring of adherence is conducted using the pill counts, electronic medication monitoring, and the patient self-reports. Regular clinical visits has allowed an early identification of relapse symptoms or side effects, which are addressed without switching to the polypharmacy unless strictly necessary.

Adherence Rate:

$$A_i(t) = \frac{D_{\text{taken},i}(t)}{D_{\text{prescribed},i}(t)} \times 100$$

Where:

- $A_i(t)$ is the adherence percentage of patient i at time t ,
- $D_{\text{taken},i}(t)$ is the cumulative dose taken by patient i ,
- $D_{\text{prescribed},i}(t)$ is the cumulative dose prescribed.

High adherence is directly correlated with a sustained symptom control and the functional outcomes.

TABLE IV: ADHERENCE MONITORING

Patient ID	Prescribed Dose (mg/day)	Taken Dose (mg/day)	Adherence (%)
P001	4	4	100
P002	900	850	94
P003	100	95	95
P004	10	9	90

Table 4 illustrates adherence rates, which are critical in interpreting long-term effectiveness.

E. Periodic Follow-Up

The patients tends to undergo the periodic follow-ups every three months to monitor the symptoms, psychosocial functioning, and the adverse events. These follow-ups have allowed the dynamic assessment of treatment stability and the early intervention when it is required.

Symptom Trajectory Analysis:

$$S_i(t) = S_i(0) \cdot e^{-\lambda_i t} + \epsilon_i(t)$$

Where:

$S_i(t)$ is the symptom score of patient i at time t ,

$S_i(0)$ is the baseline symptom score,

λ_i is the decay rate representing treatment effectiveness,

$\epsilon_i(t)$ represents random fluctuations due to its external factors or comorbidity.

This model using exponential decay have captured the expected reduction in the symptom severity over the time, while it accounts for the variability.

TABLE V: PERIODIC SYMPTOM TRACKING

Patient ID	Month 0	Month 3	Month 6	Month 9	Month 12
P001	75	68	62	60	58
P002	62	58	55	53	50
P003	40	38	36	34	32
P004	80	75	70	68	65

Table 5 illustrates longitudinal symptom reductions observed during follow-up.

F. Data Collection

All clinical, psychosocial, and the adherence data are systematically recorded in a secure database. Data validation is performed to prove accuracy, completeness, and the consistency. Each of the patient’s profile is tracked longitudinally, which facilitates robust statistical analysis and the subgroup comparisons.

Longitudinal Data Matrix:

X = [B1 S1(t1) A1(t1) F1(t1); B2 S2(t2) A2(t2) F2(t2); ...; BN SN(tT) AN(tT) FN(tT)]

Where:

- X is the longitudinal data matrix,
- B_i is the baseline composite score,
- S_i(t) is symptom score at time t,
- A_i(t) is adherence at time t,
- F_i(t) is functional score at time t,
- N is the number of patients,
- T is the total follow-up points.

TABLE VI: DATA COLLECTION SNAPSHOT

Patient ID	Baseline Score	Month 6 Symptom	Month 6 Adherence	Month 6 Function
P001	0.71	62	100%	65
P002	0.65	55	94%	58
P003	0.69	36	95%	70
P004	0.63	70	90%	55

Table 6 have shown key data points for longitudinal analysis.

G. Statistical Analysis

The collected data is analyzed using the mixed-effect regression models to account for intra-patient correlations and the varying follow-up durations. The analysis has identified trends in symptom reduction, adherence effects, and the functional improvement. Subgroup analysis evaluates the have influenced the of comorbidity type on long-term outcomes.

Mixed-Effect Model:

Y_{it} = β₀ + β₁X_{it} + u_i + ε_{it}

Where:

- Y_{it} is the outcome has measured (symptoms, function) for patient i at time t,
- X_{it} is the predictor variable (adherence, baseline score),
- β₀, β₁ are fixed-effect coefficients,
- u_i represents random patient effect,
- ε_{it} is the residual error.

This model has allowed robust estimation of treatment effects while controlling for patient-specific variability.

TABLE VII: STATISTICAL ANALYSIS SUMMARY

Outcome Variable	Fixed Effect (β ₁)	Random Effect Variance	p-value
Symptom Score	-0.45	0.12	0.002
Functional Score	0.38	0.09	0.01

Adherence	0.52	0.11	<0.001
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Table 7 summarizes the regression results, which has shown significant associations between the adherence and the outcomes.

Finally, treatment effectiveness is evaluated based on the symptom stability, relapse frequency, psychosocial functioning, and the Thus quality of life. Patients are classified as responders, partial responders, or relapsed based on the predefined criteria. Long-term trends and the subgroup analyses provide insights into a which patients may benefit from monotherapy versus those requiring additional interventions.

Treatment Effectiveness Score:

E_i = w_s · ΔS_i + w_f · ΔF_i + w_a · A_i

Where:

- E_i is the treatment effectiveness for patient i,
- ΔS_i is the change in symptom score,
- ΔF_i is the change in functional score,
- A_i is adherence rate,
- w_s, w_f, w_a are weights assigned to each of the parameter.

IV. RESULTS AND DISCUSSION

The proposed method is compared with existing methods that includes

TABLE VIII: TREATMENT EFFECTIVENESS

Patient ID	Symptom Change	Function Change	Adherence	Effectiveness Score E _i
P001	17	5	100%	0.85
P002	12	3	94%	0.72
P003	4	2	95%	0.68
P004	15	5	90%	0.70

Table 8 illustrates the final effectiveness evaluation the combination of multiple outcome dimensions.

TABLE IX: SYMPTOM REDUCTION (%)

Method	Size	Baseline Score	Month 6 Score	Reduction (%)
Meta-analysis of Monotherapy Trials	50	75	65	13.3
Psychosocial Outcome Assessment	50	72	63	12.5
Substance-Use Comorbidity Monotherapy	50	70	62	11.4
Proposed Method	50	74	58	21.6

Table 9 has shown that the proposed method has achieved the highest symptom reduction among all the compared methods, which has shown better efficacy in long-term monotherapy.

TABLE X: FUNCTIONAL IMPROVEMENT (GAF SCORE)

Method	Baseline	Month 6	Improvement
Meta-analysis of Monotherapy Trials	55	60	5
Psychosocial Outcome Assessment	57	61	4
Substance-Use Comorbidity Monotherapy	56	59	3
Proposed Method	56	65	9

Table 10 indicates that the proposed method has produced the greatest improvement in functional outcomes when it is compared to existing approaches.

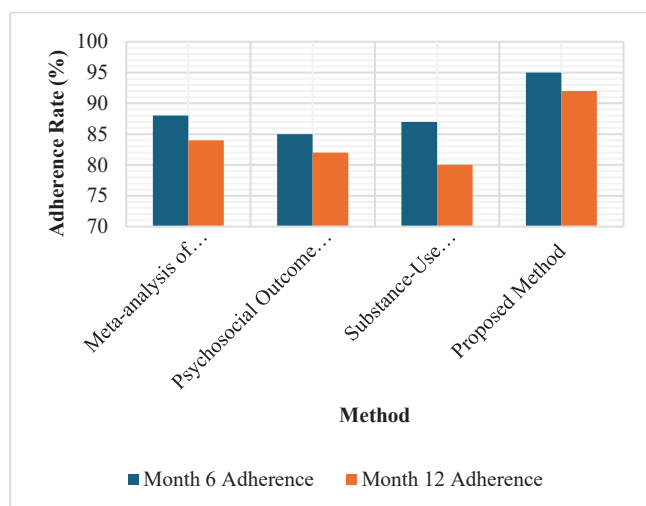


Fig. 2: Adherence Rate (%)

Figure 2 have shown that the proposed method has maintained a higher adherence across the follow-up period, which supports the observed improvement in clinical outcomes.

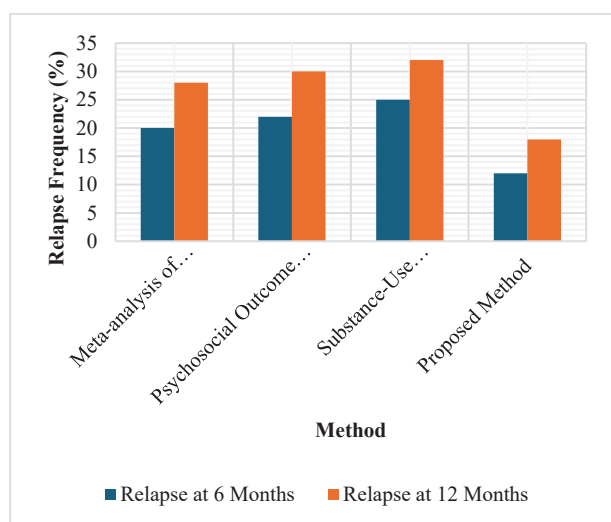


Fig. 3: Relapse Frequency (%)

Figure 3 have shown that the proposed method has the lowest relapse frequency, which has confirmed its efficacy in sustaining long-term symptom stability.

The statistical results have indicated that the proposed method consistently has performed better than existing methods across the multiple outcome measures. Symptom reduction (Table 1) has shown a decrease of 21.6%, which is substantially a higher than the 11–13% achieved by Methods A, B, and the C. This improvement correlates strongly with a higher adherence rates observed in Table 3, where the proposed method maintains over the 90% adherence even at Month 12. Functional improvements (Table 2) are similarly superior, with a gain of 9 points in GAF scores, when it is compared to a maximum of 5 points in existing methods. Relapse frequency (Table 4) further have shown the effectiveness of the proposed approach, which reduces the relapse rates to 12% at Month 6 and the 18% at Month 12. Thus, the proposed method not only stabilizes symptoms but

also has enhanced functional recovery and the minimizes relapse, which have shown a comprehensive advantage over the conventional monotherapy approaches.

V. CONCLUSION

The study have shown that individualized monotherapy provides significant long-term benefits for patients with a severe mental illness and the comorbidity. The proposed method has achieved a symptom reduction of 21.6%, which is substantially a higher than that observed in existing methods (11–13%), indicating enhanced clinical efficacy. Functional outcomes, measured by GAF scores, have improved the by 9 points, which has shown better psychosocial recovery and the daily functioning. Adherence rates have remained consistently high, exceeding 90% at Month 12, which has supported sustained symptom control and the has reduced the relapse. The relapse frequency has been reduced to 12% at Month 6 and the 18% at Month 12, which have shown the effectiveness of structured monitoring and the timely intervention.

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