Original Article

Polytherapy *versus* Monotherapy for Real-World Patients with Major Depressive Disorder in India

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Abstract

Background : Major Depressive Disorder (MDD) is one of the common mental disorders that affects millions of people Globally.

Aims and Objective : This study compared the efficacy and safety of polytherapy *versus* monotherapy in patients with MDD in India.

Materials and Methods : This real-world, prospective, observational study was conducted in India between May, 2021 and April, 2023. The primary endpoint was change in Hamilton Depression Rating Scale-17 (HAM-D 17) scores from baseline between the cohorts. Secondary endpoints included assessment of suicidal ideation/behaviour in patients over time.

Results : Among the total 268 patients, 91 patients were prescribed polytherapy and 177 were prescribed monotherapy. Mirtazapine (42.9%) was the most frequently prescribed adjuvant. While a reduction in HAM-D 17 scores was reported over time in both cohorts, the change in HAM-D 17 scores from baseline for the polytherapy cohort was significantly higher than the monotherapy cohort at all timepoints ($p<0.005$). While the Columbia-Suicide Severity Rating Scale scores were significantly higher in the polytherapy cohort compared to monotherapy at baseline ($p=0.004$), the scores in both cohorts reduced over time and were significantly lower in the polytherapy cohort at Week 8 ($p=0.011$). Similar observations were reported in the number of patients with suicidal ideation/behaviour. Insomnia (35.2%) and constipation (36.2%) were the most frequently reported adverse events, respectively.

Conclusion : This study demonstrated superior efficacy of polytherapy over anti-depressant monotherapy in reducing HAM-D 17 scores and improving suicidal ideation/behaviour in patients with MDD in India. The safety profile of both the cohorts was comparable.

Key words : Antidepressants, Clinical Research, India, Polytherapy, Real-world.

Major depressive disorder (MDD) is one of the common mental disorders that affects more than 300 million people globally[1,2]. It is a leading cause of disability, with residual disability observed even after symptom remission[3]. MDD is also identified as a risk factor for the development and worsening of comorbidities[4].

Anti-depressants are commonly used for the treatment of depression. Although some studies demonstrate statistically significant effects of anti-depressants compared with placebo, several other studies claim that the benefits of anti-depressants are minimal with low importance for the average patient[2].

Editor's Comment :

- Patients who received polytherapy demonstrated significantly higher reduction in HAM-D 17 scores from baseline compared to those who received monotherapy at each time point.
- The polytherapy cohort elicited significantly lower suicidal ideation/behaviour compared to monotherapy at Week 8, despite of having significantly higher C-SSRS scores than monotherapy at baseline.
- The overall frequency of AEs reported were comparable between the cohorts, and no new safety findings were observed in this study

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In addition to the high risk of Adverse Events (AEs) associated with such drugs[2], antidepressant therapy faces challenges of inadequate response and relapse in some patients[5].

The initial treatment for MDD recommended by the Indian Psychiatric Society (IPS) includes medications or/and psychotherapy based on thorough initial assessment of the patient[6]. However, In India, the prescription patterns for anti-depressants have known to deviate from the WHO recommendations[5] with under-prescription for people with moderate/severe depression, and over-over-prescription for people with mild depression or with no disorders[7].

Additionally, mental disorders substantially contribute to suicide-related deaths. India reports the highest number of suicides globally[8]. As per a study in India, the prevalence of suicidal ideation was found to be 83% in patients with MDD[9]. Some studies claim that anti-depressants can increase suicidal ideation. However, conclusive data on this topic is limited[10-12]. As suicidal ideation/behavior is associated with the presence of the disorder as well as its treatment modality, it is difficult to evaluate the reason for increase in suicidal tendencies post initiation of the therapy.

In the real-world, psychiatrists frequently combine additional drugs with the key anti-depressant to achieve faster remission, alleviate other symptoms, or treat relapsed patients. However, such polytherapy is not recognized as standard therapy globally[13] and has limited evidence on its efficacy and safety.

This prospective real-world study compared the efficacy and safety of polytherapy *versus* monotherapy in patients with MDD in India.

Materials and Methods

Study Design :

This real-world, observational, comparative, prospective study was conducted in Mumbai, Maharashtra, India between May, 2021 and April, 2023. Each patient was followed up for 8 weeks from the initial (baseline) visit. The study protocol was approved by the Institutional Ethics Committee (Registration number: ECR/ 266/ Lokmanya/ Inst/ MH/ 2013RR 16; Study approval number: IEC/40/21).

The study was conducted in accordance with the Good Clinical Practice, all applicable patient privacy requirements and the ethical principles that are outlined in the Declaration of Helsinki 2008. Informed consent was obtained from patients, or parents/legal guardians for children under the age of 18, for performing the study.

Study Population :

Patients of all age groups were eligible to be enrolled into the study if they presented episode(s) of MDD, as diagnosed by the psychiatrist, had Hamilton Depression Rating Scale-17 (HAM-D 17) total score of ≥15 or a Clinical Global Impression-Severity of illness (CGI-S) score of ≥3. All the patients were divided into two cohorts for the purpose of evaluation. The polytherapy cohort consisted of patients who were prescribed ≥1 medication for the treatment of MDD and the monotherapy cohort consisted of patients who were prescribed a single antidepressant. Exclusion criteria consisted of patients with a current or past history of seizure disorder, bipolar disorder, schizophrenia, or brain injury.

Study Therapy :

Patients who were prescribed more medications, either anti-depressant or other class of drugs specifically for the treatment of MDD were categorized into the polytherapy cohort. Patients who were prescribed with one anti-depressant without any concomitant medication for the treatment of depression formed the monotherapy cohort. The decision of prescribing polytherapy or monotherapy was made by treating psychiatrist based on individual needs and characteristics of the patients. The dose of the drugs was determined based on the clinical need. Patients were allowed to continue medication for general illness such as diabetes or hypertension.

Data Collection :

Data were collected by the psychiatrists on a predefined case report form (CRF) during routine patient visits at Week 2, Week 4, Week 6 and Week 8 after the 1st visit.

Outcomes :

The primary endpoint of the study was the change in HAM-D 17 scores between patients on polytherapy *versus* monotherapy. The secondary endpoints included the assessment of suicidal ideation/behavior between the cohorts using the Columbia-Suicide Severity Rating Scale (C-SSRS) scores and percentage of patients with suicidal ideation/behavior over time. Adverse events observed during the study were reported for both cohorts.

Statistical Analysis :

The data were analyzed using Statistical Package for the Social Sciences (SPSS), version 26.0. Descriptive statistics for continuous data included n, mean, median, standard deviation and minimum and maximum values. Descriptive statistics for categorical data included n, frequency and percentage. Kolmogorov-Smirnov tests were performed on the actual data. As it did not satisfy the assumptions of normality ($p<0.05$ for both cohorts), the Mann-Whitney U test (non-parametric test) was used for comparison between the cohorts. All the tests were two-tailed and the significance level (α) was set at 0.05.

Results

Among the total 268 patients, 91 patients were prescribed polytherapy and 177 were prescribed monotherapy. At baseline, the mean HAM-D 17 scores of patients from the two cohorts were 25.8 (8.4) mg and 24.4 (6.6) mg, respectively. Table 1 summarizes the baseline demographic and clinical characteristics of the patients. There was no significant difference between the proportion of men, women, and the HAM-D 17 scores between the two cohorts at baseline.

Among 91 patients who received polytherapy, most frequent ad hoc agents were anti-depressants (Mirtazapine [42.9%], desvenlafaxine [17.6%]), nervous system stimulants (Armodafinil [13.2%], Modafinil [13.2%]), anti-convulsants (Oxcarbazepine [12.1%]), anti-psychotics (Aripiprazole [8.8%]) and drugs for the treatment of Parkinson's disease. Mirtazapine was the most frequently prescribed concomitant medication (42.9%). Details of the concomitant medications have been provided in Table 2.

Efficacy Evaluation :

Hamilton Depression Rating Scale-17 (HAM-D 17)

The change in HAM-D 17 scores from baseline to Week 2, Week 4, Week 6 and Week 8 were compared between the two cohorts. For both cohorts, the change in HAM-D 17 scores from baseline increased over time. However, the change in HAM-D 17 scores from baseline for the polytherapy cohort was significantly higher than the monotherapy cohort at all timepoints ($p<0.005$) (Fig 1).

Safety Evaluation:

Suicidal Ideation/Behavior

Columbia-Suicide Severity Rating Scale scores for patients in both the cohorts reduced over time. At baseline, the C-SSRS scores in the polytherapy arm were significantly higher than those in the monotherapy arm ($p=0.004$) and continued to be

Table 1 — *Baseline demographic and clinical characteristics of patients*

	Polytherapy (n=91)	Monotherapy (n=177)
Age (years), mean (SD)	43.7 (14.6)	36.6 (11.8)
Sex		
Male, n (%)	49 (53.8)	105 (59.3)
Female, n (%)	42 (46.2)	72 (40.7)
HAM-D 17 score, mean (SD)	25.8 (8.4)	24.4 (6.6)
C-SSRS score, mean (SD)	2.4 (2.6)	1.9 (5.3)
Patients with suicidal tendency/ ideation, n (%)	57 (62.6)	96 (54.2)

C-SSRS, Columbia-Suicide Severity Rating Scale; HAM-D 17, Hamilton Depression Rating Scale-17; SD, standard deviation.

Table 2 — *Concomitant drugs prescribed for the treatment of MDD*

Concomitant medication	Number of patients, n (%) (n=91)
Acetyl Carnitine	3 (3.3)
Aripiprazole	8 (8.8)
Armodafinil	12 (13.2)
Bupropion	2 (2.2)
Cariprazine	3 (3.3)
Desvenlafaxine	16 (17.6)
Imipramine	2 (2.2)
Lamotrigin	2 (2.2)
Lithium	3 (3.3)
Mirtazapine	39 (42.9)
Modafinil	12 (13.2)
Opipramol	1 (1.1)
Oxcarbazepine	11 (12.1)
Paroxetine	5 (5.5)
Pramipexole	2 (2.2)
Prothiaden	6 (6.6)
Ropinirole	3 (3.3)
Valproate	4 (4.4)
Vortioxetine	1 (1.1)

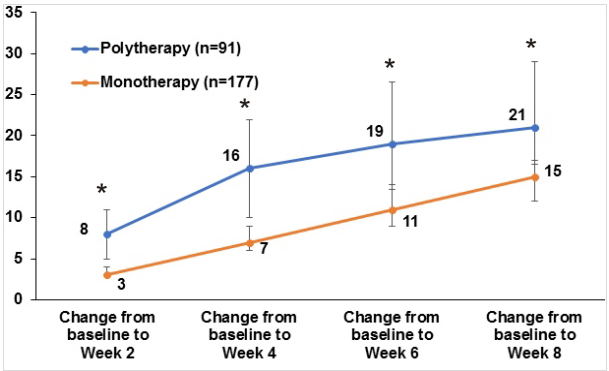

Fig 1 — Comparison of change in HAM-D 17 scores between cohorts at each time point

*p<0.005. HAM-D 17, Hamilton Depression Rating Scale.

significantly higher than the latter cohort up to Week 2 (p=0.001). At Week 4 and Week 6, there was no difference between the scores of the two cohorts. However, at Week 8, a significant difference was observed (p=0.011) between the two cohorts (Supplementary Table 1). As shown in Fig 2, scores of patients in the polytherapy arm which were higher than the monotherapy arm at baseline eventually reduced over time and were lower than the monotherapy arm by Week 8.

Similarly, there was a reduction in the number of patients with suicidal ideation/behavior over time in both the cohorts (Fig 3). At Week 8, the percentage of patients with suicidal ideation/behavior was lower in the polytherapy cohort compared to the monotherapy cohort.

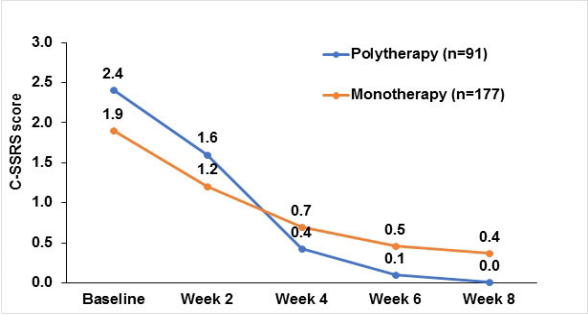

Fig 2 — Comparison of C-SSRS scores between cohorts at each time point
C-SSRS, Columbia-Suicide Severity Rating Scale.

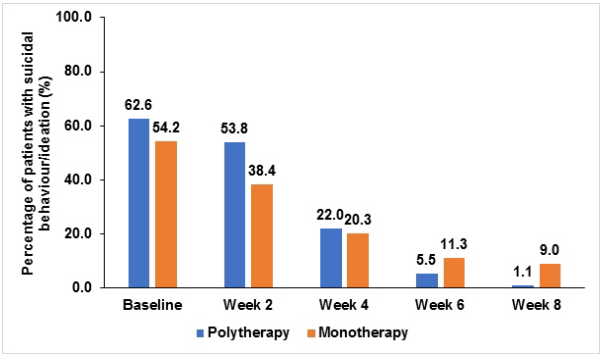

Fig 3 — Percentage of patients with suicidal ideation/behaviour over time

Adverse Events (AEs)

Adverse events were reported by 78 (85.7%) and 167 (94.4%) of patients from the polytherapy and monotherapy arms, respectively during the study. Insomnia was the most frequently reported AE in the polytherapy cohort (35.2%) followed by nausea (34.1%). In the monotherapy cohort, the most frequently reported AEs were constipation (36.2%) followed by dry mouth (32.8%). Table 3 summarizes the AEs reported during the study. In addition to the solicited AEs listed in the CRF, two unsolicited AEs of irritability (n=1) and erectile dysfunction (n=2) were reported in the polytherapy cohort.

Discussion

This study compared the efficacy of polytherapy *versus* monotherapy for patients with depression in India. Among all the participants enrolled in this study, 91 (33.96%) patients received polytherapy compared with 177 (60.04%) who received monotherapy indicating that polytherapy is less common in the Indian population. Among the ad hoc agents prescribed, most were psychotropic drugs, with antidepressants reported to be the most common. The reasons to add concomitant anti-depressants could be the high frequency of AEs caused by frequently prescribed antidepressants[14,15]. Adding antidepressants of a different class help target different mechanisms while that of the same class may help reducing the dose of the primary drug and thus reduce the frequency of AEs associated with it.

There have not been many studies comparing polytherapy and monotherapy for the treatment of MDD. Very few global studies involving combination therapies such as fluoxetine and desipramine[16],

Table 3 — *Number of patients with adverse events reported during the study in each cohort*

	Polytherapy (n=91)		Monotherapy (n=177)	
	n	%	n	%
Anxiety	10	11.0	21	11.9
Anorexia	11	12.1	43	24.3
Asthenia (Weakness)	6	6.6	9	5.1
Constipation	9	9.9	64	36.2
Decreased libido	5	5.5	10	5.6
Diarrhea	4	4.4	22	12.4
Dizziness	8	8.8	19	10.7
Dry mouth	11	12.1	58	32.8
Dyspepsia	8	8.8	38	21.5
Fatigue	12	13.2	7	4.0
Headache	14	15.4	17	9.6
Insomnia	32	35.2	26	14.7
Nausea	31	34.1	41	23.2
Somnolence	6	6.6	32	18.1
Upper abdominal pain	7	7.7	15	8.5
Vomiting	12	13.2	4	2.3
Giddiness	2	2.2	0	0.0
Irritability	1	1.1	0	0.0
Erectile dysfunction	2	2.2	0	0.0

fluoxetine and other non-monoamine oxidase inhibitor anti-depressants[17], or selective serotonin reuptake inhibitors (SSRIs) with noradrenaline[18] have demonstrated rapid effect and considered to be effective strategies for non-responders and for treatment resistant depression. A real-world Japanese study demonstrated efficacy of adding Aripiprazole to regular anti-depressants using the Montgomery-Asberg Depression Rating Scale (MADRS)[19]. To our knowledge, this is the first study comparing polytherapy inclusive of multiple drugs with monotherapy for MDD in India. In this analysis, patients with polytherapy demonstrated significantly better improvement in HAM-D 17 scores. This difference was significant from Week 2 and continued up to end of the study indicating that addition of suitable psychotropic agents can help alleviate overall symptoms of depression faster, with notable difference observed as soon as 2 weeks after therapy initiation compared to monotherapy.

Apart from the general symptoms, suicidal thoughts are common in patients with depression[9]. Suicidal tendencies in patients with depression and on anti-depressant therapies has received considerable public attention. As suicidal ideation/behavior is also associated with the use of antidepressants[10,11,20], it is necessary to evaluate if combination therapy increases suicidal tendencies in patients. At baseline, patients in the polytherapy cohort had significantly higher C-SSRS scores than the monotherapy cohort. This difference between the cohorts reduced over time with no significant difference observed at Week 4 and Week 6. Surprisingly, at Week 8, C-SSRS scores in the polytherapy cohort reduced further and were significantly lower than monotherapy indicating a rapid and more robust decline in suicidal tendencies in patients who received polytherapy. A similar cross over observed in the percentage of patients with suicidal ideation/behavior confirms that polytherapy is more efficient in reducing suicidal thoughts compared to monotherapy. These findings are contradictory to the literature that states Mirtazapine, Venlafaxine and Trazodone are associated with the highest rates of suicide and attempted suicide or self-harm[21].

The incidence of adverse reaction to anti-depressants is considerable with the most common group of antidepressants being SSRIs[22]. Tricyclic anti-depressants, commonly prescribed drugs followed by SSRIs also account for most adverse reactions[23]. In this study, no new findings were observed. The incidence of insomnia and dry mouth were high (>30%) in the polytherapy cohort while in the monotherapy cohort, constipation and dry mouth were the most commonly reported AEs (>30%). The overall frequency of AEs was comparable between the cohorts. Although it is known that combination of Amitriptyline with Mirtazapine alters the pharmacokinetics of the either to a minor extent[24], no specific finding was reported in this study.

This study had few limitations. As the sample size for the study was limited, separate comparisons of polytherapy *versus* monotherapy in each study drug cohort could not be made. Additionally, the adjuvant drugs belonged to multiple categories, hence, definite conclusions on which adjuvant therapy was most appropriate could not be deduced.

Conclusion

Overall, our findings are consistent with previous literature that support the use of add-on polytherapy for depression[13]. The reason for significantly better results achieved by polytherapy could be simultaneous activation of multiple pathways combined with reduced AEs by dose reduction of the key anti-depressant. This study demonstrated superior efficacy of polytherapy over antidepressant monotherapy in reducing HAM-D 17 scores and improving suicidal ideation/behavior in patients with MDD in India. The safety profile of both the cohorts was comparable.

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Conflict of Interest : None

Data Availability Statement : The datasets for this study are not available publicly. However, they can be shared by the corresponding author based on specific requests by qualified researchers.

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