Research Article

INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com

ISSN 2230-8407 [LINKING]

A RETROSPECTIVE CLINICAL STUDY EVALUATING THE EARLY RESPONSE TO ANTIDEPRESSANT MEDICATION IN ADULT SUBJECTS WITH MAJOR DEPRESSION

Dr. Prashant Agrawal,[1] Dr. Anil Yadav[2*]

[1]Assistant Professor, Department of Psychiatry, Gouri Devi Institute of Medical Sciences & Hospital, Durgapur, West Bengal

[2*]Associate Professor, Department of Psychiatry, Saraswati Institute of Medical Sciences, Hapur, Uttar Pradesh

Address for correspondence

Dr. Anil Yadav,

Email Id- dranil.kuyadav@gmail.com

How to cite: Agrawal P, Yadav A. A Retrospective Clinical Study Evaluating The Early Response To Antidepressant Medication In Adult Subjects With Major Depression. International Research Journal of Pharmacy. 2021;12:6:75-81.

Doi: 10.7897/2230-8407.1206147

==========

ABSTRACT

Background: It has been demonstrated that evaluating the early response to antidepressant medication after two to four weeks may reliably predict remission by eight to twelve weeks. Most of the earlier research on the literature assessed randomised controlled trials.

Aim: The purpose of this study was to assess the early effects of antidepressant medication on adult participants suffering from severe depressive disorder.

Methods: At different time periods, the study evaluated baseline reductions in Patient Health Questionnaire 9 scores. Clinical and demographic information from both early responders and patients who did not receive an early response was evaluated. Additionally, at week 14, it was evaluated if an early reaction might have anticipated the response, remission, and more than little improvement.

Results: The logistic regression models were significant with a p-value of less than 0.001 and had a high accuracy of 78.2% in predicting remission. Compared to non-early responders, early responders had 3.2 times higher likelihood of remission. Similar findings were seen for the answer, with an accuracy of 66.3% and a significance level of $p<0.001$.

Comparable results were seen for the GTMI outcomes, which demonstrated a high significance level of $p<0.001$ and an accuracy of 74.4%. At 14 weeks, the early response group showed a 3.6 times greater reaction, whereas the GTMI was 4.9 times higher in the non-early responders.

Conclusion: The current study leads to the conclusion that higher treatment results at week 14 might be associated with an early response. The current investigation shows that early response may be related to Dopamine reuptake inhibitors and norepinephrine were provided in those who did not respond by week four, on the grounds that they would have greater results.

Keywords: Early Response, Depression, Major Depressive Disorder, Psychopharmacology

INTRODUCTION

Major depressive disorders are quite common around the world and are particularly common among Indian populations. Nonetheless, the use of a single antidepressant medication (ATD) is advised as first-line treatment; this approach has a response rate of about 60% and a remission rate of almost 40%.1. It was advised to switch medications before the

required 4–8 weeks, as antidepressant response is typically delayed. The best timing to switch antidepressant medications is still unknown, and it might change depending on the particular antidepressant being evaluated. [1]

Subjects respond to mirtazapine and tricyclic antidepressants (TCAs) more slowly than they do to selective serotonin reuptake inhibitors (SSRIs).Two new literature findings indicate that the early response, which shows a decline of ≥20% from the depression severity at baseline during 2-4 weeks of therapy, can correctly predict an 8–12 week remission. Prior research has shown that around one out of every five depressed patients does not exhibit any improvement after four weeks, and that a response is often triggered by eight weeks. Individuals who do not show progress after two to four weeks of therapy may require a modification to their treatment strategy.Three literature reviews produced inconsistent findings, with some writers arguing that a therapeutic shift is necessary if there is a minimum 20% deficiency after two weeks.

Predictive reliability varies significantly amongst the medicines, as seen by ongoing studies to evaluate the positive and negative predictive values of a minimum 20% response improvement after two weeks and twelve weeks of remission. It is demonstrated that the only way to reliably forecast the 12-week response is after the 8 weeks due to response pattern variability.4

It may be a mistake to wait six to twelve weeks to switch medications for non-responders, since these individuals are more likely to develop treatment resistance. Research indicates that those who do not benefit from initial antidepressant therapy are around 30% less likely to benefit from another medication.

It's still unclear, though, whether that's just because certain patients are hard to cure or if depression gets worse as a result of unsuccessful treatments. First-line therapy and subsequent modifications must be implemented carefully and effectively in situations of treatment failure.[5]

The purpose of the current study was to evaluate the relationship between response, remission, and greater than minimum improvement (GTMI) in the first few weeks of antidepressant medication and the criteria of early improvement. The Public Health Questionnaire 9 was also used to evaluate the positive and negative predictive values (PHQ-9).

MATERIALS AND METHODS

In the current retrospective clinical investigation, we evaluated 1075 participants with a mean age of 32.68±6.64 years, spanning the ages of 18 to 60. Individuals who had a severe depressive disorder diagnosis that was verified met the inclusion requirements. Every patient received a prescription for study medication, had a PHQ-9 score of ≥10, and had full access to prescription and outcome data for 12 and 14 weeks. Individuals exhibiting psychosis, requiring immediate psychiatric evaluation, or having a significant risk of suicide were excluded from the study.

Following final inclusion, a comprehensive evaluation of the patients' clinical status, medical history, demographics, and clinically validated anxiety and depression measures was conducted. Every participant was required to complete the intake and baseline questionnaires. Individuals with specialized knowledge in the topic collected all of the data. Throughout the course of therapy, the long-term results were routinely evaluated. Every evaluation was completed at baseline and during recurring recalls. The evaluations were conducted at baseline, 12, and 14 weeks. The fifth version of the Diagnostic and Statistical Manual of Mental Disorders criteria recommended using the nine-item, self-reported PHQ-9 questionnaire to gauge the degree of depression symptoms manifesting within the first two weeks. Likert scale ratings ranged from 0 to 3, with total scores ranging from 0 to 27. Scores >9 indicated mild to minimal symptoms, whereas scores of >10 indicated moderate to severe symptoms. PHQ-9 has an 88% sensitivity and specificity, indicating good dependability.

Gender, age, duration of the present episode, history of antidepressant usage, work status, and education were the variables evaluated at baseline. Post-traumatic stress disorder, acute stress disorder, panic disorder, social anxiety disorder, obsessive-compulsive disorder, generalised anxiety disorder, and anxiety disorder unspecified were among the comorbid anxiety statuses evaluated. Fibromyalgia, persistent pain, seizures, thyroid disorders, obesity, lung disease, Crohn's disease, irritable bowel syndrome, heart problems, diabetes, hypercholesterolemia, cancer, asthma, and/or arrhythmia were among the chronic ailments evaluated.

Seven distinct sets of drugs were administered to the individuals. The most often prescribed medication was an SSRI, which was followed by atypical antipsychotics, trazodone, mirtazapine, norepinephrine and dopamine reuptake inhibitors, and serotonin-norepinephrine reuptake inhibitors. Throughout the trial, all of the medications were administered consistently and within recognised therapeutic levels. At further visits, the dosages were modified in accordance with PHQ-9 results. The PHQ-9 score, which was self-reported and evaluated at baseline, one week, two weeks, four weeks,

six weeks, twelve weeks, and fourteen weeks, was the main outcome measured. The response must show a 50% decrease in PHQ-9 scores from the baseline to week 14, meeting the standard remission standards of PHQ-9 of <5 at weeks 12 and 14. Furthermore, from baseline to 14-week PHQ-9 scores, GTMI was collected at a drop of greater than 30%. The collected data were statistically analysed using logistic regression analysis and one-way ANOVA with the SPSS software version 21.0. A significance threshold of $p<0.05$ was maintained.

RESULTS

Of the 1075 participants evaluated in this trial, 21.95% (n=236) showed signs of remission, and 57.02% (n=613) showed signs of response with a reduction of at least 50% in the baseline PHQ-9 scores and A minimum of one GTMI was present in 73.95% (n=795) of the participants (≥50% drop in baseline PHQ-9 scores). It was evident that the early reaction improved the positive predictive values. However, when time allowed for the reaction, no discernible improvement was observed. With time, a rise in the negative predictive value was seen. Subjects that did not receive an early response for a longer period of time exhibited a larger negative predictive value. Every time, the reaction intensity had no bearing on net present value. Response deficiency at 6 weeks was a more accurate predictor of endpoint deficiency and remission in all participants than it was at 4 weeks. Remission's NPV was high. According to the study's findings, an early response is when a person's initial PHQ-9 scores drop by at least 30%.

56% (n=602) of the study's individuals had an early response, defined as a fall of at least 30% in baseline PHQ-9 scores. Table 1 provides a summary of the characteristics of patients who responded early and those who did not. The early responders and non-early responders had mean ages of 33.15±2.48 and 32.53±2.64, respectively, and there was a statistically significant difference between them ($p<0.001$). In Group I, there were 70.96% (n=435) females, while in Group II, there were 66.8% (n=309) females ($p<0.001$). With 43.93% (n=203) research respondents who were not early responders and 39.96% (n=245) subjects who were graduates, the bulk of Group I subjects ($p=0.008$) had education up to that point. As shown in Table 1, the majority of respondents in the early and non-early responder groups worked full-time, with 69% (n=423) and 69.04% (n=319) participants, respectively ($p=0.22$).

Regarding illness characteristics, 10.92% (n=67) early responders and 8.87% (n=41) non-responders reported having experienced one depression episode in the past, whereas 54.97% (n=337) responders and 51.94% (n=240) non-responders reported having experienced more than one depression episode. With $p<0.001$, the difference was statistically not significant. In 99.02% (n=607) of early responders and 98.91% (n=457) of non-responders, the history of chronic systemic disorders was positive ($p<0.001$). The baseline PHQ-9 values for early and non-early responders were 18.27 and 18.04, respectively. For the majority of research participants, the duration of depression exceeded two years in 39.96% (n=245) of early responders and 40.90% (n=189) of non-responders ($p=0.002$). The first medication prescribed to early responders was mirtazapine, atypical SSRI, SNRI, NDRI, and 64.92% (n=398), 5.05% (n=31), 18.92% (n=116), 0.97% (n=6), and 1.95% (n=12) of the individuals, respectively and was 66.88% (n=309), 6.60% (n=28), 14.93% (n=69), 1.94% (n=9), and 1.94% (n=9) subjects in non-early responders as shown in Table 1.

The odds ratios for early response, duration of 2 weeks–2 months, duration of 2–12 months, duration of 1-2 years, and >2 years, as well as the age and baseline PHQ-9, were found to be 3.247, 0.747, 0.615, 0.532, 0.494, 1.127, 1.042, 1.015, and 0.885, respectively, for the prediction of the remission. The 95% confidence intervals were found to be 2.943–3.583, 0.581–0.962, 0.424–0.692, 0.394–0.617, 0.973–1.306, 0.947–1.148, 1.014–1.024, and 0.8760.894, respectively. With the exception of depression episodes of 1 and >1, which had $p=0.12$ and 0.35, respectively, none of these measures were statistically significant (Table 2).

The study's findings demonstrated that logistic regression models were significant with a p-value of less than 0.001 and had a high accuracy of 78.2% for predicting remission. Compared to non-early responders, early responders had 3.2 times higher likelihood of remission. Similar findings were seen for the answer, with an accuracy of 66.3% and a significance level of $p<0.001$. Comparable results were seen for the GTMI outcomes, which demonstrated a high significance level of $p<0.001$ and an accuracy of 74.4%. At 14 weeks, the early response group showed a 3.6 times greater response, whereas the GTMI was 4.9 times higher in the non-early responders (Table 2).

In the current study, 21.95% (n=236) of the individuals showed remission, 57.02% (n=613) of the subjects showed a response (≥50% reduction in initial PHQ-9 scores), and 73.95% (n=795) of the subjects showed at least one GTMI (≥50% reduction in original PHQ-9 values). It was evident that the early reaction improved the positive predictive values. With time permitting the reaction, no discernible improvement was observed.

DISCUSSION

With time, a rise in the negative predictive value was seen. Subjects that did not receive an early response for a longer period of time exhibited a larger negative predictive value. Every time, the reaction intensity had no bearing on net present value. Response deficiency at 6 weeks was a more accurate predictor of endpoint deficiency and remission in all participants than it was at 4 weeks. Remission's NPV was high. According to the study's findings, an early response is when a person's initial PHQ-9 scores drop by at least 30%. These findings were in line with research conducted in 1987 by Quitkin FM et al. and in 2013 by Fabbri C et al., who proposed positive and negative predictive values for antidepressant medications that were similar to those of the current study.

The study results showed that 56% (n=602) of subjects had an early response in the study. Early responders and non-early responders had mean ages of 33.15±2.48 and 32.53±2.64, respectively, and there was a statistically significant difference between them ($p<0.001$). In Group I, there were 70.96% (n=435) females, while in Group II, there were 66.8% (n=309) females ($p<0.001$). With 43.93% (n=203) research respondents who were not early responders and 39.96% (n=245) subjects who were graduates, the bulk of Group I subjects ($p=0.008$) had education up to that point. 69% (n=423) and 69.04% (n=319) of the participants in the early and non-early responder groups, respectively, were full-time workers ($p=0.22$). The findings aligned with the earlier research conducted by Rothschild AJ9 in 2022 and Henkel V et al. 10 in 2009, whereby the authors proposed similar demographic information for early and non-early responders in their individual investigations.

Regarding the illness features, 10.92% (n=67) of the early responders and 8.87% (n=41) of the non-responders reported having experienced one prior episode of depression, whereas 54.97% (n=337) of the responders and 51.94% (n=240) of the non-responders reported having experienced more than one episode of depression. With $p<0.001$, the difference was statistically not significant. In 99.02% (n=607) of early responders and 98.91% (n=457) of non-responders, the history of chronic systemic disorders was positive ($p<0.001$). In early responders, the baseline PHQ-9 was 18.27; in non-early responders, it was 18.04. Most research participants had depression for more than two years: 39.96% (n=245) of early responders and 40.90% (n=189) of non-responders ($p=0.002$).

The initial medication used in early responders was mirtazapine, atypical SSRI, SSRI, SNRI, and 64.92% (n=398), 5.05% (n=31), 18.92% (n=116), 0.97% (n=6), and 1.95% (n=12) of the subjects, respectively; in non-early responders, it was 66.88% (n=309), 6.60% (n=28), 14.93% (n=69), 1.94% (n=9), and 1.94% (n=9) of the subjects. These results corroborated those of Sun Y et al.11 in 2021 and Spies M et al.12 in 2017, whose writers hypothesised illness features in their research subjects that were seen in the study subjects.

Regarding the prognosis for the remission, the odds ratio for an early response, the lengths of time from 2 weeks to 2 months, 2 months to 12 months, 1-2 years, and >2 years, the number of preceding depressive episodes—1 or more—the age, and 95% CI was 2.943-3.583, 0.581-0.962, 0.485-0.779, 0.424-0.692, 0.394-0.617, 0.973-1.306, 0.947-1.148, 1.014-1.024, and 0.8760.894, respectively. Baseline PHQ-9 were 3.247, 0.747, 0.615, 0.532, 0.494, 1.127, 1.042, 1.015, and 0.885. With the exception of depression episodes of 1 and >1, which had p values of 0.12 and 0.35, respectively, all of these factors were statistically significant. These findings were consistent with research conducted in 2019 by Browning M et al. and in 2012 by Kudlow PA et al., where the authors showed good prediction for remission rates for the factors they studied.

The study's findings demonstrated that logistic regression models were significant with a p-value of less than 0.001 and had a high accuracy of 78.2% for predicting remission. Compared to non-early responders, early responders had 3.2 times higher likelihood of remission.

For the response, similar results were noted where the accuracy was 66.3% and the significance was seen with $p<0.001$. Comparable results were seen for the GTMI outcomes, which demonstrated a high significance level of $p<0.001$ and an accuracy of 74.4%. At 14 weeks, the early response group showed a 3.6 times greater reaction, whereas the GTMI was 4.9 times higher in the non-early responders. The present findings are in line with the earlier research conducted by Hensler J et al. (2018) and Olgiati P et al. (2018), who observed comparable outcomes in terms of remission, response, and GTMI.

CONCLUSION

Taking into account its limitations, the current study suggests that, by week 14, an early response may be associated with improved treatment results. For participants who did not show a response by week 4, dopamine reuptake inhibitors and norepinephrine were administered in the hopes of improving outcomes.

REFERENCES

1. Uher R, Mors O, Rietschel M, et al. Early and delayed onset of response to antidepressants in individual trajectories of change during treatment of major depression: a secondary analysis of data from the Genome-Based Therapeutic Drugs for Depression (GENDEP) study. J Clin Psychiatry. 2011;72:1478–1484.
2. Murray CJ, Atkinson C, Bhalla K, et al. The State of US health, 1990–2010: burden of diseases, injuries, and risk factors. JAMA. 2013;310:591–608.
3. Wagner S, Engel A, Engelmann J, et al. The early improvement as a resilience signal predicting later remission to antidepressant treatment in patients with major depressive disorder: systematic review and meta-analysis. J Psychiatr Res. 2007;94:96–106.
4. Davidson JR. Major depressive disorder treatment guidelines in America and Europe. J Clin Psychiatry. 2010;71(suppl E1):e04.
5. Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001;16:606–613.
6. Papakostas GI, Fava M. A meta-analysis of clinical trials comparing milnacipran, a serotonin—norepinephrine reuptake inhibitor, with a selective serotonin reuptake inhibitor for the treatment of the major depressive disorder. Eur Neuropsychopharmacol. 2007;17:32–36.
7. Quitkin FM, Rabkin JD, Markowitz JM, et al. Use of pattern analysis to identify true drug response. A replication. Arch Gen Psychiatry. 1987;44:259–64.
8. Fabbri C, Marsano A, Balestri M, et al. Clinical features and drug-induced side effects in early versus late antidepressant responders. J Psychiatr Res. 2013;47:1309–1318.
9. Rothschild AJ. Should antipsychotic medications be prescribed to patients with nonpsychotic depression? J Clin Psychopharmacol. 2012;42:231–233.
10. Henkel V, Seemuller F, Obermeier M, et al. Does early improvement triggered by antidepressants predict response/remission? Analysis of data from a naturalistic study on a large sample of inpatients with major depression. J Affect Disord. 2009;115:439–49.
11. Sun Y, Tao S, Tian S, et al. Serotonin 2A receptor polymorphism rs3803189 mediated by dynamics of default mode network: a potential biomarker for antidepressant early response. J Affect Disord. 2012;283:130–8.
12. Spies M, Kraus C, Geissberger N, et al. Default mode network deactivation during emotion processing predicts early antidepressant response. Transl Psychiatry. 2017;7:e1008.
13. BrowningM, Kingslake J, Dourish CT, et al. Predicting treatment response to antidepressant medication using early changes in emotional processing. Eur Neuropsychopharmacol. 2015;29:66–75.
14. Kudlow PA, Cha DS, McIntyre RS. Predicting treatment response in major depressive disorder: the impact of early symptomatic improvement. Can J Psychiatry. 2012;57:782–8.
15. Henssler J, Kurschus M, Franklin J, et al. Trajectories of acute antidepressant efficacy: how long to wait for a response?A systematic review and meta-analysis of long-term, placebo-controlled acute treatment trials. J Clin Psychiatry. 2014;79:17r11470.
16. Olgiati P, Serretti A, Souery D, et al. Early improvement and response to antidepressant medications in adults with major depressive disorder. Meta-analysis and study of a sample with treatment-resistant depression. J Affect Disord. 2013;227:777–86.

TABLES

Characteristics	Subgroup	Early responders % (n=613)	Non-early responders % (n=462)	p-value
Mean age (years)		33.15±2.48	32.53±2.64	<0.001
Gender	Males	29.03 (178)	32.90 (152)	<0.001
	Females	70.96 (435)	66.8 (309)	
Education status	Uneducated	0.97 (6)	1.94 (9)	0.008
	Schooling	33.93 (208)	43.93 (203)	
	Graduate	39.96 (245)	35.93 (166)	
	Post-graduate	24.95 (153)	17.96 (83)	
Employment status	Unemployed	20.06 (123)	20.99 (97)	0.22
	Part-time	10.92 (67)	9.95 (46)	

	Full-time	69.00 (423)	69.04 (319)	
Previous depression episodes	None	33.93 (208)	38.96 (180)	<0.001
	One	10.92 (67)	8.87 (41)	
	>1	54.97 (337)	51.94 (240)	
Chronic systemic diseases	Yes	99.02 (607)	98.91 (457)	<0.001
	No	0.97 (6)	1.08 (5)	
Baseline PHQ-9		18.27	18.04	
Depression duration	<2 weeks	0.97 (6)	1.08 (5)	0.002
	2 weeks-2months	14.02 (86)	12.98 (60)	
	2 months-1year	24.95 (153)	24.89 (115)	
	1-2 years	18.92 (116)	19.91 (92)	
	>2 years	39.96 (245)	40.90 (189)	
Initial drug	SSRI	64.92 (398)	66.88 (309)	
	SNRI	5.05 (31)	6.06 (28)	
	NDRI	18.92 (116)	14.93 (69)	
	Atypical SSRI	0.97 (6)	1.94 (9)	
	Mirtazapine	1.95 (12)	1.94 (9)	

Table 1: Characteristics of early responder and non-early responder study subjects

Characteristics	Parameter	OR (odd's ratio)	95% CI (confidence interval)	p-value
Remission	Early response	3.247	2.943-3.583	<0.001
	Duration (2weeks-2months)	0.747	0.581-0.962	0.02
	Duration (2-12 months)	0.615	0.485-0.779	<0.001
	Duration (1-2 years)	0.532	0.424-0.692	<0.001
	>2 years	0.494	0.394-0.617	<0.001
	Prior depression episode -1	1.127	0.973-1.306	0.12
	Prior depression episode >1	1.042	0.947-1.148	0.35
	Age	1.015	1.014-1.024	<0.001
	Baseline PHQ-9	0.885	0.8760.894	<0.001
Response	Early response	3.603	3.344-3.883	<0.001
	Duration (2weeks-2months)	0.493	0.394-0.627	<0.001
	Duration (2-12 months)	0.475	0.381-0.592	<0.001
	Duration (1-2 years)	0.402	0.321-0.504	<0.001
	>2 years	0.374	0.303-0.463	<0.001
	Prior depression episode -1	1.243	1.085-1.415	0.001
	Prior depression episode >1	1.121	1.035-1.214	0.003
	Age	0.993	0.981-0.997	<0.001
	Baseline PHQ-9	1.013	1.012-1.017	0.02
GTMI	Early response	4.874	4.464-5.321	<0.001
	Duration (2weeks-2months)	0.642	0.492-0.836	0.001
	Duration (2-12 months)	0.674	0.525-0.866	0.003
	Duration (1-2 years)	0.583	0.451-0.753	<0.001
	>2 years	0.552	0.431-0.702	<0.001
	Prior depression episode -1	1.286	1.101-1.503	0.001
	Prior depression episode >1	1.153	1.053-1.262	0.003
	Age	1.013	1.012-1.022	<0.001
	Baseline PHQ-9	1.007	0.997-1.017	0.05

Table 2: Logistic regression analysis for remission, response, and GTMI in the study subjects