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ANTIDEPRESSANT THERAPY AND DEPRESSION DISORDER

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ABSTRACT

Introduction: Treatment-resistant depression represents a serious clinical problem and a significant public health challenge. Research highlights the importance of combining selective serotonin reuptake inhibitors (SSRIs) with antidepressants that act as antagonists of presynaptic α2-autoreceptors and α2-heteroreceptors, such as Mianserin, Trazodone, and Mirtazapine.

Aim: to evaluate the effectiveness of combined therapy using Mirtazapine (α2-autoreceptor antagonist) and Sertraline (serotonin reuptake inhibitor) in treating depression.

Materials and Methods: This prospective study included 30 patients of both sexes, aged between 21 and 39 years, diagnosed with depressive disorder (F32). Patients were evaluated at the private psychiatric institution "Dr. Zora Mitic" over a period of three months. Participants were assessed at baseline and after one and three months of treatment with combined antidepressant therapy consisting of Mirtazapine (15-30 mg/day) and Sertraline (50-100 mg/day). Sociodemographic characteristics (age, sex, marital status, education level, and employment) were collected using a specifically designed questionnaire. Depressive symptoms were evaluated using the Hamilton Depression Rating Scale (HDRS), and sexual dysfunction was assessed using the Sexual Dysfunction Scale.

Results: A Wilcoxon signed-rank test indicated a statistically significant decrease in Hamilton Rating Scale (HRS) scores after one month ($Z = -4.717$, $P \leq 0.001$) and three months ($Z = -4.787$, $P \leq 0.001$) of treatment compared to pre-treatment scores. Additionally, the difference in HRS scores between one-month and three-month treatment periods was also significant ($Z = -4.717$, $P \leq 0.001$).

Conclusion: The results of our study demonstrate that initiating combined antidepressant therapy at the outset of treatment is highly effective.

Keywords: antidepressant therapy, depression, patients, sexual dysfunction

INTRODUCTION

Treatment-resistant depression represents a serious clinical problem and a significant public health challenge. Although controversial, combined antidepressant therapy remains a popular clinical strategy due to its reported effectiveness in treatment-resistant depression cases [1, 2]. Numerous studies support the efficacy of antidepressant combinations when following established clinical guidelines. However, physicians must carefully consider pharmacokinetic and pharmacodynamic interactions, particularly the risk of serotonin syndrome. Despite these risks, combined therapy remains an effective treatment option when the mechanisms of action are appropriately matched [3, 4]. Although many types of antidepressants are currently available, monotherapy achieves remission in only about 40% of patients after 12 weeks of treatment. Recent meta-analyses indicate that combined antidepressant therapy as a first-line treatment is more effective than monotherapy for acute depression, resulting in higher remission rates and lower dropout rates [5, 6]. Research highlights the importance of combining selective serotonin reuptake inhibitors (SSRIs) with antidepressants that act as antagonists of presynaptic α2-autoreceptors and α2-heteroreceptors, such as Mianserin, Trazodone, and Mirtazapine. Particularly, sedating α2-adrenergic receptor antagonists like Mirtazapine have demonstrated superior effectiveness in managing restlessness, agitation, and sexual dysfunction commonly associated with SSRI [7, 8]. A study has further confirmed positive outcomes when combining Mirtazapine or Bupropion with SSRI. Therefore, the AIM of this study is to evaluate the effectiveness of combined therapy using Mirtazapine (α2-autoreceptor antagonist) and Sertraline (serotonin reuptake inhibitor) in treating depression.

MATERIAL AND METHODS

This prospective study included 30 patients of both sexes, aged between 21 and 39 years, diagnosed with depressive disorder (F32). Patients were evaluated at the private psychiatric institution "Dr. Zora Mitic" over a period of three months. All participants provided written informed consent before entering the study. Patients with other psychiatric or organic disorders were excluded. Participants were assessed at baseline and after one and three months of treatment with combined antidepressant therapy consisting of Mirtazapine (15-30 mg/day) and Sertraline (50-100 mg/day). Sociodemographic characteristics (age, sex, marital status, education level, and employment) were collected using a specifically designed questionnaire. Depressive symptoms were evaluated using the Hamilton Depression Rating Scale (HDRS), which includes 21 items. HDRS scores were classified into four severity categories: scores below 8 indicate no depression, 8-16 indicate mild depression, 17-24 moderate depression, and above 24 severe depression. Body Mass Index (BMI) was also recorded, and sexual dysfunction was assessed using the Sexual Dysfunction Scale, suitable for both genders and available in clinician-rated and self-rated formats. Scores range from 5 to 30, with scores of 19 or higher indicating sexual dysfunction. Normality of data distribution was tested with the Shapiro-Wilk test. Differences between normally distributed variables were analyzed using the t-test, while the Mann-Whitney test was applied for non-normally distributed variables. Comparisons of HDRS scores before and after 1 and 3 months of treatment were made using the Wilcoxon Signed Rank test. Spearman's correlation coefficient (ρ) assessed the relationship between treatment response (defined as ≥50% reduction in HDRS scores after 3 months) and observed variables. A P-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS for Windows (version 25).

RESULTS

AThere was no significant difference in the distribution of gender, living with partner or alone, employment, obesity, sexual dysfunction, therapy induced side effects and age between the Hamilton Rating score before the treatment and the scores after one and three months of treatment. Increased body weight was represented in 26.7% of the patient, sexual dysfunction was registered in 26.7% and 23.3 % of the patients had side effects of the therapy (Table 1).

HMRS p-Hamilton Rating Scale score before the treatment, HMRS 1-Hamilton Rating

Scale score after one month treatment, HMRS 3-Hamilton Rating Scale score after three months treatment.

A Wilcoxon signed-rank test showed that after one month (Z = -4.717, P<= 0.001) and 3 months treatment (Z = -4.787, P<= 0.001), compared to the pre-treatment score as well as the HRS score difference between 1- and 3-months therapy (Z = -4.717, P<= 0.001), elicited a statistically significant decrease in the HRS score. Indeed, the median score rating was 28.2 before the treatment and reduced to 20.67 after one month and 12.63 median score after three months treatment (Table 3).

Table 1. *Distribution of depression severity ratings score (Hamilton Rating Scale score -HM) for the baseline and outcome groups in relation to independent observed variables.*

Parameter	Category	N	%	HMp (Mean±SD)	P	HM1 (Mean±SD)	P	HM3 (Mean±SD)	P
Gender	Female	15	50	27.1 ±4.4	0.122	20.4±2.9	0.587	12.4±2.5	0.632
	Male	15	50	29.4 ±3.3		20.9±3.7		12.9±2.8	
Partner	No	11	36.7	28.1 ±3.5	0.858	20.1±3.4	0.423	12.6±2.6	0.891
	Yes	19	63.3	28.4±4.3		20.9±3.2		12.7±2.7	
Employment	No	10	33.3	28.4±3.5	0.900	20.8 ±3.0	1.000	12.2±2.7	0.529
	Yes	20	66.7	28.2±4.3		20.6 ±3.5		12.9±2.6	
Increased body wight	No	22	73.3	28.5±4.3	0.677	20.7 ±3.4	0.723	12.7±2.9	0.869
	Yes	8	26.7	27.8±3.1		20.4 ±3.2		12.5±1.6	
Sexual dysfunction	<19	22	73.3	27.8±4.2	0.268	20.0 ±3.5	0.093	12.5±2.8	0.543
	>19	8	26.7	29.6±3.2		22.5 ±1.9		13.1±2.2	
Age (years)	<33years	14	46.7	28.3±4.4	0.981	20.1±3.8	0.476	12.9±3.1	0.668
	>33years	16	53.3	28.3±3.7		21.1±2.9		12.4±2.2	
Education (years)	High S.	14	46.7	28.1±4.4	0.438	20.2±3.6	0.117	12.3±2.6	0.218
	Graduate	11	36.7	27.5± 3.8		21.0±2.8		13.4±2.7	
	Masters	3	10	29.0 ±3.5		18.7±3.1		10.3±1.5	
	PhD	2	6.6	32.5±0.7		25.7±3.3		14.5±2.1	

Table 2. *Distribution of the Hamilton Rating Scale score before the treatment, after one month and after three months treatment*

HMRS	N	Mean	Std. Deviation	Median	Minimum	Maximum
HMRSp	30	28.27	3.991	29	18	34
HMRS1	30	20.67	3.325	21.5	14	25
HMRS3	30	12.63	2.606	12	8	18

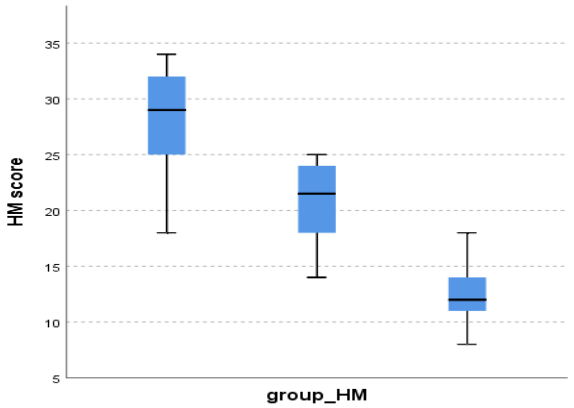

Figure 1. *Distribution of HRS score in pre and post treatment*

Table 3. *Pairwise comparison of the Hamilton Rating Scale score pre- and -post treatment*

HMRS score	*Z*	*P*
HMRS1 – HMRS p	-4.717	0.000
HMRS3 – HMRS p	-4.787	0.000
HMRS3 - HMRS1	-4.805	0.000

HMRS p- Hamilton Rating Scale score before the treatment, HMRS1- Hamilton Rating Scale score after one month treatment, HMRS3- Hamilton Rating Scale score after three months treatment

Response to therapy after 3 months treatment, defined as ≥50% reduction in HRSD scores, (Pigott HE 2023) was registered in 66.7% of the patients (Graph 2).

The response to therapy was insignificantly correlated to male gender, older age, living with a partner, higher education, unemployment, lower body weight, sexual dysfunction and side effects.

A positive response to therapy (reduction in score by more than 50%) was insignificantly correlated to male gender, older age, living with the partner, higher education, unemployment, lower body weight and sexual dysfunction (table 4).

The patients with sexual dysfunction were significantly older (35.0 ± 3.5years) then the patients without sexual dysfunction (30.4±4.5 years) (F=1.434, df=2, P=0.015).

DISCUSSION

Our study revealed that only a small percentage of patients lived alone (36.7%) or were unemployed (33.3%), contrasting with previous studies reporting higher depression rates among individuals who live alone or are unemployed [7, 9]. In our study, increased body weight and sexual dysfunction were each observed in 26.7% of the patients after antidepressant therapy. These relatively low percentages may be attributed to the sedative and α2-adrenergic antagonist properties of Mirtazapine, potentially mitigating sexual dysfunction commonly associated with antidepressants. Although these results appear modest, some research reports higher occurrences of weight gain, sexual dysfunction, and other side effects in combined

Graph 2. *Distribution of response to therapy in the total number of included patients after 3 months treatment*

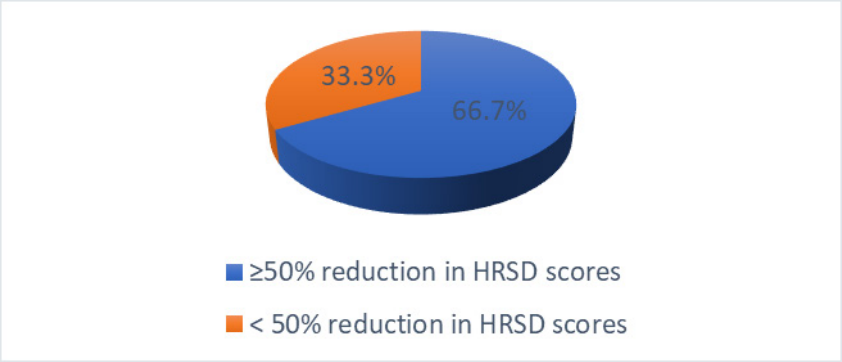

Table 4. *Correlation between therapy and socio-demographic and clinical characteristic*

Correlation	Gender	Age	Partner	Education	Employed	Increased b. weight	Sexual dysfunction
Spearmen's	0.141	0.144	0.049	0.111	-0.350	-0.053	0.267
P level	0.456	0.448	0.797	0.558	0.058	0.780	0.155

antidepressant therapies [10, 11]. Nonetheless, our study demonstrated statistically significant improvements in depression scores on the Hamilton Rating Scale (HRS) after just one month of treatment, with 66.7% of patients experiencing at least a 50% reduction in HRS scores by three months. These outcomes align with research supporting the effectiveness of combining selective serotonin reuptake inhibitors (SSRIs, e.g., Sertraline) with antidepressants acting through presynaptic α2 receptor antagonism (e.g., Mirtazapine) [2, 3]. Contradictory findings have emerged in some studies, suggesting combined therapy is particularly effective for patients unresponsive to monotherapy, such as those with impaired volition, or individuals living alone. Despite our patients generally being responsible, with fewer living alone, we employed combined therapy from the outset to achieve rapid symptom relief. Studies also suggest combined antidepressant therapy results in fewer side effects, lower dropout rates, and reduces the need for additional medication, such as lithium or second-generation antipsychotics [11, 12]. Although only a minority of our patients were unemployed or living alone and none had diagnosed personality disorders, we chose combined therapy based on evidence indicating better remission rates. Indeed, other studies show faster therapeutic responses when combining Mirtazapine and SSRIs from treatment initiation, matching our results [13, 14]. Furthermore, a double-blind study indicated that discontinuing one drug in patients who responded well to combined therapy led to relapse in 40% of cases, highlighting the benefits of initiating treatment with combined therapy. Notably, combined use of antidepressants resulted in increased body weight in 8 patients, yet only one patient discontinued treatment due to weight gain. This is consistent with other findings reporting manageable weight gain with combined therapy. Some studies suggest that after achieving initial remission with combined therapy, continuation with monotherapy could prevent relapse, offering practical clinical flexibility [15, 16]. Notably, our patients required fewer anxiolytics and no antipsychotics, reflecting significant treatment success compared to typical monotherapy outcomes. We observed that positive treatment response correlated slightly, though insignificantly, with factors such as male gender, older age, living with a partner, higher education, unemployment, lower body weight, and reduced sexual dysfunction. These results support claims that strong family support and education positively influence depression stabilization. The observed correlation with unemployment could be due to reduced stress in these individuals. Despite societal stigma labeling combined antidepressant treatments negatively, similar strategies in conditions such as HIV treatment are viewed positively as effective combinations [14, 17]. Emphasizing the effectiveness of combined antidepressant therapy is crucial, as untreated depression significantly increases suicide risk and exacerbates comorbid medical conditions. Therefore, timely and appropriate use of combined therapy can significantly enhance treatment outcomes within a short timeframe.

CONCLUSION

The results of our study demonstrate that initiating combined antidepressant therapy at the outset of treatment is highly effective. This approach rapidly reduces depressive symptoms while maintaining a low incidence of side effects, potentially preventing suicide and the development of associated comorbid conditions.

REFERENCES

1. Seetal D, David H, Gin S M, Michael B. To combine or not to combine? A literature review of antidepressant combination therapy Meta-Analysis J Affect Disord. 2005 Dec;89(1-3):1-11. doi: 10.1016/j.jad.2005.08.012. Epub 2005 Sep 16
2. Grote N.K. Difficult-to-treat depression: the role of contexts and comorbidities. Biol. Psychiatry 2003 2003 Apr 15;53(8):660-70. doi: 10.1016/s0006-3223(03)00006-4.
3. Nelson J.C. . Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. Biol. Psychiatry 2004 Feb 1;55(3):296-300.doi: 10.1016/j.biopsych.2003.08.007.
4. Perlis H.S .Effect of medical comorbidity on response to fluoxetine augmentation or dose increase in outpatients with treatment-resistant depression Psychosomatics. 2004 May-Jun;45(3):224-9.doi: 10.1176/appi.psy.45.3.224.
5. Jonathan H , Alexander D , Bushor T , Beatare CH. Combining Antidepressants vs Antidepres-

sant Monotherapy for Treatment of Patients With Acute Depression JAMA Psychiatry. 2022 Feb 16; 79(4): 300–312. doi: 10.1001/jamapsychiatry.2021.4313
6. Gelenberg AJ, Freeman MP, Markowitz JC, et al. Practice guideline for the treatment of patients with major depressive disorder: third edition. Published October 2010. Accessed January 11 2022 https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf
7. American Psychological Association. Depression treatments for adults. Published August 2019. Accessed October 13, 2020. https://www.apa.org/depression-guideline/adults
8. Xiao L, Zhu X, Gillespie A, et al. Effectiveness of mirtazapine as add-on to paroxetine v. paroxetine or mirtazapine monotherapy in patients with major depressive disorder with early non-response to paroxetine: a two-phase, multicentre, randomized, double-blind clinical trial. Psychol Med. 2021; 51(7): 1166–1174. doi: 10.1017/S0033291719004069 [DOI] [PubMed] [Google Scholar]
9. Pierre B, Ward E, Combination of Antidepressant Medications From Treatment Initiation for Major Depressive Disorder: A Double-Blind Randomized Study Publication: American Journal of Psychiatry 2021; 5(6): 12–321.
10. Pigott HE, Kim T, Xu C, Kirsch I, Amsterdam J. What are the treatment remission, response and extent of improvement rates after up to four trials of antidepressant therapies in real-world depressed patients? A reanalysis of the STAR*D study's patient-level data with fidelity to the original research protocol. BMJ Open. 2023 Jul 25; 13(7): e063095. doi: 10.1136/bmjopen-2022-063095
11. Nemeroff CB, Entsuah R, Benattia I, Demitrack M, Sloan DM, Thase ME: Comprehensive analysis of remission (COMPARE) with venlafaxine versus SSRIs. Biol Psychiatry 2008; 63:424–434
12. Wang Qi,, Liang Yao, M Yaolong Combination Antidepressant Therapy vs Monotherapy—Further Considerations JAMA Psychiatry. 2022; 79(8): 831–832. doi:10.1001/jamapsychiatry.2022.1391
13. Elisa F 1, Amir H , Pierre B Treatment of depression: antidepressant monotherapy and combination therapy Psychiatry (Edgmont) . 2007 Nov; 4(11): 25–7.
14. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STARD: Implications for clinical practice. Am J Psychiatry. 2006; 163: 28–40. - PubMed
15. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRs for depression. N Eng J Med. 2006; 354: 1243–52. - PubMed
16. Evans DL, Charney DS. Mood disorders and medical illness: A major public health problem. Biol Psychiat. 2003; 54: 177–80. - PubMed
17. Wittchen HU, Jacobi F, Rehm J, et al. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. 2011; 21(9): 655–679.

Резиме

АНТИДЕПРЕСИВНА ТЕРАПИЈА И ДЕПРЕСИВНИ СОСТОЈБИ

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Вовед: Депресијата отпорна на третман претставува сериозен клинички проблем и значаен предизвик за јавното здравје. Истражувањата ја нагласуваат важноста од комбинирање на селективните инхибитори за повторно земање на серотонин (SSRI) со антидепресиви што дејствуваат како антагонисти на пресинаптичките α2-авторецептори и α2-хетерорецептори, како што се миансеринот, тразодонот и миртазапинот.

Цел: Целта на ова истражување е да се оцени ефективноста на комбинираната терапија со употреба на миртазапин (антагонист на α2-авторецептор) и сертралин (инхибитор на повторно земање серотонин) во лекувањето на депресијата.

Материјал и методи: Пациентите беа евалуирани во приватната психијатриска установа „Д-р Зора Митиќ“ во период од три месеци. Учесниците беа евалуирани на почетокот, по еден и по три месеци од третманот со комбинирана антидепресивна терапија: миртазапин (15-30 mg/ден) и сертралин (50-100 mg/ден). Социодемографските карактеристики (возраст, пол, брачен статус, ниво на образование и вработување) беа собрани со помош на специјално дизајниран прашалник. Депресивните симптоми беа одредеувани со помош на скалата за оцена на депресија на Хамилтон (HDRS), а сексуалната дисфункција со помош на скалата за сексуална дисфункции.

Резултати: Тестот Wilcoxon покажа статистички значајно намалување на резултатите на Хамилтоновата скала (HRS) по еден месец ($Z = -4{,}717$, $P \leq 0{,}001$) и по три месеци ($Z = -4{,}787$, $P \leq 0{,}001$) од третманот. Разликата во резултатите од HRSомеѓу едномесечен и тримесечен период на третманот беше, исто така, значајна ($Z = -4{,}717$, $P \leq 0{,}001$).

Заклучок: Резултатите од нашата студија покажуваат дека третманот со комбинирана антидепресивна терапија на самиот почеток од третманот покажува многу брз и ефикасен антидепресивен учинок.

Клучни зборови: антидепресивна терапија, депресија, пациенти, сексуална дисфункција