



Mirtazapine Combination in Treatment-Resistant Major Depressive Disorder: A Retrospective Evaluation of Six Weeks

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ÖZET:

Tedaviye dirençli major depresif bozuklukta mirtazapin eklemeye tedavisi: Altı haftalık geriye dönük değerlendirme

Amaç: Yeterli süre ve dozda tedaviye karşın, majör depresif bozukluğu bulunan hastaların yaklaşık üçte biri tedaviye yanıt vermemektedir. Önceki çalışmalarda, yeterli doz ve süreyle en az iki farklı sınıftan antidepresan tedaviye yanıt alınamayan tedaviye dirençli hastalarda mirtazapin eklemeye tedavisi etkili olduğu bildirilmiştir. Bu çalışmada, tedaviye dirençli majör depresif bozukluğu olan hastalarda mirtazapin eklemeye tedavisinin etkisinin geriye dönük kayıt taraması yöntemiyle ortaya konması amaçlanmıştır.

Yöntem: Ağustos 2004 ile Temmuz 2005 tarihleri arasındaki dönemde tedaviye dirençli majör depresif bozukluk tanısı konmuş hastaların dosyaları seçilmiştir. Hastaların değerlendirilmesinde, Hamilton Depresyon Derecelendirme Ölçeği (HAM-D) ve Klinik Global İzlenim (KGI) kullanılmıştır. Yan etki değerlendirilmesinde hastanın bildirimini dikkate alınmıştır. Daha önceden iki ayrı gruptan antidepresan tedaviye yanıt vermeyen (HAM-D değerlendirilmesinde <50% belirti azalması) yatarak ya da ayaktan majör depresif depresif bozukluğu bulunan 43 hasta çalışma için değerlendirilmiştir. Araştırmaya alma ölçütlerine uyan 43 hastadan, verileri tam olan 39 hasta değerlendirilmeye alınmıştır. Hastalardan 18 (%41.9)'i venlafaksin, 25 (%58.1)'i ise SSRI (15 sitalopram, 6 sertralin, 4 paroksetin) kullanmaktadır.

Bulgular: Araştırma grubunun yaş ortalaması 42.2 ± 12.9 'dur ve %74.4'ü (s=32) kadındır. Altı haftalık değerlendirme sonunda HAM-D puanı 23.1 ± 5.1 'den 7.3 ± 5.6 'ya düşmüştür ve 21 (%53.8) hastanın remisyon (HAM-D < 7) elde ettiği belirlenmiştir. Başlangıçtaki antidepresan ilaç tedavisi göz önüne alındığında, venlafaksin kullanan hastalar, seçici serotonin geri alım inhibitörü (SSRI) kullanan hastalara göre daha yüksek oranda remisyon elde etmişlerdir. Hastaların 12 (%27.9)'sinde çalışma sırasında yan etki gözlenmiştir ve yan etkilerin başında 8 hastada ortaya çıkan kilo alma gelmektedir. Yan etki nedeniyle çalışma dışı bırakılan hastalardan birisinde neden kilo alma iken, diğerinde anksiyete ve ajitasyondur.

Tartışma: Mirtazapin eklemeye tedavisi, tedaviye dirençli majör depresif bozuklukta etkili ve iyi tolere edilen bir seçenektir. Başlangıç ilacı venlafaksin olduğunda, bu eklemeye tedavisinin etkisi daha da artmaktadır.

Anahtar sözcükler: Mirtazapin, eklemeye tedavisi, tedaviye dirençli depresyon

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ABSTRACT:

Mirtazapine combination in treatment-resistant major depressive disorder: a retrospective evaluation of six weeks

Objective: Despite the adequate time and dose of antidepressant treatment, approximately one-third of the patients with major depression do not respond. In previous trials, mirtazapine combination was found to be efficacious in treatment-resistant depression which is non-response to two previous adequate antidepressant drug treatments from different classes. In this present study, it is aimed to assess the efficacy and the tolerability of mirtazapine combination treatment in patients with treatment-resistant major depression by retrospective chart review.

Method: During the period between August 2004 and July 2005, all the charts of the patients with treatment resistant major depressive disorder were selected. For the assessment, Hamilton Depression Rating Scale (HAM-D) and Clinical Global Impression (CGI) were used. For the assessment of adverse effects, the report of the patients was considered. Forty-three in- or outpatients with major depression who previously received two antidepressants of different groups and did not respond (<50% of symptom reduction in HAM-D) to either treatment were assessed. Of the 43 patients who fulfilled the inclusion criteria, 39 patients had complete data for the assessment. The study was based on the chart records of 39 patients. At the time of assessment, 18 (41.9%) patients were receiving venlafaxine, and 25 (58.1%) patients were receiving an SSRI (15 on citalopram, 6 on sertraline, and 4 on paroxetine).

Result: The mean age of the study group was 42.2 ± 12.9 , and 74.4% (n=32) female. Of the whole sample, 14 (32.6%) patients were having their first episode, whereas 29 (67.4%) patients had a recurrent major depression. Ten (23.3%) patients were inpatients and 33 (76.7%) patients were outpatients. The mean HDRS score was decreased from 23.1 ± 5.1 to 7.3 ± 5.6 at the end of the assessment of six weeks, and 21 (53.8%) patients achieved remission (HDRS < 7). When the primary antidepressant was taken into consideration, patients on venlafaxine had significantly more remission rate compared to patients on selective serotonin reuptake inhibitors (SSRI). In 27.9% (n=12) of the patients, adverse events were emerged, and weight gain was predominant with 8 patients. In two patients who were dropped out due to adverse events, one patient experienced weight gain (8 kg/4 weeks) and the other had anxiety and agitation.

Discussion: Mirtazapine combination treatment is an efficacious and well-tolerated alternative in treatment-resistant major depression. When the primary antidepressant is venlafaxine, this combination therapy seems to be more effective.

Key words: Mirtazapine, combination treatment, treatment-resistant depression

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INTRODUCTION

Despite the adequate time and dose of antidepressant treatment, approximately one-third of the patients with major depression do not respond, and another one-third only achieves a partial response (1). When a depressed patient fails to respond or only does so partially to an adequate trial of antidepressant monotherapy, a variety of strategies have been proposed as regards what to do next. Unfortunately, the majority of these recommendations are unsupported by evidence (2). Posternak and Zimmerman (3) suggested that switching antidepressants was somewhat less effective than augmentation, although this difference was not statistically significant. Therefore, when depressions do not respond adequately to treatment with an antidepressant, clinicians may choose to keep the same antidepressant and add another "augmenting" compound (4). Such augmentation strategies involve the use of a pharmacologic agent that is not considered to be a standard antidepressant but may boost or enhance the effect of an antidepressant. Alternatively, clinicians may choose combination strategies, in which they combine the antidepressant that did not produce adequate response with another antidepressant, typically of a different class (5).

Mirtazapine is a dual-action antidepressant whose mechanism involves the enhancement of central noradrenergic and 5-HT₁ serotonergic neurotransmission via blockade of α_2 -adrenergic auto- and heteroreceptors, without activity at the serotonin transporter (6). Blockade of inhibitory presynaptic α_2 -adrenergic autoreceptors increases neuronal release of norepinephrine. Norepinephrine subsequently stimulates excitatory α_1 -adrenergic receptors on serotonergic cell bodies in the raphe nuclei, potentiating serotonin release. With long-term administration, mirtazapine is thought to increase serotonergic neurotransmission by desensitizing inhibitory 2-heteroreceptors located on serotonergic nerve terminals (7). This unique mechanism of action makes mirtazapine a compelling candidate for augmentation treatment in patients who fail to achieve adequate response with other antidepressant medications (8). Moreover, the combination of mirtazapine with venlafaxine in treatment-resistant depression is suggested to be the most effective combination by Stahl (9). Thus, Carpenter and colleagues performed a placebo-controlled study on mirtazapine augmentation in treatment-

refractory depression and found that mirtazapine appears safe and effective for short-term antidepressant augmentation (10).

Combination strategies are commonly used in clinical practice, but most have been poorly studied. There are some studies concerning augmentation strategies with atypical antipsychotics in treatment-resistant depression in current literature (11), but no combination strategies have been studied. In this present study it is aimed to determine the effect of mirtazapine combination in patients with major depressive disorder who do not respond to adequate courses of at least two different antidepressant treatments. This is a retrospective evaluation study with duration of six weeks; and to our knowledge, this is the first study on effectiveness of mirtazapine combination in treatment-resistant depression in Turkey. In this study, treatment-resistance is described as non-response to two adequate courses of antidepressant drug treatments from different classes.

MATERIALS AND METHOD

The study was carried out in Department of Psychiatry, School of Medicine, Celal Bayar University, Manisa, Turkey with the evaluation of chart records between August 2004 and July 2005.

Subjects

In- or outpatients with major depressive disorder according to DSM-IV who previously received two antidepressants of different classes and did not respond fully (<50% of symptom reduction in HDRS) to either treatment, and who were decided to be administered add-on treatment of mirtazapine in addition to their ongoing antidepressant treatment were assessed. As a criterion of resistance of depressive symptoms, patients with a score of Hamilton Depression Rating Scale (HDRS) ≥ 17 despite their ongoing treatment were considered for the inclusion criterion to the study. The exclusion criteria were having any substance use disorder (other than nicotine and caffeine) or any neurological or physical disease requiring a chronic treatment. All patients were asked to give their verbal consent at the time of combination treatment as a principle of good clinical practice.

As a result, 43 patients were included in the study, but 39 of the patients with a mean age of 42.2 ± 13.7 , and 78.9% (n=30) being women had all their records complete. Of the whole study sample, 11 (28.9%) patients were having their first episode, whereas 27 (71.1%) patients had a recurrent major depression described as having more than one depressive episode according to DSM-IV. Ten (25.6%) patients were inpatients and 29 (74.4%) patients were outpatients. In 43.5% (n=17) of the patients a comorbid anxiety disorder diagnosis were given concurrently according to DSM-IV at the time of diagnostic assessment. Demographical and clinical features of the patients are shown in Table 1.

Table 1: Demographical and clinical features of the patients.

Age	42.2±13.7	
Gender		
female	30	78.9%
male	9	21.1%
Type of depression		
single episode	13	33.3%
recurrent	26	66.7%
Primary antidepressant (current episode)		
SSRI	16	41.0%
venlafaxine	23	59.0%
Patient type		
inpatient	10	25.6%
outpatient	29	74.4%
Comorbid anxiety disorder	17	43.5%

Instruments

In the assessment of depression, 17-item Hamilton Depression Rating Scale (HDRS) with structured interview guide used; and the reliability and validity study for the Turkish version was performed by Aydemir et al (12). HDRS is the most widely used depression scale in antidepressant drug trials. It assesses anxiety symptoms beside core depressive symptoms. The Turkish version of HDRS does not have a cut-off point. Beside HDRS, Clinical Global Impression (CGI) was used for global severity and change assessment. It is originally developed by Guy and colleagues (13). It contains seven rating between 1 and 7 where 1 means “normal, not at all ill”, and 7 means “among the most extremely ill subjects”. In Clinical Global Improvement, there is also 7 ratings where 1 means “very much improved” and 7 means “very

much worse”. For assessing adverse events, no formal assessment or scale was administered. The subjective report of the patients is considered. Patients were assessed with the 17-item Hamilton Depression Rating Scale (HDRS) and the Clinical Global Impression (CGI) at the beginning, in the 2nd, 4th and 6th weeks.

Procedure

At the time of combination, 16 (41.0%) patients were receiving venlafaxine, and 23 (59.0%) patients were receiving a selective serotonin reuptake inhibitor (SSRI) (14 patients were on citalopram, 5 patients were on sertraline, and 4 patients were on paroxetine). Primary antidepressants were continued at their pre-study doses throughout the combination and no other psychotropic agents were given during the six weeks. The mean venlafaxine dose was 195.8 with a range of 75-300 mg/day. One patient was on venlafaxine with a dose of 75 mg/day and since he partly benefited from this dose of venlafaxine but could not tolerate a higher dose, we did not want to exclude the patient from the study; instead, we evaluated his results with caution. The mean dose of citalopram was 42.8 with a range of 40-60 mg/day, and of sertraline was 142.8 with a range of 100-200 mg/day. All four patients receiving paroxetine were on a dose of 40 mg/day. Mirtazapine was first given with a dose of 15-30 mg/day according to the clinician’s judgment, and it was raised by 15 mg/day at the follow-up visits according to the response obtained. The response was accepted as 50% decrease in the HDRS score. The remission was accepted as HDRS score < 7 (14).

Statistical Analysis

Before performing the statistical analyses, to test the normality of the distribution of the sample, Kolmogorov-Smirnov Test and Shapiro-Wilk Test are calculated. In statistical analysis, since the distribution of the sample is not normal, Wilcoxon Test for paired samples was performed. For the comparison of the subgroup scores, since the distribution was not equal, Wilcoxon Test for paired samples was used. Fisher’s exact tests were applied for comparisons involving dichotomous data and the subjective assessment of the clinicians and the comparison of the remission rate were applied to Fisher’s exact test.

RESULTS

Of the records of 43 patients, 39 patients had their complete records of six-week follow-up visits. Two patients were stopped medication before six weeks due to adverse events and the two patients were lost follow-up visits. The statistical analysis was performed for the 39 patients who completed the study.

The mean total score changes of the patients were summarized in Table 2 and Figure 1. At the index assessment, the mean HDRS score was 23.1 ± 5.1 , and the mean CGI score was 5.1 ± 0.6 ; and the mean starting dose of mirtazapine was 25.1 ± 8.4 mg/day. In the second week assessment the mean HDRS score was decreased significantly to 13.9 ± 6.7 , and the CGI score to 4.2 ± 0.9 ($p < 0.0001$). In the fourth week assessment, the mean

Table 2: Change of mean and median scores of HDRS and CGI during the study.

	HDRS	CGI	Mirtazapine dose (mg/day)
Index visit			
mean \pm s.s.	23.1 ± 5.1	5.1 ± 0.6	25.1 ± 8.4
median	22.5	5.0	
2nd week visit			
mean \pm s.s.	13.9 ± 6.7	4.2 ± 0.9	
median	14.0*	4.0*	
4th week visit			
mean \pm s.s.	10.5 ± 6.4	3.6 ± 1.0	
median	11.0*	4.0*	
6th week visit			
mean \pm s.s.	7.3 ± 5.6	2.9 ± 1.0	27.6 ± 10.1
median	5.5*	3.0*	

* $p < 0.0001$

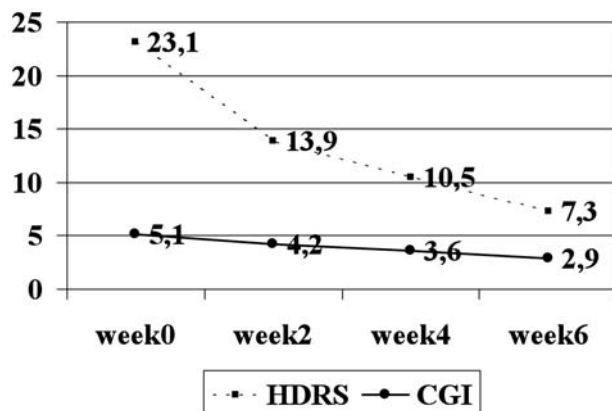


Figure 1: Change of HDRS and CGI scores during mirtazapine augmentation

HDRS score was found to be 10.5 ± 6.4 , and the mean CGI score to be 3.6 ± 1.0 ; and the decrease was statistically significant ($p < 0.0001$). In the last visit at the sixth week, the mean HDRS score was 7.3 ± 5.6 , the mean CGI score was 2.9 ± 1.0 . The mean mirtazapine dose at the last visit was 27.6 ± 10.1 mg/day. Of the patients who had complete records, 21 (53.8%) patients achieved remission (HDRS < 7). Also the patient subgroup with a comorbid anxiety disorder had a significant decrease in total HDRS score from 23.8 to 7.6 ($p < 0.0001$).

When the primary antidepressant was taken into consideration, patients on venlafaxine (remission rate 76.5%) had significantly more remission rate compared to patients on SSRI (remission rate 36.4%) ($p = 0.014$) (Fig 2). Total HDRS score in the venlafaxine group was decreased from 22.9 to 4.6, and in the SSRI group the decrease was from 23.1 to 9.4; the venlafaxine group had a significantly higher decrease than the SSRI group ($p = 0.041$).

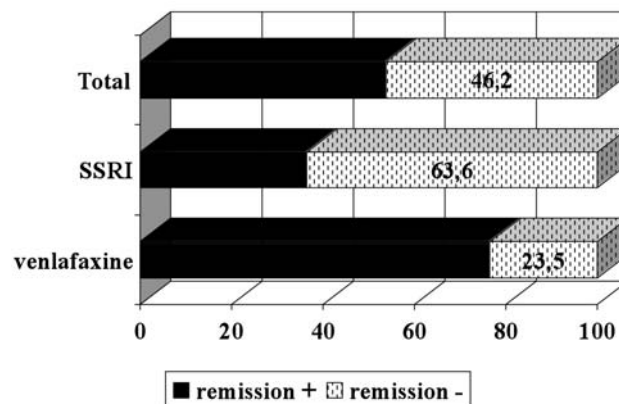


Figure 2: Rate of remission according to the primary antidepressant

In 27.9% ($n = 12$) of the patients, adverse events were emerged, and weight gain was predominant with 8 patients. In two patients who were excluded due to the adverse events, one patient experienced weight gain (8 kg/4 weeks) and the other patient had anxiety and agitation.

DISCUSSION

In this present study, mirtazapine combination in major depressive disorder previously non-responsive to two antidepressant treatment was found to be efficacious and safe in a six-week follow-up. At the end of six weeks,

the HDRS score was decreased by one-third, and more than half of the patients achieved remission. Previous studies on mirtazapine combination in treatment-resistant depressive patients reported that mirtazapine appears to be effective and safe when combined with other antidepressants (8,10), and the response and the remission rates of this present study are also similar. Furthermore, Thase and colleagues reported 37.8% remission rate for SSRI non-responders who were subsequently treated with mirtazapine monotherapy in a multicenter controlled study (15). However, Wan and colleagues found 38% symptomatic improvement in treatment-resistant depression treated with mirtazapine monotherapy (16).

Also, the patient subgroup with comorbid anxiety disorder showed significant decrease in the HDRS scores, as the pure major depressive group. It is well-documented that mirtazapine is effective in severe depression with high baseline anxiety symptoms (17). Also it was reported that mirtazapine is efficacious in the treatment of comorbid major depression and generalized anxiety disorder (18). Moreover, mirtazapine monotherapy is a good alternative in the treatment of anxiety disorders (19,20). Having improvement in depressive patients with comorbid anxiety disorder seems to support this evidence.

When the primary antidepressant was taken into consideration, there was a significant difference between venlafaxine and SSRIs, and in terms of remission rate the venlafaxine group was separated from the SSRI group by two-fold. In previous studies on mirtazapine combination with paroxetine, both Debonnel and colleagues (21) and Carpenter and colleagues (8) found this combination was effective with a response rate of over 50%. On the other hand, venlafaxine and mirtazapine combination is known to be one of the most potent antidepressant combinations, and Hannan and colleagues reported that mirtazapine-venlafaxine combination has more than 50% response at six-month review in more difficult to treat patients with depression (22). In another study performed by Malhi et al. (23), it was reported that in an 8-week study, the venlafaxine-mirtazapine combination produced a response rate of 81.8% and a remission rate of 27.3% in 22 patients with treatment-resistant depression. Our findings also support this finding and suggest that

mirtazapine-venlafaxine combination works well in treatment-resistant depression. However, our sample size is relatively small to make definitive conclusions.

Similar with previous studies (10), the combination of mirtazapine with other antidepressants such as SSRIs or venlafaxine, shows less side effects than either alone. Especially, during the study no sexual side effects were detected which are very common with SSRIs or venlafaxine (24). Moreover, bodyweight gain experienced with mirtazapine is much less common when in combination. Two patients were dropped out due to side effects and one was weight gain which can be expected. But, the other was anxiety and agitation which seems paradoxical, and sometimes, serotonergic synergism may cause such a side effect.

The most important limitation of this present study is the retrospective design, and for more objective and reliable results, prospective studies on the combination of mirtazapine in treatment-resistant depression are needed. Other limitations of the study include the small sample size, the heterogeneous nature of the sample, the variety of primary antidepressants and the range of primary antidepressant doses which were augmented. Since there possibly are many confounding factors, the results of the subgroup analyses such as comorbid anxiety group or primary antidepressant group should be cautiously handled and commented on. The heterogeneous nature of the study group is another limitation of the study since the design is based on retrospective analyses of the data of the patients. Also, the six-week design only supports short term response, but long-term data for treatment-resistant depression are missing.

In conclusion; the current study suggests that mirtazapine augmentation is an efficacious and well-tolerated alternative in treatment-resistant major depression. When the primary antidepressant is venlafaxine, this combination therapy especially seems to be more effective, however this requires further longitudinal studies. Long-term prospective follow-up studies are needed to establish the role of mirtazapine combination in the maintenance of antidepressant response and clinical remission in treatment-resistant depression where long-term data are needed.

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