

## 주요 우울증 환자에서 Mirtazapine 치료 중 Benzodiazepine의 불필요한 사용

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### ABSTRACT

#### Superfluous Use of Benzodiazepines in Patients with Major Depression Treated with Mirtazapine

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**Objective** : The purpose of this study is to evaluate the usefulness of administration of benzodiazepines in patients with major depression being treated with the antidepressant mirtazapine. **Methods** : The subjects of this study included 503 patients between 18 and 65 years of age. They were diagnosed with major depression according to the ICD-10 and scored over 18 at baseline on the 17-item HAM-D scale. They were among the 925 patients who have participated in the Remeron (mirtazapine) post-marketing surveillance carried out between September 1999 and December 2000 at 33 institutes in Korea. The patients were initially started on 15 mg/day or 30 mg/day of mirtazapine orally and the dosages could be changed according to clinical judgment during the trial. Benzodiazepines could also be administered according to clinical judgment. The clinical effects were evaluated before and 1, 2 and 6 weeks after treatment initiation. The therapeutic action of mirtazapine was evaluated using the 17-item HAM-D and CGI. The adverse effects were rated according to patient reports. **Results** : Their mean age was 45 years old and 61.6% were women. 391 subjects (77.3%) from a total of 503 patients completed the trials. 313 (62.2%) patients were administered benzodiazepines during the trial. These were alprazolam 37.0%, lorazepam 12.5%, clonazepam 9.1% and diazepam 7.0%. The reasons for prescribing benzodiazepines were : anxiety 43.1%, insomnia 18.3% and somatic symptoms 3.8%. The HAM-D scores of total patients were reduced from 26.1 to 10.9, and CGI scores from 4.5 to 3.0 after 6 weeks with significant changes beginning after 1 week of treatment. No significant differences were found in terms of each interval changes on the HAM-D and CGI scores between the groups with and without benzodiazepines. There were no significant differences of each interval changes of anxiety/agitation factors and sleep disturbance factors between the two groups. The occurrence of side effects was not significantly different between the two groups. **Conclusion** : Administration of benzodiazepines in patients with major depression being treated with mirtazapine may not be useful in reducing depressive symptoms, even for anxiety/agitation and sleep disturbance symptoms. (Korean J Psychopharmacol 2004;15(1):58-65)

**KEY WORDS** : Depression · Mirtazapine · Benzodiazepine · Antidepressant.

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## 서론

1) benzodiazepine  
 2,3) (serotonin - specific reuptake inhibitors ; SSRI)가 benzodiazepine 가 가 4) SSRI , SSRI benzodiazepine , SSRI benzodiazepine 가 5-7) benzodiazepine diazepine 가 8) 가 NaSSA(norenergic and specific serotonergic antidepressant) mirtazapine 9,10) Mirtazapine 2 - autoreceptor 가 2 - heteroreceptor 가 5 - HT<sub>2</sub> 5 - HT<sub>3</sub> HT<sub>1A</sub> 가 , 11) mirtazapine SSRI 1 12-15) mirtazapine HT<sub>2A</sub> 5 - HT<sub>2C</sub> H<sub>1</sub> 16,17) , SSRI benzodiazepine mirtazapine 가

benzodiazepine , mirtazapine benzodiazepine mirtazapine benzodiazepine 가

## 대상 및 방법

### 1. 연구 대상

1999 9 2000 12 Re-meron(mirtazapine) post - marketing surveillance (PMS) 33 925 503 1) 18 65 10th revision of International Statistical Classification of Diseases and Related Health Problems(ICD - 10)<sup>18)</sup> , 2) 17 - item Hamilton Rating Scale for Depression(HAM - D)<sup>19)</sup> 가 18 , 3) 가 1) benzodiazepine , 2) 가 , 3) , 4) , 5) , 6)

### 2. 연구 방법

mirtazapine 6 (open), (non - comparative), mirtazapine 1 15 mg 30

Mirtazapine      Benzodiazepine

mg      6 가

zodiazepine      , ben- 45.3(±11.9) , 193 (38.4%) , 310 (61.6%) . mirtazapine

1, 2, 138 (27.4%) ,

6 가 271 (53.9%) ,

가 41.0(±12.2) .

HAM - D , Clinical Global Impression 384 (76.3%), 7 101 (20.1%) .

(CGI) 6 . 6 mir- (mild)가 46 (9.1%),

tazapine 가 , 가 (moderate)가 328 (65.2%),

(adverse experience) (severe without psychotic symptoms) 78 (15.5%), (severe with psy-

가 last observation carried for- chotic symptoms) 51 (10.2%) ( 1). 212

ward(LOCF) intent - to - treat(ITT) (42.1%) mirtazapine

. 17 - item HAM - D, CGI re- , parox-

peated measures ANOVA , etine 23.6%, amitriptyline 20.3%, sertraline 17.5%,

Bonferroni fluoxetine 16.0%, trazodone 11.8% venlafaxine

. 17 - item HAM - D / 5.2% . 112 (22.7%)

(anxiety/agitation factor), / (an- 가 64

xiety/somatization factor) (sleep (57.1%), 19 (17.0%),

disturbance factor) . 7 (7.1%)

6 benzodiazepine

17 - item HAM - D

CGI ANOVA

(responders) 17 item -

HAMD 가 50%

(remitters) 17 item -

HAMD 가 7

SPSSWIN(Statistical Package for the Social

Science for Windows) package 11.5

, 0.05

**결 과**

1. 인구사회학적 자료

503 391 (77.3%)

**Table 1.** Demographic characteristics of total subjects (N=503)

Characteristics	Number (%)
Age*	45.3 (± 11.9)
Gender	
Male	193 (38.4)
Female	310 (61.6)
Previous history of depression	271 (53.9)
Age of onset of depression*	41.0 (± 12.2)
Duration of the present episode	
<1 month	18 ( 3.6)
1 - 6 months	384 (76.3)
>7 months	101 (20.1)
Patients hospitalized at baseline	138 (27.4)
Severity of symptoms	
Mild	46 ( 9.1)
Moderate	328 (65.2)
Severe without psychotic features	78 (15.5)
Severe with psychotic features	51 (10.2)

\* : Data are means (± standard deviations)

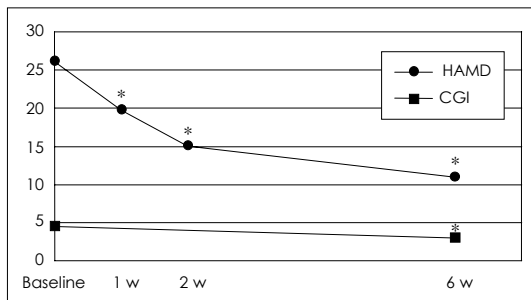
**2. Benzodiazepine 투여**  
 313 (62.2%) benzodiazepine . Benzodiazepine  
 pine 67% mirtazapine  
 benzodiazepine , 15.5%  
 mirtazapine benzodiazepine  
 benzodiazepine alprazolam 37.0%,  
 lorazepam 12.5%, clonazepam 9.1% diazepam  
 7.0% ( 2). benzodiazepine  
 alprazolam 0.84 mg (± 0.68), lorazepam 1.08  
 mg (± 0.51), clonazepam 1.01 mg (± 0.64) diaze-  
 pam 6.52 mg (± 3.81) ,  
 2 . Benzodiazepine  
 43.1%, 18.3% 3.8% .

**3. 임상 효과**

Mirtazapine 20.0 mg (± 7.5),  
 29.0 mg (± 10.4) . Mir-

**Table 2.** Administrated benzodiazepines (N=313)

Benzodiazepines	%	Mean daily dosage (mg)	Mean duration of administration (days)
Alprazolam	37.0%	0.84 (± 0.68)	27.4 (± 15.2)
Lorazepam	12.5%	1.08 (± 0.51)	30.1 (± 15.4)
Clonazepam	9.1%	1.01 (± 0.64)	28.7 (± 14.9)
Diazepam	7.0%	6.52 (± 3.81)	24.9 (± 16.2)
Others	34.4%		

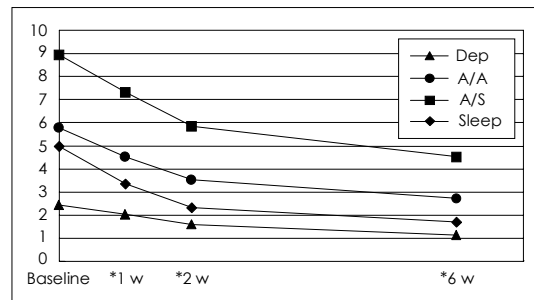


**Figure 1.** Change of efficacy variables for 6 weeks of treatment with mirtazapine (N=503). HAMD : Total score of 17-item Hamilton Rating Scale for Depression, CGI : Total score of Clinical Global Impression. \* : Repeated measure ANOVA, Bonferroni test, p<0.01.

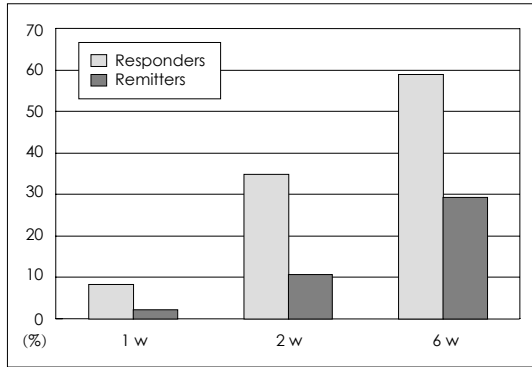
tazapine 6 17 - item HAM -  
 D, CGI (p<0.01) . 17 -  
 item HAM - D 26.1  
 6 10.9, HAM - D 1 ( )  
 ) 2.4 6 1.1, CGI  
 4.5 6 3.0  
 (p<0.01) .  
 1 , 가  
 17 - item HAM - D, CGI  
 ( 1). 17 - item HAM - D  
 mirtazapine 6  
 / 5.8 2.7, /  
 9.0 4.5, 5.0  
 1.7 (p<0.01) . 17 - item  
 HAM - D 1  
 ( 2).  
 17 - item HAM - D 가 50%  
 (responders) 1  
 42 (8.3%), 2 175 (34.8%), 6  
 297 (59.0%) . , 17 - item HAM - D  
 가 7 (remitters) 1  
 11 (2.2%), 2 54 (10.7%), 6 147  
 (29.2%) ( 3).

**4. Benzodiazepine 군과 비 Benzodiazepine 군 간의 비교**

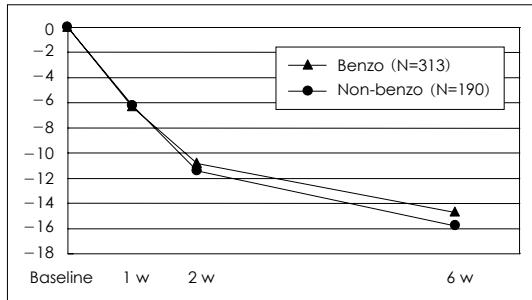
benzodiazepine 313



**Figure 2.** Change of each factors of 17-item Hamilton Rating Scale for Depression for 6 weeks of treatment with mirtazapine (N=503). Dep : Depressed mood item, A/A : Anxiety/agitation factor, A/S : Anxiety/somatization factor, Sleep : Sleep disturbance factor. \* : Repeated measure ANOVA, Bonferroni test, p<0.01.



**Figure 3.** Responders and remitters on 17-item HAM-D during 6 weeks of treatment with mirtazapine (N=503).



**Figure 4.** Interval changes on the 17-item HAM-D scores between the groups with and without benzodiazepines (N=503).

190  
benzodia-  
zepine  
46.5  
43.3 가  
1, 2, 6 17-  
item HAM-D  
가, 6 CGI  
가 (4, 3).  
17-item HAM-D / (anxiety/agi-  
tation factor), / (anxiety/somatization  
factor)  
(sleep disturbance factor)  
6  
가 (3),  
가 .

**Table 3.** Changes from baseline of efficacy variables at endpoint : estimated Treatment Differences (ITT group, LOCF analysis)

Efficacy variable	Estimated treatment differences*	95% CI	p value
17-HAM-D	1.05	-0.23 to 2.33	.108
Anxiety/Agitation factor	0.15	-0.22 to 0.52	.427
Anxiety/Somatization factor	0.14	-0.39 to 0.67	.598
Sleep disturbance factor	-0.06	-0.37 to 0.24	.681
CGI	-0.13	-0.38 to 0.11	.276

\* : Estimated Treatment Differences (Benzodiazepine-Non-benzodiazepine)  
ITT : Intent to treat, LOCF : Last Observation Carried Forward, CI : Confidence Interval, 17-HAM-D : 17-item Hamilton Rating Scale for Depression, CGI : Clinical Global Impressions

**Table 4.** Adverse events in benzodiazepine group and non-benzodiazepine group

Adverse events	Benzodiazepine group (N=313)	Non-benzodiazepine group (N=190)	Total (N=503)
Total	32.3%	28.9%	31.0%
Drowsiness	10.9%	10.0%	10.5%
Dizziness	4.8%	8.4%	6.2%
Somnolence	5.8%	4.7%	5.4%
Asthenia	2.9%	3.7%	3.2%
Weight gain	3.8%	1.1%	2.8%

5. 이상반응

6 503 156  
(31%) 가 adverse events  
, 가 53  
(10.5%) 가  
6.2%, 5.4%, 3.2%, 가  
2.8% . benzodiazepine  
가 (4).

고 찰

mirtazapine

1 . mirtazapine 가

(feedback mechanism) SSRI

가 ,<sup>20)</sup> benzodiazepine , mirtazapine

mirtazapine , benzodiazepine

12 - 15) . ben-

mirtazapine 503 zodiazepine

62% .

benzodiazepine . ben- post - marketing surveillance(PMS)

zodiazepine . ,

SSRI benzo- 가 mirtazapine ,

diazepine 가 가 mirtazapine

가 . (p= ,

0.052) 17 - item HAM - D / ,

가 benzodiazepine 5.89 925 18 65

5.56 17 - item

benzodia- HAM - D 가 18

zepine . ben- benzodiazepine

zodiazepine 43%, 18%

503

17 - item HAM - D / . PMS

1 , 2 6 가

가 . 17 - item HAM - D

가 . , mirtazapine

benzodiazepine 가 , benzodiazepine

,

mirtazapine . Nutt<sup>21)</sup> 가 , 17 - item HAM -

zapine 5 - HT<sub>2A</sub> 5 - HT<sub>2C</sub> mirta- D / 가 가

H<sub>1</sub> . PMS

,<sup>16,17)</sup> ,

가

가 mirtazapine , mirtazapine

benzodiazepine

가

가 mirtazapine 가 .

Mirtazapine Benzodiazepine

요약

목적 : mirtazapine benzodiazepine 가

방법 : 1999 9 2000 12 Remeron (mirtazapine) post - marketing surveillance 33 925 503

18 65 mirtazapine 1 15 mg 30 mg

, benzodiazepine 1, 2, 6 가 가 17 - item HAM - D , CGI 6 가 가 adverse experience 가

결과 : 45 , 61.6% 가 503 391 (77.3%) 6 가 . 313 (62.2%) benzodiazepine benzodiazepine alprazolam 37.0%, lorazepam 12.5%, clonazepam 9.1% diazepam 7.0% . HAM - D 26.1 6 10.9, CGI 4.5 6 3.0 1

HAM - D, CGI benzodiazepine 1 , 2 , 6 HAM - D 가 , 6 CGI 가 HAM - D / , 6 가

가 benzodiazepine

가

결론 : mirtazapine benzodiazepine

중심 단어 : Mirtazapine Benzodiazepine.

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