



## Efficacy and safety of mirtazapine in university students with depression: a comparison with elderly patients

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### ABSTRACT

When clinicians are concerned about an increased risk of suicidality induced by antidepressants in young patients, mirtazapine is considered a suitable option because of its low risk of provoking suicidality and its sedative effect. However, mirtazapine often needs to be discontinued or the dose reduced because of drowsiness, especially in young persons. This study retrospectively compared the clinical effects of mirtazapine in 16 young university students to those in 16 elderly patients with depression. Drowsiness was the most frequent side effect, and was observed more often in the students. Greater numbers of students also had their doses reduced or stopped using mirtazapine specifically because of oversedation. Furthermore, the final dose of mirtazapine was much lower in the student group even though the therapeutic effects were similar to those in the elderly group, suggesting that lower doses of mirtazapine should be administered to young depressed patients as starting or maintenance doses to avoid sedation and achieve a minimal level of therapeutic efficacy.

**Keywords:** *mirtazapine, young patients, drowsiness, suicidality, histamine receptor*

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### INTRODUCTION

Nearly 17,000 students are enrolled at the University of Tsukuba. Approximately 30% of students visiting the Mental Health Service at the Tsukuba University Health Center do so because of mood disorders, mostly involving depression.

In general, there are concerns about suicidal ideation and behaviors in young patients during antidepressant therapy [1, 2]. A review by the United States Food and Drug Administration (FDA) revealed that use of antidepressants in pediatric patients is likely associated

with an increased risk of suicidality [3]. Furthermore, even in adult patients, the risk of suicidality was increased among individuals under 25 years old [4]. It is therefore imperative to select an antidepressant that does not provoke suicidality for use in young patients. According to a 2005 National Institute for Health and Clinical Excellence guidance, significant increases in suicidality were not observed in a systematic review of mirtazapine treatment among young people compared to placebo. Furthermore, according to an assessment of the relative risk for suicidality of pharmacological treatments for depression that was

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performed by the FDA, mirtazapine was ranked low on the list, next to fluoxetine and citalopram [3]. Mirtazapine has also exhibited a lower suicide risk profile than placebo in short-term placebo-controlled studies in patients with major depressive disorder [5]. Mirtazapine can therefore be a useful option for treating depression even in younger patients.

Mirtazapine acts as an antagonist of the histamine H<sub>1</sub> receptor, causing sedation [6]. This pharmacological action may improve agitation, but can also produce adverse events such as drowsiness and weight gain. In the normal clinical setting, mirtazapine often needs to be discontinued in young patients because of drowsiness, whereas in elderly patients such effects are frequently viewed as being favorable anxiolytic and hypnotic effects. According to the package insert for mirtazapine in the United States [7], the most common side effects of mirtazapine include somnolence (approximately 50%), weight gain (approximately 10%), and dizziness (approximately 10%), with the high incidence of somnolence being notable. This finding is comparable to that of a double-blind, placebo-controlled study conducted in 280 Japanese patients [8]. Although various studies have reported that mirtazapine treatment is safe and effective in elderly patients [9, 10, 11], few studies have examined its clinical effects in young patients [12]. Furthermore, no comparative studies for mirtazapine treatment have been yet conducted between young and elderly patients. In the present study, therefore, we examined whether young patients are more likely to experience oversedation and treatment discontinuation in mirtazapine therapy than elderly patients.

## SUBJECTS AND METHODS

We investigated 16 university student patients with depression who were treated with mirtazapine in the Mental Health Service at Tsukuba University Health Center during the period between April 2011 and June 2013 (the student group). The control group consisted of 16 elderly patients treated with mirtazapine in the Department of Psychosomatic Medicine at Tsukuba Gakuen Hospital who were randomly selected during the same period (the elderly group). These patients were selected from patients treated at a different institution, because the University Health Center only treats young patients. All patients met the International Classification of Diseases-10 criteria for a depressive episode. Furthermore, all participants were Japanese and were evaluated based on the same criteria by the same co-author responsible for diagnosis and

treatment.

The student group consisted of 5 men and 11 women (mean age, 22.6 years), and the elderly group consisted of 3 men and 13 women (mean age, 61 years). Although female patients outnumbered male patients in both groups, no significant gender differences between groups were evident. Physical comorbidities were not found in any patients in the student group, but the following physical comorbidities were found in the elderly group: liver dysfunction (1 case), diabetes mellitus (1 case), and rheumatoid arthritis (2 cases). The disposition of concomitant medications in the student group was: selective serotonin reuptake inhibitors (SSRIs) in 4 cases, serotonin and norepinephrine reuptake inhibitors (SNRIs) in 2 cases, and benzodiazepine hypnotics in 5 cases. The disposition of concomitant medications in the elderly group was: SSRIs in 5 cases, and benzodiazepine hypnotics in 10 cases. The dosage of each concomitant medication was fixed during the observation period.

All patients were started at 15 mg/day of mirtazapine at bedtime. The clinical course was assessed at 1 or 2 week-intervals. The dose was halved if the side effects were too severe, and was increased if the therapeutic effect was insufficient. Information about all patients was collected retrospectively from medical records. Decisions on dose reduction or discontinuation of mirtazapine were made by the psychiatrist based on response and tolerance to the drug. Evaluations of Clinical Global Impressions-Global Improvement (CGI-GI) and side effects, and the selection of the final dose of mirtazapine, were performed 8-10 weeks after treatment initiation.

Statistical analyses were performed using Statistical Package for Social Sciences version 19 software (SPSS Japan, Tokyo, Japan). Differences in the mean values were compared using the t-test, and the chi-squared test was used for categorical variables. Each type of analysis was tested at a two-sided significance level of 0.05. Patients who discontinued treatment were treated as showing no change in the CGI-GI and as having received a final dose of 0 mg.

The present study was approved by the ethics committees of the Faculty of Medicine at the University of Tsukuba (No. 785) and Tsukuba Gakuen Hospital (No. 13-4).

## RESULTS

The overall results are summarized in Table 1. Mirtazapine was effective against depression in both groups. Improvement as evidenced by the CGI-GI

was moderate, and did not differ significantly between the student and elderly groups.

Meanwhile, a greater number of patients in the student group (56.3%) needed to have their mirtazapine doses reduced than in the elderly group (12.5%), and mirtazapine treatment discontinuation was more frequently observed in the student group (43.8%) than in the elderly group (12.5%). The final dose of mirtazapine was much lower in the student group ( $8.4 \pm 9.0$  mg/day) than in the elderly group ( $17.8 \pm 11.3$

mg/day). Mirtazapine dose reduction and treatment discontinuation were attributable to drowsiness in all cases.

Drowsiness was the most frequent side effect in both groups, seen in 14 students (87.5%) and 8 elderly patients (50%), which indicated that there was a significant difference in the frequency between the two groups. None of the patients in either group had complained of drowsiness prior to drug treatment.

**Table 1. Results of treatment with mirtazapine**

	Student group (n=16)	Elderly group (n=16)	P*
Number of side effects (%)			
Drowsiness	14 (87.5)	8 (50)	< .05
Weight gain	3 (18.8)	1 (6.3)	.29
Dizziness	2 (12.5)	1 (6.3)	.54
Numbness	1 (6.3)	0	.14
Dry mouth	1 (6.3)	0	.31
Constipation	0	1 (6.3)	.31
Improvement (CGI-GI)	2.1±1.2	2.8±1.0	.08
Dose reduction, n (%)	9 (56.3)	2 (12.5)	< .01
Discontinuation, n (%)	7 (43.8)	2 (12.5)	< .05
Final dosage (mg/day)	8.4±9.0	17.8±11.3	< .05

CGI-GI: Clinical Global Impression-Global Improvement

\*P values for comparisons between student and elderly groups were calculated using t or chi-squared tests.

## DISCUSSION

Mirtazapine was effective at reducing depressive symptoms for both groups, consistent with previous studies [9, 10, 11, 12]. However, tolerability to mirtazapine was much lower in the student group than in the elderly group. Mirtazapine dose reduction and treatment discontinuation resulting from drowsiness were more frequent in the student group. Even though young patients received benzodiazepines as concomitant medication less often, they experienced drowsiness more frequently than elderly patients. Drowsiness thus seems likely to have been mainly induced by mirtazapine in young patients.

We did not investigate plasma levels of mirtazapine in this study. In general, elderly patients show higher plasma levels of drugs than young patients due to decreased metabolic capacity, and are thus assumed to more easily suffer from side effects than young patients. In fact, it has been pointed out that the area under the blood concentration-time curve for mirtazapine is higher in elderly patients than in young patients [13]. This may be explained by a reduction in hepatic clearance due to aging. The elimination half-life of mirtazapine is also prolonged by hepatic

impairment and renal failure [14]. In this study, hepatic dysfunction was only identified in 1 patient in the elderly group, and none of the elderly patients had renal dysfunction. Taking all this information together, oversedation in mirtazapine treatment appears less attributable to aging or physiological effects.

Mirtazapine is thought to induce drowsiness through histamine H<sub>1</sub> receptor antagonism in the brain. According to Yanai *et al.* [15], H<sub>1</sub> receptors decrease in number by 13% every decade in the frontal, parietal, and temporal lobes of the cerebral cortex in the human brain. H<sub>1</sub> receptor levels are thus higher in the brains of young individuals than in the elderly, suggesting that the influence of H<sub>1</sub> antagonism would be stronger in young individuals. This higher sensitivity to H<sub>1</sub> antagonism by mirtazapine treatment may be one reason why mirtazapine-induced drowsiness was more frequent in young individuals.

In the present study, the mean final dose of mirtazapine was much lower in the student group than in the elderly group. This suggests that the risk of dropout from mirtazapine treatment can be avoided without sacrificing efficacy by starting the drug at a lower dose of 7.5 mg/day (0.5 tablets/day).

A key limitation of this study was the small sample

size and retrospective nature of the investigation. Data were not consecutively collected, and standard scales for comprehensively assessing both therapeutic efficacy and side effects were not used. The reliability of the study thus may not necessarily be sufficient due to possible defects in data, biased sample collection and overly general assessments. Furthermore, ethnicity needs to be included as a factor, and it is also possible that potential bipolarity in younger patients may have been associated with hypersensitivity to antidepressants, although none displayed a change to a manic state.

### CONCLUSION

Suicidality is a major concern when antidepressants are used to treat depression in young patients. Although mirtazapine is suitable for young patients because of its lower risk of increased suicidality, drowsiness occurs more frequently in young individuals than in the elderly. However, this side effect may be avoidable by initiating and maintaining mirtazapine treatment at a low dose.

### CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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