Efficacy, tolerability, and preference of mirtazapine orally disintegrating tablets in depressed patients: a 17-week naturalistic study in Lithuania

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Key words: *mirtazapine orally disintegrating tablet; depression; naturalistic study; efficacy; tolerability.*

Summary. *Mirtazapine is an established antidepressant with well-documented efficacy demonstrated in controlled clinical trials. However, the gap between the results obtained in controlled clinical trials and everyday clinical practice exists. Therefore, the importance of naturalistic studies in psychiatry is becoming recognized. The aim of present naturalistic study was to acquire data on efficacy, safety, and preference of mirtazapine orally disintegrating tablets during a 17-week treatment of depression. This prospective, open-label, multicenter study in patients with mild to severe depression was conducted at 47 mental health centers of Lithuania by 78 psychiatrists. Patients were initially given 15 mg or 30 mg of mirtazapine orally disintegrating tablets; the maximum allowed dose was 45 mg per day. The primary efficacy measure was the total score on the Hamilton Depression Rating Scale-17 (HAMD-17), the Clinical Global Impression-Severity (CGI-S), and Clinical Global Impression-Improvement (CGI-I) scales. Tolerability was primarily measured by assessing the incidence of treatment-emergent adverse events. Patients were evaluated at baseline, at weeks 1, 5, 9, 13, and 17. A total of 779 patients (595 women [76.4%] with a mean [SD] age of 50.2 [13.65] and 184 men [23.6%] with a mean [SD] age of 52.4 [14.6] years) were enrolled into the study; 687 (88.2%) patients completed the study. The mean (SD) daily dose of mirtazapine orally disintegrating tablets was 29.0 (3.8) mg. The mean total (SD) HAMD-17 score improved significantly from 25.7 (4.6) to 7.3 (4.3) (P<0.005). At each visit, the mean HAMD-17 score was significantly lower than that at the preceding visit. At week 17, remission (HAMD-17 score < or =7) was observed in 436 (56%) patients. The mean (SD) CGI-S score improved significantly from 4.9 (1.0) at baseline to 1.5 (0.6) at endpoint (P<0.001). According to the CGI-I assessments, 621 patients (89.4%) improved and improved very much. The vast majority of patients (80%) preferred the new formulation of mirtazapine – mirtazapine orally disintegrating tablet. Treatment-emergent adverse events occurred in 106 patients (13.6%). The most frequent adverse events were weight gain, sedation, dizziness, and dry mouth. In this study conducted in Lithuania with depressed patients, a significant improvement was shown in all efficacy measures. In addition, mirtazapine orally disintegrating tablet was a well-tolerated and preferable formulation for the treatment of depressed patients.*

Introduction

Depression is one of the most common psychiatric disorders. The analysis of epidemiological data of 27 studies revealed that 6.9% of the adult European Union population had been suffering from depression during the past 12 months (1). These data are almost identical to other recent epidemiological studies from the United States, namely the National Comorbidity Survey with a 12-month depression rate of 8.6% and the National Comorbidity Survey Replication study with a 6.6% prevalence rate of depression for 12 months (2, 3). The World Health Organization (WHO) reported that depression was the fourth leading cause of health-related disability in 1990. It is estimated that in 2020 depression would become the second leading cause of disability worldwide after the first one – heart disease (4). It is generally accepted that depressive disorders also influence the outcome of comorbid

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medical illnesses such as cardiac disease, cancer, diabetes, and other chronic illnesses (5–8). It is widely recognized that depression is often underdiagnosed and undertreated. It is well known that depressed patients need long-term treatment and good compliance. New formulations of antidepressants are developed with the aim to increase the convenience and the compliance of patients with the treatment.

Mirtazapine orally disintegrating tablet (ODT) was developed for convenience of depressed patients. Mirtazapine is an established antidepressant with well-documented efficacy demonstrated in controlled clinical trials (9). However, the gap between the results obtained in controlled clinical trials and everyday clinical practice is well recognized. Therefore, the importance of naturalistic studies in psychiatry is becoming recognized. Until now, the results of limited number of the naturalistic studies with mirtazapine ODT have been published. These studies were done under naturalistic conditions with observation duration of 6 to 12 weeks (10–12). However, depression is a condition requiring long-term treatment, and more prolonged observation of depressed patients is important. Thus, the objective of this naturalistic study was to acquire data on efficacy, safety, and preference of mirtazapine ODT during the 17-week treatment of depression. We also evaluated the effects of mirtazapine ODT on depressed mood, suicidal ideation, insomnia, and anxiety clusters (i.e. features of depression increasing risk of suicide) after one week.

Material and methods

Study design

This was a prospective, open-label, multicenter, 17-week duration study in patients with mild to severe depression. The study was conducted in Lithuania under naturalistic conditions at the primary health care level in mental health centers (MHCs). In Lithuania, MHC is a specialized mental health institution providing mental health care for outpatients. The team of MHC specialists includes psychiatrists, nurses, psychologists, and social workers. The study was approved by the Lithuanian Bioethics Committee and State Medicines Control Agency. Seventy-eight psychiatrists from 47 MHCs participated in this study. Before study initiation, the investigators were informed about study objectives, procedures, and they were trained to use the Hamilton Depression Rating Scale-17 (HAMD-17), the Clinical Global Impression-Severity (CGI-S), and Clinical Global Impression-Improvement (CGI-I) scales. Patients with depressive disorders who visited the MHC on their own or were referred to MHC by other physicians (general practitioners, neurologists, etc.) were suggested to take part in the study. The diagnosis of depression was made by psychiatrists according to the ICD-10 (13). The following clinical features of depression were evaluated during the study: severity (mild, moderate, and severe), recurrence and duration of the current depressive episode. Inclusion criterion was a physician's diagnosis of depression of sufficient severity to start pharmacological treatment with an antidepressant. Eligible patients had to be older than 18 years. Pregnant or breast-feeding women, depressed patients with nonstabilized somatic disease, history of blood dyscrasias, known allergic reaction to mirtazapine, current severe suicidal risk were not included. Patients were not included if they had alcohol/substance abuse or epilepsy or if they had a history of seizure disorder. Patients with a new depressive episode were offered treatment with mirtazapine ODT. Patients who had already been treated with another antidepressant were offered to switch to mirtazapine ODT, if prior treatment was considered not effective.

Data collection

Patients were evaluated at baseline, at weeks 1, 5, 9, 13, and 17. Data were collected using the case report forms (CRFs). At baseline, the following data were recorded: gender, age, duration of the current episode, the number and severity of depressive episodes. The severity of depression was assessed using the Hamilton Depression Rating Scale-17 (HAMD-17) and the Clinical Global Impression-Severity (CGI-severity) scale. At weeks 1, 5, 9, 13, and 17, patients were reassessed using clinical psychiatric evaluation and the HAMD-17. In addition, at week 17, patients were assessed using the CGI-Severity and CGI-Improvement scales. Clinical psychiatric and psychometric evaluations were performed by psychiatrists.

Data on treatment dosage, concomitant medication, adverse events, and tolerability were recorded into CRFs. Date and reasons for premature termination of the study were documented. Patients were asked about their preference to mirtazapine ODT once during the study.

Treatment

Treatment with mirtazapine ODT was started with a dose of 15 mg or 30 mg at bedtime; after 1 week, the dose of mirtazapine ODT could be increased to 30 mg per day. After 5 weeks, the dose of mirtazapine ODT could be increased to 45 mg per day according to the clinical response and the judgment of the treating physician.

Concomitant psychotropic medications were al-

lowed during this study at the discretion of psychiatrist. However, study patients could not take other antidepressants (tricyclic antidepressants, TCAs; selective serotonin reuptake inhibitors, SSRIs; serotonin and norepinephrine reuptake inhibitors, SNRIs; etc.) If there was a need, previous somatic treatments were continued with dosages adapted if necessary.

Statistical analysis

Improvement was defined as the reduction in the total HAMD-17 score by 20–50%. Response was defined as the reduction in the HAMD-17 score by ≥50%. Remission was defined as the reduction in the HAMD-17 score to 7 or less at any visit after baseline. Stable remission was defined as the reduction in the HAMD-17 score to 7 or less at two consecutive visits covering a time period of 4 weeks.

The data analysis was carried out on an intention-to-treat (ITT) basis using observed-cases method in order to include all study patients with all available information. To be included in analyses of change from baseline to endpoint, the patient must have had both a baseline score and at least one postbaseline score. Analyses of the total HAMD-17 scores, the HAMD-17 items of depressed mood and suicide ideation, clusters of anxiety and insomnia, also on improvement, remission, and stable remission were carried out. The missing data were compensated where necessary through the last observation carried forward procedure. Changes between the total HAMD-17 score, clusters, and items during different visits were analyzed using the Wilcoxon signed-rank test (two-sided). The significance level was set at 0.05. Data were expressed as means ± standard deviations (SD). Statistical analysis was performed using the SAS software (version 9.1).

Results

Characteristics of patients at baseline

A total of 779 patients with depressive disorders were included into the study (Table 1). There were 595 (76.4%) women and 184 (23.6%) men among the patients enrolled. The mean age of the study population was 51.9 years (SD 14.4). To participate in this study, all patients provided written informed consent after the study was described in detail. Six hundred eighty-seven (88.2%) patients completed the study. Eighty-five patients (11%) discontinued study participation: 2 (0.3%), 14 (1.8%), 43 (5.5%), 70 (9.0%), and 85 (10.9%) patients discontinued at visits 2, 3, 4, 5, and 6, respectively. The reasons of withdrawals were as follows: adverse events (n=34, 4.4%), refusal by patient (n=18, 2.3%), worsening of the depression (n=1, 0.1%), lack of efficacy (n=9, 1.2%), and other reasons (n=24, 3.1%).

Three hundred sixty patients (46.2%) experienced their first depressive episode, and the remaining 419 patients (53.8%) experienced a recurrent episode of depression. The mean duration of the current episode of depression was 2.9 months (SD 3.3). The mean duration of the depressive illness with repeated episodes was 3.4 years (SD 3.2). Depression was mild in 36 patients (4.6%), moderate in 306 patients (39.3%), and severe in 437 patients (56.1%). At baseline, the mean total HAMD-17 score was 25.7 (SD 4.6) (Table 2). The mean score of the HAMD-17 on depressed mood was 3.0 (SD 0.8); on suicide ideation, 1.1 (SD 0.9); on the sleep cluster (4, 5, 6 items of the HAMD-17), 5.0 (SD 1.2); on the anxiety cluster (9, 10, 11 items of the HAMD-17), 5.4 (SD 1.7). The mean score of CGI-Severity scale was 4.9 (SD 1.0).

Table 1. **Summary demographic data and patient disposition**

Characteristic	Number	%
Enrolled patients	779	100
Completed patients	687	88.2
Gender:		
women	595	76.4
men	184	23.6
Mean age (years):		
women (SD)	50.2 (13.65)	–
men (SD)	52.4 (14.6)	–
Discontinued (total):	85	10.9
side effects	34	4.4
refusal by patient	18	2.3
lack of effect	1	0.1
other reasons	24	3.1

SD – standard deviation.

Table 2. **Changes in the mean HAMD-17 score at baseline, weeks 1, 5, 9, 13, and 17**

Evaluation	Mean HAMD-17 score (SD)
Baseline	25.7 (4.6)
Week 1	22.2 (5.2)
Week 5	16.3 (5.8)
Week 9	12.1 (5.4)
Week 13	9.1 (4.9)
Week 17	7.3 (4.3)

SD – standard deviation;
HAMD – Hamilton Depression Rating Scale-17.

Changes after 1 week of treatment

After the first week of treatment with mirtazapine ODT, clinically significant changes in HAMD-17 scores, including depressed mood and suicidal ideation items, sleep and anxiety clusters, were observed (Table 2).

Evaluation of total HAMD-17 scores at consecutive visits

The mean total HAMD-17 score consistently decreased from 25.7 (SD 4.6) at baseline to 7.3 (SD 4.3) at the endpoint ($P<0.05$). At each visit, the mean HAMD-17 score was significantly lower than that at the preceding visit (Table 2).

Response and remission

At week 17, remission (the decrease in HAMD-17 scores to < or =7) was observed in 436 patients (56%). Stable remission lasting at least 4 weeks was observed in 371 (41.6%) depressed patients treated with mirtazapine ODT. At study endpoint, the mean score of the CGI-Severity scale was 1.5 (SD 0.6). The mean CGI-Severity score improved significantly from 4.9 (SD 1.0) at baseline ($P<0.001$). As evaluated by the CGI-Severity scale, 413 (59.4%) patients were without disorder, 247 (35.5%) patients had borderline disorder, 28 (4.0%) patients were mildly ill, and 7 (1%) patients had moderate depressive disorder. According to CGI-Improvement assessments, 621 patients (89.4%) improved and improved very much.

No differences in the rates of remission and stable remission were observed between age groups. The efficacy of treatment was similar in patients with depression of different severity. At the end of the study, there were 671 responders (86.1%) and 436 remitters (56%).

Comedication

Data were recorded only for psychotropic concomitant medication. In total, 437 patients (56.1%) were treated with comedication. The main reason for concomitant medication was the presence of anxiety. Benzodiazepines were recommended for 318 patients (40.8%). For augmentation of antidepressant action of mirtazapine ODT, 94 patients (12.1%) were recommended to take antipsychotics at minimal doses (risperidone, 0.5 mg/day; Olanzapine, 0.25–0.5 mg/day; or chlorprothixene, 25 mg/day).

Preference of mirtazapine ODT

The vast majority of patients (80%) preferred the new formulation of mirtazapine ODT. The principal reasons given by patients for the preference of mirtazapine ODT were as follows: easy opening (n=520, 66.8%), choice of tablet (n=604, 77.5%), taste (n=687, 88.2%), texture (n=537, 68.9%), and ease of use (n=644, 82.7%).

Safety

The mean dose of mirtazapine ODT was 29.0 (SD 3.8) mg/day. The majority of the patients (n=701, 90.0%) received a dose of 30 mg per day. Mirtazapine ODT was well tolerated. Only small number of patients (4.4%) discontinued the study due to adverse events. In total, 106 patients (13.6%) experienced 130 treatment-emergent adverse events. The most frequent adverse events were weight gain, sedation, dizziness, and dry mouth (Table 3). All other adverse events occurred at low frequency and were mostly of mild and moderate intensity.

Table 3. **Most frequently reported treatment-emergent adverse events**

Adverse event	Number	Incidence (%)
Weight gain	39	5.0
Sedation	31	4.0
Dizziness	14	1.8
Dry mouth	7	0.9

Discussion

The results of controlled clinical trials are complemented by naturalistic observations in various countries. Although naturalistic studies lack of double-blind controlled treatment condition, they offer the advantage of including a broader range of patients and yielding results, which represent better usual everyday clinical practice in mental health care. Such naturalistic studies are especially important for clarifying the efficacy and tolerability profiles associated with medications because double-blind clinical trials usually exclude patients with comorbid disorders. Naturalistic observations provide an opportunity to collect data on patients who are treated with combinations of psychotropic medications. Despite benzodiazepines do not have direct action on depression, their anxiolytic and/or hypnotic action helps to bridge the time lag until the onset of antidepressant action. Relatively rapid onset of action of mirtazapine ODT reduces this time lag and makes the use of benzodiazepines necessary only in rare cases. Although 40% of the patients in our study got benzodiazepines, we have not compared the patients receiving and not receiving benzodiazepines, because we considered the role of benzodiazepines to be negligible in the treat-

ment of depression. It has been reported that comedication with antianxiety agents does not improve the antidepressant response (14).

The results of our observational study, conducted under naturalistic conditions, have shown that patients with depressive disorders treated with mirtazapine ODT experienced a significant improvement in depressed mood, suicidal ideation, insomnia, and anxiety clusters already after the first week of treatment, as assessed by the HAMD-17 scale. The consistent decrease in the total HAMD-17 score through the entire study period (17 weeks) indicated the effectiveness of prolonged treatment with mirtazapine ODT. Remission achieved under the treatment with mirtazapine ODT was stable in the majority of study patients. Mild, moderate, and severe depression was successfully treated with mirtazapine ODT. Majority of the patients preferred the new formulation of mirtazapine ODT.

A rapid onset of action of antidepressant medication is of high importance. Presence of early improvement on the HAMD-17 is significant with active study medication treatment but not with placebo (15). In our study, we have observed significant changes in mood, suicidal ideation items, anxiety and insomnia clusters during the first week of treatment with mirtazapine ODT. Rapid reduction of suicidal thoughts and anxiety is in line with data of other naturalistic studies and previous clinical studies, showing that mirtazapine has a faster onset of action compared to paroxetine, sertraline, or venlafaxine extended-release tablets (16–19). Referring to the Lithuanian situation with a very high number of suicides, it is important to have rapid acting antidepressants like mirtazapine ODT (20). The relationship between suicide rate and mirtazapine treatment is not convincingly outlined. However, it is well known that suicidal patients need medication with fast onset of action on depression, anxiety, and insomnia. Therefore, an indirect relationship between the use of mirtazapine and suicide rate cannot be excluded.

Therapeutic experience over the past decade has proved that remission is the optimal outcome of depression (21). In the treatment of depression, the main goal is to achieve stable remission. Many patients treated with antidepressants show a response but do not achieve remission. A lack of complete remission can be detrimental to a patient's well-being. This naturalistic study was oriented to achieve remission as recommended in various publications (22, 23). Although all registered antidepressants have shown effectiveness, remission was only achieved in one-third of the patients within 8 weeks of therapy (21). In our study, remission was achieved by 21.2% of patients at week 9. Moreover, remission was achieved by 56.0% of patients at week 17. Stable remission with duration of at least 4 weeks was observed in 41.59% of the study population. These results confirm that the treatment of depression should be of adequate duration.

Mirtazapine ODT was effective in the treatment of depression of different severity. Severe depression was experienced by more than 50% of the patients. However, the average dose of mirtazapine ODT was only 29.0 mg/day. This looks like that some depressions were undertreated, and it is in line with data of other authors (24). The undertreatment of depression is a common problem sometimes leading to the impression of treatment resistance. Treatment with mirtazapine ODT was an effective, well-tolerated treatment with a patients' preference for the new formulation. These data correspond with the results of other naturalistic studies with mirtazapine (10–12).

Conclusion

In this naturalistic, open-label study in patients with depression in Lithuania, treatment with mirtazapine orally disintegrating tablet was an effective therapy for depressions of different severity and has a good safety profile. Improvement of depressed mood, suicidal ideation, anxiety, and sleep had been already observed after the first week of treatment. Mirtazapine orally disintegrating tablet was well tolerated in these patients. In addition, mirtazapine orally disintegrating tablet is a preferable formulation for the treatment of depressed patients.

Burnoje disperguojamojo mirtazapino veiksmingumas gydant depresiją, jo toleravimas ir pirmumo teikimas (septyniolikos savaičių natūralistinis tyrimas Lietuvoje)

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Raktažodžiai: mirtazapinas, veiksmingumas, toleravimas, depresija, natūralistinis tyrimas.

Santrauka. Mirtazapinas – tai antidepresantas, kurio veiksmingumas nustatytas ir dokumentuotas kontroliuojamųjų klinikinių tyrimų metu. Nepaisant to, klinikinių tyrimų metu gautus rezultatus ne visada galima pritaikyti klinikiniame darbe. Todėl pripažįstama natūraliomis sąlygomis atliktų tyrimų svarba. Šio tyrimo tikslas – 17 savaičių rinkti mirtazapino burnoje disperguojamųjų tablečių, vartojamų depresijai gydyti, veiksmingumo, saugumo ir farmacinės formos parinkimo duomenis. Tai prospektyvusis, daugiacentris tyrimas su depresija (nuo lengvos iki sunkios formos) sergančiais ligoniais, atliktas 47 Lietuvos psichikos sveikatos centruose, kuriame dalyvavo 78 psichiatrai. Ligoniams buvo skirta 15–30 mg burnoje disperguojamo mirtazapino, didžiausia leistina dozė – 45 mg per parą. Pagrindiniai veiksmingumo kriterijai buvo bendras Hamiltono depresijos vertinimo skalės-17 (HAMD-17) balai, Bendrojo klinikinio įspūdžio (sunkumo) (CGI-S) ir Bendrojo klinikinio įspūdžio (pagerėjimo) (CGI-I) balai. Ar vaistas buvo gerai toleruojamas, vertinta pagal vaistų sukeltų nepageidaujamų reiškinių skaičių. Ligoniai vertinti tyrimo pradžioje ir 1, 5, 9, 13, 17 savaitę. Tyrime dalyvavo 779 ligoniai (595 moterys (76.4 proc.), kurių vidutinis amžius (standartinis nuokrypis) buvo 50,2 metų (13,65) ir 184 vyrai (23,6 proc.), kurių vidutinis amžius (standartinis nuokrypis) – 52,4 metų (14,6) metai). 687 (88,2 proc.) ligoniai baigė tyrimą. Vidutinė (standartinis nuokrypis) burnoje disperguojamojo mirtazapino dienos dozė buvo 29,0 (3,8) mg. Pagal bendrąjį vidutinį HAMD-17 balą (standartinis nuokrypis) būklė pagerėjo nuo 25,7 (4,6) tyrimo pradžioje iki 7,3 (4,3) tyrimo pabaigoje ($p<0,005$). Kiekvieno vizito metu HAMD-17 vidutinis balas buvo reikšmingai mažesnis nei ankstesnio vizito metu. 17-ąją savaitę remisija (HAMD-17 balas ≤7) pasireiškė 436 (56 proc.) ligoniams. Vidutinis (standartinis nuokrypis) CGI-S skalės balų pokytis rodė reikšmingą būklės pagerėjimą (nuo 4,9 (1,0) balo tyrimo pradžioje iki 1,5 (0,6) pabaigoje ($p<0,001$). Remiantis vertinimu pagal CGI-I skalę, 621 ligoniams (89,4 proc.) būklė pagerėjo ir labai pagerėjo. Dauguma ligonių (80 proc.) rinktųsi naująją mirtazapino farmacinę formą – burnoje disperguojamąjį mirtazapiną. 106 ligoniams (13,6 proc.) pasireiškė vaistų sukeltų nepageidaujamų reiškinių. Dažniausias nepageidaujamas reiškinys buvo svorio prieaugis, mieguistumas, galvos svaigimas ir burnos džiūvimas. Šio tyrimo, atlikto Lietuvoje su depresija sergančiais pacientais, duomenimis, nustatytas reikšmingas visų veiksmingumo rodmenų pagerėjimas. Be to, burnoje disperguojamasis mirtazapinas buvo gerai toleruojamos ir šiai farmacinei formai teikiamas pirmumas.

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Received 23 March 2009, accepted 6 October 2009
Straipsnis gautas 2009 03 23, priimtas 2009 10 06