

Characteristics of the treatments for each severity of major depressive disorder: A real-world multi-site study

Hiroyuki Muraoka^a, Fumitoshi Kodaka^b, Naomi Hasegawa^c, Norio Yasui-Furukori^{d,*}, Kentaro Fukumoto^e, Hiroko Kashiwagi^f, Hiromi Tagata^g, Hikaru Hori^h, Kiyokazu Atakeⁱ, Hitoshi Iida^h, Kayo Ichihashi^j, Ryuji Furihata^k, Takashi Tsuboi^l, Masahiro Takeshima^m, Hiroshi Komatsuⁿ, Chika Kubota^o, Shinichiro Ochi^p, Yoshikazu Takaesu^q, Masahide Usami^r, Tatsuya Nagasawa^s, Manabu Makinodan^t, Toshinori Nakamura^u, Mikio Kido^{v,af}, Ikki Ueda^w, Hirotaka Yamagata^x, Toshiaki Onitsuka^y, Takeshi Asami^z, Akitoyo Hishimoto^z, Kazuyoshi Ogasawara^{aa}, Eiichi Katsumoto^{ab}, Kenichiro Miura^c, Junya Matsumoto^c, Kazutaka Ohi^{ac}, Hisashi Yamada^{ad}, Koichiro Watanabe^l, Ken Inada^a, Katsuji Nishimura^a, Ryota Hashimoto^{c,ae}

^a Department of Psychiatry, Tokyo Women's Medical University, Tokyo, Japan

^b Department of Psychiatry, The Jikei University School of Medicine, Tokyo, Japan

^c Department of Pathology of Mental Diseases, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo, Japan

^d Department of Psychiatry, Dokkyo Medical University School of Medicine, Tochigi, Japan

^e Department of Neuropsychiatry, School of Medicine, Iwate Medical University, Iwate, Japan

^f Department of Forensic Psychiatry, National Center Hospital, National Center of Neurology and Psychiatry, Tokyo, Japan

^g Department of Neuropsychiatry, Toho University Graduate School of Medicine, Tokyo, Japan

^h Department of Psychiatry, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

ⁱ Nippon Telegraph and Telephone West Corporation Kyushu Health Administration Center, Fukuoka, Japan

^j Department of Neuropsychiatry, University of Tokyo Hospital, Tokyo, Japan

^k Kyoto University Health Services, Kyoto, Japan

^l Department of Neuropsychiatry, Kyorin University School of Medicine, Mitaka, Japan

^m Department of Neuropsychiatry, Akita University Graduate School of Medicine, Akita, Japan

ⁿ Department of Psychiatry, Tohoku University Hospital, Sendai, Japan

^o National Center of Neurology and Psychiatry Hospital, Tokyo, Japan

^p Department of Neuropsychiatry, Molecules and Function, Graduate School of Medicine, Ehime University, Ehime, Japan

^q Department of Neuropsychiatry, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan

^r Department of Child and Adolescent Psychiatry, Kohnodai Hospital, National Center for Global Health and Medicine, Ichikawa, Chiba, Japan

^s Department of NeuroPsychiatry Kanazawa Medical University, Ishikawa, Japan

^t Department of Psychiatry, Nara Medical University School of Medicine, Nara, Japan

^u Department of Psychiatry, Shinshu University School of Medicine, Nagano, Japan

^v Toyama City Hospital, Toyama, Japan

^w Miyagi Psychiatric Center, Miyagi, Japan

^x Division of Neuropsychiatry, Department of Neuroscience Yamaguchi University School of Medicine, Yamaguchi, Japan

^y Department of Neuroimaging Psychiatry, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan

^z Department of Psychiatry, Yokohama City University Graduate School of Medicine, Yokohama, Japan

^{aa} Center for Postgraduate Clinical Training and Career Development, Nagoya University Hospital, Nagoya, Japan

^{ab} Katsumoto Mental Clinic, Osaka, Japan

^{ac} Department of Psychiatry, Gifu University Graduate School of Medicine, Gifu, Japan

^{ad} Department of Neuropsychiatry, Hyogo College of Medicine, Hyogo, Japan

^{ae} Molecular Research Center for Children's Mental Development, United Graduate School of Child Development, Osaka University, Suita, Japan

^{af} Department of Neuropsychiatry, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences, Toyama, Japan

* Correspondence to: Department of Psychiatry, Dokkyo Medical University, School of Medicine, Mibu, Shimotsuga, Tochigi 321-0293, Japan.

E-mail address: furukori@dokkyomed.ac.jp (N. Yasui-Furukori).

ARTICLE INFO

Keywords:
Depression
Severity
ECT
Guideline
EGUIDE

ABSTRACT

Purpose: In the treatment guidelines for major depressive disorder (MDD), the recommended treatment differs based on the severity. However, the type of treatment provided based on the severity of MDD in real-world clinical practice has not been investigated. In this study, we clarified the actual situation of MDD treatment in clinical practice and compared the treatment based on the severity of MDD.

Methods: We used data from 1484 patients with MDD at discharge from October 2016 to March 2020.

Results: The number of psychotropic prescriptions tended to be lower in those diagnosed with MDD in the severe group compared to in the non-severe group. There were significant differences among the three groups (mild, moderate/severe, and psychotic) in the percentage of patients who were not prescribed antipsychotics ($p = 1.9 \times 10^{-6}$), a combination of antipsychotics and antidepressants ($p = 5.0 \times 10^{-4}$), and the implementation rate of modified electroconvulsive therapy (m-ECT) ($p = 3.4 \times 10^{-9}$). The percentage of patients with a severe diagnosis who underwent m-ECT was higher, which corresponded to the severity.

Conclusion: Our findings showed that the use of psychotropics decreased when the severity of MDD was diagnosed, and the rate of a combination of antipsychotics and antidepressants and the implementation rate of m-ECT increased with the severity. However, this study suggests that there is still an evidence-practice gap in the treatment of MDD in Japan, and guidelines are only partially adhered to in the treatment of depression.

1. Introduction

Major depressive disorder (MDD) is a psychiatric disorder that affects 264 million people worldwide (James and Abate, 2018). Since patients with MDD suffer both social and economic losses, they require appropriate treatment (König et al., 2019). To standardize the treatment of MDD, treatment guidelines have been developed in various countries (National Collaborating Centre for Mental Health, 2010; Kennedy et al., 2016). In Japan, these treatment guidelines were developed in 2012, based on guidelines from other countries (Japanese Society of Mood Disorders, 2018). The Japanese MDD treatment guidelines are particularly unique as they recommend different treatments for mild, moderate/severe, and psychotic depression. The definitions of severity follow the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (American Psychiatry Association, 2015). They are defined as the number of symptoms and functional impairment. Mild depression is defined as generally meeting the diagnostic criteria for a depressive episode with only minor impairment of social functioning, such as employment. Severe depression is defined as having a sufficiently high number of symptoms and significantly impaired social functioning. Moderate depression is defined as a degree between mild and severe depression regarding the number of items and the degree of social function impairment. Depression with psychotic features (psychotic depression) is defined as the presence of delusions and/or hallucinations, regardless of the severity of the depressive episode.

The Japanese MDD treatment guidelines (Japanese Society of Mood Disorders, 2018) recommend environmental adjustment and psychoeducation for the treatment of mild depression. Monotherapy with antidepressants is recommended for patients with moderate and severe depression. A combination of antidepressants and antipsychotics is recommended for the treatment of psychotic depression. The use of modified electroconvulsive therapy (mECT) is recommended for patients with moderate and severe depression and psychotic depression. Regardless of the severity of depression, patients are cautioned not to take anxiolytics or sleeping pills indiscriminately.

The effectiveness of the Guidelines for Dissemination and Education (EGUIDE), an educational program to disseminate treatment guidelines for MDD and schizophrenia, has been implemented in Japan (Takaesu et al., 2019; Numata et al., 2021). A total of 240 medical hospitals with psychiatric wards compiled a yearly database of treatment details at admission and discharge. The database was stratified before and after the educational program of the treatment guidelines, and the changes in the treatment were analyzed. The proportion of patients with schizophrenia and MDD who received multiple antipsychotics and antidepressants, respectively, varied by hospital (Iida et al., 2020; Ichihashi et al., 2020; Furihata et al., 2021). Prior to the educational program of the guidelines, 43% of the patients with schizophrenia were on

polytherapy with antipsychotics (Ichihashi et al., 2020), and 40% of the patients with depression were on polytherapy with antidepressants (Iida et al., 2020).

Since the Japanese MDD treatment guidelines recommend different treatments based on the severity of the disease, we hypothesized that there were different treatments between severities, even in real-world clinical practice in Japan. However, there is little information on the treatment for each severity of MDD. Therefore, in this study, we used the data set at the time of hospital discharge before the educational program of the MDD treatment guidelines to clarify the actual treatment of MDD in Japan and compare the treatment between the severities.

2. Methods

2.1. Study design and subjects

This was a cross-sectional retrospective study. We created a dataset of the treatment at discharge between October 2016 to March 2020 from the 240 hospitals that participated in the EGUIDE project. The study extracted data from the dataset of the treatment by psychiatrists prior to attending the EGUIDE educational program. We analyzed treatment data from 1484 patients with MDD from 51 hospitals. Of the 1484 patients with MDD, 518 (34.9%) were males and 966 (65.1%) were females. The mean (\pm standard deviation) age was 57.9 ± 17.7 years. All patients with MDD were allocated into two groups based on the presence or absence of a diagnosis of MDD. Patients with MDD in the severity diagnosis group were classified into three groups based on DSM-5: mild, moderate/severe, and psychotic depression. As for the treatment contents, we recorded whether antidepressants, anxiolytics/sleeping pills, and antipsychotics were prescribed and their equivalent doses (Inada and Inagaki, 2015), whether antidepressants and antipsychotics were used together, whether mood stabilizers were used, and whether mECT was performed.

The study was approved by the ethics committees of the National Center for Neuropsychiatry and Neurology and at the participating EGUIDE sites. This study was conducted in compliance with the Declaration of Helsinki and its future amendments. The study protocol was registered in the University Hospital Medical Information Network Registry (UMIN000022645).

2.2. Data analysis

All statistical analyses were performed using Excel (Microsoft, Redmond, WA, USA) or JMP Pro 15 (SAS Institute, Cary, NC, USA). The significance level was set at $P < 0.05$. The Anderson-Darling test was used for normality, the Wilcoxon signed ranked test for continuous variables between the two groups, the Kruskal-Wallis test for continuous

variables between the three groups, a chi-square test for categorical variables, and the Cochran-Armitage trend test for trend analysis of categorical variables. A Bonferroni correction was used for multiple tests.

2.3. Rate of severity diagnosis of MDD among the hospitals

To investigate the actual status of severity diagnosis of MDD in Japan, we examined the rate of severity diagnosis of MDD among the hospitals.

2.4. Comparison of the treatment of MDD between the groups with and without severity diagnosis

We compared the treatment contents of the “with severity diagnosis” and the “without severity diagnosis” groups to determine whether there were any differences in the treatment.

2.5. Comparison of the treatment of MDD with difference in each severity diagnosis

We compared the treatment between the three groups of patients with mild, moderate/severe, and psychotic depression.

2.6. Comparison of the treatment of MDD with difference of moderate and severe depression

As a post-hoc analysis, those with moderate and severe depression were grouped and their treatments were compared.

2.7. Correspondence between the severity of MDD and mECT implementation

As a post-hoc analysis, those from the “with severity diagnosis” group were grouped into mild, moderate, severe, and psychotic depression, and the trend in the rate of mECT implementation among the four groups was evaluated using the Cochran-Armitage trend test.

3. Results

3.1. Rate of severity diagnosis of MDD diagnosis among the hospitals

Approximately half of the hospitals included had a rate of severity diagnosis of MDD of less than 50%. The mean severity diagnosis of MDD was 56.8% (range: 0–100%) (Fig. 1).

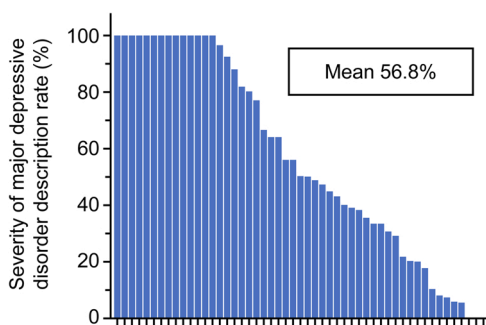


Fig. 1. Proportion of the patients with major depressive disorder who had severity rating from 51 hospitals. This figure shows that the rate of severity diagnosis in each facility varied from 0% to 100%.

3.2. Comparison of treatment of MDD between the groups with and without severity diagnosis

The number of psychotropic drugs prescribed tended to be lower in the “with severity diagnosis” group compared to the “without severity diagnosis” group. The percentage of antipsychotics or mood stabilizers prescribed was significantly lower in the “with severity diagnosis” group compared to the “without severity diagnosis” group ($p = 4.5 \times 10^{-5}$, $p = 4.6 \times 10^{-3}$). The percentage of no prescriptions for antidepressants was significantly lower in the “with severity diagnosis” group compared to the “without severity diagnosis” group ($p = 1.5 \times 10^{-3}$). The rate of mECT was significantly higher in the “with severity diagnosis” group compared to the “without severity diagnosis” group ($p = 5.1 \times 10^{-5}$) (Table 1).

3.3. Comparison of the treatment of MDD with difference in each severity diagnosis

The characteristics of the treatment differed by severity in the “with severity diagnosis” group. In the mild depression group, all patients were prescribed psychotropic drugs, and the rate of antidepressant monotherapy was 13.6% ($n = 6$). In the moderate/severe depression group, the rate of antidepressant monotherapy was 7.0% ($n = 44$), the rate of mECT was 0.5% ($n = 3$), and the combined rate of antidepressant monotherapy and mECT was 1.9% ($n = 12$). In patients with psychotic depression, the combined treatment rates of antidepressant and antipsychotic monotherapy were 13.6% ($n = 15$), mECT monotherapy was 1.8% ($n = 2$), and the combined treatment rate of antidepressant monotherapy, antipsychotic monotherapy, and mECT was 4.5% ($n = 5$).

There were significant differences in the percentage of the patients for whom antipsychotics were not prescribed ($p = 1.9 \times 10^{-6}$), CP equivalent ($p = 3.4 \times 10^{-3}$), antipsychotics and antidepressants were combined ($p = 5.0 \times 10^{-4}$), and mECT was conducted ($p = 3.4 \times 10^{-9}$) among the three groups (mild, moderate/severe, and psychotic depression). The post hoc test for those who were not prescribed antipsychotics showed that the percentage of patients with mild depression and moderate/severe depression were significantly higher compared to patients with psychotic depression ($p = 5.9 \times 10^{-5}$, and $p = 1.8 \times 10^{-6}$), respectively. The Cochran-Armitage trend test showed a significant linear decreasing trend in the order of mild, moderate/severe, and psychotic depression ($p = 4.0 \times 10^{-4}$). The post-hoc analysis of the

Table 1 Comparison of treatment in major depression disorder between groups with and without severity description.

	Without severity description N = 702	With severity description N = 782	p value
Number			
no prescription of antidepressant (%)	N = 138 (19.7%)	N = 106 (13.5%)	6.3×10^{-3} [†]
mono prescription of antidepressant (%)	N = 404 (57.5%)	N = 490 (62.7%)	
poly prescription of antidepressant (%)	N = 160 (22.8%)	N = 186 (23.8%)	
no prescription of anxiolytic and hypnotic drug (%)	N = 164 (23.4%)	N = 199 (25.5%)	0.35 [†]
no prescription of antipsychotic drug (%)	N = 308 (43.9%)	N = 426 (54.5%)	4.5×10^{-5} [†]
no prescription of mood stabilizer and antiepileptic drug (%)	N = 576 (82.1%)	N = 683 (87.3%)	4.6×10^{-3} [†]
Implementation of m-ECT (%)[*] 1	N = 68 (9.7%)	N = 132 (16.9%)	5.1×10^{-5} [†]

Abbreviations: m-ECT, modifide electroconvulsive therapy. Significance level was set at two-sided $P < 1.0 \times 10^{-2}$ with Bonferroni’s correction applied. Significant p-values are shown in bold.

[†] : chi-square test.

proportion of antipsychotics and antidepressants combined showed that psychotic depression was significantly more common than mild depression ($p = 2.4 \times 10^{-3}$) and moderate/severe depression ($p = 1.8 \times 10^{-3}$). The Cochran-Armitage trend test showed that the proportion of antipsychotics and antidepressants combined showed a significant linear increasing trend in the order of mild, moderate/severe, and psychotic depression ($p = 7.93 \times 10^{-7}$). The mECT post-test showed that mild depression and severe/moderate depression were significantly lower than psychotic depression ($p = 1.5 \times 10^{-5}$ and $p = 3.1 \times 10^{-8}$), respectively. The Cochran-Armitage trend test showed a significant linear increasing trend in the percentage of mECT performed in the order of mild, moderate/severe, and psychotic depression ($p = 1.0 \times 10^{-9}$). (Table 2).

3.4. Comparison of the treatment of MDD with difference of moderate and severe depression

In the “with severity diagnosis” group, the percentage of patients who received mECT was significantly higher in the severe depression group compared to the moderate depression group ($p = 5.1 \times 10^{-9}$). The diazepam equivalent value was significantly lower in the severe depression group compared to the moderate depression group ($p = 6.5 \times 10^{-4}$). (Table 3).

Table 2

Comparison of treatment in major depression disorder with difference of each severity description.

Number	mild N = 44	moderate/ severe N = 628	psychotic N = 110	p value
age (SD)(years)	58.4 (18.5)	58.3 (18.0)	62.6 (14.6)	0.11 [‡]
Male (%)	N = 10 (22.7%)	N = 222 (35.4%)	N = 37 (33.6%)	0.23 [‡]
no prescription of antidepressant (%)	N = 7 (15.9%)	N = 76 (12.1%)	N = 23 (20.9%)	0.065 [‡]
mono prescription of antidepressant (%)	N = 25 (56.8%)	N = 396 (63.1%)	N = 69 (62.7%)	
poly prescription of antidepressant (%)	N = 12 (27.3%)	N = 156 (24.8%)	N = 18 (16.4%)	
imipramine equivalent for antidepressants (SD)(mg/day)	157.9 (96.8)	181.2 (109.2)	172.8 (92.8)	0.5 [‡]
no prescription of anxiolytic and hypnotic drug (%)	N = 8 (18.2%)	N = 159 (25.3%)	N = 32 (29.1%)	0.37 [‡]
diazepam/nitrazepam equivalent for anxiolytics and hypnotics (SD)(mg/day)	10.16 (8.54)	11.17 (11.67)	9.19 (6.93)	0.22 [‡]
no prescription of antipsychotic drug (%)	N = 30 (68.2%)	N = 360 (57.3%)	N = 36 (32.7%)	1.9 × 10⁻⁶ [‡]
chlorpromazine equivalent for antipsychotics (SD) (mg/day)	112.6 (101.7)	176.1 (187.9)	248.0 (224.1)	3.4 × 10⁻³
combination with antidepressant and antipsychotic drug (%)	N = 11 (25.0%)	N = 227 (36.2%)	N = 57 (51.8%)	5.0 × 10⁻⁴ [‡]
no prescription of mood stabilizer and antiepileptic drug (%)	N = 39 (88.6%)	N = 550 (87.6%)	N = 94 (85.5%)	0.8 [‡]
Implementation of m-ECT (%)	N = 1 (2.3%)	N = 91 (14.5%)	N = 40 (36.4%)	3.4 × 10⁻⁹ [‡]

Abbreviations: m-ECT, modifide electroconvulsive therapy.

‡: chi-square test, †: Wilcoxon test.

The significance level was set at two-tailed $P < 4.5 \times 10^{-3}$ with Bonferroni's correction applied. Significant p-values are shown in bold.

Table 3

Comparison of treatment in major depression disorder with difference of moderate and severe.

	moderate N = 393	severe N = 235	p value
age (SD)(years)	56.8 (18.5)	60.7 (17.0)	9.6 × 10⁻³ [‡]
Male (%)	N = 131 (33.3%)	N = 91 (38.7%)	0.17 [‡]
no prescription of antidepressant (%)	N = 47 (12.0%)	N = 29 (12.3%)	0.31 [‡]
mono prescription of antidepressant (%)	N = 256 (65.1%)	N = 140 (59.6%)	
poly prescription of antidepressant (%)	N = 90 (22.9%)	N = 66 (28.1%)	
no prescription of anxiolytic and hypnotic drug (%)	N = 95 (24.2%)	N = 64 (27.2%)	0.39 [‡]
no prescription of antipsychotic drug (%)	N = 232 (59.0%)	N = 128 (54.5%)	0.26 [‡]
combination with antidepressant and antipsychotic drug (%)	N = 136 (34.6%)	N = 91 (38.7%)	0.3 [‡]
no prescription of mood stabilizer and antiepileptic drug (%)	N = 345 (87.8%)	N = 205 (87.2%)	0.84 [‡]
Implementation of m-ECT (%)	N = 32 (8.1%)	N = 59 (25.1%)	5.1 × 10⁻⁹ [‡]
imipramine equivalent for antidepressants (SD)(mg/day)	173.1 (102.2)	194.9 (119.0)	0.08 [‡]
diazepam/nitrazepam equivalent for anxiolytics and hypnotics (SD) (mg/day)	12.0 (11.8)	9.50 (11.3)	6.7 × 10⁻⁴ [‡]
chlorpromazine equivalent for antipsychotics (SD) (mg/day)	176.9 (203.7)	157.6 (152.6)	0.74 [‡]

Abbreviations: m-ECT, modifide electroconvulsive therapy.

‡: chi-square test, †: Kruskal-Wallis test.

The significance level was set at two-tailed $P < 4.5 \times 10^{-3}$ with Bonferroni's correction applied. Significant p-values are shown in bold.

3.5. Correspondence between the severity of MDD and mECT implementation

In the Cochran-Armitage trend test, the percentage of patients who underwent mECT showed a significant linear increasing trend in the order of mild, moderate, severe, and psychotic depression. ($p = 3.1 \times 10^{-13}$). (Fig. 2).

4. Discussion

We used a discharge data set to determine the actual treatment of MDD in clinical practice in Japan and compared the treatment by the severity. In this study, we confirmed that there were large differences in

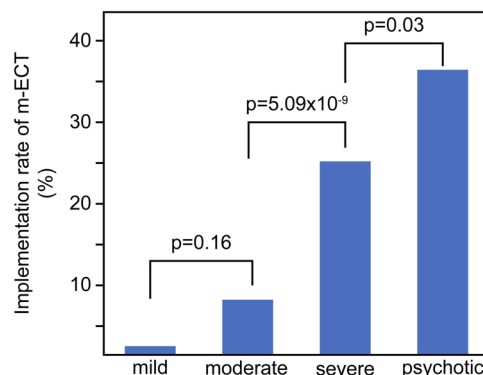


Fig. 2. Implementation rate of mECT among severity of depression. The bar graph shows the implementation rate of mECT for each severity of major depressive disorder. The results of the chi-square test are shown. The Cochran-Armitage trend test indicates an increasing trend in the severity and implementation rate of mECT ($p = 3.11 \times 10^{-13}$).

the treatment of MDD based on the severity of MDD.

The mean rate of severity diagnosis of MDD among hospitals was 56.8% (range: 0–100%). Iida et al. reported that the mean rate of antidepressant monotherapy in Japan was 58.6% (range: 0–100%) (Iida et al., 2020). This suggested that the guidelines for the treatment of depression were not being followed in approximately half of the hospitals. In addition, the number of psychotropic medications prescribed tended to be lower in the “with severity diagnosis” group compared to the “without severity diagnosis” group. The number of psychotropic drugs prescribed tended to be lower in the “with severity diagnosis” group compared to the “without severity diagnosis” group. Yasui-Furukori et al. reported that clozapine prescriptions in Japan increased when the diagnosis of treatment-resistant schizophrenia was assessed (Yasui-Furukori et al., 2022). In this study, diagnosing the severity of MDD may have changed the treatment to follow the guidelines.

The Japanese MDD treatment guidelines recommend 1) antidepressant monotherapy, 2) mECT alone, and 3) a combination of antidepressant monotherapy and mECT for moderate/severe depression. However, in this survey, only 9.4% of the patients were fully compliant with all the recommended treatments. Similarly, for the treatment of psychotic depression, 1) combination treatment with antidepressant monotherapy and antipsychotic monotherapy, 2) mECT alone, and 3) a combination treatment with antidepressant monotherapy or antipsychotic monotherapy and mECT are recommended. However, in this survey, only 19.9% of the patients were fully compliant with all the recommended treatments. This suggests that there is still an evidence-practice gap in the treatment of MDD in Japan, and guidelines are only partially adhered to in the treatment of depression.

In a comparison between the three groups of mild, moderate/severe, and psychotic depression, in the “with severity diagnosis” group the rate of combined antidepressant/antipsychotic use and the rate of mECT use increased with increasing severity. The Japanese MDD treatment guidelines recommend mECT for the treatment of moderate/severe psychotic depression. The combination of antipsychotics and antidepressants is recommended only for the treatment of psychotic depression. In this study, the increased rates of antidepressants and antipsychotics use and of mECT based on the severity of MDD suggest that, despite the evidence-practice gap, there is a tendency for the “with severity diagnosis” group to adhere to the MDD treatment guidelines.

Griffiths et al. reported that patients may have negative attitudes toward mECT compared to its usefulness in the treatment of MDD (Griffiths and O’Neill-Kerr, 2019). The choice of antidepressant and antipsychotic combination over mECT in the treatment of moderate/severe depression in this study may reflect the avoidance of mECT treatment among patients with depression in Japan.

In a comparison between the moderate and severe depression groups, the rate of mECT use was higher in the severe depression group. In addition, when the four groups of mild, moderate, severe, and psychotic depression were compared the rate of mECT implementation increased with severity. Kautzky et al. reported that severe depression was more resistant to antidepressants compared to moderate depression (Kautzky et al., 2019). In addition, severe depression is associated with a higher risk of suicide, and early improvement is desirable (Hawton et al., 2013). Regarding the efficacy of mECT, a high remission rate of MDD has been reported, regardless of severity (Kho et al., 2003; Tsuchiyama et al., 2005; Pinna et al., 2018). Therefore, we believe that the treatment options may differ between moderate and severe depression.

The results of this study showed that the rate of mECT implementation increased with increasing severity from mild to psychotic depression. This suggested that the treatment behavior changed based on the severity of MDD. As for future issues, we consider that the dissemination of guidelines should be promoted to standardize pharmacotherapy and improve the quality of treatment. Conversely, it is necessary to identify the factors that contribute to the evidence-practice gap pointed out and explore ways to address them. In other words, the

factors that lead to the selection of antipsychotics and mECT should be examined.

4.1. Limitations

This study has several limitations. First, although this study was conducted in hospitals throughout Japan, it may not reflect the prescribing practices of all hospitals. Therefore, the risk of selection bias could not be ruled out. Second, we used the diagnostic criteria of the DSM-5 for the severity of MDD. However, we did not assess the severity using a rating scale such as the Hamilton Depression Rating Scale. Third, we did not distinguish between the first and recurrent episodes. Compared to the first episode, recurrent cases are more difficult to treat and have been reported to have increased suicidal ideation (Courtet, 2010). Fourth, Altunsoy et al. reported that MDD was associated with a discrepancy between symptomatic remission and improvement in psychosocial functioning (Altunsoy et al., 2021). However, we did not assess the psychosocial functioning using the Sheehan Disability Scale or the Short Form Health Survey - 36. Fifth, this study did not take into account the effect of psychotropic pro re nata medications. Ichihashi et al. reported that 31.1% of depressed patients were prescribed psychotropic pro re nata medications (Ichihashi et al., 2022). It is possible that psychotropic pro re nata medications may have influenced the prescribing behavior of regular medications in this study. Further studies and international collaborations with designs that address these limitations are required. In addition, increasing the number of institutions participating in the EGUIDE study may help reduce selection bias.

5. Conclusion

This study showed that there were significant differences in the treatment of MDD based on the severity. The results showed that the use of antidepressants increased and the use of antipsychotics and mood stabilizers decreased when the severity of MDD was diagnosed. Regarding the differences in the treatment by severity, the rates of concomitant use of antipsychotics and mECT increased with severity. Nevertheless, this study suggests that there is still an evidence-practice gap in the treatment of MDD in Japan, and guidelines are only partially adhered to in the treatment of depression. Further research is required to determine whether treatment for each severity of MDD is closer to the guideline recommendations after attending the guideline education program.

Financial disclosure

This study was supported by the Japan Agency for Medical Research and Development (AMED) under Grant Number JP16dk0307060, and AMED under Grant Number JP19dk0307083, the Health and Labor Sciences Research Grants (H29-Seishin-Ippan-001, 19GC1201), the Japanese Society of Neuropsychopharmacology, the Japanese Society of Mood Disorders and the Japanese Society of Clinical Neuro-psychopharmacology. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

The authors thank the following psychiatrists belonging EGUIDE members.

Declaration of Competing Interest

The authors report no declarations of interest.

Conflict of interest

The authors declare no conflict of interest.

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