[J Tokyo Wom Med Univ
86 (Extra 1) E82～E85 (2016)]

Original

Rapid-cycling of Antidepressants in Bipolar Disorder: A Retrospective Study of 359 Patients

Hiroyuki MURAOKA, Ken INADA, Takaaki KAWANO, Kentaro MATSUI, Masahiko KAWANO, Daisuke HASEGAWA and **Jun ISHIGOOKA**

Department of Psychiatry, School of Medicine, Tokyo Women's Medical University

(Accepted January 6, 2016)

To examine whether the administration of antidepressants to patients with bipolar disorder triggers rapid cycling, we conducted a retrospective study, targeting 1,060 patients who had been prescribed antiepileptic drugs and lithium between January 1 and December 31, 2011, at the departments of psychiatry and psychosomatic medicine in the Tokyo Women's Medical University hospital. Of 1,060 subjects, 359 were diagnosed with bipolar disorder based on the DSM-IV-TR diagnostic criteria. Of these, 227 had a history of antidepressant use, while we could not confirm the history of antidepressant use in 132 patients. Among 227 patients with a history of antidepressant use, 24 (10.6%) manifested rapid cycling. In contrast, of 132 patients who had no history of antidepressant use, only 3 (2.3%) manifested rapid cycling. Our results showed a statistically significant difference in rapid cycling between antidepressant users and those with no history of antidepressants in bipolar disorder ($p = 0.006$). These findings indicate the need to exercise caution when considering the use of antidepressants in patients with bipolar disorder.

Key Words: bipolar disorder, rapid cycling, antidepressant

Introduction

Bipolar disorder is a mood disorder characterized by depressive and manic (bipolar I disorder, or "BPI") to hypomanic episodes (bipolar II disorder, or "BPII")[1)2)]. Most patients initially develop the disease with a depressive episode, and then visit a medical institution[3)4)]. From a long-term study of bipolar disorder, the proportion of depression phase to the total time elapsed before diagnosis has been reported as 30-50%[5)], suggesting that the patients may spend a major part of their life in a depressive phase. Antidepressants are often considered as useful treatment tools for depression in bipolar disorder. However, opinions are split regarding the use of antidepressants, with some recommending[6)] and the others opposing their use[7)]. Results of recent meta-analyses have failed to prove that antidepressants can improve depressive episodes in bipolar disorder[8)]. As a result, for the treatments of bipolar disorder, various guidelines currently maintain a cautious stance toward the use of antidepressants that show no benefits[9)~11)]. However, taking only an antidepressant can increase the risk of switching to mania or hypomania, or of developing rapid-cycling symptoms[12)].

Most reports on the use of antidepressants for bipolar disorder are from around the world. Racial differences in the effects of antidepressants[13)] are known to occur. In Japanese patients with bipolar disorder, the relationship between rapid-cycling and antidepressants has not been shown in the past. Therefore, in this study, we examined whether the

✉ : Hiroyuki MURAOKA Department of Psychiatry, School of Medicine, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, 162-8666
E-mail: muraoka.hiroyuki@twmu.ac.jp

Table 1 The relationship between history of antidepressant use and rapid-cycling

	History of antidepressant use			
	BPI (n = 136)		BPII (n = 223)	
	Yes	No	Yes	No
Rapid-cycling				
Yes	6	3	18	0
No	55	72	148	57

Unit: number of patients.

use of antidepressants would create a future risk of inducing rapid cycling in Japanese bipolar disorder.

Materials and Methods

This study was conducted with the approval of the Tokyo Women's Medical University Ethics Committee. We enrolled outpatients undergoing treatment at the psychiatry and psychosomatic medicine departments of the Tokyo Women's Medical University Hospital as subjects, if they were prescribed lamotrigine, valproic acid, carbamazepine, or lithium carbonate between January 1 and December 31, 2011. For conducting this study, we did not use a structured research design, but recorded our findings from actual clinical practice.

The medical records of all target patients were confirmed retrospectively. We selected those individuals whose diagnosis of bipolar disorder was confirmed by the attending doctors using the text revision of Diagnostic and Statistical Manual of Mental Disorder, 4th ed. (DSM-IV-TR), diagnostic criteria[1)]—by two psychiatry specialists who were certified both as a Japanese Society of Psychiatry and Neurology specialist physician and as a psychiatrist designated by Japan's Ministry of Health, Labour and Welfare.

We investigated the age, sex, diagnosis, number of depressive and manic episodes, history of antidepressant use, and presence/absence of rapid cycling in patients selected for analysis. Rapid cycling was defined as developing at least four episodes of major depression, mania, mixed type, or hypomania during the past 12 months[1)2)]. Because of this, data from patients whose course could be followed for at least a year were included in the analysis. Statistically significant differences were examined using Fisher's exact test, with a level below 5% in a two-sided test being regarded as statistically significant.

Table 2 Number of patients exhibiting or not exhibiting rapid-cycling type bipolar disorder, and list of antidepressants used

Medicine	Rapid-cycling	
	Yes	No
Paroxetine	67	2
Sertraline	56	5
Duloxetine	13	3
Milnacipran	56	2
Mirtazapine	32	2
Fluvoxamine	56	4
Sulpiride	43	2
Trazodone	56	5
Nortriptyline	4	0
Maprotiline	16	0
Mianserin	47	2
Imipramine	4	1
Amitriptyline	12	1
Amoxapine	39	0
Clomipramine	23	3
Setiptiline	1	0

Unit: number of patients.

Results

A total of 1,060 patients had been prescribed investigational drugs. Of these, 359 were diagnosed with bipolar disorder and were eligible for the analysis (136 with BPI and 223 with BPII). There were 181 men (BPI: 70 and BPII: 111) and 178 women (BPI: 66 and BPII: 112). Their ages ranged from 16-86 years (mean: 49.9 ± 15.0 years), and, in terms of age distribution, approximately 70 subjects were between 40-79 years for each type of bipolar disorder and sex, leading to a total of 280 people, which accounted for the majority of subjects. A total of 227 patients had a history of antidepressant use (BPI: 61 and BPII: 166). Twenty-seven subjects manifested rapid-cycling bipolar disorders, of whom 24 (BPI: 6 and BPII: 18) had a history of antidepressant use. All three subjects without a history of antidepressant use who presented with rapid-cycling bipolar disorder had BPI (Table 1). We found no clear patterns as to the relationship between the type of antidepressant used and the risk of inducing rapid cycling (Table 2).

A Fisher's exact test was performed to examine

the influence of antidepressants on inducing rapid cycling. The results showed that a significantly large number of subjects who manifested rapid cycling had a history of antidepressant use ($p = 0.006$). When the subjects were divided into BPI and BPII groups, a significant difference in rapid cycling was seen only with the BPII group in terms of the p value ($p = 0.180$ for BPI and $p = 0.008$ for BPII).

Discussion

Our results show that, although rapid cycling was seen more frequently in patients with BPII, the relationship between rapid-cycling and either BPI or BPII was not statistically significant ($p = 0.68$). This result suggests that, in Japan, antidepressant administration is not recommended more frequently for BPII than for BPI. Among the reports published previously, Kupka et al presented similar results[14]. In contrast, Serretti et al and Schneck et al reported that rapid cycling was seen more frequently in BPI[15][16]. This suggests that, no agreement between results has been obtained so far.

One factor contributing to the differences in results could be the usage status of antidepressants. Based on our findings, the use of antidepressants did not lead to significant differences in inducing rapid cycling, at least among subjects with BPI. This may have been partly due to the small number of subjects in the sample. In contrast, the influence of antidepressants on inducing rapid cycling was observed in patients with BPII. Therefore, the difference in the influence of antidepressants on inducing rapid cycling may be attributable to differences in the pathophysiology between BPI and BPII.

No differences were identified in the type of medication. Past reports have noted the risk of tricyclic antidepressants (TCAs) in inducing manic switches and rapid cycling[17][18]. Indeed, the World Federation of Societies of Biological Psychiatry guidelines recommend that bipolar disorder should not be treated solely with TCAs[19]. In the current study, no differences were apparent between TCAs and other antidepressants, likely because only 27 patients showed rapid cycling, making it impossible to correlate any observed differences to individual drugs.

Nevertheless, the current findings point to the need for considering the risk that antidepressants might trigger rapid-cycling, especially, the danger of non-TCAs inducing mania in ways similar to TCAs.

Conclusion

The important findings in the current study suggest that a history of antidepressant use can cause rapid-cycling in outpatients with bipolar disorder in Japan. Therefore, prescription of antidepressants to patients with bipolar disorder should be carefully considered. However, the relationship between rapid-cycling and class of antidepressant is yet to be shown. The limitations of this study include a small sample size and the retrospective design. Hence, it is necessary to conduct a prospective study in the future with a larger sample size.

The authors indicated no conflicts of interest.

References

1) **Association AP**: Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR, American Psychiatric Association, Washington (2000)
2) **Association AP**: Diagnostic and Statistical Manual of Mental Disorders: DSM-5, American Psychiatric Association, Arlington (2013)
3) **Hantouche EG, Akiskal HS, Lancrenon S et al**: Systematic clinical methodology for validating bipolar-II disorder: data in mid-stream from a French national multi-site study (EPIDEP). J Affect Disord **50**: 163–73, 1998
4) **Ghaemi SN, Sachs GS, Chiou AM et al**: Is bipolar disorder still underdiagnosed? Are antidepressants overutilized? J Affect Disord **52**: 135–144, 1999
5) **Judd LL, Akiskal HS, Schettler PJ et al**: A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. Arch Gen Psychiatry **60**: 261–269, 2003
6) **Gijsman HJ, Geddes JR, Rendell JM et al**: Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry **161**: 1537–1547, 2004
7) **Schneck CD, Miklowitz DJ, Miyahara S et al**: The prospective course of rapid-cycling bipolar disorder: findings from the STEP-BD. Am J Psychiatry **165**: 370–377; quiz 410, 2008
8) **Sidor MM, Macqueen GM**: Antidepressants for the acute treatment of bipolar depression: a systematic review and meta-analysis. J Clin Psychiatry **72**: 156–167, 2011
9) **Hirschfeld RM, Lewis L, Vornik LA**: Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of indi-

viduals with bipolar disorder. J Clin Psychiatry **64**: 161–174, 2003
10) **Hirschfeld MAR, Bowden CL, Gitlin MJ et al**: Practice Guideline for the Treatment of Patients With Bipolar Disorder (Revision), Amer Psychiatric Pub (1995)
11) **National Collaborating Centre for Mental Health**: Bipolar Disorder: The Management of Bipolar Disorder in Adults, Children and Adolescents, in Primary and Secondary Care, British Psychological Society, Leicester (2006)
12) **El-Mallakh RS, Vöhringer PA, Ostacher MM et al**: Antidepressants worsen rapid-cycling course in bipolar depression: A STEP-BD randomized clinical trial. J Affect Disord **184**: 318–321, 2015
13) **Johnson JA**: Influence of race or ethnicity on pharmacokinetics of drugs. J Pharm Sci **86**: 1328–1333, 1997
14) **Kupka RW, Luckenbaugh DA, Post RM et al**: Rapid and non-rapid cycling bipolar disorder: a meta-analysis of clinical studies. J Clin Psychiatry **64**: 1483–1494, 2003
15) **Serretti A, Mandelli L, Lattuada E et al**: Rapid cycling mood disorder: clinical and demographic features. Compr Psychiatry **43**: 336–343, 2002
16) **Schneck CD, Miklowitz DJ, Calabrese JR et al**: Phenomenology of rapid-cycling bipolar disorder: data from the first 500 participants in the Systematic Treatment Enhancement Program. Am J Psychiatry **161**: 1902–1908, 2004
17) **Yatham LN, Kennedy SH, O'Donovan C et al**: Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies. Bipolar Disord **7**(Suppl 3): 5–69, 2005
18) **Peet M**: Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry **164**: 549–550, 1994
19) **Grunze H, Vieta E, Goodwin GM et al**: The World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the biological treatment of bipolar disorders: update 2012 on the long-term treatment of bipolar disorder. World J Biol Psychiatry **14**: 154–219, 2013

双極性障害患者359症例への抗うつ薬投与と急速交代型の後方視的検討

東京女子医科大学医学部精神医学講座

村岡（ムラオカ） 寛之（ヒロユキ）・稲田（イナダ） 健（ケン）・河野（カワノ） 敬明（タカアキ）・松井健太郎（マツイケンタロウ）
河野（カワノ） 仁彦（マサヒコ）・長谷川大輔（ハセガワダイスケ）・石郷岡（イシゴウオカ） 純（ジュン）

双極性障害患者への抗うつ薬投与が急速交代型を惹起する危険因子であるか検討することを目的に，2011年1月1日から同年12月31日までに当院精神科，心身医療科で抗てんかん薬および，リチウムを処方されている1,060名の患者を対象に後方視的に検討を行った．1,060名のうち，DSM-IV-TRの診断基準で双極性障害と診断された患者は359名であった．抗うつ薬使用歴を確認された患者は227名，使用歴の確認できなかった患者は132名であった．抗うつ薬使用歴を有する227名中，急速交代型を呈していたのは24名（10.6%）であった．一方で抗うつ薬使用歴のない132名において急速交代型を呈したのは3名（2.3%）であり，抗うつ薬使用歴のある患者群において，急速交代型が有意に多かった（$p=0.006$）．以上の結果は双極性障害患者において，抗うつ薬の使用は慎重に検討すべきであるという考えの一助となると考えられた．