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Influence of comorbid alcohol use disorder on treatment response of depressive patients

Eri Hashimoto · Masaya Tayama · Hiromi Ishikawa · Megumi Yamamoto · Toshikazu Saito

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Abstract Patients with major depressive disorder (MDD) frequently also have alcohol use disorder (AUD) and they are more likely to experience symptomatic recurrence and resist treatment. How the two disorders interrelate has not yet been fully examined in Japanese subjects. The treatment response of 47 MDD patients was followed for 12 weeks. Depressive symptoms were rated by the 17-item Hamilton Rating Scale for Depression (HAM-D) and those whose HAM-D score was less than 16 were excluded. The MDD patients were divided into a non-alcohol use disorder (NAUD) and an alcohol use disorder (AUD) group according to the Alcohol Use Disorder Identification Test (AUDIT). We applied a cutoff score of 12 in the AUDIT scale. After 8 weeks, HAM-D NAUD group scores were significantly lower compared with AUD patients. The NAUD group, 23 individuals, prescribed therapeutic doses of antidepressant (equivalent to more than 150 mg of imipramine per day) significantly improved their HAM-D scores but no improvement occurred in the AUD subjects. Correlation analysis in all subjects revealed a significant negative correlation between AUDIT score and improved HAM-D score at endpoint. Moreover, a significant negative correlation was found between total alcohol consumption during the study period and improvement of HAM-D score at endpoint in AUD patients. These results suggest that co-occurrence of MDD and AUD is associated with a lower response to antidepressant treatment and it may reflect an inhibitory effect of ethanol on antidepressants action in the brain.

Keywords Alcohol use disorder · Depression · Comorbidity · Antidepressant

E. Hashimoto (✉) · M. Tayama · H. Ishikawa · M. Yamamoto · T. Saito
Department of Neuropsychiatry, School of Medicine, Sapporo Medical University, S.1, W.16, Chuo-ku, Sapporo 060-8543, Japan
e-mail: ehasimot@sapmed.ac.jp

Introduction

In recent years, suicide has claimed nearly 30,000 victims per year in Japan and strong effective preventative measures are urgently required. Multinational research indicates mood disorders and substance-related disorders are strongly related to the risk of suicide and comorbidity with MDD and AUD further increases its risk (Bertolote 2002).

Major depressive disorder (MDD) is a common psychiatric illness whose 12-month prevalence in developed countries falls between 3.1 and 9.6 % according to the World Health Organization (Nandi 2009). New antidepressants are introduced frequently and other psychotropic drugs, i.e. antipsychotics and mood stabilizers are probably effective against the symptoms of MDD. However, treatment outcomes in MDD patients have not improved in spite of this therapeutic progress and this lack of improvement is mostly caused by the existence of treatment-resistant MDD. Various factors contribute to this treatment-resistance including the co-occurrence of other psychiatric problems.

The clinical picture of MDD is complicated by the co-occurrence of other mental disorders and it is often observed that alcohol use disorder (AUD) is comorbid with the disease (Grant and Hartford 1995; Kessler et al. 1997; Sullivan et al. 2005; Davis et al. 2010). Hasin, reported that people with a history of AUD have a high prevalence rate of MDD (Hasin et al. 2002; Hasin and Grant 2002).

Moreover, there appears to be a close interrelation between the two diseases, for example, it has been observed that growing severity in MDD is associated with growing severity in AUD and vice versa (Grant and Hartford 1995; Gilman and Abraham 2001).

Patients with both MDD and AUD are more likely to have more severe depressive symptoms and disturbed functions, experience symptomatic recurrence, resist antidepressant treatment, possess an increased risk of suicide, and are less likely to recover and adhere to treatment (Cornelius et al. 1996; Davis et al. 2005, 2006; Conner et al. 2008; Sher et al. 2008). Moreover, subjects with the dual diagnosis tend to have high rates of medical comorbidity and increased use of public and medical health services including psychiatric hospitalizations (Fortney et al. 1999; Sullivan et al. 2005). Clearly, the presence of AUD has a tremendous adverse influence on the clinical course and treatment outcome of MDD, and there is an urgent need to investigate the effects of alcohol intake on the pathophysiology of MDD and elucidate the mechanism of treatment-resistance induced by comorbidity with AUD in MDD.

Past trials in which the effects of antidepressants in MDD with AUD were evaluated produced inconsistent results; however, most recent studies indicate that the use of antidepressants in this population can effectively control depressive symptoms (Iovieno et al. 2011; Pettinati et al. 2013). Unfortunately, the available data at present are based on relatively small sample numbers and larger studies are needed to determine the optimal pharmacologic treatment of MDD with AUD. There has been little research addressing the confounding interplay of MDD and AUD and the efficacy of antidepressants in treating MDD patients with comorbid AUD has not yet been thoroughly examined in the Japanese population. Therefore, in the present study, we investigated treatment outcomes in MDD patients with or without AUD.

Subjects and methods

This study was conducted at the Department of Neuropsychiatry, Sapporo Medical University Hospital and its affiliated hospitals and subjects were inpatients or outpatients diagnosed as MDD using ICD-10 criteria (World Health Organization 1992). Data for this report were collected between October 2011 and October 2013, and we examined 47 individuals (male/female = 24/23).

At the beginning of the investigation, depressive episodes were assessed by the Mini International Neuropsychiatric Interview (M.I.N.I.) (Otsubo et al. 2005) and the symptoms of MDD were rated by 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton 1960; Tabuse et al. 2007) and those whose HAM-D score was less than 16 were excluded.

Patients who were diagnosed with MDD, were then divided into 2 groups: non-alcohol use disorder (NAUD) group ($n = 27$) and alcohol use disorder (AUD) group ($n = 20$) according to Alcohol Use Disorder Identification Test (AUDIT) and a cutoff score of 12 in AUDIT was adopted as the best approximation for problem drinking including hazardous drinking and suspected alcohol dependence (ADS) (NAUD < 12, AUD $\geqq 12$) (Saunders et al. 1993; Hiro and Shima 1996, 1997; Donovan et al. 2006). There were no significant differences between the NAUD and AUD groups in gender, age, original HAM-D score as shown in Table 1.

Pharmacotherapy for MDD was conducted at the discretion of the attending physicians without instruction on any specified agents. Prescribed antidepressants and their dose were converted to imipramine equivalents (Inagaki and Inada 2006). The effect of medication on depressive symptoms was monitored at 2, 4, 8 and 12 weeks by the change of HAM-D score.

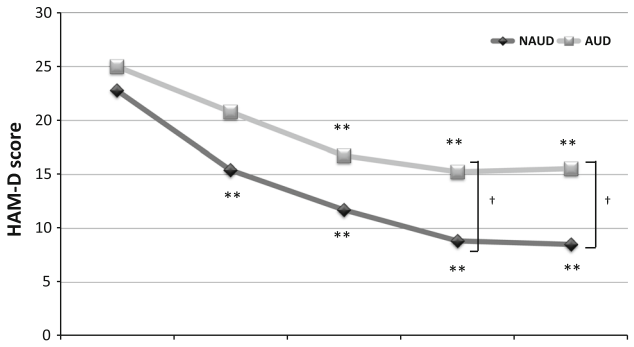
Supportive psychotherapy was combined with pharmacotherapy in all cases and abstinence was not absolutely required, however, the AUD group patients who had alcohol-related psychosomatic problems and could be diagnosed as alcohol dependence were encouraged to abstain and treated in cooperation with self-help groups such as Alcoholics Anonymous and the Giving-up drinking society of Japan.

Moreover, regarding alcohol consumption during the study period, the subjects were asked whether they were drinking and the total amounts of alcohol consumption were checked at 2, 4, 8 and 12 weeks. The total alcohol consumption was described as an amount of absolute alcohol (g).

Statistical analyses in the present study were performed with commercially available software, Stat Flex version 6 (Osaka, Japan). Subjects characteristics were compared using a Fisher's exact test. All repeated measures in HAM-D scores from baseline to endpoint in NAUD and AUD groups were examined by Dunnett-test and changes in HAM-D scores between the two groups were compared by Welch's t test. Furthermore, remission rate and correlation

Table 1 Subjects characteristics

	NAUD	AUD	p
n	27	20	
Male/Female	12/15	12/8	0.29
Age	43.3 ± 13.1	47.2 ± 13.8	0.33
AUDIT score	1.6 ± 1.9	23.5 ± 8.1	
HAM-D baseline	22.8 ± 4.1	25.0 ± 5.8	0.17



	baseline	week 2	week 4	week 8	week 12
NAUD	22.8±4.1	15.4±6.1	11.7±7.0	8.9±6.0	8.5±5.6
AUD	25.0±5.8	20.8±10.5	16.7±9.7	15.3±11.0	15.6±11.2

Fig. 1 The HAM-D score of each group from baseline through endpoint. $^{**}p < 0.01$ Significant difference compared with baseline (Dunnett-test). $^{\dagger}p < 0.05$ Significant difference between the two groups (Welch's t test)

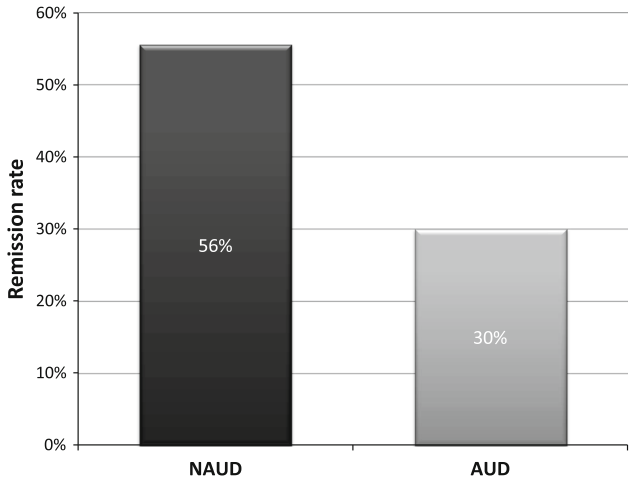


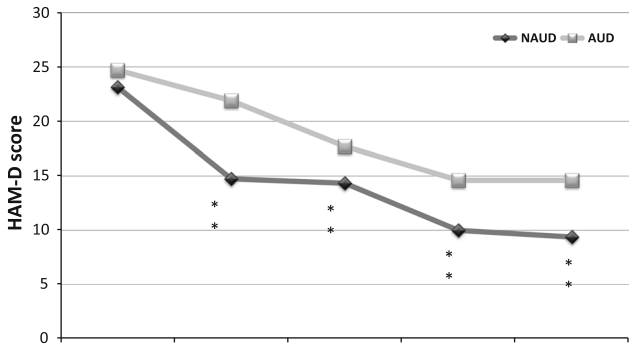
Fig. 2 The percentage of patients in remission defined as an HAM-D score below 7 at the end of the treatment period

between the improvement of HAM-D scores at 12 weeks and other measures (AUDIT score, total alcohol consumption during study) were also assessed by correlation analysis. For all analyses, statistical significance was set at $P < 0.05$.

Sapporo Medical University ethics committee approved the study protocol and written informed consent was obtained from all patients. Subjects were limited only by those who were over 20 years old and had no somatic or mental disturbance in making a decision to participate voluntarily in the investigation.

Results

Figure 1 shows the change of HAM-D scores in each group throughout the study. HAM-D scores significantly



	baseline	week 2	week 4	week 8	week 12
NAUD	23.1±4.3	14.7±5.1	14.3±7.0	10.0±6.0	9.3±5.1
AUD	24.7±4.6	21.9±13.1	17.7±12.5	14.6±12.5	14.6±14.4

Fig. 3 The effect of therapeutic doses of antidepressants on the improvement in HAM-D scores. $^{**}p < 0.01$ (Dunnett-test) compared with study baseline

improved in the NAUD group from 2 weeks to endpoint ($P < 0.01$). However, no significant improvement of HAM-D score occurred in the AUD group until 4 weeks ($P < 0.01$) and the HAM-D scores were significantly lower in NAUD group than in the AUD group in 8 and 12 weeks ($P < 0.05$); thus, the response rate to medication is lower in the AUD patients. We defined remission as an HAM-D score below 7 at the end of the treatment period and compared the remission rate in each group at the endpoint of the investigation as shown in Fig. 2. Although the remission rate tended to be higher in the NAUD group than in AUD group after 12 weeks treatment, the difference (56 vs. 30 %) was not statistically significant ($\chi^2 = 3.05$, $p = 0.08$).

We then analyzed the data of subjects who received therapeutic doses of antidepressants, i.e. equivalent to more than 150 mg of imipramine per day. Twenty-three individuals met the criteria ($n = 16$ in NAUD; $n = 7$ in AUD), and there were no significant differences between NAUD and AUD groups in gender, age, initial HAM-D score, or in the average dose of prescribed antidepressant (data not shown).

Therapeutic doses resulted in significantly improved HAM-D scores through the study period in the NAUD group ($P < 0.01$) but failed to improve HAM-D scores in the AUD subjects (Fig. 3). We concluded that antidepressants were less effective in depressive patients with AUD.

Figure 4 shows a correlation analysis of the relationship between AUDIT score and improved HAM-D score after 12 weeks of treatment in all subjects and a significant negative correlation was observed between the two variables ($P < 0.05$). Moreover, a significant negative correlation ($P < 0.01$) was observed between total alcohol consumption during the study period in AUD patients and improved HAM-D score at 12 weeks of the treatment as shown in Fig. 5.

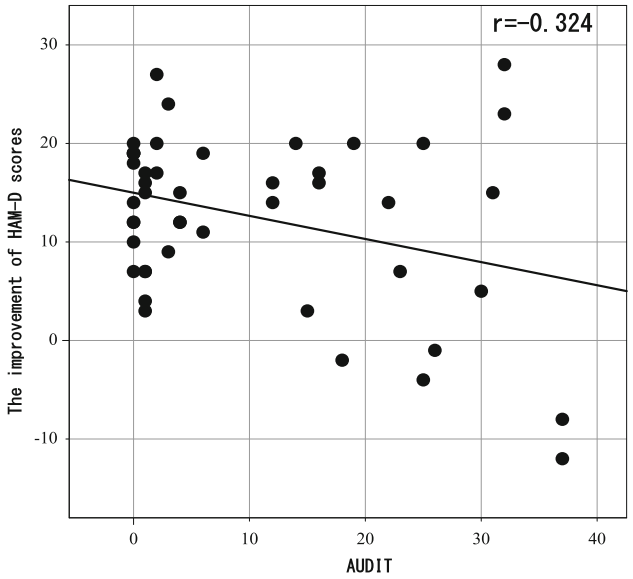


Fig. 4 Correlation analysis of the relationship between AUDIT score and improvement of HAM-D score at 12 weeks

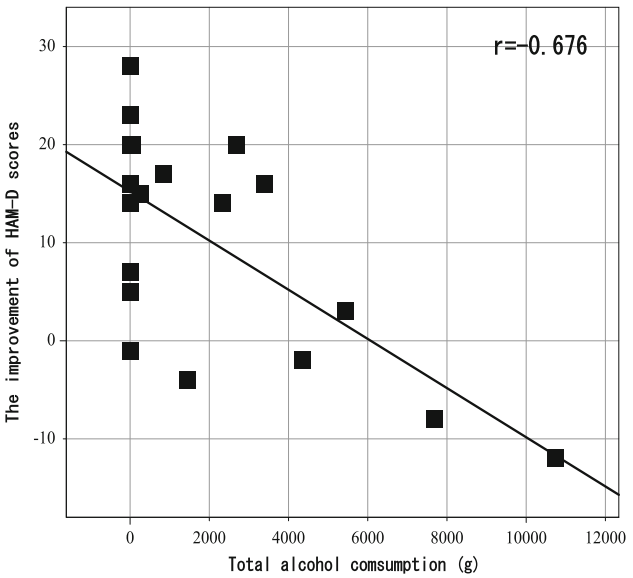


Fig. 5 Correlation analysis of the relationship between total alcohol consumption during the study period and improvement of HAM-D score at 12 weeks in AUD

Discussion

This is the first attempt to compare the efficacy of antidepressants for the treatment of MDD in Japanese patients with or without comorbid AUD. The present findings suggest that antidepressives are less effective in treating depression in patients with comorbid AUD than in those without alcohol problems.

Previous relatively small scale studies suggest that treatment with antidepressants for managing depressive symptoms can be effective in patients with substance dependence including AUD. However the evidence is conflicting and other investigators have reported a decreased response to treatment in depressive patients with comorbid AUD (Nunes and Levin 2004; Pettinati 2004, 2013). A 10-year epidemiological survey found that rates of improved depressive symptoms in subjects with AUD was about half of those in depressive patients without any alcohol problems (Mueller et al. 1994). Our present observations that showed a lower response to antidepressant medication in AUD patients than in NAUD group agree with the previous findings and it is possible that the action of antidepressants in AUD patients differ fundamentally from the actions in NAUD subjects.

We considered that determining the difference in actions of antidepressants between the two groups and the factors that explain the decreased treatment response in AUD patients to be important in developing better therapeutics for MDD with comorbid AUD. Therefore, patients who were prescribed therapeutic doses of antidepressant, i.e. as defined above, were analyzed separately and the effect of the pharmacotherapy was compared between the AUD and NAUD groups. Therapeutic doses of antidepressant resulted in significantly improved HAM-D scores during the study period in NAUD patients, but in equal doses failed to reduce HAM-D scores in AUD subjects. The results confirm the conclusion that antidepressants are less effective in the treatment of MDD in AUD patients than in NAUD patients.

A possible explanation for the diminished antidepressants action observed in AUD subjects could be biological alterations in brain induced by toxic effects of alcohol. The present result showing negative correlations between total alcohol consumption and improved HAM-D score at endpoint in the AUD group could be considered as supporting evidence for this speculation. Moreover, the negative correlation observed between AUDIT score and improved HAM-D score at 12 weeks in all subjects also seems to support the possibility that the alcohol induced biological brain changes could be related closely with the amount of alcohol intake. Questions in the AUDIT address the amount of alcohol consumption and frequency during the past year and the test is used to detect heavy drinking for evaluating alcohol problems. Thus it is suggested that the negative correlation between the AUDIT score and improved HAM-D score found in all subjects that alcohol might interfere with antidepressants action in a dose response manner.

We previously reported that chronic alcohol intake impairs the intracellular cyclic AMP (cAMP) signaling cascade in the postmortem brains of alcoholics (Pandey et al. 2001; Ukai et al. 2009). Similar alteration in the cAMP signaling pathway was also demonstrated in

postmortem brains of depressed subjects (Ozawa et al. 1993). These findings suggest a common pathophysiological background between alcoholism and depression and the cAMP signaling system in brain might be significantly impaired by chronic ethanol exposure in MDD patients with comorbid AUD. Possibly alterations in the brain cAMP signaling in MDD subjects with comorbid AUD could considerably weaken the antidepressants action which is thought to involve intracellular signal transduction pathways via stimulation of Gs protein in brain (Ozawa et al. 1993; Pandey et al. 2001).

Recent neuroimaging studies found that both alcohol dependence and MDD are associated with brain atrophy in the prefrontal cortex and hippocampal region (Agartz et al. 1999; Bremner 2002) implying a loss of neural network in those regions and possible altered intracellular signal transduction systems including cAMP signaling. This would reduce production of brain-derived neurotrophic factor (BDNF) presumed to occur in both alcohol dependence and MDD. Furthermore decreased cognitive function is associated with brain atrophy in the prefrontal cortex and hippocampal region in alcohol dependence and MDD patients (Bremner 2002; Nixon and Crews 2004). Consequently, the impaired neural network in brain is likely more severe in MDD patients with comorbid AUD than in MDD alone and this profound change could underlie the decreased response to treatment in MDD subjects with comorbid AUD.

Another possibility must be considered. Ethanol may directly interrupt the effect of antidepressants in brain. The present observation of a negative correlation between total alcohol consumption during the study period and improved HAM-D score at the endpoint in the AUD group suggests the possible disturbance of antidepressants action by increased ethanol in brain. Although it is unclear how ethanol might block the effect of antidepressants, it was suggested that the neural transmissions in brain thought to be altered in depression may also be affected by ethanol as alcohol intake may decrease the availability of tryptophan the serotonin precursor (Badawy et al. 2009).

We must also consider a possible influence of alcohol withdrawal on depressive symptoms in the AUD group. Depressed patients often drink greater amounts of alcohol as an inadequate self-medication and physical dependence can quickly develop. Withdrawal states can easily occur after one drink. Alcohol withdrawal may induce sleep disturbance, malaise, anxiety, agitation, dysphoric mood, etc. and it may be possible that withdrawal symptoms were induced and affected the assessment of HAM-D scores in the AUD patients.

Other possibilities should be kept in mind. AUD subjects are often non-compliant with drug treatment (Grant and Dawson 1998) and non-compliance could explain our results. A recent meta-analysis suggests that antidepressant medications are more effective than placebo in treating depression among subjects with comorbid AUD and supports the view that antidepressants should represent first-choice for treating depressive symptoms in patients with MDD and concurrent AUD (Iovieno et al. 2011). However, our results did not suggest significant efficacy of antidepressant treatment in the AUD group and the effects of the different types of antidepressants prescribed should also be considered. Large-scale studies with more subjects should help to answer the questions about the influence of alcohol intake on depressive symptoms and the response to pharmacotherapy in MDD comorbid with AUD and should contribute to more effective treatment for MDD concurrent with AUD.

Conclusion

The present study suggests that co-occurrence of MDD and AUD is associated with a lower response to antidepressant treatment. It may reflect an inhibitory effect of ethanol on antidepressants action in the brain. In addition, cognitive dysfunction, socioeconomic problems of patients, adherence to treatment, and type of antidepressant may all be related to the decreased treatment response of MDD patients with comorbid AUD. Further large-scale investigations with more subjects are needed to clarify the influence of comorbid AUD on depressive symptoms and the treatment response.

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