

Prevalence of problem drinking in patients with depression and association between depression severity and problem drinking: a cross-sectional survey

Susumu Higuchi¹, Izuru Nakamura², Yoshiyuki Shibasaki²

¹National Hospital Organization, Kurihama Medical and Addiction Center, Japan

²Medical Affairs, Otsuka Pharmaceutical Co., Ltd., Japan

ABSTRACT

Purpose: There has been little research into the effects of therapies for alcohol dependence in Japanese patients with depression and drinking problems. The aim of this study was to: 1) assess the prevalence of problem drinking in patients with depression and 2) evaluate the association between depression severity and problem drinking.

Methods: This cross-sectional survey was conducted in Japanese patients aged ≥ 20 years old with depression. Survey 1 identified those who engaged in habitual drinking and these individuals completed survey 2, which assessed alcohol consumption, depression severity and alcohol dependence or abuse.

Results: Overall, 2354 patients completed survey 1 and 425 patients completed survey 2. Of the patients who completed survey 2, 112 (26.4%; 95% confidence interval 22.2, 30.8) had alcohol dependence. Survey 2 showed that the severity of depression was significantly associated with the prevalence of alcohol dependence ($p < 0.0001$), suspected alcohol dependence ($p = 0.0001$) and high or very high drinking risk level (DRL; $p < 0.0001$). Univariate logistic regression analysis showed that alcohol dependence ($p < 0.0001$), suspected alcohol dependence ($p = 0.0112$), high DRL ($p = 0.0027$) and very high DRL ($p = 0.0004$) were significantly associated with severity of depression.

Conclusions: Among patients with depression who engaged in habitual drinking, the prevalence of alcohol dependence and suspected alcohol dependence were substantially higher than in the general population. Depression severity was significantly associated with alcohol dependence, suspected alcohol dependence and high or very high DRL.

Keywords: *alcohol dependence, alcohol use disorder, depression, Japanese, survey*

Received February 19, 2019 / Accepted April 8, 2019 / Published May 24, 2019.

Introduction

Worldwide, 7% and 13 – 18% of the general population experience current and lifetime problems with alcohol, respectively [1], while in Japan the prevalence of hazardous drinking is around 10%,

with 1.1% of the population experiencing alcohol dependence in their lifetime [2].

Among patients with depression, approximately 16% have current problems with alcohol such as at-risk drinking, alcohol abuse and alcohol depend-

Corresponding Author: Izuru Nakamura, Medical Affairs, Otsuka Pharmaceutical Co., Ltd., Shinagawa Grand Central Tower, 2-16-4 Konan, Minato-ku, Tokyo 108-8241, Japan; Tel: +81-3-6361-7344, Fax: +81-3-6717-1398, e-mail: Nakamura.Izuru@otsuka.jp

ence, while approximately 30% experience such problems in their lifetime [1]. An association between depression and problem drinking has been recognized since 1990 [3, 4]; however, whether there is a causal relation remains to be established [5]. Sullivan and colleagues found that alcohol problems were associated with worse outcomes in some depression-related indexes [1], while other publications support these findings [6-8]. In Japan, a survey conducted among 775 patients with depression (285 men and 491 women) treated at general psychiatric institutions on an outpatient basis, showed that 8.8% of men and 4.7% of women had alcohol dependence [9]. However, to our knowledge there are few other studies that have investigated the association between alcohol dependence and depression in Japan.

The current study was undertaken to examine the relationship between depression and hazardous drinking specifically among Japanese individuals. The study had two aims; the first was to assess the prevalence of problem drinking in patients with depression, and the second was to evaluate the association between the severity of depression and problem drinking.

Patients and Methods

Design and ethics

This study was a cross-sectional survey conducted in patients 20 years old or older who had depression according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), and were being treated at outpatient psychiatric clinics in Japan. Patients whose responses could not be considered credible were excluded (UMIN registration number UMIN 000025558).

This study was conducted in accordance with the protocol and the ethical principles outlined in the Declaration of Helsinki. The protocol was approved by the institutional review board in December 2016. Between 10 January 2017 and 30 May 2017, all patients provided verbal (survey 1) or written (survey 2) informed consent before entering the study.

Assessments

Survey 1 was administered to all eligible patients attending the outpatient psychiatric clinics and was designed to identify those who engaged in habitual drinking. Habitual drinking was defined as con-

sumption of at least 180 mL of alcohol (sake or equivalent) per day for at least 3 days per week, which is the criterion for a drinking habit according to the National Health and Nutrition Survey by the Ministry of Health, Labour and Welfare of Japan.

Survey 2 was administered only to patients who met the criteria for habitual drinking in survey 1. Patient's sex, age, duration of depression, psychiatric comorbidities (schizophrenia, anxiety disorder, eating disorder, bipolar disorder, posttraumatic stress disorder, sleep disorder, drug dependence) and drinking guidance (whether the patient had been instructed to abstain from or reduce drinking, or had received no guidance) were obtained from medical records. Information about average daily alcohol consumption (amount of pure alcohol, g/day), number of days per month when alcohol consumption exceeded 60 g for men and 40 g for women, history of treatment for alcohol dependence, marital status and presence of physical comorbidities (hypertension, hyperlipidaemia, diabetes mellitus, hepatic disorder, gout, chronic pancreatitis, others) was collected during in-person interviews.

Patients who completed survey 2 were also assessed for severity of depression, presence of alcohol dependence or abuse, presence of alcohol use disorder, drinking risk level (DRL), health-related quality of life, work productivity and activity impairment, and their desire to improve the drinking habit. Severity of depression was assessed using the Sequenced Treatment Alternative to Relieve Depression (STAR*D) [10] version of the Structured Interview Guide for the Hamilton Depression Rating Scale (SIGH-D) [11], where scores 0–7 are normal, scores 8–13 indicate mild depression, 14–18 indicate moderate depression, 19–22 indicate severe depression, and scores higher than 23 indicate very severe depression. Severity of depression was also assessed by the Clinical Global Impression – Severity (CGI-S) scale [12]. Alcohol dependence and abuse were assessed using item J (alcohol dependence and abuse) of the Japanese version of the Mini International Neuropsychiatric Interview (MINI) questionnaire [13]. Patients who answered at least one of the questions 3a–d in the affirmative were diagnosed with alcohol abuse. Patients who answered at least three of the questions 2a–g in the affirmative were diagnosed with alcohol dependence. Alcohol use disorder was diagnosed using the Japanese version of the Alcohol Use Disor-

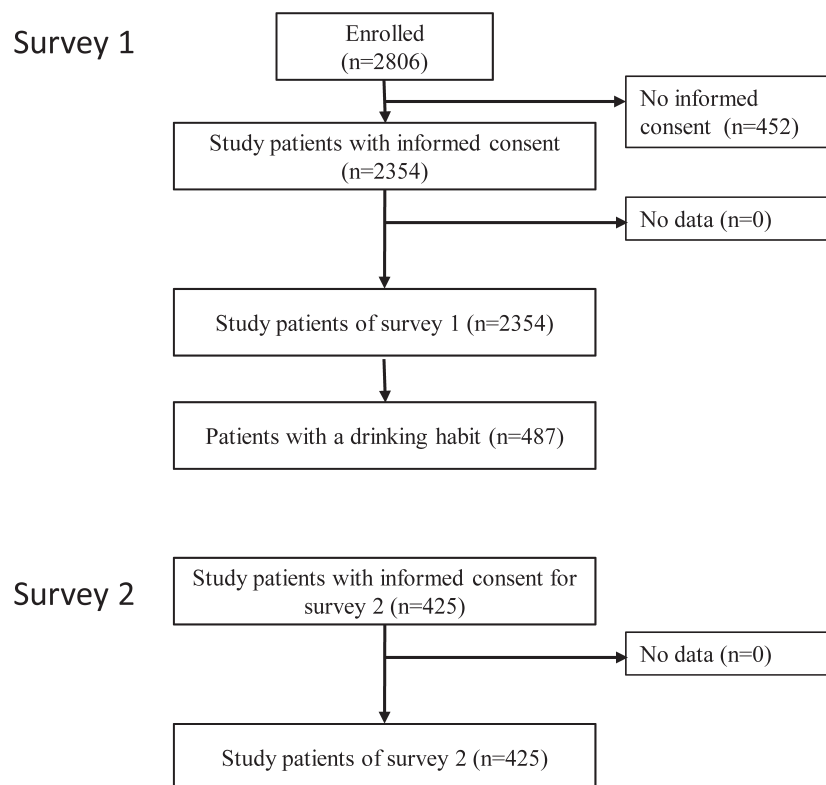


Figure 1. Patient disposition

ders Identification Test (AUDIT) [14]. Patients who scored 15 or higher were diagnosed with suspected alcohol dependence. DRL was determined using the World Health Organization methodology [4]. Health-related quality of life (HRQoL) was assessed using the EuroQol-5D (EQ-5D) questionnaire [15]. Work productivity and activity impairment (WPAI), specifically presenteeism, absenteeism and missed work hours due to health problems, were assessed using the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI-GH), version 2.2 [16].

Primary and secondary outcomes

The primary outcome of this study was the prevalence of alcohol dependence, suspected alcohol dependence and alcohol abuse in patients with depression and habitual drinking. The secondary outcome was the association between the severity of depression and alcohol dependence, suspected alcohol dependence and abuse.

Statistical analysis

Prevalence was assessed by calculating the proportion of patients with alcohol dependence, suspected dependence and abuse and 95% CI. In addition, the proportions of patients with depression of each SIGH-D level were calculated in a post hoc analy-

sis. The association between the prevalence of each SIGH-D level of depression and alcohol dependence, suspected alcohol dependence, alcohol abuse and $DRL \geq$ high was assessed using the Cochran-Armitage Trend test. To evaluate the association between severity of depression and alcohol dependence or patients' physical, social and psychological characteristics, a univariate logistic regression analysis was performed with SIGH-D score as the response variable (14 or higher vs lower than 14) and patient characteristics as the explanatory variable. Spearman's rank correlation was used to assess the relationship between parameters of depression severity, drinking behaviour, HRQoL and work productivity and impairment. The significance level was set at 5% using a two-sided test. JMP version 11.0 or later, Microsoft Excel 2013 and SAS version 9.3 or later were used for statistical calculations.

Results

Survey results

Overall, 2354 patients with depression who were treated at 23 outpatient psychiatric clinics agreed to participate in survey 1 (Figure 1). Of these, 487 had a drinking habit and 425 agreed to participate in survey 2 (Table 1). The mean (standard deviation

Table 1. Demographics of patients in survey 2

	Survey participants (n=425)
Age (years), mean (range)	48.1 (20.0-86.0)
Male, n (%)	283 (66.6)
Duration of depression (years), mean (range)	3.75 (0.0-24.1)
Psychiatric comorbidities, n (%)	
Schizophrenia	3 (0.7)
Anxiety disorder	97 (22.8)
Eating disorder	5 (1.2)
Bipolar disorder	33 (7.8)
Posttraumatic stress disorder	4 (0.9)
Sleep disorder	125 (29.4)
Drug dependence	5 (1.2)
Other	12 (2.8)
None	190 (44.7)
Drinking guidance, n (%)	
Abstinence	31 (7.3)
Drinking reduction	153 (36.0)
No guidance	241 (56.7)
History of treatment for alcohol dependence, n (%)	15 (3.5)
Married, n (%)	247 (58.1)
Lives with others (family, partner, etc.), n (%)	307 (72.2)
Physical comorbidities, n (%)	
Hypertension	87 (20.5)
Hyperlipidaemia	36 (8.5)
Diabetes mellitus	24 (5.6)
Hepatic disorder	35 (8.2)
Gout	23 (5.4)
Chronic pancreatitis	0
Other	48 (11.3)
None	264 (62.1)
Number of major depressive episodes, mean (range)	1.6 (0-10)
TAC (g/day), mean (range)	37.78 (8.57-285.71)
HDD (days/month), mean (range)	8.60 (0.0-31.0)
WHO Drinking Risk Level, n (%)	
Very high	32 (7.5)
High	43 (10.1)
Medium	88 (20.7)
Low	262 (61.6)

HDD, heavy drinking day; TAC, total alcohol consumption; WHO, World Health Organization.

[SD]) SIGH-D score for depression severity was 11.8 (7.2) in these 425 patients.

Prevalence of severe depression and alcohol dependence

Of the 425 patients included in survey 2, 44 patients (10.4%; 95% CI 7.6, 13.6) engaged in alcohol abuse, 112 patients (26.4%; 95% CI 22.2, 30.8) had alcohol dependence and 135 patients (31.8%; 95% CI 27.4, 36.4) had suspected alcohol dependence (Table 2).

The mean (SD) SIGH-D score was 16.5 (7.6) in

patients with alcohol dependence (n = 112), 13.9 (7.8) in patients with suspected alcohol dependence (n = 135), 11.2 (5.9) in patients with alcohol abuse (n = 44) and 15.1 (7.7) in patients with high or very high DRL (n = 75). As the severity of depression increased there was a significant increase in the prevalence of patients with alcohol dependence ($p < 0.0001$), suspected alcohol dependence ($p = 0.0001$) and high or very high DRL ($p < 0.0001$), suggesting a significant association between depression and these drinking problems. On the other hand, there was no significant association between the severity of depression and the prevalence of al-

Table 2. SIGH-D scores and the number of patients with alcohol drinking problems

SIGH-D score	Total	Alcohol dependence*	Suspected alcohol dependence**	Alcohol abuse*	Patients with DRL ≥High***
	425	112 (26.4%)	135 (31.8%)	44 (10.4%)	75 (17.6%)
0-7: Normal	135	15 (11.1%)	32 (23.7%)	13 (9.6%)	14 (10.4%)
8-13: Mild depression	129	26 (20.2%)	40 (31.0%)	15 (11.6%)	21 (16.3%)
14-18: Moderate depression	79	24 (30.4%)	21 (26.6%)	10 (12.7%)	10 (12.7%)
19-22: Severe depression	41	18 (43.9%)	21 (51.2%)	4 (9.8%)	15 (36.6%)
≥23: Very severe depression	41	29 (70.7%)	21 (51.2%)	2 (4.9%)	15 (36.6%)
Cochran-Armitage Trend test	–	<0.0001	0.0001	0.5815	<0.0001

*Alcohol dependence and abuse were assessed using item J (alcohol dependence and abuse) of the Mini International Neuropsychiatric Interview (MINI) questionnaire, Japanese version. Patients who answered at least one of the questions 3a-d in the affirmative were diagnosed with alcohol abuse. Patients who answered at least three of the questions 2a-g in the affirmative were diagnosed with alcohol dependence.

**Suspected alcohol dependence was diagnosed using the Alcohol Use Disorders Identification Test (AUDIT), Japanese version. Patients who scored 15 or higher were diagnosed with suspected alcohol dependence.

***Patients not diagnosed with alcohol dependence, suspected alcohol dependence or alcohol abuse. DRL was determined using the World Health Organization methodology

CI, confidence interval; DRL, drinking risk level; SD, standard deviation; SIGH-D, Structured Interview Guide for the Hamilton Depression Rating Scale.

Table 3. Univariate logistic regression analysis of factors associated with depression severity

Category	Odds ratio	95% CI	p-value
Age (vs individuals aged 1 year older)	0.99	0.97, 1.00	0.1096
Females (vs males)	1.88	1.24, 2.84	0.0027
Living with someone (vs living alone)	0.77	0.50, 1.19	0.2373
Marital status			
Married/cohabiting (vs never married)	0.73	0.45, 1.17	0.1879
Single/living alone (vs married/cohabiting)	1.57	0.86, 2.86	0.1411
Physical comorbidities (vs no physical comorbidities)	1.33	0.89, 1.98	0.1610
Psychiatric comorbidities (vs no psychiatric comorbidities)	1.00	0.67, 1.50	0.9985
Alcohol abuse (vs no alcohol abuse) *	0.93	0.49, 1.78	0.8264
Suspected alcohol dependence (vs no suspected dependence)	1.71	1.13, 2.60	0.0112
Alcohol dependence (vs no alcohol dependence)	4.29	2.72, 6.77	<0.0001
DRL ≥Medium (Medium + High + Very high) (vs Low)	1.36	0.91, 2.03	0.1364
DRL ≥High (High + Very high) (vs Medium + Low)	2.16	1.31, 3.58	0.0027
DRL ≥Very High (vs High + Medium + Low)	4.02	1.85, 8.73	0.0004
HDD ≥4 (vs <4)	1.24	0.83, 1.83	0.2909

() represents denominator.

*“No alcohol abuse” included all patients except those with alcohol abuse, as diagnosed with MINI questionnaire. Analogous definitions applied to “no suspected alcohol dependence” and “no alcohol dependence”.

CI, confidence interval; DRL, drinking risk level; HDD, heavy drinking day

cohol abuse ($p = 0.5815$; Table 2).

Variables associated with depression severity

Factors identified as being significantly associated with depression severity in the univariate logistic regression analysis were female sex ($p = 0.0027$), alcohol dependence ($p < 0.0001$), suspected alcohol dependence ($p = 0.0112$), high DRL ($p = 0.0027$) and very high DRL ($p = 0.0004$) (Table 3). Consistent with the analysis of prevalence, no association

was found between depression severity and alcohol abuse ($p = 0.8264$).

Significant correlations were identified between total SIGH-D and CGI-S scores and the number of patients who gave affirmative answers to MINI question 2 ($p = 0.0012$ and $p = 0.0019$, respectively). Consciousness of a drinking problem was significantly associated with the total AUDIT score ($p < 0.0001$). The SIGH-D score was significantly

associated with EQ-5D ($p = 0.0007$), EQ-5D Visual Analogue Scale (EQ-5D-VAS; $p = 0.0001$), WPAI presenteeism ($p = 0.0041$), WPAI missed work hours due to health problems ($p = 0.0042$), CGI-S score ($p < 0.0001$) and sex ($p < 0.0001$) (Supplementary Table 1).

Discussion

The findings of this cross-sectional study show that the prevalence of habitual drinking in adult outpatients with depression was 20.7%. Among those patients who engaged in habitual drinking, the prevalence of alcohol dependence, suspected alcohol dependence and alcohol abuse was 26.4%, 31.8% and 10.4%, respectively. In this group, depression severity was significantly associated with alcohol dependence, suspected alcohol dependence and high or very high DRL. There was no significant association between severity of depression and alcohol abuse.

The prevalence of alcohol dependence in the Japanese general population was studied by Osaki and colleagues in 2003, 2008 and 2013 [2]. They defined alcoholism according to the AUDIT test, whereby a score of 15 or more denoted suspected alcoholism, and found a prevalence of 2.7% in 2013 [2]. Compared with these data, the prevalence of suspected alcohol dependence in patients with depression in the present study was 10 times higher. The prevalence of “current alcohol dependence” using ICD-10 diagnostic codes was 0.6% in the 2013 study by Osaki and colleagues and 26.4% in patients with depression in the present study (diagnosed with MINI). In a systematic review published in 2005, the median prevalence of current alcohol problems in patients with depression was 16% (range 5–67%), while it was 7% in the general population [1]. Comparable results were obtained in the present study.

The existence of a statistical association between alcohol use disorders and depression has been discussed since 1990 [3-5]. A meta-analysis of longitudinal and cross-sectional studies conducted by Boden and colleagues suggested the existence of this association and the authors concluded that it was robust to variations in study design and assessment methods [17]. The connection between alcohol use disorders and depression may be explained by a causal relation; however, this remained to be confirmed [17]. An analysis of the survey of a na-

tionally representative population of 17,276 individuals conducted in Canada over a period of 12 years showed that this causal relationship is bidirectional in men, but not in women [18]. The results of a household survey of 43,083 individuals conducted in the US indicate that major depressive episodes are more strongly associated with alcohol dependence than with alcohol abuse [19]. These findings echo those of the present study, in which the severity of depression was significantly associated with alcohol dependence, but not abuse.

There is a debate about whether antidepressant treatments are less effective in patients with co-occurring depression and alcohol use disorder. In a meta-analysis of 14 randomized, double-blind, placebo-controlled clinical trials, antidepressants were found to produce a moderately-sized improvement in depressive symptoms (pooled effect size 0.38; 95% CI 0.18, 0.58) [20]. In a systematic review conducted by Foulds and colleagues, the pooled effect size of anti-depressant therapy compared to placebo was estimated at less than 0.2, with CI including zero [21]. In another systematic review that included controlled trials of antidepressants in patients with depression and alcohol dependence, antidepressants were shown to significantly improve some measures of alcohol dependence, although the quality of the included studies was low or moderate [22].

On the other hand, little research has been conducted on the effects of therapies for alcohol use disorders and it is possible that these therapies will lead to some improvement in depression in patients with co-occurring depression and alcohol use disorder. According to some estimates, up to 10% of the overall burden of major depression could be due to an alcohol use disorder [17]. One of the problems in the treatment of alcohol dependence is that abstinence is difficult to achieve and maintain, particularly in patients with comorbid depression. It would be interesting to investigate whether reducing alcohol consumption with the help of drugs would affect depression. The findings of the present study suggest that reducing alcohol consumption from high or very high DRL to moderate or mild could lead to reductions in the severity of depression. Further research into this area is warranted.

This study had a number of limitations. Firstly, patients with both independent and alcohol-induced depression were included in this study and all data

were analysed collectively. While the present study did not focus on the nature of causality, data on the natural histories of both disorders would be useful. Previous studies found sex differences in the prevalence of alcohol use disorders and depression [18]; however, the present study did not investigate these differences. Furthermore, no data on the use of treatments such as antidepressants, cognitive behavioural therapy, interpersonal psychotherapy or electroconvulsive therapy at baseline or during the study, which may confound the results was analyzed. Finally, because the present study was conducted exclusively in Japanese patients, the generalisability of its results may be limited in other populations.

Conclusions

The results of this study indicate that among patients with depression who engaged in habitual drinking the prevalence of alcohol dependence and suspected alcohol dependence were substantially higher than in the general population. In this group, depression severity was significantly associated with alcohol dependence, suspected alcohol dependence and high or very high DRL, but not with alcohol abuse. Further research into the effects of treatments for alcohol dependence, including on the symptoms of depression, is warranted.

Funding

This study was funded by Otsuka Pharmaceutical Co., Ltd. The publication fee was also covered by Otsuka Pharmaceutical Co., Ltd.

Author contributions

Susumu Higuchi conceived and designed the study. Yoshiyuki Shibasaki was the study statistician. Izuru Nakamura and Yoshiyuki Shibasaki contributed to the study design, preparation of the study report, writing of the manuscript, and read and approved the drafts. All authors participated in the interpretation of the data and in the writing, critical review and revision of the manuscript. All authors approved the final manuscript for publication.

CONFLICT OF INTEREST

Susumu Higuchi has received personal fees, grants and other fees from Otsuka Pharmaceutical, as well as grants and other fees from Lundbeck Japan

during the conduct of the study, as well as personal fees from Nippon Shinyaku, MSD, Yoshitomi Pharmaceutical, Jansen Pharma, Eli-Lilly Japan, Mochida Pharmaceutical, and Meiji-Seika Pharma, and other fees from Nippon Shinyaku, and Eisai. Izuru Nakamura and Yoshiyuki Shibasaki are full-time employees of Otsuka Pharmaceutical Co., Ltd. A California winery, Ridge Vineyards, Inc., is a subsidiary company of Otsuka Pharmaceutical Co., LTD.

ACKNOWLEDGEMENT

We would like to thank Yoshiko Okamoto, PhD and Georgii Filatov of inScience Communications, Springer Healthcare, who wrote the outline and the first draft of this manuscript, respectively. This medical writing assistance was funded by Otsuka Pharmaceutical Co., Ltd.

REFERENCES

- [1] Sullivan LE, Fiellin DA, O'Connor PG. The prevalence and impact of alcohol problems in major depression: a systematic review. *Am J Med.* 2005; 118(4): 330-341.
- [2] Osaki Y, Kinjo A, Higuchi S, et al. Prevalence and trends in alcohol dependence and alcohol use disorders in Japanese adults: results from periodical nationwide surveys. *Alcohol Alcohol.* 2016; 51(4): 465-473.
- [3] Regier DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. *JAMA.* 1990; 264(19): 2511-2518.
- [4] World Health Organization, Department of Mental Health and Substance Dependence. International guide for monitoring alcohol consumption and related harm. 2000. <http://apps.who.int/iris/handle/10665/66529> Accessed 8 August 2018.
- [5] Davis L, Uezato A, Newell JM, et al. Major depression and comorbid substance use disorders. *Curr Opin Psychiatry.* 2008; 21(1): 14-18.
- [6] Åhlin J, Hallgren M, Öjehagen A, et al. Adults with mild to moderate depression exhibit more alcohol related problems compared to the general adult population: a cross sectional study. *BMC Public Health.* 2015; 15: 542.
- [7] Johannessen EL, Andersson HW, Bjørngaard JH, et al. Anxiety and depression symptoms

- and alcohol use among adolescents - a cross sectional study of Norwegian secondary school students. *BMC Public Health*. 2017; 17(1): 494.
- [8] Subramaniam M, Mahesh MV, Peh CX, et al. Hazardous alcohol use among patients with schizophrenia and depression. *Alcohol*. 2017; 65: 63-69.
- [9] Matsumoto T, Kobayashi O, F. I, et al. Prevalence of problem drinking in outpatients with depressive disorder: a study using a literature control. *Seishin Igaku*. 2012; 54(1): 29-37.
- [10] Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Control Clin Trials*. 2004; 25(1): 119-142.
- [11] Williams JB. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry*. 1988; 45(8): 742-747.
- [12] Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, and Welfare. 1976: 534-537.
- [13] Otsubo T, Tanaka K, Koda R, et al. Reliability and validity of Japanese version of the Mini-International Neuropsychiatric Interview. *Psychiatry Clin Neurosci*. 2005; 59(5): 517-526.
- [14] Hiro H, Shima S. [Availability of the Alcohol Use Disorders Identification Test (AUDIT) for a complete health examination in Japan]. *Nihon Arukoru Yakubutsu Igakkai Zasshi*. 1996; 31(5): 437-450.
- [15] EuroQol Group. EQ-5D questionnaire. <https://euroqol.org/eq-5d-instruments/>. Accessed 27 March 2019.
- [16] Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993; 4(5): 353-365.
- [17] Boden JM, Fergusson DM. Alcohol and depression. *Addiction*. 2011; 106(5): 906-914.
- [18] Bulloch A, Lavorato D, Williams J, et al. Alcohol consumption and major depression in the general population: the critical importance of dependence. *Depress Anxiety*. 2012; 29(12): 1058-1064.
- [19] Cranford JA, Nolen-Hoeksema S, Zucker RA. Alcohol involvement as a function of co-occurring alcohol use disorders and major depressive episode: evidence from the National Epidemiologic Survey on Alcohol and Related Conditions. *Drug Alcohol Depend*. 2011; 117(2-3): 145-151.
- [20] Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *JAMA*. 2004; 291(15): 1887-1896.
- [21] Foulds JA, Adamson SJ, Boden JM, et al. Depression in patients with alcohol use disorders: Systematic review and meta-analysis of outcomes for independent and substance-induced disorders. *J Affect Disord*. 2015; 185: 47-59.
- [22] Agabio R, Trogu E, Pani PP. Antidepressants for the treatment of people with co-occurring depression and alcohol dependence. *Cochrane Database Syst Rev*. 2018; 4: CD008581.

Supplementary Table 1. Association between parameters in alcohol dependent patients. *Spearman's rank correlation coefficient

	MLN.I Y to Q2 (n)	AUDIT total score	SIGH-D total score	EQ-5D value	EQ-5D (VAS)	WPAI (presenteeism)	WPAI (absenteeism)	WPAI (missed work hours due to health problem)	TAC	HDD	CGI-S	WPAI: GH Y to Q1	living status	Marital status	Age	Gender	History of treatment for alcohol dependence	Presence of physical complications	Presence of psychiatric complications	Status of drinking guidance	Status of consciousness on the drinking problem	Consciousness on the drinking problem	
MLN.I Y to Q2 (n)	Correlation	0.3350	0.3028	0.1780	0.2010	0.2350	0.2499	0.2376	0.2497	0.2871	0.2904	0.0689	0.0991	0.0449	0.0924	0.0799	0.0111	-0.1551	-0.0317	0.3516	-0.1652	0.1170	
	p value	0.0003	0.0012	0.0604	0.0336	0.0812	0.0585	0.0779	0.0079	0.0021	0.0019	0.4703	0.2988	0.6385	0.3324	0.4021	0.9073	0.1024	0.7399	0.0001	0.0817	0.2192	
AUDIT total score	Correlation		0.0156	0.4046	0.1392	0.2766	0.3688	0.3021	0.5852	0.5494	0.1146	0.0908	0.0456	0.1313	0.2990	0.1873	0.1872	-0.2212	0.0873	0.3068	-0.4651	0.2132	
	p value		0.8704	<0.0001	0.1432	0.0391	0.0044	0.0237	<0.0001	<0.0001	0.2291	0.3411	0.6533	0.1677	0.0014	0.0480	0.0481	0.0191	0.3601	0.0010	<0.0001	0.0240	
SIGH-D total score	Correlation			0.3148	0.3571	0.3776	0.2248	0.3771	0.1129	0.0470	0.6025	0.2337	0.1224	0.1043	0.1723	0.4234	-0.0389	-0.0149	0.0848	0.1854	-0.0184	-0.0075	
	p value			0.0007	0.0001	0.0041	0.0899	0.0042	0.2359	0.6225	<0.0001	0.0132	0.1987	0.2736	0.0693	<0.0001	0.6840	0.8758	0.3740	0.0503	0.8477	0.9778	
EQ-5D value	Correlation				0.5309	0.5540	0.0975	0.5464	0.2073	-0.1153	0.2708	0.1169	0.1049	0.2128	0.2725	0.3047	-0.2026	0.2185	-0.1447	0.2398	0.1905	-0.2546	
	p value				<0.0001	<0.0001	0.4666	<0.0001	0.0283	0.2262	0.0039	0.2197	0.2712	0.0243	0.0036	0.0011	0.0232	0.0206	0.1279	0.0109	0.0443	0.0068	
EQ-5D (VAS)	Correlation					0.4658	0.0593	0.4706	0.0251	-0.0125	-0.2029	0.1510	0.1071	0.1900	0.1453	0.1667	-0.2236	0.0682	-0.1587	0.1516	-0.0168	-0.1819	
	p value					0.0003	0.6584	0.0003	0.7932	0.8959	0.0319	0.1119	0.2609	0.0448	0.1264	0.0790	0.0178	0.4750	0.0947	0.1107	0.8605	0.0550	
WPAI (presenteeism)	Correlation						0.3143	0.9960	0.0049	0.0769	0.1483	0.1119	0.1422	0.1743	0.2431	0.1531	0.1233	-0.2663	-0.1396	0.2287	0.0123	0.2284	
	p value						0.0183	<0.0001	0.9715	0.5731	0.2754	0.2958	0.2958	0.1988	0.0710	0.2600	0.3653	0.0473	0.3047	0.0899	0.9282	0.0904	
WPAI (absenteeism)	Correlation							0.3720	0.4313	0.4190	0.3950	0.0016	0.0016	0.0468	0.1977	0.1593	-0.0585	-0.0028	0.0706	0.1615	-0.1640	0.1949	
	p value							0.0048	0.0007	0.0011	0.0022	0.9906	0.9906	0.7272	0.1369	0.2323	0.6629	0.9832	0.5986	0.2259	0.2185	0.1426	
WPAI (missed work hours due to health problem)	Correlation								0.0231	0.1004	0.1606	0.1308	0.1308	0.1711	0.2400	0.1635	0.1196	-0.2556	-0.1427	0.2316	-0.0145	0.2405	
	p value								0.8658	0.4615	0.2369	0.3367	0.3367	0.2074	0.0749	0.2286	0.3798	0.0573	0.2942	0.0858	0.9154	0.0742	
TAC	Correlation									0.7130	0.2900	0.2097	0.0858	0.0438	0.2571	0.1564	-0.0009	-0.1124	0.0067	0.2584	-0.3557	0.1007	
	p value									<0.0001	0.0019	0.0265	0.3683	0.6465	0.0062	0.0996	0.9925	0.2382	0.9441	0.0059	0.0001	0.2908	
HDD	Correlation										0.2077	0.1042	0.0834	0.0393	0.1592	0.0837	0.0996	-0.0511	-0.0221	0.3134	-0.3621	0.0453	
	p value										0.0280	0.2741	0.3822	0.6811	0.0937	0.3802	0.2960	0.5928	0.8175	0.0008	<0.0001	0.6356	
CGI-S	Correlation										0.1601	0.0696	0.0071	0.2181	0.2765	-0.0318	-0.0109	0.3930	0.3824	-0.0957	0.1661	0.1661	
	p value										0.0918	0.4658	0.9412	0.0079	0.0590	0.0785	0.0392	-0.0706	<0.0001	<0.0001	0.3153	0.0800	
WPAI: GH Y to Q1	Correlation											0.0079	0.0590	0.2136	0.0785	0.0392	-0.0706	-0.1317	0.0065	-0.2036	0.1713	0.1713	
	p value											0.9338	0.5365	0.0237	0.4107	0.6813	0.4596	0.1663	0.9454	0.0313	0.0710	0.0710	
living status	Correlation												0.6463	0.1017	0.1354	0.1443	-0.0108	0.1057	0.1327	-0.1376	-0.1766	-0.1766	
	p value												<0.0001	0.2860	0.1548	0.1289	0.9100	0.2672	0.1631	0.1479	0.0625	0.0625	
Marital status	Correlation													0.2200	0.1652	-0.0544	-0.0337	0.0085	0.1304	-0.0423	0.2548	0.2548	
	p value													0.0197	0.0687	0.7245	0.9294	0.2779	0.2779	0.6576	0.0067	0.0067	
Age	Correlation														0.3701	0.0795	0.4990	-0.2309	0.1827	0.0875	-0.2052	-0.2052	
	p value														<0.0001	0.4047	<0.0001	0.0143	0.0538	0.3588	0.0300	0.0300	
Gender	Correlation															-0.0298	-0.2075	0.1391	0.0944	-0.2319	0.2000	0.2000	
	p value															0.7550	0.0281	0.1435	0.3221	0.0139	0.0345	0.0345	
History of treatment for alcohol dependence	Correlation															0.0639	0.1369	0.1369	0.1013	-0.2115	-0.1796	-0.1796	
	p value															0.5031	0.1501	0.1501	0.2787	0.0252	0.0580	0.0580	
Presence of physical complications	Correlation																		-0.0520	0.2704	0.0558	-0.2077	-0.2077
	p value																		0.5863	0.0039	0.5589	0.0280	0.0280
Presence of psychiatric complications	Correlation																			0.0887	0.0245	0.0225	0.0225
	p value																			0.3635	0.7975	0.8140	0.8140
Status of drinking guidance	Correlation																				-0.1707	0.1147	0.1147
	p value																				0.0719	0.2286	0.2286
Consciousness on the drinking problem	Correlation																					-0.1522	-0.1522
	p value																					0.1091	0.1091
Consciousness to improve habitual drinking	Correlation																						

AUDIT, Alcohol Use Disorders Identification Test; CGI-S, Clinical Global Impression - Severity; EQ, EuroQol; HDD, heavy drinking day; MINI, Mini International Neuropsychiatric Interview; Q, quarter of the year; SIGH-D, Structured Interview Guide for the Hamilton Depression Rating Scale; TAC, total alcohol consumption; VAS, visual analogue scale; WPAI-GH, Work Productivity and Activity Impairment Questionnaire-General Health