Interaction of Heavy Drinking Patterns and Depression Severity Predicts Efficacy of Quetiapine Fumarate XR in Lowering Alcohol Intake in Alcohol Use Disorder Patients

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ABSTRACT

BACKGROUND: Shared etiological pathways of dopamine and serotonin neurotransmission play a central role in heavy alcohol intake and exacerbation in the symptoms of depression.

We investigated the treatment efficacy of Quetiapine fumarate extended release (XR) in lowering alcohol intake in alcohol use disorder (AUD) patients indicated by the shared alleviation of depression ratings and patterns of heavy drinking.

METHODS: Hundred and eight male and female heavy drinking AUD patients in the age range of 18 to 64 years. participated in a randomized clinical trial (RCT) to receive 12 weeks of quetiapine XR or placebo (N = 115). Participants were sub-grouped by the severity grading of depression using Montgomery-Asberg Depression Rating Scale (MADRS) (clinically relevant ⩾8 [CR], clinically non-relevant ⩽7 [CNR]) at baseline in both the groups. Drinking history and depression ratings were assessed at the patients' visits.

RESULTS: Heavy drinking days (HDD) and total drinks (TD) were significantly fewer in CR patients at the treatment end. A true positive response in AUROC analysis supported the lowering of TD in CR patients. The number of drinking days (NDD) and average drinks per drinking day (AvgD) were lower in the CNR patients at treatment-end. Significant associations with increasing effect sizes were observed for all the heavy drinking measures (HDD, TD, NDD, and AvgD) and MADRS scores by the end of the treatment course.

CONCLUSIONS: Baseline elevated depressive symptoms could likely predict the course of heavy alcohol drinking during the treatment, and efficacy outcome of a treatment. AUD patients with baseline clinically significant depression had a progressive lowering in heavy drinking markers significantly corresponding to the lowering of depression symptoms by the end of treatment with Quetiapine fumarate XR.

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KEYWORDS: Alcohol dependents, alcohol use disorder, depression, drinking-markers, MADRS, quetiapine *fumarate* XR

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Introduction

Alcohol use disorder (AUD) is an important mental and medical health concern in the United States. Heavy prolonged alcohol intake can cause organ injury, including neurodegenerative and adverse neurocognitive effects.[1] Currently, the FDA approved medications for treatment of alcohol use disorder (AUD), that is, disulfiram, acamprosate, and oral and injectable naltrexone,[2,3] have not been proven to be efficacious for all patients. Around 30% of the patients with bipolar depression and schizophrenia conditions report higher susceptibility to heavy alcohol drinking.[4,5] Heavy alcohol intake and depression have been shown to have close comorbid susceptibility thus there is a high likelihood finding depression symptoms in alcohol dependents (AD).[6]

Some studies have shown this propensity with the involvement of dopamine D2 and serotonin 5-HT2 pathways in such mental comorbid conditions along with heavy alcohol intake.[7,8] This propensity of alcohol and mental health condition has

been mechanistically explained using the same pathways both in human and animal studies.[9-11] Alcohol intake in excessive amounts could also adversely impact the prognosis in these conditions.[12,13] Among the clinical trials conducted to date, Quetiapine has been shown to have positive effects on alcohol consumption—increased days of abstinence from alcohol during the two to seven months of treatment[14]; increased abstinent days and improvement in depression, anxiety, and insomnia[15]; and increased abstinent days and fewer hospitalizations in alcohol-dependent patients with disturbed sleep.[16] Such mental health conditions are difficult to manage and have shown broad co-morbidity.[17]

Heavy alcohol drinking has been well characterized by the recent drinking history using Timeline Followback (TLFB) for past 90 days in AUD patients in recent research on AUD.[18,19] These markers have also been tested on AUD patient cohorts who also exhibited other forms of addiction such as cocaine, pathophysiological or behavioral symptomology including depression.[20-22] Heavy drinking markers derived from TLFB do not only characterize the drinking behavior, consequences, and pathological course but are also highly useful as therapeutic targets of treatment efficacy.[23,24] Thus, in this study, we used TLFB as our primary assessment of endpoints for treatment efficacy.

A pharmacotherapeutic drug that could reduce alcohol consumption and adequately manage complications of chronic alcohol consumption would be a desirable treatment alternative for lowering alcohol intake. A pilot study had shown reduction of alcohol consumption with Quetiapine treatment in heavy drinkers.[25] The preliminary results described above suggest that Quetiapine may have potential in treatment for alcohol dependence, especially among heavy drinkers (of more complicated Type B, early-onset alcoholics). Quetiapine is an FDA approved treatment for depression, bipolar disorder, and schizophrenia. Thus, we postulated that Quetiapine may be a useful intervention to reduce heavy alcohol drinking in alcohol dependents who also exhibit symptoms of depression following previous literature.[6,26]

This study was conducted as a secondary analysis of a larger clinical trial on quetiapine efficacy for reducing alcohol consumption.[27] The primary aim of this study was to determine if baseline and longitudinally reported depression ratings (as assessed by Montgomery-Asberg Depression Rating Scale [MADRS]) and corresponding heavy drinking patterns could predict efficacy of Quetiapine XR in reducing heavy alcohol drinking to a moderate level. Our other aim was to identify the specific markers/patterns of heavy drinking that show affinity with the symptoms of depression in AUD patients.

Methods

Study participants

This study is one of the investigational arms of a larger protocol (ClinicalTrials.gov: NCT#00498628) that was supported by National Institute on Alcohol Abuse and Alcoholism (NIAAA). This investigation was a double-blind placebo-controlled (Randomized Clinical Trial) parallel group design with two treatment groups: (1) Quetiapine XR as an active drug, and (2) placebo as control that was approved by the institutional review board of all the participating sites. One hundred and seventy-nine men and 45 women (N = 224) were randomized in this larger study after the completion of consenting, and 218 started the treatment.[27] One hundred and eight patients who received Quetiapine fumarate XR among the total randomized were included specific for this study (and only 105 participants took at least first dose). Placebo group had 115 subjects enrolled (however eventually 113 only took at least first dose). Data of one participant was excluded from this study. We have not used placebo data in this study apart from Figure 5. Participants were recruited with initially assessment either telephonically/in-person to determine basic eligibility and further with a screening visit scheduled as a clinic appointment. Participants who met the participation criteria and agreed to participate, were consented to enroll in the study.

Inclusion criteria included diagnosis with alcohol dependence (using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) and age between 18 and 64 years. Other inclusion criteria were 10 or more drinks per day for men and 8 or more drinks per day for women for at least 40% of the last 60 days of the 90-day drinking assessment (Timeline Follow-back, TLFB90). Having a 0.00 breath alcohol level at the time of consenting was also a requirement. Major exclusions were: other psychoactive drug dependence within the last year, positive urine screen for drugs, participation in other pharmacological/behavioral study within the last three months, lifetime diagnosis of major depression or eating disorder, use of antidepressants (last 30 days) and antipsychotics (last 14 days) before randomization, other significant medical conditions such as panic disorder with or without agoraphobia, schizophrenia, bipolar disorder, or other psychosis, or a past-year diagnosis of major depression or eating disorder, and Clinical Institute Withdrawal Assessment of Alcohol score $\geqslant$10.

Procedures and assessments

The active drug, Quetiapine XR (Seroquel XR® AstraZeneca, Wilmington DE) was provided to the participants for three months in 50- and 200-mg tablets with identical matching non-active pills for the placebo group.[27] Blood chemistry; clinical and subjective assessments from baseline (0W, start of the trial treatment); end of four week (4W, post 3-weeks of dose titration or dose escalation $\pm$1 week); end of eight weeks (8W, mid of maintenance phase of dosing); and end of week 12 (12W, end of maintenance phase of dosing when dose tapering phase commenced) were evaluated. Dose was titrated in the first three weeks up to a target dose of 400 mg/day, which was maintained from the start of week 4 until the end of week 12. Some patients received lower dose (50 mg daily depending on

the tolerability). Details on dose titration, protocol for delay in titration reaching maintenance dose, and dose adjustments have been details also in the parent publication of this study.[28] All individuals received medical management (MM) that included assessment of medication side effects, participant education and advice on drinking.[29] Safety and adverse events have already been discussed in a parent publication[28] and thus is not within the interest of this study.

Data collection, statistical paradigm and analysis

Individual demographics—age (years), sex (male or female), weight (lbs.), and drinking history (TLFB90) were collected at the time of screening evaluation and were included in this study to estimate their role as pre-existing conditions and factors in the Quetiapine XR pharmacodynamics. Recent TLFB90 measures[30] developed from the raw data included Total Drinks (TD90), Drinking Days past 90 Days (NDD90), Average Drinks per Drinking Day in past 90 Days (AvgDPD90), and Heavy Drinking Days (defined as five or more drinks per day for a man and four or more drinks per day for a woman) in the past 90 Days (HDD90). Additionally, we analyzed drinking history at each timepoint : baseline (−2-0W, between screening and baseline for two weeks); week 4 (4W, for an interval of four weeks, from baseline to the end of week 4); week 8 (8W, with an interval of two weeks from the beginning of the 7th week to the end of 8th week); and week 12 (12W, with an interval of two weeks starting from the beginning of the 11th week to the end of 12th week). We also used the TLFB questionnaire during the treatment period they have been termed as following: Total Drinks (TD), Drinking Days (NDD), Average Drinks per Drinking Day (AvgD), and Heavy Drinking Days (defined as five or more drinks per day for a man and four or more drinks per day for a woman, HDD).

Demographic and drinking history assessment were collected. Difference in Quetiapine treated and placebo group were analyzed using univariate analysis (Table 1). The MADRS scale was included in this study as the primary tool for grouping the AD patients. Patients were grouped based on the MADRS score reported at baseline as having clinically not relevant (CNR) or clinically relevant (CR) depression. MADRS was selected as an instrument for assessment of depression symptoms since it has only one item pertaining to sleep disturbance, due to which clinical investigations and regulatory authorities favor the MADRS to discriminate any prominent nonspecific sedative effects.[31] The scale was constructed to be sensitive to changes in treatment effects. Its capacity to differentiate between responders and non-responders to antidepressant treatment has been shown to be comparable to the Hamilton Rating Scale for Depression,[32] another established measure of depressive symptomatology, but the MADRS has greater sensitivity to change during the course. It has exhibited high inter-rater reliability and appears to be oriented more towards psychic as opposed to somatic aspects of depression.[33]

Participants were grouped by the severity grading of depression using Montgomery-Asberg Depression Rating Scale (MADRS) (clinically relevant $\geqslant$8 [CR], clinically non-relevant $\leqslant$7 [CNR]) at baseline in both the active and placebo groups. Since there were some patients who could have taken antidepressants more than 30 days back (not an exclusion criteria), we also included the between the scale steps' score for each question (1, 3, 5) to include any subtle elevations (thus $\leqslant$7) in place of defined scale steps (0, 2, 4, 6) for patients.[34] This assessment was used in various between-group univariate, and repeated ANOVA analyzes. MADRS scores were used as covariates in the between group (and by time-course analyzes, as applicable) for multiple comparisons. Multiple comparisons were conducted to estimate the increase in effect sizes of the outcome measures (post-treatment drinking markers) only. Association analyzes were conducted using linear and multivariable regression models. Data analysis platforms used in this study were SPSS 26.0 version (IBM, Chicago IL), MS Office 365 (MS Corp. Redmond WA) and GraphPad prism 7 (GraphPad Software, Inc., La Jolla CA). Figures were created using MS Office PowerPoint 2016 (MS Corp. Redmond WA) and GraphPad prism 7 (GraphPad Software, Inc., La Jolla CA), and converted to TIFF file. Statistical significance was set at $P < .05$. Data are presented as Mean ± Standard Deviation (M ± SD).

Results

Patient characterization and drinking profile

Demographic measures were comparably similar in all the subgroups differentiated by treatment, and sex (Table 1). At the baseline, 31 out of 108 alcohol dependent patients showed clinically relevant depression based on the MADRS scores in the active treatment group, and 44 in the placebo arm. As anticipated, males weighed more and numbered more than females in each arm. There was no significant main effect of any of the demographic or drinking history markers in these analyzes. There were no statistical differences at baseline in the heavy drinking markers between the AD patients with clinically relevant (CR) depression and those without (CNR) depression.

Changes in heavy drinking patterns in quetiapine treated AD patients

There was no difference in any of the drinking markers recorded at baseline 9 for a period of two weeks prior: −2-0W) between the CR and CNR groups (Figures 1a, 2a, 3a, 4a). We found a time-dependent response in the drinking patterns between the CR group compared to the CNR group across all the timepoints (Figures 1–4).

HDD (7.45 ± 6.2 at baseline versus 2.68 ± 3.8 at 12W) was lower in CR group compared to the CNR group (7.61 ± 6.1 at baseline versus 3.87 ± 4.6 at 12W) (Figure 1a and d). On average, this drop was around 1.34 heavy drinking episode per

Table 1. Baseline demographic and drinking history markers in alcohol dependent patients by MADRS group and sex.

TREATMENT AND MEASURES	QUETIAPINE				PLACEBO			
	CNR		CR MADRS		CNR		CR MADRS	
	MALES (63)	FEMALES (14)	MALES (27)	FEMALES (4)	MALES (56)	FEMALES (15)	MALES (32)	FEMALES (12)
Age (**years**)	44.4 ± 10.0	49.9 ± 8.5	46.0 ± 8.1	41.8 ± 4.3	46.7 ± 9.7	46.8 ± 5.7	42.3 ± 10.4	46.4 ± 11.4
Weight (lb.)	194.9 ± 40.8	153.2 ± 27.6	195.1 ± 35.0	174.3 ± 35.4	201.1 ± 45.5	162.0 ± 31.8	198.0 ± 47.1	163.0 ± 38.5
Drinking history								
TD90	1268.9 ± 503.5	1030.0 ± 507.8	1370.0 ± 587.3	1064.8 ± 309.1	1206.2 ± 461.9	949.3 ± 358.4	1242.8 ± 479.5	955.2 ± 255.0
AvgD90	14.1 ± 5.6	11.4 ± 5.6	15.2 ± 6.5	11.8 ± 3.4	13.4 ± 5.1	10.6 ± 4.0	13.8 ± 5.4	10.6 ± 2.8
HDD90	63.1 ± 22.7	72.1 ± 13.1	67.7 ± 24.7	76.0 ± 16.2	68.6 ± 21.5	66.9 ± 24.5	70.5 ± 19.4	73.1 ± 22.3
NDD90	80.5 ± 15.1	81.3 ± 13.7	79.1 ± 13.6	83.8 ± 6.5	79.6 ± 14.4	83.5 ± 7.7	79.5 ± 14.1	81.9 ± 15.0
Depression assessment								
MADRS	2.71 ± 2.4	3.14 ± 2.1	13.48 ± 4.0	16.0 ± 5.7	2.7 ± 2.3	2.40 ± 2.4	13.22 ± 4.6	12.58 ± 5.2

TD90, total drinks past 90 days; AvgD90, average drinks per drinking day past 90 days; HDD90, heavy drinking days past 90 days; NDD90, number of drinking days past last 90 days.

week (~HDD) at 12 week. We found a significant within-subjects contrast ($P \leq .001$) in the HDD values across all the four timelines between CR and CNR groups. HDD values gradually decreased numerically in the CR group with highest changes observed at week 8 (3.1 ± 4.7) versus CNR (4.87 ± 5.0) (Figure 1c). HDD values were significantly lower at week 8 (Figure 1c) and week 12 (Figure 1d) in the CR group versus CNR group when co-varied with the MADRS scores.

Progressive lowering of TD by time and treatment was well observed in the CR group (111.89 ± 109.6 at baseline versus 32.72 ± 43.2 at week 12) compared to the CNR group (103.53 ± 94.9 at baseline versus 42.36 ± 49.9 at week 12) (Figure 2, all subfigures). On average, this drop was around 16.36 drinks per week (~TD) at week 12 timepoint in the CR group. A significant within-subjects contrast was observed also in the TD values ($P \leq .001$) across all the four time points between CR and CNR groups when we used repeated measures ANOVA analysis. TD values were significantly lower at week 8 (Figure 2c) and week 12 (Figure 2d) in the CR group versus CNR group with MADRS scores being co-varied.

Baseline NDD (8.26 ± 6.3) lowered initially at week 4 (end of drug titration, Figure 3b) then increased at week 8 (Figure 3c). It eventually decreased to 5.75 ± 5.2 at 12 week (Figure 3d) in the CR group. NDD showed similar response in the CNR group by time and treatment (6.3 ± 6.1 at baseline versus 3.8 ± 4.6 at week 12) (Figure 3). CR group patients drank more frequently but in moderation (reduced heavy drinking days [HDD] and total drinks [TD] as mentioned before). There was a significant interaction effect of NDD values across all the four timepoints by both the groups, $P = .026$ (along with a main effect: $P < .001$ across all the four time points). Higher NDD levels were statistically significant at week 8 ($P = .035$ [when co-varied with MADRS augmented $P = .004$]) (Figure 3c); and week 12 (non-significant $P = .106$ [when co-varied with MADRS augmented $P = .006$]) (Figure 3d) compared to the CNR group.

AvgD (12.38 ± 6.2 at baseline versus 7.65 ± 4.6 at week 12) remained higher in the CR group compared to the CNR group (11.25 ± 4.6 at baseline versus 7.06 ± 3.3 at week 12) by the end of the treatment (Figure 4a and d). Average drinking remained higher in the CR group at week 4 of the treatment due to lower number of drinking days, when total drinks were not significantly different between the two groups (Figure 4b). At week 8, number of drinking days went up coupled with lowering of total drinks (Figures 2c and 3c), which likely brought the average drinks to slightly lower level in CR group, this trend persisted till the end of treatment (Figure 4c).There was a significant interaction effect of time in the average drinks per drinking day (AvgD) values between the CR and CNR groups, $P = .038$; and a main effect of AvgD values, $P < .001$ across all the four times. AvgD changes with treatment showed a numerical lowering in CNR group at each time (Figure 4a–d), similar to NDD values. However, none of the comparisons between

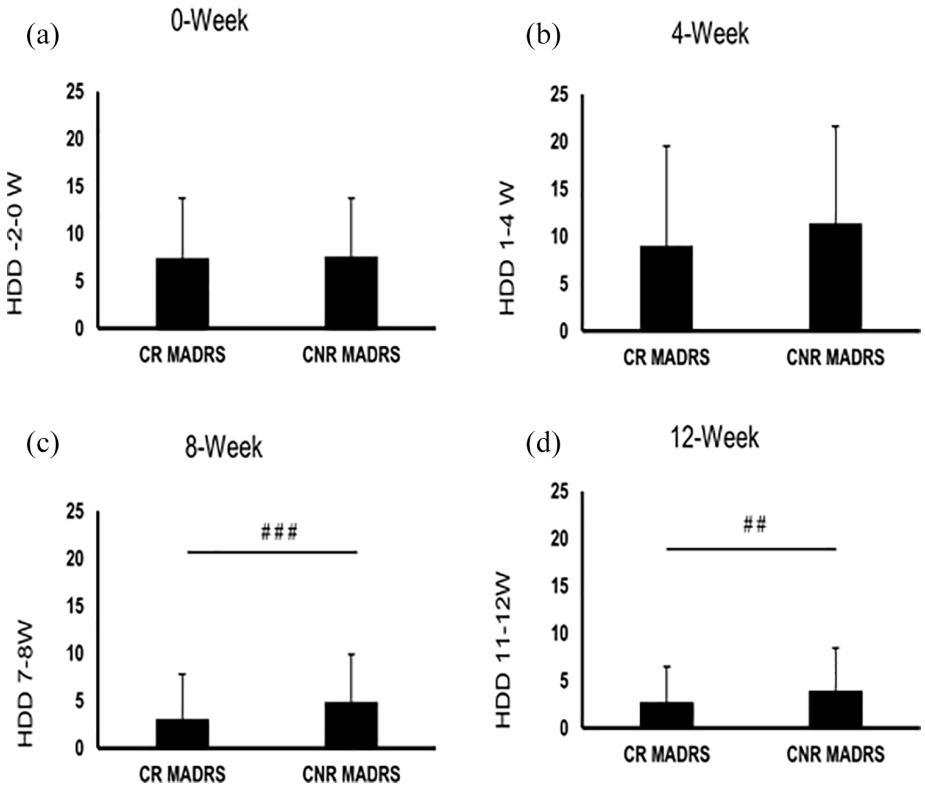

Figure 1. Changes in heavy drinking marker, heavy drinking days (HDD) in alcohol dependent patients receiving quetiapine as treatment, grouped as with clinically relevant MADRS (CR) and without any (CNR) recorded at each of the following timepoint: week 0 (a), week 4 (b), week 8 (c), and week 12 (d). With covariate MADRS score $^{###}P = .001$; and $^{##}P = .007$. Data presented as Mean ± SD. Statistical significance was set at $P \leqslant .05$.

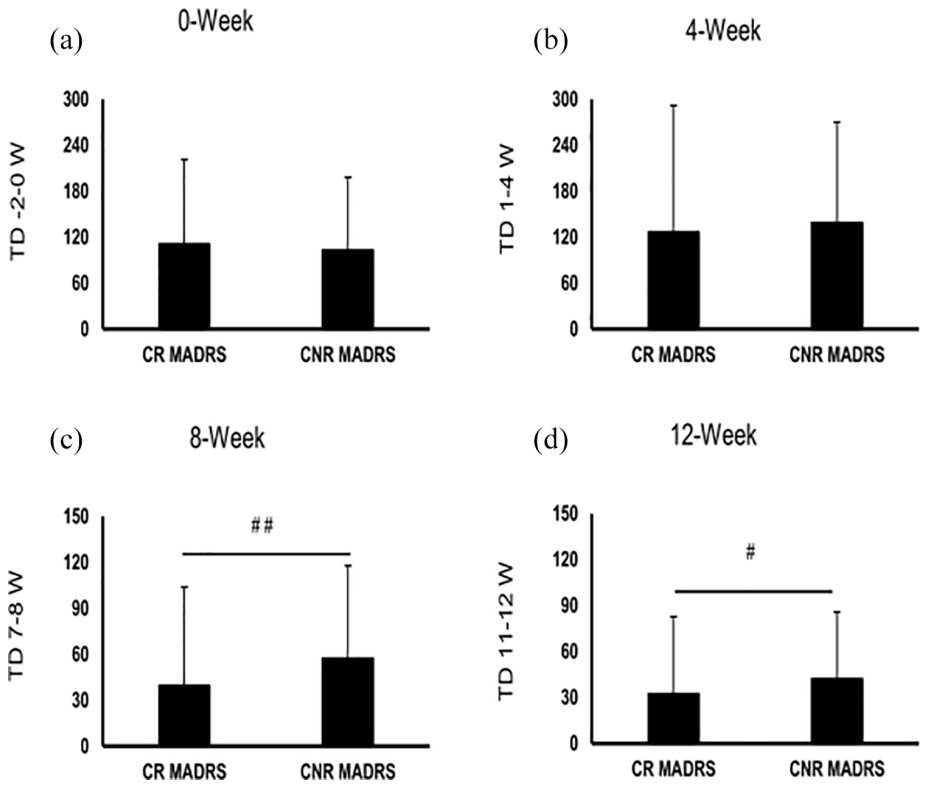

Figure 2. Changes in heavy drinking marker, total drinks (TD) in alcohol dependent patients receiving quetiapine as treatment, grouped as with clinically relevant MADRS (CR) and without any (CNR) recorded at each of the following timepoint: week 0 (a), week 4 (b), week 8 (c), and week 12 (d). With covariate MADRS score; $^{##}P = .010$, $^{#}P = .020$. Data presented as Mean ± SD. Statistical significance was set at $P \leqslant .05$.

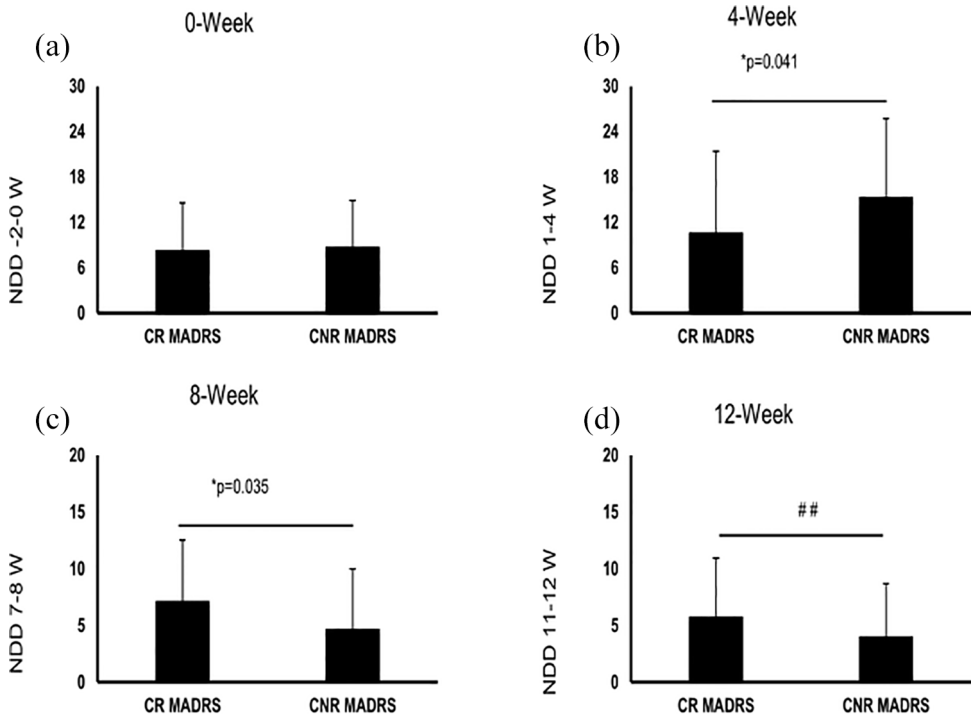

Figure 3. Changes in heavy drinking marker, number of days of drinking (NDD) in alcohol dependent patients receiving quetiapine as treatment, grouped as with clinically relevant MADRS (CR) and without any (CNR) recorded at each of the following timepoint: week 0 (a), week 4 (b), week 8 (c), and week 12 (d). With covariate MADRS score; and $^{\#\#}P = .006$. Data presented as Mean ± SD. Statistical significance was set at $P \leqslant .05$.

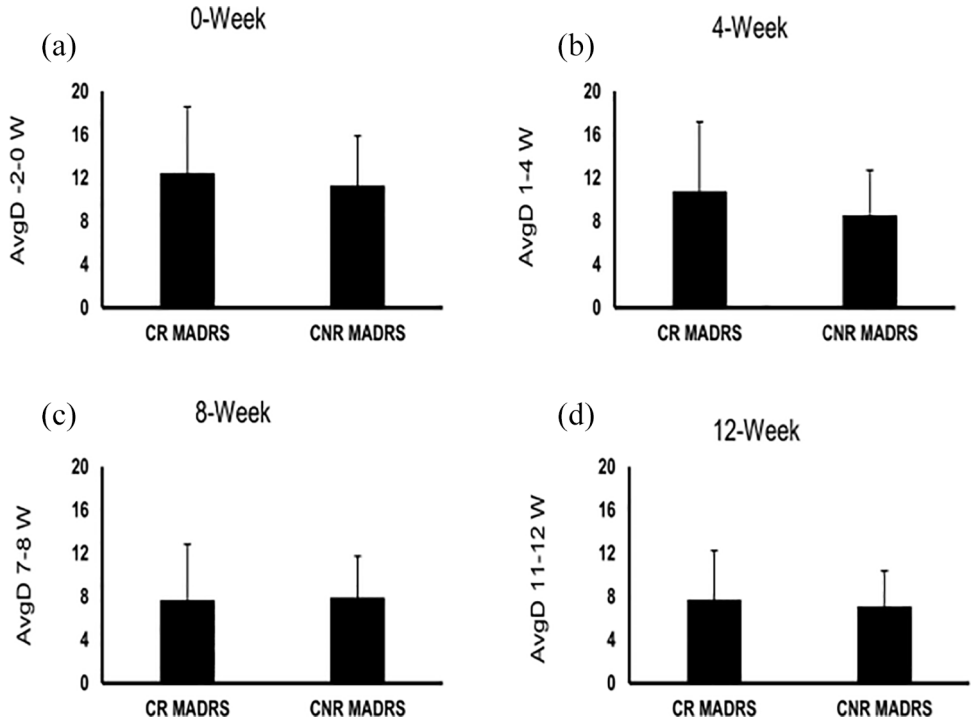

Figure 4. Changes in heavy drinking marker, average drinks (AvgD) in alcohol dependent patients receiving quetiapine as treatment, grouped as with clinically relevant MADRS (CR) and without (CNR) recorded at each of the following timepoint: week 0 (a), week 4 (b), week 8 (c), and week 12 (d). Data presented as Mean ± SD. Statistical significance was set at $P \leqslant .05$.

the CR and CNR groups for the AvgD marker were statistically different.

We assessed both numerically and statistically the values of the drinking markers in CNR and CR groups between the treatment and placebo arms for the last two week (11th-12th) of treatment (Table 2; Figure 5). We found lowering of TD, HDD, and NDD in the CR group of quetiapine treated patients, whereas same markers showed higher numerical

Table 2. Drinking patterns reported in treatment and placebo arms in NCR and CR (MADRS) groups.

DRINKING MARKERS	QUETIAPINE ARM		PLACEBO ARM	
	CNR GROUP	CR GROUP	CNR GROUP	CR GROUP
TD 11-12W	42.35 ± 49.94	32.73 ± 43.17	33.49 ± 45.63	42.19 ± 50.23
AvgD 11-12W	7.06 ± 3.29	7.64 ± 4.63	6.85 ± 4.23	7.43 ± 3.86
HDD 11-12W	3.87 ± 4.62	2.68 ± 4.62	2.72 ± 3.86	3.52 ± 4.48
NDD 11-12W	5.75 ± 5.17	4.00 ± 4.65	4.63 ± 5.20	5.50 ± 5.20

TD 11-12W, total drinks in 11 to 12 weeks; AvgD 11-12W, average drinks per drinking day in 11 to 12 weeks; HDD 11-12W, heavy drinking days in 11 to 12 weeks; NDD90 11-12W, number of drinking days in 11 to 12 weeks.

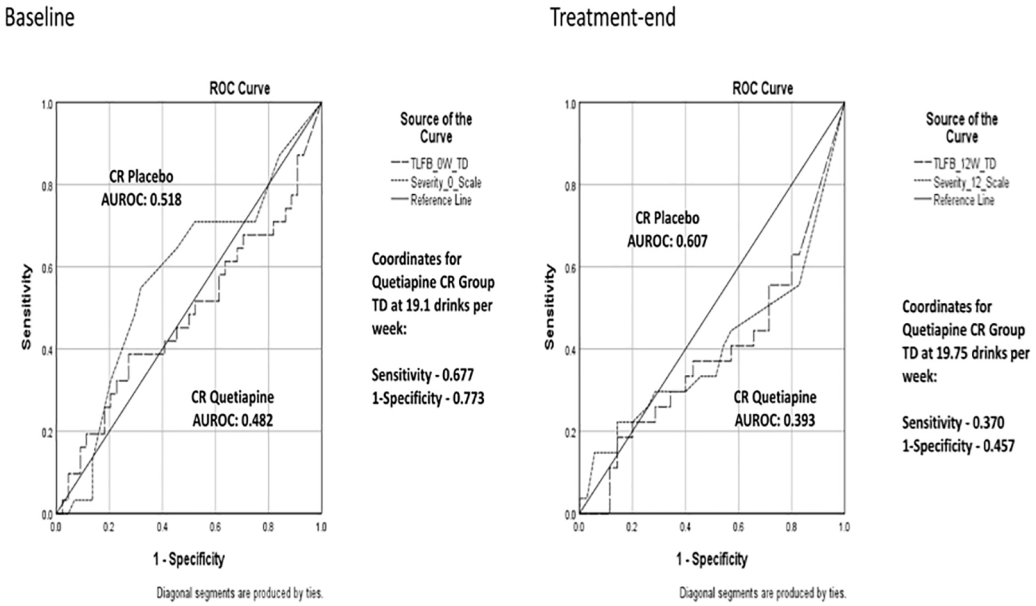

Figure 5. Drinking profile assessment for total drinks at baseline and treatment-end for the sub-groups categorized by the baseline reported MADRS (treated with Quetiapine or placebo) using area under the curve plot. Coordinates for TD (at ~20 drinks per week) has also been mentioned for both the timelines.

values in the CR group of placebo treated patients. There was not much variability found in AvgD values across the CNR and CR groups of each arm. In placebo arm, TD value remained at more than 20 drinks per week in the CR group at the end of the treatment assessment (Table 2). We verified this lowering by using AUC-ROC response (Figure 5). We found that the response was positive consistent with the lowering (Table 2), however it was weak only (0.607) at the study end compared to baseline (0.518) in CR placebo group with respect to the CR quetiapine group patients.

Association of heavy drinking and depression in quetiapine treated AD patients

There was a significant association (adjusted $R^2 = 0.162$ at $P = .024$) of depression ratings and heavy drinking days (HDD) at week 4 assessment in CR patients. This association grew progressively stronger over the treatment course, with the effect size increasing to adjusted $R^2 = 0.801$ at $P \leqslant .001$ at week 12 (Table 3). In addition, over the same period in the CR group, significant associations with increasing effect sizes were observed for all other measures of drinking: total drinks, number of drinking days, and average drinks per day (Table 3). Increasing effect sizes were significantly observed with TD (adjusted $R^2 = 0.403$ at week 8 to adjusted $R^2 = 0.776$ at week 12), and NDD (adjusted $R^2 = 0.294$ at week 8 to adjusted $R^2 = 0.497$ at week 12). Such increasing effect sizes in patients with high MADRS support the fact that the efficacy of active treatment in heavy drinkers goes along with the greater association of both the lowering of drinking markers and the lowering of depressions scores. No such association was observed in CNR group patients (Table 3).

Quetiapine has sedative effects, thus we also tested if the results are not due to quetiapine acting primarily on sleep itself (by significantly augmenting the MADRS scores). In CR patients (with clinically relevant baseline MADRS scores), the raw scores reported for sleep score (one item in the MADRS scale) was significantly associated with heavy drinking markers

Table 3. Regression analysis of drinking markers at each timepoint and baseline CR and CNR MADRS scores in patients treated with Quetiapine XR.

VARIABLES/GROUPS	HIGH MADRS SCALE (CR) (MEAN ± SD, SUBJECT NUMBER)	LOW MADRS SCALE (CNR) (MEAN ± SD, SUBJECT NUMBER)
Week 4 assessment		
	(4.85 ± 4.451, n = 26)	(1.74 ± 2.55, n = 73)
TLFB_0-4W_TD	Mean(SD) = 140.5(177.0), adjusted R^2 = 0.077, *P* = .092; B = 13.4 ± 7.6; CI (95%) for B: −2.4 to 29.2	Mean(SD) = 138.4(131.2), adjusted R^2 = 0.015, *P* = .152; B = 8.705 ± 6.006; CI (95%) for B: −3.271 to 20.681
TLFB_0-4W_NDD	Mean(SD) = 11.7(11.4), adjusted R^2 = 0.055, *P* = NS; B = 0.783 ± 0.500; CI (95%) for B: −0.248 to 1.815	Mean(SD) = 15.2(10.3), adjusted R^2 = −0.006, *P* = .235; B = 0.569 ± 0.475; CI (95%) for B: −0.379 to 1.516
TLFB_0-4W_AvgD	Mean(SD) = 10.2(6.8), adjusted R^2 = 0.034, *P* = NS; B = 0.414 ± 0.317; CI (95%) for B: −0.249 to 1.077	Mean(SD) = 8.5(4.2), adjusted R^2 = −0.007, *P* = .445; B = 0.156 ± 0.203; CI (95%) for B: −0.250 to 0.562
TLFB_0-4W_HDD	Mean(SD) = 9.92(11.2), adjusted R^2 = 0.162, ***P* = .024**; B = 1.114 ± 0.461; CI (95%) for B: 0.163 to 2.065	Mean(SD) = 11.2(10.1), adjusted R^2 = −0.002, *P* = .291; B = 0.494 ± 0.464; CI (95%) for B: −0.432 to 1.421
Week 8 assessment		
	(6.38 ± 8.691, n = 26)	(1.84 ± 3.03, n = 64)
TLFB_7-8W_TD	Mean(SD) = 45.9(67.7), ***adjusted R^2* = 0.403**, ***P* = .000**; B = 5.091 ± 1.203; CI (95%) for B: 2.608 to 7.573	Mean(SD) = 63.0(60.3), adjusted R^2 = 0.006, *P* = .244; B = 2.939 ± 2.502; CI (95%) for B: −2.061 to 7.940
TLFB_7-8W_NDD	Mean(SD) = 5.4(5.4), ***adjusted R^2* = 0.294**, ***P* = .002**; B = 0.355 ± 0.105; CI (95%) for B: 0.138 to 0.573	Mean(SD) = 7.8(5.2), adjusted R^2 = −0.009, *P* = .517; B = 0.141 ± 0.216; CI (95%) for B: −0.291 to 0.573
TLFB_7-8W_AvgD	Mean(SD) = 7.5(5.3), adjusted R^2 = 0.183, ***P* = .039**; B = 0.263 ± 0.117; CI (95%) for B: 0.0150 to 0.511	Mean(SD) = 8.0(3.9), adjusted R^2 = 0.044, *P* = .063; B = 0.310 ± 0.163; CI (95%) for B: −0.017 to 0.638
TLFB_7-8W_HDD	Mean(SD) = 3.5(5.0), ***adjusted R^2* = 0.663**, ***P* = .000**; B = 0.476 ± 0.067; CI (95%) for B: 0.3370 to 0.615	Mean(SD) = 5.3(4.9), adjusted R^2 = 0.008, *P* = .228; B = 0.247 ± 0.203; CI (95%) for B: −0.158 to 0.652
Week 12 assessment		
	(5.556 ± 7.92, n = 27)	(1.523 ± 2.29, n = 65)
TLFB_11-12W_TD	Mean(SD) = 36.1(44.9), ***adjusted R^2* = 0.776**, ***P* = .000**; B = 5.014 ± 0.525; CI (95%) for B: 3.933 to 6.094	Mean(SD) = 46.2(49.1), adjusted R^2 = −0.012, *P* = .606; B = −1.394 ± 2.691; CI (95%) for B: −6.772 to 3.983
TLFB_11-12W_NDD	Mean(SD) = 4.4(4.7), ***adjusted R^2* = 0.497**, ***P* = .000**; B = 0.433 ± 0.084; CI (95%) for B: 0.261 to 0.606	Mean(SD) = 6.4(5.0), adjusted R^2 = −0.009, *P* = .525; B = −0.174 ± 0.272; CI (95%) for B: −0.719 to 0.370
TLFB_11-12W_AvgD	Mean(SD) = 7.5(4.7), ***adjusted R^2* = 0.322, *P* = .010**; B = 0.321 ± 0.109; CI (95%) for B: 0.088 to 0.554	Mean(SD) = 7.0(3.3), adjusted R^2 = −0.020, *P* = .960; B = −0.012 ± 0.238; CI (95%) for B: −0.490 to 0.466
TLFB_11-12W_HDD	Mean(SD) = 2.9(4.0), ***adjusted R^2* = 0.801**, ***P* = .000**; B = 0.449 ± 0.044; CI (95%) for B: 0.359 to 0.539	Mean(SD) = 4.2(4.5), adjusted R^2 = −016, *P* = .960; B = 0.013 ± 0.248; CI (95%) for B: −0.484 to 0.590

Drinking assessment for the first four weeks of treatment: 0-4W, drinking assessment for the 7th and 8th week of treatment: 7-8W, Drinking assessment for the 11th and 12th week of treatment: 11-12W. TLFB, timeline followback; TD, total drinks; NDD, drinking days; AvgD, average drinks per drinking day; and heavy drinking days (defined as five or more drinks per day for a male and four or more drinks per day for a female, HDD).

only at week 8 (albeit effects were mild or low): HDD (adjusted R^2 = 0.259, *P* = .005), TD (adjusted R^2 = 0.252, *P* = .005), and NDD (adjusted R^2 = 0.179, *P* = .018). However, there was no association of sleep score and heavy drinking measures at baseline, week 4 and specially at the end of the study (at week 12). Similarly, we did not find any significant association of heavy drinking measures and depression scale at each timepoint in CNR group.

Discussion

Most of the study patients showed uniformed drinking at baseline and none of the drinking markers showed any obvious baseline differences between the two groups. Furthermore, patients in our study who were prescribed antidepressants at least 30 days prior to the study were also eligible, who might show some elevation during the treatment/evaluation course. Even though the patients in this study were not diagnosed with depression based on the DSM-IV TR criteria, they exhibited some symptoms of depression, which is anticipated in heavy drinkers.[26] Thus, MADRS which does not diagnose depression, but measures intensity of certain symptoms was employed.

Clozapine has been reported to reduce alcohol use in schizophrenic patients with alcohol use disorder.[35,36] In our treatment study, one group of alcohol dependent patients also exhibited clinically relevant symptoms of depression indicating presence of comorbid condition (CR). We found separation in

the treatment efficacy of quetiapine based on the level of depression symptoms recorded at baseline. Both total drinks (by one-fourth) and heavy drinking days (by one third) continued to be reduced significantly over the treatment course. Average drinking and number of drinking days also dropped in the CR group compared to baseline, but levels were higher than those in the CNR group.

Quetiapine (Seroquel®), like clozapine, is another atypical antipsychotic medication that, in addition to decreasing alcohol intake, has also been reported to decrease craving and psychiatric symptoms in alcoholic patients with a concurrent axis I disorder[37] in a four-month open label trial. This study suggests that the lowering of craving by quetiapine could be involved in lowered consumption of alcohol as well. In our findings, lowering of heavy drinking markers showed increasing effect sizes and significance of association when regressed with MADRS during the course of treatment only in CR patients. We also found a statistically and numerically significant elevation in total amount of drinking and the pattern of heavy drinking persisted at each time point until the end of the treatment in CNR patients. This response was in contrast to that observed in the CR group. Quetiapine might be an effective treatment in AD patients who also have depression symptoms (CR) but may not be effective in AD patients without any significant level of depression symptoms (CNR). Kampman and colleagues also reported a higher therapeutic value of quetiapine in treatment of Type B alcoholics, the more complex of the two types of alcoholism characterized by earlier onset of problematic drinking, more severe alcohol dependence, and greater psychopathology.[25] Another potential indirect mechanism that quetiapine lowers MADRS simultaneously is by lowering alcohol consumption (which itself is a depressant[38]).

One study demonstrated that aripiprazole decreased drinking in alcoholic patients who were not seeking treatment[39] while another study showed that aripiprazole proved to be as effective as the currently FDA approved drug, naltrexone, in treating alcohol dependence.[40] A parent study of this manuscript reported that quetiapine could overall lower the drinking in AD patients on quetiapine, although not to a level that is considered to be moderate drinking.[27] Based on our findings, we observed that quetiapine selectively targets and lowers the alcohol consumption in alcohol dependents who also show baseline signs of depression. This suggests that drinking markers are good therapeutic targets to assess treatment efficacy and corresponding lowering of depression scores in heavy drinkers could be a positive sign of drug efficacy. Similar findings were also reported in a study comparing aripriprazole and placebo in a multicenter drug trial.[41] Scope of that study did not include investigating the results in context of the presence of depression symptoms. HDD at baseline was roughly four times per week that reduced to roughly one episode per week at the end of the treatment. Similarly, baseline NDD was four times a week that reduced to roughly three times per week. Importantly TD reduced from roughly 56 drinks per week at baseline to 16.5 drinks per week, which was lower than the heavy drinking criteria of 20 drinks per week for men (we had almost all male participants in the CR group [27/31]).[18] Thus, treatment efficacy of anti-depressants should also be evaluated in context of depression symptoms apart from overall outcomes. Efficacy of Quetiapine in lowering the heavy drinking patterns was evident in the subset of patients who exhibited baseline clinically relevant MADRS scores.

A clinical study showed that olanzapine reduced the urge to drink in heavy social drinkers post exposure to alcohol cues[42] as well as diminished alcohol craving and consumption in alcohol-dependent patients, especially in those with the 7-repeat allele of the D4 receptor gene.[43] In our study, we found a corresponding lowering in the number of drinking days during treatment) in CNR patients. While quetiapine could not lower drinking from heavy to moderate levels in this group, there was a non-significant lowering in total drinks at the 12-week assessment compared to baseline. Another study showed similar findings with no differences in drinking outcomes between olanzapine and placebo groups in alcohol dependent patients.[44] In that study, the authors used Beck's Depression Inventory (BDI), however association between BDI and heavy drinking was not discussed. It seems that the potential effectiveness of an anti-depressant drug should be evaluated in the context of both lowering alcohol consumption and improving depression symptoms.

This study had several limitations. There were three-fold more men in this study compared to women, which shifted balance of the sex ratio disproportionally. Though since this occurred in all the groups evenly, thus it did not restrain the analysis. However, it is indicative that the results of the CR sub-group (of quetiapine treated patients) mostly reflected the trends in males. Previously publications support vulnerability in females with alcohol drinking and its neurological manifestations,[45] this has not been analyzed in this study due to very low numbers of females enrolled. There were a few dropouts during the course of the study and 4% to 5% of the total data points could not be included in this study due to missing values. In our study, AD patients with clinically relevant depression symptoms (-CR group) were far fewer (<50%) than the group who did not have clinically relevant depression symptoms (CNR group). This could have tilted the weight of findings toward the CNR group in the analyzes. AUROC curve supports the positive response thus, we believe that the findings are still significant. There is a likelihood of type I error (false positive) results in multiple comparisons for TD and HDD comparisons. We see numerical drops regardless that were lower than the heavy drinking criteria, and ROC curve showed positive response for true positivity (This response was weak by category). We did not include MDD patients with comorbid diagnosis of alcohol in this study, which might have also revealed if Quetiapine has dual efficacy, however this was not

part or scope of this study and its design. We did not evaluate sleep comprehensively (there is only one on sleep in the MADRS scale, which was not significantly associated in CR group apart from 8-week stage) for its role in the treatment.[31] This study has used DSM-IV criteria going along with the criteria used by the parent publication,[28] however latest version DSM-V is the presently used criteria. Thus, the results are limited in interpretations based on the previous criteria. We did not perform any race/ethnicity based analyzes, however the information on these measures are available in the parent publication.[27] Scope of this study was limited to interaction of depression and drinking on treatment efficacy. In a separate study, we would address using a comprehensive questionnaire on the interaction of sleep and quetiapine in alcohol consumption (Pittsburg sleep quality index).

Conclusions

Quetiapine fumarate XR reduced markers of heavy drinking, namely, (1) heavy drinking days and (2) total drinks at the end of treatment compared to baseline albeit only in alcohol dependent patients who exhibited clinically relevant depression symptoms at baseline (sub-set efficacy is evident that generalized efficacy). In AD patients without any relevant level of baseline signs of depression, quetiapine could reduce the frequency of drinking days during the treatment, however, little effect was observed in heavy drinking days and total drinks. Quetiapine fumarate treatment showed therapeutic dimorphism in alcohol dependent patients and could be an effective intervention for those who have clinical signs of depression along with heavy alcohol intake.

Authors' note

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Authors' contribution

VV is the project PI and designed the study. VV, MLS, MK, ZK, and LMM provided data acquisition, management and analysis. VV, KVC, MK, VAR, and CJM interpreted the outcomes. VV, KVC, LMM, and CJM wrote the manuscript. VV, VAR, KVC, CJM, MK, and MLS contributed scientifically. All the authors have approved the submission version of this manuscript.

Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Disclosure

This article is present on a university repository website and can be accessed on https://onlinelibrary.wiley.com/doi/abs/10.1111/acer.14059. This article is not published nor is under publication elsewhere. Only the abstract was published related to a conference presentation.

Ethics approval and consent to participate

Study was approved by the site/s' Institutional Review Board (Ethics committee). All patients included in this study consented to participate before the beginning of the study.

Proprietorship

This article is a work of the University of Louisville Alcohol Research Center and is in the public domain in the USA.

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