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Prazosin and cyproheptadine in combination in the treatment of alcohol use disorder: A randomized, double-blind, placebo-controlled trial

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Abstract

Background and aims: Pre-clinical studies suggest that the simultaneous blockade of the α 1b and 5HT2A receptors may be effective in reducing alcohol consumption. This study aimed to assess the efficacy and safety of prazosin (α 1b blocker) and cyproheptadine (5HT2A blocker) combination in decreasing total alcohol consumption (TAC) in alcohol use disorder (AUD).

Design, setting and participants: This was a double-blind, parallel group, placebo-controlled, Phase 2, randomized clinical trial conducted in 32 addiction treatment centres in France. A total of 108 men and 46 women with severe AUD took part.

Intervention: Participants were randomly assigned to one of the following 3-month treatments: (1) low-dose group (LDG) receiving 8 mg cyproheptadine and 5 mg prazosin extended-release (ER) formulation daily; (2) high-dose group (HDG) receiving 12 mg cyproheptadine and 10 mg prazosin ER daily; and (3) placebo group (PG) receiving placebo of cyproheptadine and prazosin ER. A total of 154 patients were randomized: 54 in the PG, 54 in the LDG and 46 in the HDG.

Measurements: The primary outcome was TAC change from baseline to month 3.

Findings: A significant main treatment effect in the change in TAC was found in the intent-to-treat population ($P = 0.039$). The HDG and LDG showed a benefit in the change in TAC from baseline to month 3 compared with PG: -23.6 g/day, $P = 0.016$, Cohen's $d = -0.44$; -18.4 g/day, $P = 0.048$ (Bonferroni correction $P < 0.025$), Cohen's $d = -0.36$. In a subgroup of very high-risk drinking-level participants (> 100 g/day of pure alcohol for men and > 60 g/day for women), the difference between the HDG and

For affiliations refer to page 11

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the PG in the primary outcome was -29.8 g/day ($P = 0.031$, Cohen's $d = -0.51$). The high and low doses were well-tolerated with a similar safety profile.

Conclusions: A randomized controlled trial of treatment of severe alcohol use disorder with a cyproheptadine–prazosin combination for 3 months reduced drinking by more than 23 g per day compared with placebo. A higher dose combination was associated with a larger magnitude of drinking reduction than a lower dose combination while showing similar safety profile.

KEYWORDS

Alcohol reduction, alcohol use disorder, cyproheptadine, prazosin, randomized controlled trial, risk drinking level

INTRODUCTION

The addictive properties of alcohol and other addictive substances are generally considered to be mediated by an increased release of dopamine in the ventral striatum [1]. Evidence indicates the implication of both $\alpha 1b$ -adrenergic and 5HT2A serotonergic receptors in dopamine-mediated behavioural and rewarding responses to psychostimulants and opiates [2]. The concept of coupling between noradrenergic and serotonergic systems on the dopaminergic subcortical system derives from the observation of a reciprocal control of locus coeruleus noradrenergic cells by serotonergic neurones arising from the raphe nuclei and, conversely, a noradrenergic control of raphe cells by means of the stimulation of $\alpha 1b$ -adrenergic receptors (Supporting information, Figure S1) [1, 3].

Uncoupling between noradrenergic and serotonergic systems occurs when they become independent after repeated injections of alcohol, psychostimulants or opiates, explaining behavioural sensitization [1, 3, 4]. It has been suggested that in people with substance use disorder, because of noradrenergic and serotonergic uncoupling, each system would react as if they were independent and undergo desynchronized activations, thus inducing discomfort and distress: in the absence of the addictive substance, over-activation of noradrenergic neurones would be associated with craving, whereas the lack of a synchronized activation of serotonergic neurones would impede the regulation of impulsivity, resulting in an increased drive for substance use. In this view, consumption would restore the interaction between noradrenergic and serotonergic neurones, thus inducing a temporary relief [1].

It has been proposed that the simultaneous blockade of $\alpha 1b$ -adrenergic and 5HT2A-serotonergic receptors may facilitate a re-coupling of these systems and thus inhibit addictive substance-seeking behaviours [1]. This hypothesis has been tested in alcohol-preferent mice. The combination of prazosin (0.5 mg/kg), which blocks $\alpha 1b$ -adrenergic receptors, and cyproheptadine (1 mg/kg), which blocks 5-HT2A receptors, reversed alcohol preference, whereas prazosin or cyproheptadine alone exhibited no significant effect [5].

These findings suggest that combined blockade of the $\alpha 1b$ and 5HT2A receptors is a promising avenue in the treatment for alcohol use disorder (AUD). Cyproheptadine is used as an anti-histaminic, anti-allergic medication. Prazosin is used to treat hypertension and

urinary urgency. The extended-release (ER) formulation of prazosin used in this trial allows avoiding titration and reduces the risk of orthostatic hypotension [6]. Both drugs have been marketed for 40+ years in most countries, consistently showing a favourable safety profile.

The primary aim of this Phase 2 trial was to investigate the efficacy of simultaneous blockade of $\alpha 1b$ and 5HT2A receptors using prazosin ER and cyproheptadine in reducing alcohol consumption among individuals with severe AUD. The study employed a three-arm parallel group, placebo-controlled design, evaluating two different treatment doses.

METHODS

Study design

This was a 16-week double-blind, double-dummy, randomized, parallel-group, three-arm, multi-centre, placebo-controlled study. The study was conducted in France in 32 addiction treatment centres and primary care offices.

The study was approved by the Ethics Committee of Ile-de-France on 13 September 2016, as well as by the French regulatory authority (Agence Nationale de Sécurité du Médicament et des Produits de Santé). The study was registered in [ClinicalTrials.gov](https://clinicaltrials.gov), NCT04108104.

Participants

Participants were recruited from substance abuse clinics and from the community through social media and newspaper advertisements. They were enrolled and followed-up by the study investigators; all were physicians specialized in substance use disorders. To be included, participants had to be aged 18–65 years; meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria for severe AUD [7]; and have a high-risk drinking level (RDL) defined by the World Health Organization (WHO) as a total alcohol consumption (TAC) > 60 g/day for men and > 40 g/day for women in the 2 weeks preceding screening and the 2 weeks preceding randomization [8].

The main exclusion criteria were hypotension, anti-hypertensive treatment, history of severe psychiatric disorders, cardiovascular disease not under control, generalized seizures, alcohol withdrawal (as defined by DSM-5, including criterion C, i.e. clinically significant distress or impairment of functioning), and/or substance use disorder (other than alcohol or nicotine) during the previous year. Concomitant labelled and off-label medications for AUD (e.g. naltrexone, acamprosate, disulfiram, nalmefene, baclofen, varenicline, gabapentin) were prohibited. Benzodiazepines were allowed if they had been prescribed for at least 4 weeks before starting the study. Most antidepressants were allowed if they had been prescribed for at least 2 months before randomization. A comprehensive account of the inclusion/exclusion criteria is in the study protocol (Supporting information, Data S1). The participants gave written informed consent before being included.

Randomization and masking

Participants were randomized in the three groups according to a 1:1:1 ratio and a block size of 3. Each group received an equal number of capsules in their morning/noon/evening regimen, as follows.

1. The low-dose group (LDG) received one 4-mg capsule of cyproheptadine in the morning and the evening, one capsule of cyproheptadine placebo at noon and one 5-mg capsule of prazosin ER and one capsule of prazosin ER placebo in the evening.
2. The high-dose group (HDG) received one 4-mg capsule of cyproheptadine in the morning, noon and evening and two capsules of 5-mg slow-release prazosin ER in the evening.
3. The placebo group (PG) received one capsule of cyproheptadine placebo in the morning, noon and evening and two capsules of prazosin ER placebo in the evening.

All treatments were administered for 12 weeks.

Randomization was stratified by centre. The study medications were supplied to the sites by the sponsor of the study and numbered according to the allocation sequence. The investigators assigned the eligible subjects to interventions using the lowest unassigned number available in the site. The randomization list was prepared using the software nQuery Advisor version 7.0 by a person independent from the study. A restricted access to an individual participant's randomization code was implemented via the electronic Case Report Form (eCRF), that should be used by the investigator in case of a serious adverse event (SAE) necessitating unblinding treatment allocation. The randomization list was communicated to the treatment manufacturing company for clinical packaging and labelling and integrated blindly into the eCRF. A double-dummy technique was used for treatment concealment. The tablets of the two active products were inserted into capsules of different colours and further completed by lactose. The placebo capsules, identical in size, form, weight and colour than those containing the active products, were entirely filled in with lactose. Clinicians, study personnel and participants were

blinded to drug treatment allocation. The data monitoring was performed blinded. The statistical analysis was started once the database was locked and unblinded.

An independent Data Safety Monitoring Board (DSMB) regularly examined in a blinded manner the individual safety data provided for each treatment arm (undefined groups A, B and C) and advised the sponsor to continue, prematurely or definitely interrupt the study according to its appreciation of the groups' AEs profile.

Procedures

A total of nine visits was planned. Potential participants attended a screening visit for eligibility that included a 2-week retrospective assessment of alcohol consumption with the time-line follow-back (TLFB) method [9]. Two weeks later, at the second eligibility and inclusion visit (day 0), alcohol consumption was again assessed with the TLFB to ensure that the participants maintained a high or very high RDL until randomization. Included participants were scheduled for six additional visits: weeks 1, 2, 3, 4, 8 and 12 (end of treatment), and one post-treatment visit at week 16.

Participants received psychosocial support following the BRENDA model, for which all investigators were trained. BRENDA is a relatively brief and simple approach suitable for specialized or primary care physicians. It was chosen for this trial because of its focus on treatment adherence and reducing alcohol consumption. The BRENDA model comprises six components: (1) biopsychosocial evaluation, (2) patient report of findings, (3) empathy, (4) addressing patient needs, (5) providing advice and (6) adjusting treatment as needed [10].

After randomization, daily alcohol consumption and daily medication intake were assessed with either an eDiary (daily questionnaire on the participant's smartphone, tablet, laptop or computer) or a paper diary. Alcohol craving was assessed monthly with the Obsessive Compulsive Drinking Scale (OCDS) [11]. Depressive symptoms and sedation (a probably adverse effect of cyproheptadine) were assessed at each visit with the Beck Depression Inventory (BDI) [12] and by a 10-cm visual analogue scale (VAS), respectively. Orthostatic hypotension (OH), a possible adverse effect of prazosin ER, was systematically assessed at each visit by a checklist reporting symptoms when changing from the supine to the standing position and by measuring blood pressure. OH was defined as a drop of the systolic blood pressure by at least 20 mmHg after 1 or 3 minutes standing when changing from supine to standing position.

Amendments to the protocol authorized the use of a paper diary for participants feeling unable to use the eDiary and controlled cirrhosis was allowed at enrolment (April 2020); the exclusion criterion 'History of uncontrolled hypertension: systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 90 mmHg' was changed to 'History of uncontrolled hypertension' (November 2020). The exclusion criteria were softened in order to facilitate enrolment (Supporting information, Data S1).

Outcomes

The primary outcome was the change in TAC from baseline to the last month of treatment (i.e. month 3 defined as weeks 9–12). The secondary objectives included the assessment of the safety (AEs, SAEs, sedation, body weight and OH) and surrogates of efficacy: heavy drinking days (HDDs; i.e. days with alcohol consumption > 60 g for men or > 40 g for women), number of abstinence days, OCDS and BDI scores, the responder rate, defined as a two-level reduction in WHO RDLs [8] between baseline and month 3 and the proportion of patients with a TAC decrease by at least 50% between baseline and month 3.

Statistical analysis

We based our effect size assumptions on the Phase 3 nalmefene efficacy trials, where nalmefene showed a reduction in the change in TAC from baseline to month 6 of -14.3 g/day [95% confidence interval (CI) = 7.8–20.8] compared to placebo, representing a standardized effect size of 0.36 [13]. In order to be clinically relevant, we aimed a TAC reduction difference of 20 g/day for the HDG and 10 g/day for the LDG compared to the PG. This Phase 2 trial's duration being shorter than the Phase 3 nalmefene trials, we expected a lower variance. We based the estimation of the standard deviation (SD) on the assumption of a CI range of 5.5 g/day, yielding a SD = 15. A sample size of 45 participants by group would have 80% power to detect a mean difference of 10 or 20 g/day, assuming that the common SD is 15 g/day (LDG, HDG versus PG, respectively), using a two-group *t*-test with a $P = 0.025$ two-sided significance level (Bonferroni's adjustment for multiplicity—see below). Taking into account the above-mentioned hypotheses and a dropout rate of 20–30%, 60 participants per group were needed to be randomized (i.e. 180 participants) to detect a difference versus placebo.

The primary analysis was that of the intention-to-treat (ITT) sample, defined as participants having been randomized, having been treated for at least 1 day and for whom data were available at visit 3 (week 1). The per protocol (PP) population included participants having completed the study, who did not qualify for a major deviation from the protocol, for whom the primary end-point was available and whose compliance was at least 80% during the whole treatment period. Efficacy was also explored in the subgroup of patients with a very high (VH) WHO RDL at baseline (> 100 g/day for men and > 60 g/day for women).

The primary and secondary outcomes were analyzed using a mixed-effects model for repeated measures (MMRM) with an unstructured covariance matrix for the residuals. Treatment, time and their interaction were included as fixed effects and baseline values as covariate. Participant was included as a random effect with a random intercept. A MMRM model on observed cases was applied for the primary analysis of the primary end-point and a correction for multiplicity was applied for the pairwise comparisons between each active treatment group and the PG (Bonferroni's correction $P < 0.025$). No

correction for multiplicity was performed for the analysis of secondary end-points. Two sensitivity analyses were conducted for the primary outcome in the ITT population: the first analysis used an analysis of covariance (ANCOVA) model with multiple imputation, while the second analysis used a MMRM model with the last observation carried forward (LOCF) method for handling missing data. For the multiple imputation, and as the pattern of missingness in TAC was monotone, a monotone data imputation using a predictive mean matching method was applied with treatment, age, gender and baseline TAC as predictors. A total of 100 imputed data sets were generated and treatment effect was estimated from these imputed data. In the MMRM and multiple imputation models missing data were assumed to be missing at random, whereas in the LOCF model they were considered to be missing completely at random. The primary outcome was also analyzed in the PP population. The dose–response relationship in the primary end-point was explored a posteriori with an ANCOVA model, with dose as fixed effect and baseline TAC as covariate. In this analysis, dose was a continuous variable with the following values: 0 for patients in the PG, 1 for patients in the LDG and 2 for patients in the HDG. The rationale was that patients in the HDG received approximately twice the dose of those in the LDG. Standardized effect sizes were estimated using the standardized mean difference (Cohen's *d*) method for continuous end-points (Supporting information, Figure S1). Response odds ratios (OR) were obtained with a logistic mixed model. Safety end-points and post-treatment TAC change were analyzed using descriptive statistics. The principal statistical software used was SAS® version 9.4. PROC MIXED was used for performing MMRM models. The statistical analysis plan was finalized in December 2021, before locking the database (Supporting information, Data S1).

RESULTS

Because of major difficulties in recruiting participants in the context of the COVID-19 pandemic, the recruitment was stopped before reaching the planned sample size of 180 randomized participants. A total of 154 people (108 men and 46 women) were randomized throughout 32 centres between 29 November 2019 and June 2021; the last patient visit was on 28 October 2021. Of these participants, 142 were recruited from 17 addiction treatment centres and the remaining 12 were recruited from five primary care centres. They constituted the ITT population (54, 54 and 46 in the PG, LDG and HDG, respectively). Sixty-one participants were excluded from the PP analysis for reasons shown in the CONSORT diagram (Figure 1). The PP sample included 93 participants (29, 36 and 28 in the PG, LDG and HDG groups, respectively) and the VH RDL subgroup 95 participants (36, 28 and 31 in the PG, LDG and HDG groups, respectively). A total of 104 participants completed the study (36, 40 and 28 in the PG, LDG and HDG groups, respectively). The follow-up rates did not differ significantly across treatment groups (57, 74 and 61%, respectively, $P = 0.18$). Baseline characteristics of the ITT sample are shown in Table 1.

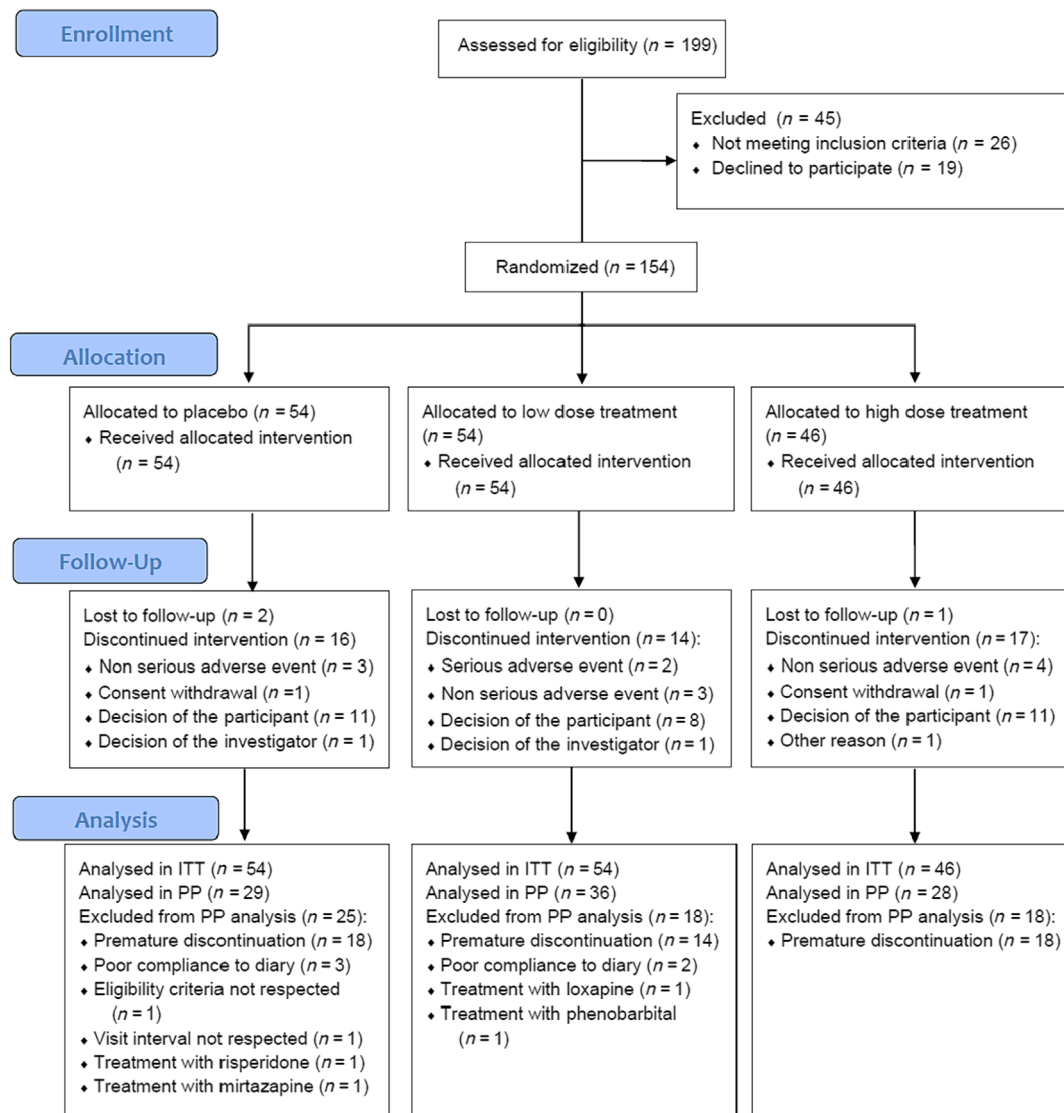


FIGURE 1 CONSORT diagram. ITT, intention-to-treat sample; PP, per protocol sample.

Primary outcome

Observed TAC values are shown in Table 2. In the ITT population, the pre-specified primary analysis (MMRM model on observed cases) showed a significant main effect of treatment ($P = 0.039$) and a significant effect of time ($P < 0.001$) in the change from baseline in TAC. Although the treatment \times time interaction was not significant ($P = 0.087$), the group differences increased numerically with time (Table 3; Figure 2). The main effect of treatment was also significant in the sensitivity analysis using multiple imputation ($P = 0.048$), and was close to statistical significance in the sensitivity analysis using LOCF ($P = 0.053$).

In the primary analysis, the group differences in the change in TAC from baseline to month 3 were significantly in favour of the HDG compared to the PG in the ITT population: -23.6 g/day, $P = 0.016$. Due to multiplicity correction, no significant difference was

observed between the LDG and the PG: -18.4 g/day, $P = 0.048$ (Figure 2; Table 3). Standardized effect sizes with respect to PG increased from -0.07 to -0.36 from months 1 to 3 in the LDG and from -0.31 to -0.44 in the HDG. These results were supported by the sensitivity analyses. Only the HDG showed a significant effect compared to the PG in the primary end-point in the LOCF model and in the model using multiple imputation (Supporting information, Table S1).

A significant dose-response relationship in the primary end-point was identified ($P = 0.027$), with a reduction in the change in TAC by -9.9 g/day by unit of dose (i.e. 0 g/day for the placebo, -9.9 g/day for the low dose and -19.8 g/day for the high dose).

In the VH RDL subgroup, the group differences in the change in TAC from baseline to month 3 were -29.8 g/day ($P = 0.031$) between the HDG and the PG and -18.9 g/day ($P = 0.183$) between the LDG and the PG. Standardized effect sizes with respect to PG increased

TABLE 1 Baseline characteristics of the intention-to-treat sample.

	Placebo group n = 54	Low-dose group n = 54	High-dose group n = 46
Age (years)	47.5 (8.7)	49.1 (8.8)	51.8 (7.4)
Sex			
Female	13 (24)	16 (30)	17 (37)
Male	41 (76)	38 (70)	29 (63)
Marital status			
Living alone	14 (25.9)	18 (33.3)	17 (37.0)
Living with a partner	24 (44.4)	17 (31.5)	19 (41.3)
Living in family or with friends	15 (27.7)	17 (31.5)	8 (17.4)
Information missing	1 (1.9)	2 (3.7)	2 (4.3)
Education level			
No diploma	4 (7.4)	3 (5.6)	3 (6.5)
National vocational qualification 1–3	24 (44.4)	26 (48.1)	17 (37.0)
College	26 (48.1)	24 (44.4)	26 (56.5)
Information missing	0 (0.0)	1 (1.9)	0 (0.0)
Employment status			
Unemployed	12 (22.2)	5 (9.3)	3 (6.5)
Employed	37 (68.5)	35 (64.8)	35 (76.1)
Retired	2 (3.7)	5 (9.3)	5 (10.9)
Disabled	1 (1.9)	2 (3.7)	1 (2.2)
On sick leave	2 (3.7)	6 (11.1)	2 (4.3)
Information missing	0 (0.0)	1 (1.9)	0 (0.0)
Body mass index (kg/m ²)	24.9 (3.7)	25.2 (4.2)	25.6 (5.3)
Total alcohol consumption (g/day)	110.7 (43.5)	110.8 (56.4)	106.0 (41.1)
WHO drinking risk level			
Very high risk	36 (66.7)	28 (51.9)	31 (67.4)
High risk	16 (29.6)	25 (46.3)	15 (32.6)
Moderate risk	2 (3.7)	1 (1.9)	0 (0.0)
Heavy drinking days last month	23.0 (5.1)	23.1 (6.2)	22.4 (5.1)
Alcohol use disorder (AUD) duration (years)	11.5 (8.2)	12.0 (8.7)	15.7 (12.4)
Time since last treatment for AUD (months)	32.3 (58.9)	32.1 (47.5)	81.3 (294.7)
Smoking status			
Non-smoker	9 (17)	12 (22)	5 (11)
Former smoker	12 (22)	8 (15)	12 (26)
Current smoker	33 (61)	34 (63)	29 (63)
Obsessive Compulsive Drinking Scale (OCDS) total score, range = 0–56	20.9 (6.1)	20.8 (5.7)	19.6 (4.9)
Beck Depression Inventory score, range = 0–63	6.3 (4.9)	7.1 (6.2)	6.7 (6.0)
Heart rate (beats/min)	80 (12)	81 (14)	78 (10)
Respiratory rate (breaths/min)	17 (4)	16 (4)	17 (4)
Systolic blood pressure (mmHg) (supine)	139 (16)	138 (18)	137 (17)
Systolic blood pressure (mmHg) standing			
1 minute	139 (16)	137 (19)	138 (17)
3 minutes	140 (16)	137 (21)	139 (20)
Diastolic blood pressure (mmHg) (supine)	84 (10)	86 (11)	84 (12)

TABLE 1 (Continued)

	Placebo group <i>n</i> = 54	Low-dose group <i>n</i> = 54	High-dose group <i>n</i> = 46
Diastolic blood pressure (mmHg) standing			
1 minute	88 (12)	88 (14)	89 (14)
2 minutes	90 (11)	88 (12)	89 (15)
Sedation, visual analogue scale (cm), range 0–10	1.8 (2.4)	1.4 (1.9)	1.3 (2.0)

Note: Data are means (standard deviation) or *n* (%). Low-dose group: 8 mg cyproheptadine and 5 mg prazosin ER per day. High-dose group: 12 mg cyproheptadine and 10 mg prazosin ER per day. WHO drinking risk levels: very high risk if TAC \geq 101 g/day in males and \geq 61 g/day in females, high risk if TAC 61–100 g/day in males and 41–60 g/day in females, moderate risk if 41–60 g/day in males and 21–40 g/day in females [8].
ER = extended-release; TAC = total alcohol consumption.

TABLE 2 Observed total alcohol consumption (TAC) in the intention-to-treat population and in participants with very high RDL at baseline.

ITT Observed cases	PG		LDG		HDG	
	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)	<i>n</i>	Mean (SD)
ITT population						
Baseline	54	110.7 (43.8)	54	110.8 (56.4)	46	106.0 (41.4)
Month 1	54	89.3 (56.2)	53	85.2 (55.1)	46	72.3 (43.3)
Month 2	45	80.0 (53.9)	47	69.6 (56.5)	37	61.0 (44.0)
Month 3	35	77.7 (56.3)	41	66.3 (55.0)	33	57.8 (44.8)
Participants with very high RDL at baseline						
Baseline	36	126.5 (45.6)	28	143.8 (60.6)	31	119.2 (43.3)
Month 1	36	106.0 (59.9)	27	117.5 (58.6)	31	78.9 (46.9)
Month 2	29	94.3 (56.7)	23	101.4 (63.0)	25	64.0 (46.3)
Month 3	24	89.0 (61.5)	21	93.1 (62.4)	23	66.9 (47.3)

Note: Very high RDL: alcohol consumption > 100 g/day for men or > 60 g/day for women.

Abbreviations: ER = extended-release; HDG = high-dose group (12 mg cyproheptadine and 10 mg prazosin ER per day); ITT = intention-to-treat; LDG = low-dose group (8 mg cyproheptadine and 5 mg prazosin ER per day); PG = placebo group; RDL = risk-drinking level; SD = standard deviation.

TABLE 3 Primary outcome: time \times time comparisons (from the mixed-effect model) of changes from baseline in the total alcohol consumption (TAC) per day in the low-dose and high-dose groups versus the placebo group (reference).

TAC change from baseline	LDG versus PG					HDG versus PG				
	Estimate	95% CI		P-value	Cohen's <i>d</i>	Estimate	95% CI		P-value	Cohen's <i>d</i>
		Lower	Upper				Lower	Upper		
ITT population										
Month 1	-3.0	-16.2	10.2	0.655	-0.07	-13.5	-26.8	0.6	0.086	-0.31
Month 2	-13.4	-30.9	4.0	0.130	-0.27	-24.6	-42.9	-6.4	0.009	-0.46
Month 3	-18.4	-36.6	-0.2	0.048	-0.36	-23.6	-42.7	-4.5	0.016	-0.44
Participants with very high RDL at baseline										
Month 1	-0.9	-21.4	19.6	0.929	-0.02	-21.3	-40.9	-1.7	0.034	-0.45
Month 2	-11.5	-38.1	15.2	0.395	-0.09	-34.8	-60.5	-9.1	0.009	-0.61
Month 3	-18.9	-46.8	9.1	0.183	-0.31	-29.8	-56.8	-2.8	0.031	-0.51

Note: Very high RDL: alcohol consumption > 100 g/day for men or > 60 g/day for women.

Abbreviations: CI = confidence interval; ER = extended-release; HDG = high-dose group (12 mg cyproheptadine and 10 mg prazosin ER per day); ITT = intention-to-treat; LDG = low-dose group (8 mg cyproheptadine and 5 mg prazosin ER per day); PG = placebo group; RDL = risk-drinking level.

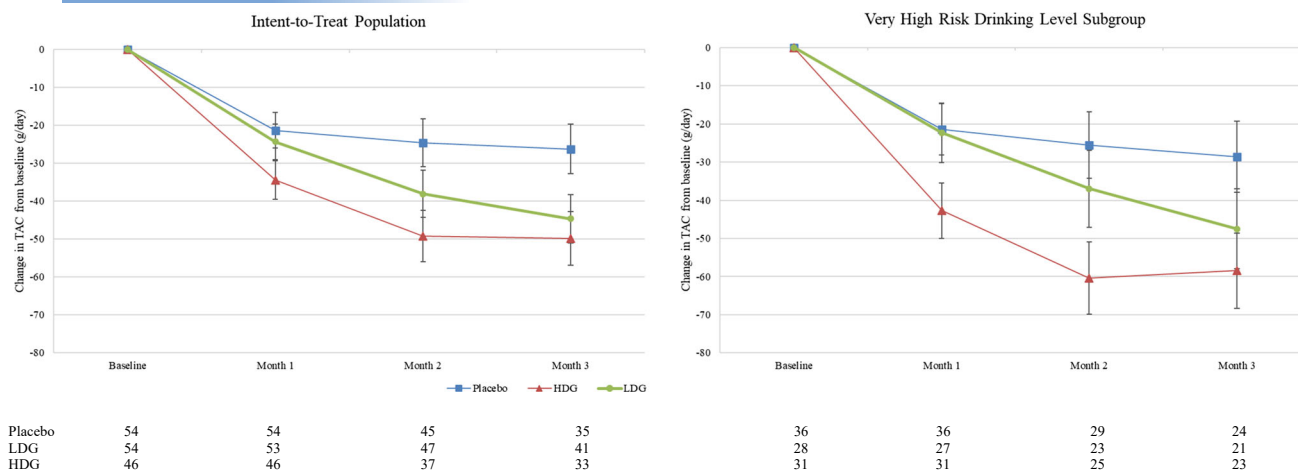


FIGURE 2 Change from baseline in total alcohol consumption (TAC) in the intent-to-treat population (left panel) and in the subgroup of patients with a very high-risk drinking level at baseline (right panel). The low-dose group (LDG) received 8 mg cyproheptadine and 5 mg prazosin per day; the high-dose group (HDG) received 12 mg cyproheptadine and 10 mg prazosin per day; the placebo group received placebo of cyproheptadine and placebo of prazosin. Adjusted means. Bars indicate standard error. Participant numbers contributing to each monthly period are shown below the x-axis for each treatment group

from -0.02 to -0.31 in the LDG and from -0.45 to -0.51 in the HDG from months 1 to 3 (Tables 2 and 3).

In the PP population results were very similar to those in the ITT population, with a significant benefit only for the HDG (Supporting information, Table S2).

Secondary outcomes

The responder rates defined as a two-level reduction in WHO RDLs between baseline and month 3 using observed cases were 20.0, 34.2 and 42.4% in the PG, LDG and HDG, respectively, in the ITT population. Using a logistic mixed model for repeated measures, the ORs comparing responder rates between LDG or HDG and PG were 2.21 (95% CI = 0.80–6.11) and 2.97 (95% CI = 1.04–8.51), respectively. A reduction of at least 50% in TAC between baseline and month 3 was observed in 25.7, 39.0 and 45.5% of participants still present at month 3 in the PG, LDG and HDG groups, respectively. In the logistic mixed model for repeated measures, the ORs comparing response rates between LDG or HDG and PG were 1.91 (95% CI = 0.74–4.89) and 2.18 (95% CI = 0.82–5.80).

All other secondary outcomes shown in Table 4 improved numerically in all groups. Pairwise comparisons showed a significant effect ($P < 0.05$) of the HDG in the change in OCDS total score and in the change in OCDS subscores from baseline to month 2 and also to month 3 for the obsessional subscore, compared to the PG. Statistical significance was also reached for the change in BDI score from baseline to month 3 for the comparison between the LDG and the PG, indicating a benefit for the LDG (Table 4). Effect sizes were globally larger in the HDG than in the LDG for drinking outcomes (HDD and days abstinent), whereas they were quite similar for the OCDS and BDI outcomes,

Five participants (3.2%) were continuously abstinent by month 3 (one in the PG, two in the LDG and two in the HDG) (ITT and PP populations). The smoking status or cigarette consumption (cigarettes/day) did not change significantly during the study.

Safety

A total of 342 AEs were reported by 113 (73.4%) participants: 84 AEs by 35 (64.8%) participants in the PG, 127 AEs by 43 (79.6%) participants in the LDG and 131 AEs by 35 (76.1%) participants in the HDG (Supporting information, Table S3). More than 90% of AEs were mild or moderate. Six SAEs have been reported in five participants: one SAE in the PG (1.9%) and five SAEs in four participants in the LDG (7.4%). No SAE was reported in the HDG. All SAEs were considered unlikely to be related to the study drugs after review by the DSMB (further details in Supporting information, Data S1). The sedation level was similar in all groups (Supporting information, Table S4).

Symptoms of OH were reported in one (1.9%), four (7.4%) and two (4.3%) participants in the PG, LDG and HDG, respectively. Of the 1785 measures of OH at 1 and 3 minutes of standing after the supine position, 60 (3.4%) were compatible with the definition of an OH in 22 participants: eight (14.8%), eight (14.8%) and six (13.0%) participants in the PG, LDG and HDG, respectively; of these, only one participant reported clinical symptoms suggestive of OH (details in Supporting information).

Body weight increased by 0.1 kg (SD = 2.8) in the PG, by 2.5 kg (SD = 2.5) in the LDG and by 2.4 kg (SD = 4.2) in the HDG between baseline and month 3. Weight increase was significantly higher ($P \leq 0.003$) in both active treatment groups compared to the

TABLE 4 Secondary outcomes: time by time comparisons (from the mixed effect model) of changes from baseline in the low-dose and high-dose groups versus the placebo group (reference).

	LDG versus PG					HDG versus PG				
	Estimate	95% CI		P-value	Cohen's <i>d</i>	Estimate	95% CI		P-value	Cohen's <i>d</i>
		Lower	Upper				Lower	Upper		
HDD change from baseline										
Month 1	-1.94	-5.17	1.30	0.239	-0.19	-1.47	-4.83	1.89	0.390	-0.14
Month 2	-1.33	-5.01	2.34	0.474	-0.12	-2.91	-6.77	0.94	0.138	-0.25
Month 3	-2.60	-6.70	1.50	0.211	-0.22	-3.34	-7.66	0.97	0.128	-0.27
Days abstinent change from baseline										
Month 1	0.32	-1.62	2.25	0.747	0.05	1.67	-0.34	3.68	0.102	0.27
Month 2	1.29	-1.57	4.15	0.374	0.15	2.59	-0.42	5.61	0.091	0.28
Month 3	0.87	-2.10	3.83	0.564	0.10	2.34	-0.79	5.47	0.142	0.25
OCDS total score change from baseline										
Month 1	-1.64	-3.95	0.68	0.163	-0.25	-2.03	-4.48	0.41	0.102	-0.29
Month 2	-1.72	-4.23	0.79	0.177	-0.24	-3.22	-5.85	-0.58	0.017	-0.43
Month 3	-2.78	-5.60	0.05	0.054	-0.36	-2.95	-5.98	0.08	0.056	-0.35
OCDS obsessional subscore change from baseline										
Month 1	-1.20	-2.48	0.08	0.066	-0.32	-1.24	-2.60	0.11	0.071	-0.32
Month 2	-0.62	-2.01	0.77	0.377	-0.16	-1.48	-2.94	-0.03	0.046	-0.36
Month 3	-1.39	-2.83	0.05	0.058	-0.36	-1.56	-3.10	-0.01	0.048	-0.37
OCDS compulsive subscore change from baseline										
Month 1	-0.44	-1.79	0.91	0.519	-0.11	-0.89	-2.32	0.53	0.218	-0.22
Month 2	-1.10	-2.56	0.36	0.138	-0.26	-1.84	-3.37	-0.31	0.019	-0.42
Month 3	-1.41	-2.98	0.16	0.078	-0.33	-1.57	-3.25	0.11	0.066	-0.33
BDI score change from baseline										
Month 1	-1.09	-2.50	0.32	0.130	-0.26	-0.64	-2.13	0.85	0.398	-0.14
Month 2	-0.48	-1.99	1.03	0.530	-0.11	-0.59	-2.18	1.00	0.464	-0.13
Month 3	-1.45	-2.78	-0.12	0.033	-0.43	-1.04	-2.48	0.40	0.155	-0.28

Abbreviations: BDI = Beck Depression Inventory; CI = confidence interval; ER = extended-release; HDD = heavy drinking days; HDG = high-dose group (12 mg cyproheptadine and 10 mg prazosin ER per day); LDG = low-dose group (8 mg cyproheptadine and 5 mg prazosin ER per day); OCDS = obsessive compulsive drinking scale; PG = placebo group.

PG. There was no statistically significant difference between the two active treatment groups.

DISCUSSION

The primary analysis of the primary outcome (change in TAC from baseline to month 3) showed a significant benefit of the prazosin ER–cyproheptadine combination in the ITT population, with a statistically significant and clinically relevant reduction of 23.6 g/day for HDG compared to the PG. In addition, a significant dose–response relationship was identified for this primary end-point, indicating that the effect size increased with the dose.

Prolonged abstinence has long been considered the imperative outcome of AUD treatment [14, 15], and most clinical trial designs have focused historically on abstinence as a primary outcome measure of treatment efficacy, often limiting the inclusion to recently

detoxified participants [16]. However, many individuals with AUD are unwilling or feel unable to engage in abstinence, and are increasingly interested in drinking reduction goals [14, 17]. In addition, drinking reduction, as objectified by a reduction in WHO RDL, has been shown to be sustainable and associated with long-term clinical and functioning improvements [18–20]. This led the European Medicines Agency (EMA) to allow harm reduction, such as TAC or HDD reduction, as a goal in the development of medications for AUD [8]. The US Food and Drug Administration determined a low risk-drinking outcome of no HDD as the acceptable drinking end-point [21]. In France, the growing popularity of alcohol reduction versus abstinence drinking goal among AUD individuals seeking treatment is such that it has become difficult to aim for a complete abstinence drinking goal in a clinical trial [22]. Therefore, we opted for an alcohol-reduction trial design with no prior detoxification requirement, similar to the design used in the nalmefene development programme, and with TAC change as the primary outcome [13, 17, 23, 24].

All groups showed substantial improvement in all drinking outcomes; this was expected, as large placebo responses are usually reported in AUD trials [25, 26]. The primary end-point's (TAC) effect size for the HDG (Cohen's $d = 0.44$) is somewhat higher than those reported with naltrexone (Cohen's $d = 0.09$ – 0.21) [27–29], nalmefene (Cohen's $d = 0.18$ – 0.37) [17, 28, 29] or baclofen (Cohen's $d = 0.28$) [30]. Similarly, the high-dose medication effect size on the HDD (Cohen's $d = 0.27$) was in the same range as those reported with naltrexone (Cohen's $d = 0.15$) [29], nalmefene (Cohen's $d = 0.33$ to 0.34) [17, 29] or baclofen (Cohen's $d = 0.26$) [30].

As proposed by the EMA [8] and several authors [19, 31–33], the responder analysis used the percentage of individuals who reduced their WHO RDL by at least two levels. The response rate increased both in the LDG (OR = 2.21, 95% CI = 0.80–6.11) and HDG (OR = 2.97, 95% CI = 1.04–8.51) compared to PG, further supporting to a potential therapeutic efficacy.

Importantly, the high-dose medication effect sizes relative to placebo were clinically relevant (Cohen's $d > 0.20$) for other drinking outcomes derived from the same drinking diary (ranging from Cohen's $d = 0.25$ to 0.27), and also for OCDS and BDI scores (ranging from Cohen's $d = 0.28$ to 0.35).

Interestingly, the exploratory analysis of the primary end-point in the subgroup of patients with a VH RDL at baseline yielded a greater treatment effect size than observed in the ITT population, but only in the HDG (Cohen's $d = -0.51$ versus -0.44), with an estimated TAC change close to 30 g/day compared to PG. A larger effect size in this subgroup is relevant, as subjects with VH RDL suffer from the particularly high burden of disease and mortality: 54% of all liver cirrhosis, 44% of all pancreatitis and 41% of oral cavity and pharyngeal cancers, 21–35 years reduction in life expectancy compared with the general population [34].

The number of participants with AE did not seem to increase as a function of dose exposure (PG: 64.8%, LDG: 79.6%, HDG: 76.1%). Only five SAE were recorded (four in the LDG, one in the PG) and none of them was considered by the investigator and/or the DSMB to be associated with the active treatment. OH, a potential adverse effect of prazosin, was recorded in 22 participants, with similar distribution among all groups. The utilization of the ER formulation of prazosin probably contributed to minimizing the incidence of OH in the active treatment groups. The most prominent adverse effect of the prazosin–cyproheptadine combination appears to be weight gain, an anticipated AE of cyproheptadine. Unlike prazosin, cyproheptadine spurs appetite and subsequent weight gain [35]. Considering the comparable extent of weight gain in both active treatment groups, this adverse effect should not deter future studies from concentrating on the high-dose regimen of the treatment combination.

The study had several strengths, as follows.

- a. The study clinically validates a concept originated from pre-clinical animal studies suggesting the critical role of the noradrenergic and serotonergic systems' uncoupling after repeated exposure to drugs of abuse, including alcohol, and the possibility of re-coupling these

systems by simultaneously blocking the $\alpha 1b$ -adrenergic and 5HT2A-serotonergic receptors [1] and eventually showing the effectiveness of the combination of prazosin and cyproheptadine in reversing alcohol preference [5].

- b. The design of this study took advantage of the nalmefene development programme [17] while avoiding some of its initial flaws; namely, discarding moderate RDL drinkers and early responders by including only participants who maintained at least a high RDL over the 4-week period preceding randomization.
- c. The sensitivity analyses confirmed the primary analysis results.

Limitations include the fact that we could only randomize 86% ($n = 154$) of the planned sample size, mainly because of COVID-19 pandemic restrictions. Also, as a first clinical exploration of the concept of simultaneously blocking of $\alpha 1b$ and 5HT2A receptors, this trial did not include biomarker measurements. This decision was made to improve feasibility and reduce costs, particularly in a context of limited funding. However, we observed sizeable improvements in secondary outcomes not deriving from participants drinking self-reports (i.e. measuring alcohol craving and depressive symptoms), which paralleled the drinking reduction outcomes. This consistency in the findings provides additional support for the observed treatment effects. Further, the 12 weeks' treatment duration may be considered as insufficient, given the chronic nature of the AUD. A substantially longer treatment exposure should be considered in further Phase 3 trials.

Regarding generalizability, the socio-demographic characteristics of the participants were similar to previous French clinical trials in AUD [22, 36, 37]. In addition, although we have excluded individuals with a history of alcohol withdrawal syndrome or with uncontrolled hypertension, these individuals may be an appropriate target for this treatment.

Overall, these results suggest the efficacy of the combination of prazosin ER and cyproheptadine in AUD, thus providing a clinical validation of the concept of re-coupling the noradrenergic and serotonergic systems by simultaneously blocking the $\alpha 1b$ -adrenergic and 5HT2A-serotonergic receptors [1, 5]. Only the high dose of the combination showed a significant effect in the change in TAC and the dose–response indicated a larger magnitude of drinking reduction for the high dose than the low-dose combination—especially in participants with a VH RDL at baseline—while showing a similar safety profile. This clearly favours the choice of the high-dose combination when designing future trials. Considering the small number of approved medications and current limited use of pharmacotherapy for AUD, all with limited-to-moderate efficacy, patients with AUD as well as their physicians are at need for additional treatments [38]. The promising efficacy of the combination of prazosin and cyproheptadine warrants prolonging this work with Phase 3 trials.

AUTHOR CONTRIBUTIONS

Henri Jean Aubin: Conceptualization (equal); formal analysis (equal); investigation (equal); methodology (equal); supervision (equal); validation (equal); writing—original draft (equal). **Ivan Berlin:** Conceptualization

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DECLARATION OF INTERESTS

H.J.A., B.T., D.L., F.Q., M.B., P. Batel, P. Bendimerad, P.P., M.G.B., M.G.L. and R.M. were investigators for the study, and therefore their institutions received financial support from Kinnov Therapeutics. D.D. received financial support from Kinnov Therapeutics as investigator for the study. A.P., T.F., J.P.T., H.P.P., P. Bernard, I.B. and J.B. received consulting fees from Kinnov Therapeutics. H.J.A. received financial support from Kinnov Therapeutics, Ethypharm, Lundbeck, Bioprojet Pharma and Pfizer. J.G. is employed by Vergio and was employed by D&A Pharma until March 2022. M.B. received financial support from Ethypharm, Accor Pharmafield and Abbvie. P. Bendimerad received financial support from Ethypharm, Janssen and Novonordisk. P.P. received financial support from Ethypharm and Lundbeck.

DATA AVAILABILITY STATEMENT

The de-identified participant data that underlie the results reported in this article, along with a data dictionary, the study protocol, and the participant information and consent form, will be made available to researchers immediately after the publication. Request for data sharing should be addressed to Julien Guiraud jguiraud@vergioconsulting.com accompanied by a research plan specifying the research questions, aims and providing a detailed statistical analysis plan. Data sharing will be approved by the Cocktail steering committee.

CLINICAL TRIAL REGISTRATION DETAILS

The study was registered in [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT04108104), NCT04108104, <https://clinicaltrials.gov/ct2/show/NCT04108104>.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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