STATENS BEREDNING FÖR MEDICINSK OCH SOCIAL UTVÄRDERING

Bilaga till rapport

Behandling och sociala stödinsatser vid samsjuklighet mellan beroende och andra psykiatriska tillstånd, Del 1
Läkemedelsbehandling / Interventions for adults with co-occurring addictive and psychiatric disorders: A systematic review, Part 1
Pharmacological treatment, rapport 372 (2024)

Bilaga 4 Inkluderade studier/Appendix 4 Characteristics of included studies

Adamson et al. 2015

Study	**Adamson, 2015 [1]**
Study design	RCT (double blind, multi-center)
Intervention	**Pharmacotherapy: citalopram** Co-interventions: open-label naltrexone and manualized clinical case management
Trial registration	ACTRN12606000413527
Country	New Zealand
Setting	Outpatient: 7 outpatient addiction clinics spanning urban, provincial, and rural catchments.
Aims	The present study had 2 main objectives. First, we aimed to determine whether combining naltrexone with citalopram produced better treatment outcomes than naltrexone alone in patients with co-occurring alcohol dependence and major depression. Second, we investigated whether either sex or depression type (independent or substance-induced depression) was associated with a differential outcome between treatment groups.
Participants	**AUD & Depression** Alcohol dependence and major depressive episode in the past 4 weeks, DSM-IV criteria (SCID). **Baseline characteristics**

	Total	Citalopram	Placebo
n	**138**	**73**	**65**
Women: %	59.4%	60.3%	58.5%
Age: M (SD)	43.6 (9.1)	44.6 (8.6)	42.4 (9.5)
Education, years	13.5 (3.1)	13.1 (3.0)	14.0 (3.3)
Lives alone	23.9%	28.8%	18.5%
Employed	55.1%	53.4%	56.9%
Substance use status			
Alcohol dependence, onset age: M (SD)	29.8 (10.4)	30.1 (10.2)	29.3 (9.9)
Percent days abstinent: M (SD)	25.8 (27.4)	25.5 (28.4)	26.1 (26.4)
Percent days heavy drinking: M (SD)	58.9 (33.6)	60.7 (34.9)	56.8 (32.2)
Drinks per drinking day: M (SD)	14.3 (8.0)	14.3 (7.4)	14.4 (8.6)
LDQ: M (SD)	19.5 (6.5)	20.2 (6.4)	18.7 (6.6)
Mental health status			
Independent depression: %	76.1%	69.9%	83.1%
Major depressive disorder, onset age*: M (SD)	24.3 (11.4)	26.3 (12.4)	22.2 (9.9)
MADRS: M (SD)	31.0 (5.8)	31.3 (5.6)	30.6 (6.0)

SCL-90 depression: M (SD)	2.0 (0.7)	2.0 (0.7)	1.9 (0.7)
Comorbidities			
Current other substance dependence**: %	14.5%	17.8%	10.8%
Current anxiety disorder: %	47.1%	50.7%	43.1%

*Significant difference between groups.

**Current substance use disorder was almost exclusively a cannabis user disorder (13.0%) or stimulant use disorder (3.6%).

Inclusion criteria

Participants were aged 17 to 65 years, met DSM-IV criteria for alcohol dependence and major depressive episode in the past 4 weeks according to responses to the SCID-IV, and scored greater than 20 on MADRS for past week symptoms of depression. Subjects were not required to be abstinent from alcohol when entering the study. Depression was defined as independent or substance-induced according to SCID-IV.

Exclusion criteria

Potential participants were excluded if they had a history of the following:

A. past regular intravenous drug use for more than 2 weeks;

B. recreational use of any opioid drugs in the previous 4 weeks or a current requirement for ongoing opioid use;

C. psychosis, including psychotic delirium complicating alcohol or other drug withdrawal;

D. mania or hypomania;

E. significant current suicidality or homicidality;

F. current severe psychiatric symptoms requiring hospitalization;

G. unstable physical disease;

H. use of disulfiram, naltrexone, antidepressant, or mood-stabilizing medication in the past 4 weeks;

I. serum aspartase aminotransferase, alanine transaminase, or gamma glutamyl transpeptidase greater than 3 the upper limit of the laboratory reference range, or a bilirubin level above the upper limit of the reference range;

J. pregnancy, breastfeeding, or unwillingness to use a reliable method of contraception in female participants of childbearing age; and

K. current or pending imprisonment.

Recruitment & screening

Participants were recruited by advertising and from alcohol treatment services.

	A total of 474 potentially eligible participants were screened, of whom 237 were excluded, primarily due to subthreshold levels of depression, not meeting criteria for alcohol dependence, and being on antidepressant medication where it was not appropriate to have a washout period before commencing the current trial. A further 88 declined to participate, and 2 failed to reach the point of randomization, whereas in post randomization, 2 withdrew consent and 3 became uncontactable before commencing study medications, and outcome data were lost by research clinicians for 4 participants. Finally, 2 participants, both receiving citalopram, were unblinded before the week 12 assessment. This left 138 patients randomized to the 2 conditions who commenced treatment, 73 receiving citalopram, and 65 receiving placebo. **Remuneration** Participants were compensated for participation with vouchers worth NZ $40 during the study.
Comparison	**Citalopram vs. placebo** **Duration of treatment** 12 weeks **Follow ups** Measurements during treatment: every three weeks Endpoint / time of last treatment:12 weeks
Experimental arm	**Citalopram, adjunct** Patients took 1 capsule of 20 mg citalopram daily in week 1. If tolerated, the dose was then increased to 2 capsules. After 6 weeks, the dose could be further increased to 3 capsules if patients remained depressed. **Co-interventions:** <u>Open label Naltrexone</u> Naltrexone was prescribed for all participants as 1 component of good clinical care, given its established efficacy as a treatment for alcohol dependence. The naltrexone dose was 25 mg daily for 1 week, then increased to 50 mg in patients without significant adverse effects. The dose could be further increased to 75 or 100 mg after 6 weeks. <u>Benzodiazepines</u> Participants could be prescribed benzodiazepines to treat alcohol withdrawal. Disulfiram, acamprosate, and antidepressants other than citalopram were not permitted during the trial. <u>Clincal case management</u> All participants received manualized clinical case management delivered by experienced addiction clinicians (predominantly nursing or social work trained with postgraduate qualifications) who took a 4-day training course specific to the study. Clinical case

	management comprised motivational enhancement, education, support for improved social functioning, encouraging significant other involvement, problem solving, medication adherence, and mood management strategies. Participants were supported to work toward abstinence or to reduce their consumption, although abstinence was promoted as the most clinically appropriate goal. Participants' progress was discussed at fortnightly telephone supervision. Research clinicians also maintained contact with participants' nominated significant other to corroborate history obtained from the participant. Treatment was overseen by an addiction medicine specialist or psychiatrist at each site
Control arm	**Placebo (vitamin C), adjunct** Patients took 1 capsule of 20 mg placebo daily in week 1. If tolerated, the dose was then increased to 2 capsules. After 6 weeks, the dose could be further increased to 3 capsules if patients remained depressed. **Co-interventions** Same as for Experimental arm.
Outcomes	**Substance use** Primary outcomes: Alcohol, percent days abstinent (TLFB), self-reported, measured at baseline, 3, 6, 9, and 12 weeks Secondary outcomes: Alcohol, drinks per drinking day (TLFB), self-reported, measured at baseline, 3, 6, 9, and 12 weeks Alcohol, percent days heavy drinking (TLFB), self-reported, measured at baseline, 3, 6, 9, and 12 weeks All drinking outcomes are the summed total of available drinking data from baseline to week 12. Severity of alcohol dependence (LDQ), self-reported, measured at baseline and week 12 **Mental health** Primary outcomes: Depressive symptoms (MADRS), self-reported, measured at baseline, 3, 6, 9, and 12 weeks (primary outcome: week 12) Secondary outcomes: Remission of depression, defined as a MADRS score of less than 10 and change in SCL-90 depression score Measured at 3-week intervals from baseline to study completion at 12 weeks (baseline, 3, 6, 9, and 12 weeks). Assume self-reported, but not stated. **Quality of life** Not assessed **Function**

Results

Not assessed

Mortality

Not assessed

Compliance

Adherence was monitored via self-report and counting pills at clinic visits.

Adverse effects

Adverse effect profile form, self-reported,

Substance use

	Citalopram (ITT, n = 73)	Placebo (ITT, n = 65)	Between group Effect size	F	*P*
Primary outcomes	**12 weeks**	**12 weeks**	**Cohen d**		
Percent days abstinent, adjusted* mean (SD)	68.0 (32.0)	59.9 (32.1)	0.25	2.68	0.104
Secondary outcomes					
Drinks per drinking day, adjusted* mean (SD)	6.2 (6.1)	6.8 (6.4)	0.09	0.27	0.604
Percent days heavy drinking, adjusted* mean (SD)	16.3 (22.7)	16.8 (22.3)	0.00	0.10	0.747
LDQ, adjusted* mean (SD)	9.0 (8.9)	9.6 (8.6)	0.06	2.08	0.152

Mental health

	Citalopram (ITT, n = 73)	Placebo (ITT, n = 65)	Between group Effect size	F	*P*
Primary outcomes	**12 weeks**	**12 weeks**	**Cohen d**		
MADRS, adjusted* mean (SD)	12.8 (9.9)	11.8 (11.0)	0.10	0.00	0.992
Secondary outcomes					
SCL-90 depression, adjusted* mean (SD)	1.2 (0.9)	1.2 (0.9)	0.01	0.19	0.661
MADRS remission, %	46.6%	55.4%		Wald 0.13	0.716

* Factorial ANOVA. All models used baseline MADRS for depression outcomes, baseline drinking for drinking outcomes, and treatment location as covariates. The last observation carried forward method was used for handling missing data.

Compliance

	Citalopram N = 73	Placebo n = 65	*P**
Citalopram/placebo adherence			
Percent days medication taken, % (SD)	83.8 (22.0)	87.9 (15.7)	0.213
Maximum dose (mg)**, mean (SD)	38.3 (9.4)	40.0 (8.1)	0.271
Percent consuming on ≥80% of days, %	67.6%	76.2%	0.271
Naltrexone adherence			
Percent days medication taken, % (SD)	85.3 (20.7)	87.6 (16.4)	0.481

	Maximum dose (mg), mean (SD)	55.5 (19.2)	61.3 (22.5)	0.117
	Percent consuming on ≥80% of days, %	71.8%	77.8%	0.43
	Psychosocial component			
	Sessions attended, mean (SD)	5.2 (1.2)	5.1 (1.4)	0.745
	*Independent sample t-test			
	**Pill equivalent for placebo group			
	Adverse effects, % (N)			
	Overall, 66 patients (90.4%) who received citalopram reported one or more symptom on the self-report adverse effect profile form at some point during treatment, with an equivalent rate (87.7%) for the 57 patients who received placebo, whereas 52.1% and 35.4%, respectively, self-rated at least 1 symptom as "severe" at some point during follow-up ($\chi2 = 3.87$, df = 1, P = 0.049). Severe adverse effects reported by more than 10% of the sample were difficulty sleeping (citalopram 17.8%, placebo 7.7%; $\chi2 = 3.10$, df = 1, P = 0.078), nausea (citalopram 12.3%, placebo 7.7%; $\chi2 = 0.81$, df = 1, P = 0.368), and low energy (citalopram 16.4%, placebo 4.6%; $\chi2 = 4.961$, df = 1, P = 0.026). The 2 patients who required unblinding during the 12-week treatment, for suicidal ideation and severe abdominal cramps, were both prescribed citalopram.			
	Loss to follow up: N (%)			
	12 week: N = 34 (24.6%) There was no between group difference in the rate of attendance rate scheduled treatment appointments.			
Comments	Recruitment began in 2007 and finished in 2011 due to exhausting research funds. Targeted sample size was n=220.			
Risk of bias	Moderate			

AUD = alcohol use disorder; **ANOVA** = analysis of variance; **DSM** = Diagnostic and Statistical Manual of Mental Disorders, roman numerals indicate version number; **ITT** = intention to treat; **LDQ** = Leeds Dependence Questionnaire: a questionnaire to measure alcohol and opiate dependence in the context of a treatment evaluation package; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **SCL**-90 = Symptom Checklist – 90 items; **RCT** = randomized controlled trial; **SD** = standard deviation; **SCID** = Structured Clinical Interview for DSM, roman numerals indicate DSM version number; **TLFB** = Time Line Follow Back, self-reported substance abuse.

Back et al. 2023

Study	**Back, 2023 [2]**
Study design	Double-blind RCT
Intervention	Pharmacotherapy: doxazosin
	Co-interventions: All participants had the option to receive weekly CBT
Trial registration	NCT02500602
Country	South Carolina, USA
Setting	Outpatient (a veteran's medical center or affiliated outpatient clinics)

Aims

To determine the efficacy of doxazosin, an α1-adrenergic antagonist, for the treatment of co-occurring PTSD and AUD.

Participants

AUD & PTSD

Treatment-seeking US military veterans who met DSM-5 criteria for current moderate or severe AUD and current PTSD (CAPS-5)

Baseline characteristics

	Total	Doxazosin	Placebo
N=	141	70	71
Women: % (n)	16% (22)	11% (8)	20% (14)
Age: M (SD)	45.7 (11.1)	45.5 (11.4)	45.9 (10.8)
Substance use status			
AUDIT, total scores: M (SD)	19.4 (9.4)	19.5 (10.2)	19.3 (8.7)
% drinking days*: M (SD)	54.3 (37.1)	52.1 (39.7)	56.5 (34.4)
% heavy drinking days*: M (SD)	41.2 (37.8)	42.8 (37.7)	39.7 (38.2)
Mental health status			
CAPS-5, total scores: M (SD)	33.7 (9.0)	34.2 (9.6)	33.1 (8.3)
PCL-5, total scores: M (SD)	47.3 (14.8)	47.0 (15.2)	47.7 (14.4)
Comorbidities			
Psychotropic medications: % (n)	59.6% (84)	52.9% (37)	66.2% (47)
- Antidepressants: % (n)	82.1% (69)		
- Antianxiety meds: % (n)	4.8% (4)		
- Antipsychotics: % (n)	8.3% (7)		
Anticonvulsants**: n	21.3% (30)	22.9% (16)	19.7% (14)

* Baseline based on average over the 60 days prior to commencement of treatment

** Primarily to treat pain or migraine headaches

Comments

At baseline, 11 participants reported abstinence from alcohol in the 60 days prior to enrolment (6 in the doxazosin condition and 5 in the placebo condition). Twenty-three participants reported abstinence in the 30 days prior to enrolment (15 in the doxazosin condition and 8 in the placebo condition).

Inclusion criteria

Participants were treatment-seeking US military veterans enrolled at the Ralph H. Johnson VA Medical Center or affiliated community-based outpatient clinics. They were required to meet DSM-5 criteria for current (past 6 months) moderate or severe AUD as assessed with MINI and current (past month) PTSD as assessed by the CAPS-5. Participants were not required to report a minimum amount of

	alcohol consumption or abstain from alcohol prior to study enrolment. Veterans taking psychotropic medications were required to be maintained on a stable dose for at least 4 weeks prior to study start. **Exclusion criteria** Primary exclusion criteria included previous treatment with doxazosin, history of adverse reactions to quinazolines or other α1 antagonists, currently taking α-blockers (eg, prazosin) or a medication for AUD (eg, naltrexone), current enrolment in an evidence-based psychosocial treatment for PTSD or AUD, and significant medical/psychiatric conditions that may adversely affect safety or study participation (e.g., suicidal intent). Women who were pregnant or nursing were excluded. Individuals presenting with significant alcohol withdrawal symptoms (score ≥ 10 on the CIWA for alcohol), were referred to a higher level of care and were eligible for revaluation after stabilization. **Recruitment & screening** Recruitment methods included clinician referrals, social media, newspaper advertisements, and flyers. **Remuneration** Participants were remunerated for each component of the study they completed and could receive up to $725 in cash, gift cards, or electronic funds transfer if they completed all aspects of the study.
Comparison	**Doxazosin vs. placebo** Duration of treatment 12 weeks **Follow ups** Measurements taken weekly (TLFB, PCL-5), at week 6 and 12 (CAP-5) A 6 week follow-up measurement was taken, results published elsewhere [3]
Experimental arm	**Doxazosin** immediate-release formulation, 16 mg/d, administered in capsules to be taken at bedtime Active study medication capsules consisted of United States Pharmacopeia–grade doxazosin and 25 mg riboflavin. Titration: Doxazosin was initiated at 1 mg/d and titrated up as follows: 2 mg at week 2, 4 mg at week 3, 8 mg at week 4, and then 16 mg during weeks 5–12. The majority (87.9%) of participants reached full medication titration to 16 mg at week 5. At the end of week 12, downward titration occurred, and participants were titrated down to 8 mg on day 1, 6 mg on day 2, 4 mg on day 3, 2 mg on day 4, and 1 mg on day 5.42. **Co-interventions** Psychosocial support

Control arm	All participants are enrolled in the VA and have the option to receive weekly CBT to ensure that all participants receive adequate psychosocial support and monitoring, regardless of medication arm. Information retrieved from separate publication on study design and methods [3]. Number who opted to receive CBT was not reported. <u>Multivitamin</u> Participants interested in taking a multivitamin during the treatment phase were provided a multivitamin (Tri-Vi-Sol) that does not contain riboflavin. **Placebo** All placebo capsules were brought to proper packing level in color-matched, opaque, identically sized capsules. Presumably the titration scheme was the same for doxazosin, and the placebo capsules also contained riboflavin. **Co-interventions** Same as for Experimental arm.
Outcomes	**Substance use** <u>Primary outcomes</u>: % drinking days, any alcohol (TLFB), self-reported, collected weekly % heavy drinking days (TLFB), self-reported, collected weekly % abstinent days, no alcohol (TLFB), self-reported, collected weekly <u>Secondary outcomes</u>: Number of drinks per drinking days (TLFB), self-reported, collected weekly Alcohol craving over last week (VAS 1 to 10), self-reported, collected weekly **Mental health** <u>Primary outcomes</u>: PTSD symptom severity (CAPS-5), semi-structured interview administered by trained independent evaluators, at week 6, 12, & at follow-up PTSD severity (PCL-5), self-reported, administered weekly & at follow-up **Quality of life** Not assessed **Function** Not assessed

Results

Mortality

Not assessed

Other

Secondary outcomes:

Participants also completed a battery of measures as Common Data Elements, including military history information, trauma exposure, psychiatric symptoms, traumatic brain injury, and pain.

Compliance

Participants provided monthly urine samples to assess riboflavin for medication adherence

Participants were also asked about medication adherence during each weekly study visit and reminded to take study medication as instructed.

Adverse effects

Vital signs and adverse events were obtained weekly by the study medical clinician

Substance use

Alcohol consumption	**Doxazosin** (ITT,n = 70)			**Placebo** (ITT, n = 71)			**Doxazosin vs Placebo**
Primary outcomes	**Baseline**	**12 weeks**	**Change**	**Baseline**	**12 weeks**	**Change**	**Between group differences in change, baseline to 12 weeks**
% drinking days*, mean (SE)	52.1 (4.47)	27.2 (4.35)	25.0 (4.84)	56.5 (4.41)	29.9 (4.32)	26.6 (4.80)	−1.6 (6.81)
p=			< 0.0001			< 0.0001	0.81
Cohen's d=			0.67			0.72	-0.04
% heavy drinking days*, mean (SE)	42.8 (4.57)	13.4 (3.06)	29.3 (4.51)	39.7 (4.50)	9.5 (3.01)	30.1 (4.44)	−0.8 (6.33)
p=			< 0.0001			< 0.0001	0.90
Cohen's d=			0.78			0.80	-0.02
% who abstained, % (n)		22 (15)			7 (5)		p = 0.017 $X^2 = 5.7$
Secondary outcomes		**Endpoint**			**Endpoint**		**Difference**
Drinks / drinking day, mean (SD)		6.15 (3.51)			4.56 (2.91)		$t_{111} = 2.63$ p = 0.0096 *d* = 0.50

Mental health

PTSD	Doxazosin (ITT,n = 70)			Placebo (ITT, n = 71)			Doxazosin vs Placebo
Primary outcomes	**Baseline**	**Endpoint**	**Difference**	**Baseline**	**Endpoint**	**Difference**	**Baseline to 12 weeks**
CAPS-5* total, mean (SD)**	34.2 (1.07)	26.5 (1.72)	7.7 (1.43)	33.1 (1.07)	25.8 (1.70)	7.3 (1.40)	0.4 (2.00)
p=			< 0.0001			< 0.0001	0.84
Cohen's d=			0.86			0.81	0.04
PCL-5 Total, , mean (SD)	47.0 (1.77)	34.6 (2.36)	12.4 (1.93)	47.7 (1.76)	30.6 (2.33)	17.1 (1.89)	−4.8 (2.70)
p=			< 0.0001			< 0.0001	0.8
Cohen's d=			0.84			1.16	−0.32

* CAP-5 subscales are also reported separately, data not extracted.

** Entries are model-based estimated least-squares means and standard errors (SEs) and within-group change from baseline to week 12. Cohen d values are the estimated change and differences standardized by the baseline standard deviations. Degrees of freedom are the Kenward-Roger estimates

Comments

No analysis of the follow-up data presented in this article.

Compliance

	Total N = 132*
Riboflavin levels ≥ 900 ng/mL: % (n)	75.5 % (n)

* Participants were considered compliant when urine levels of riboflavin ≥ 900 ng/ml. Nine participants had missing riboflavin data and were not included in this analysis.

Comments

The authors state that there were no differences between medication groups.

Adverse effects

AE reported	**Doxazosin**	**Placebo**
Total: n	101	112
Serious: n (medical / psychiatric)	12 (5 / 7)	9 (3 / 6)

Comments

Common adverse events (AEs) included dizziness, gastrointestinal symptoms (eg, nausea), joint/muscle pain, cold or sinus congestion, sleep problems, and vivid dreams / nightmares. No differences in the overall frequency of side effects were observed by treatment group.

	The most common SAEs were hospital admissions for medical reasons (eg, hemorrhoids, hernia surgery, chest pain, viral gastroenteritis, diabetes complications), psychiatric problems (eg, depression, suicidal ideation, panic attack/anxiety), or inpatient treatment for alcohol use. **Loss to follow up** **At end of trial (12 weeks)** — **Total n = 141** — **Doxazosin n = 70** — **Placebo n = 71** **Completers*: % (n)** — 74.5 % (105) — 75.7 % (53) — 73.0 % (52)** **Loss to follow ups: % (n)** — 25.5 % (36) — 24.3 % (17) — 26.8 % (19) * Completers were defined as participants with complete data at the end of treatment (week 12), whether or not they remained on the medication. ** possible typo, 73.0 reported in text, however 52/71 = 73.2 %
Risk of bias	Low

AE = adverse effect; **AUD** = alcohol use disorder; **CAPS-5** = Clinician Administered PTSD Scale, number indicates DSM version; **CBT** = cognitive behavioural therapy; **CIWA** = Clinician Institute Withdrawal Assessment of Alcohol scale; **DSM** = Diagnostic and Statistical Manual of Mental Disorders, roman numerals indicate version number; **ITT** = intention to treat;**NR** = not reported; **M** = mean; **MINI** = Mini International Neuropsychiatric Interview**; PTSD** = posttraumatic stress disorder; **PCL-5** = PTSD checklist, number indicates DSM version; **RCT** = randomized controlled trial; **SAE** = serious adverse effect; **SD** = standard deviation; **TLFB** = Time Line Follow Back, self-reported substance abuse; **VAS** = visual analogue scale.

Batki et al. 2014

Study	**Batki, 2014 [4]**
Study design	RCT (double-blind, pilot trial)
Intervention	**Pharmacotherapy: topiramate** Co-interventions: weekly medical management counselling
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	To obtain a preliminary assessment of the efficacy and safety of topiramate in reducing alcohol use and PTSD symptoms in veterans with both disorders.
Participants	**PTSD and AUD** Veterans with both conditions **Baseline characteristics**

	Topiramete N = 14	Placebo N = 16
Women: % (n)	7% (1)	6% (1)
Age: M (SD)	49.5 (13.9)	50.4 (12.8)
Education level	12.9 (3.1) yrs	14.4 (1.9) yrs
Housing situation	NR	NR
Employment status	NR	NR
Attending parallel rehab program* : n	4	2
Substance use status		
AUDIT Score: M (SD)	27.1 (7.9)	23.0 (7.5)
Days abstinent between last drink and initiation of study medication	12.8 (13.6)	4.8 (9.2)
Percent DD/week M (SD)	73.3 (30.3	80.4 (21.5)
Percent HDD/week M (SD)	58.5 (33.7)	72.6 (28.5)
Drinks/day: M (SD)	11.1 (6.1)	10.9 (4.7)
Drinks/week: M (SD)	52.4 (34.2)	58.2 (25.4)
Mental health status		
BDI: M (SD)	23.4 (11.6)	26.3 (12.3)
BAI: M (SD)	20.4 (12.7)	27.4 (13.3)
CAPS Total: M (SD)	72.8 (14.3)	83.1 (17.3)
Comorbidities		
Comorbid SUD: % (n)	36% (5)	32% (5)

* Rehabilitation program included a structured living environment, group therapy and case management

Comments

Authors state that there are no significant baseline differences.

Inclusion criteria

Veterans who met DSM-IV-TR (American Psychiatric Association, 2000) diagnostic criteria for both current alcohol dependence and PTSD. All participants also reported “at-risk” or “heavy” drinking in accordance with NIH/NIAAA criteria (at least 15 standard drinks per week on average over the 4 weeks prior to study entry for men and at least 8 standard drinks per week on average for women) and all expressed a desire to reduce alcohol consumption with the possible long-term goal of abstinence. Participants included patients who were still actively drinking as well as those who had stopped in the days prior to random assignment.

Exclusion criteria

Met diagnostic criteria for psychotic disorders, bipolar disorder, and dementia; were known to have any clinically significant unstable psychiatric or medical conditions; had a suicide attempt or suicidal ideation in the six months prior to enrolment; acute alcohol withdrawal; history of either nephrolithiasis, narrow angle glaucoma or seizure disorder; current use of other anticonvulsant medications; topiramate use within the past four weeks; concurrent participation in other treatment studies.

Comparison	**Recruitment & screening** Recruitment and all procedures took place at the San Francisco Veterans Affairs Medical Center (SF VAMC) in San Francisco, CA; screened for eligibility, n = 137; randomized (stratified by gender), n = 30; no detoxification period **Remuneration** Not paid or reimbursed for participation **Topiramate vs. placebo** **Duration of treatment** 12 weeks **Follow ups** Measurements during treatment: PTSD – at baseline, week 4, 8, and 12; alcohol consumption – at baseline, thereafter weekly; alcohol craving – at baseline, week 4, 8, and 12; drinking severity – at baseline; cognition – at baseline, week 6, and 12; AE – weekly Endpoint / time of last treatment: at 12 weeks Follow up: NR
Experimental arm	**Topiramate** Provided as 25- or 100-mg capsules. The initial dose was 25 mg nightly for one week. The dose was increased to 50 mg per day in two divided doses in week 2; in week 3, the dose was increased to 100 mg per day; in week 4, to 150 mg per day; in week 5 to 200 mg per day, and in week 6, to 300 mg per day given as 100 mg in the morning and 200 mg in the evening. This final dose was maintained from week 6 through week 11. In week 12, study medication was tapered and discontinued. Dosing was flexible, in that the maximum daily dose was determined by tolerability **Co-interventions:** <u>Medical management</u> All participants also received weekly medical management counselling, a manual-driven, low-intensity supportive counselling method to promote adherence to the medication regimen and reduction in alcohol use <u>Other treatments</u> Participants were free to access any other standard psychological or pharmacologic treatments for PTSD and any psychosocial treatments for AUD, but they could not receive other AUD pharmacotherapy. <u>Comment</u>

Control arm

Four topiramate participants attended a 30-day community based residential rehabilitation treatment program that included a structured living environment with group therapy and individual case management.

Placebo

Provided as 25- or 100-mg capsules, identical to the study drug, and following the same protocol as above.

Co-interventions

Same as for Experimental arm.

Comment

Two placebo participants attended a 30-day community based residential rehabilitation treatment program that included a structured living environment with group therapy and individual case management.

Outcomes

Substance use

Number of alcohol drinking days (TLFB), interview at baseline + weekly

Number of heavy drinking days (TLFB), interview at baseline + weekly

Number of drinks per each day of drinking (TLFB), interview at baseline + weekly

Mental health

PTSD symptom severity (PTSD Checklist, PCL), self-reported at baseline, week 4, 8, and 12

Quality of life

Not assessed

Function

Auditory verbal learning, total recall (HVLT-R), self-reported at baseline, week 6 and 12

Memory, delayed recall (HVLT-R), self-reported at baseline, week 6 and 12

Mortality

Not assessed

Compliance

Self-report verified by pill count. Medication adherence rate was the total dose (mg) self-reported taken ÷ total dose prescribed × 100.

Adverse effects

Recorded weekly using a checklist of the 18 most common AEs associated with topiramate

Results

Substance use

	Topiramate (ITT, n = 14)	Placebo (ITT, n = 16)	p-value	IRR (beta)	95% CI	%Diff*

	Average weeks 1-12	Average weeks 1-12				
%DD, mean (SD)	19.5 (34.2)	39.7 (36.5)	0.036	0.38	0.15-0.94	51%
% HDD, mean (SD)	11.1 (27.1)	16.8 (26.3)	0.342	0.56	0.17-1.87	34%
Std drinks per week, mean (SD)	8.7 (19.0)	19.3 (30.5)	0.099	0.43	0.16-1.17	55%
Drinks per DD, mean (SD)	1.9 (3.3)	4.8 (6.5)	0.057	0.45	0.20-1.02	60%

* %Diff = percent difference, calculated by comparing weeks 1-12 averages between treatment groups

Comments

Adjusted for baseline alcohol consumption means. P-values from analyses where the insignificant interaction term (treatment by week) was removed

Mental health

PTSD Symptoms	Topiramate (ITT, n = 14) Average weeks 1-12	Placebo (ITT, n = 16) Average weeks 1-12	p-value	IRR (beta)	95% CI	%Diff
PCL Total score, mean (SD)	42.3 (16.0)	49.0 (16.5)	0.100	(-9.01)	-19.8 to 1.80	14%

Function

	Topiramate (ITT, n = 14) Baseline	Topiramate (ITT, n = 14) Week 6	Topiramate (ITT, n = 14) Week 12	Placebo (ITT, n = 16) Baseline	Placebo (ITT, n = 16) Week 6	Placebo (ITT, n = 16) Week 12
HVLT-R Total (learning), mean (SD)	42.3 (10.3)	31.6 (8.4)	41.0 (7.8)	41.5 (13.8)	43.4 (15.3)	44.8 (13.8)
HVLT-R Delayed Recall (memory), mean (SD)	46.4 (10.2)	31.3 (11.2)	36.8 (8.8)	44.13 (11.9)	42.4 (16.8)	45.8 (15.0)

There was a significant treatment-by-week interaction for *HVLT-R total recall* [F(1,21)=6.63, p=0.018].

There was a significant main effect of treatment [F(1,42)=5.01, p=0.031] and week [F(1,22)=6.23, p=0.021] suggesting differential treatment group performance between baseline and week 12 in *HVLT-R delayed recall*. There was no significant treatment-by-week interaction. Follow up univariate analyses indicated that the topiramate group decreased in learning and memory performance between baseline and week 6 and then regained part of that loss between week 6 and 12, whereas the placebo group did not show any significant change during these same intervals.

Compliance

Compliant	*Topiramate n = 14*	*Placebo n = 16*
Attended study visits: %	94.2%	83.1%
Medication adherence rate: %	63.1%	60.2%

Adverse effects

	Topiramate n = 14	*Placebo n = 16*
Patients experiencing treatment-emergent AE: % (n)	85.7% (12)	81.3% (13)
Sleepiness: %	36%	13%
Loss of appetite: %	29%	38%
Change in sense of taste: %	21%	31%
Itsching: %	21%	6%
Diarrhea: %	29%	19%
Abnormal vision: %	21%	19%
SAE – suicidal ideation: n		1
SAE – chest pain: n		2
SAE – died due to myocardial infarction: n		1

Comments:

The authors state: “There were no significant differences between groups on any reported emergent AE.”

Loss to follow up: N (%)

Endpoint: I: 1/14 (7.7%), C: 2/16 (12.5%).

Risk of bias

Low

AE = adverse effect; **AUD** = alcohol use disorder; **AUDIT** = Alcohol Use Disorders Identification Test; **BAI** = Beck Anxiety Inventory; **BDI** = Beck Depression Inventory; **C** = controll group; **CAPS-5** = Clinician Administered PTSD Scale, number indicates DSM version; **DD** = drinking days; **DSM-IV-TR** = Diagnostic and Statistical Manual of Mental Disorders, roman numerals indicate version number, text revised; **HDD** = heavy drinking days; **HVLT-R** = Hopkins Verbal Learning Test-Revised, tests cognition including

total recall (learning) and delayed recall (memory); **NIH** / **NIAAA** = National Institute of Health / National Institute on Alcohol Abuse and Alcoholism; **I** = intervention group; **IRR** = incidence rate ratio, average relative change in outcome per week; **NR** = not reported; **M** = mean; **SAE** = serious adverse effect;**SD** = standard deviation; **PTSD** = posttraumatic stress disorder; **RCT** = randomized controlled trial; **PCL** = PTSD checklist, number indicates DSM version.

Book et al. 2008

Study	**Book, 2008 [5–6]**
Study design	Double-blind RCT
Intervention	**Pharmacotherapy: Paroxetine (SSRI)** Co-interventions: optional individual therapy, retention and compliance
Trial registration	NR
Country	USA
Setting	Outpatient clinic
Aims	[5]: To determine the efficacy of paroxetine for social anxiety in patients with co-occurring alcohol problems. [6]: To examine whether effective treatment of social anxiety with paroxetine reduces drinking in dual-diagnosed individuals who endorse using alcohol to cope.
Participants	**AUD & Social anxiety disorder** All participants met DSM-IV criteria for current social anxiety disorder and alcohol abuse (21%) or dependence (79%), and all were seeking treatment for social anxiety and not for alcohol; participants had mild to moderate alcohol use disorders **Baseline characteristics**

	Paroxetine	**Placebo**
n	20	22
Women: % (n)	45% (9)	50% (11)
Age: M (SD)	28 (6.5)	30 (8.3)
Education level	NR	NR
Housing situation	NR	NR
Employment status	NR	NR
Substance use status		
ADS score: M (SD)	10.5 (7.3)	9.4 (5.2)
Drinks per week (TLFB): M (SD)	14.6 (11.3)	18.6 (14.3)
Drinking days (TLFB): M (SD)	5.4 (2.8)	6.6 (4.1)
SOCRATES, low recognition: % (n)	95% (19)	100% (22)
Mental health status		
LSAS, Total: M (SD)	87 (14.9)	93 (18.5)
SPIN, Total: M (SD)	45 (7.8)	45 (9.0)

	CGI severity, ≥ "markedly severe": % (n) 90% (18) 82% (18) **Comorbidities** MDD (DSM-IV): % (n) 10% (2) 9% (2) Comments There were no significant differences between groups, all p values >0.05 **Inclusion criteria** Individuals were required to meet diagnostic criteria for current social anxiety disorder (DSM-IV), generalized type, and current alcohol use disorder (abuse or dependence, DSM-IV). All individuals reported deliberate drinking to cope with social stress. **Exclusion criteria** (1) history of prior medical detoxification or treatment for alcoholism; (2) current use of psychotropic medications; (3) urine drug screen positive for illicit drugs other than marijuana; (4) liver enzymes that were elevated 3 times normal levels; and (5) current diagnosis of bipolar disorder, schizophrenia, significant suicidality, and substance abuse or dependence on drugs other than alcohol, nicotine, or marijuana. **Recruitment & screening** Recruitment: Participants were recruited from the community with advertisements. Individuals were invited to call the research center for initial telephone evaluation. Screening: The interview included questions from the Mini-SPIN to check if social anxiety disorder was likely, and questions related to their quantity and frequency of drinking. In-person interview with those who signed an informed consent agreement (N = 102) were conducted by clinically trained research personnel and by the study physician. Included evaluation using the Structured Clinical Interview for DSM-IV (SCID) to determine eligibility. Of those who were excluded based on the interview (n = 60), the most common reasons for exclusion were current use of psychotropic medications and failure to meet inclusion criteria for alcohol use. In total, 42 individuals met all inclusion criteria. **Remuneration** Participants were compensated $50 for providing week 16 research data, and 90% of randomized subjects provided data at the week 16 visit.
Comparison	**Paroxetine (SSRI) vs. placebo** **Duration of treatment** 16 weeks

Experimental arm	**Follow ups** Baseline Weekly during treatment Endpoint / time of last treatment **Paroxetine** Participants in the intervention group were initiated at a dose of 10 mg per day of paroxetine over-encapsulated by the investigational pharmacy with 100 mg of riboflavin, a biomarker used to measure medication compliance. The titration plan was to increase the dose weekly over four weeks from 10 to 20 to 40 to 60 mg daily, pending tolerability. Titration delays were also used as needed to minimize side effects. No limits were placed on number of dose reductions. The average final dose of paroxetine was 45 mg/day. The majority of participants (85%) reached their stable dose by week 6. Mean dose at week 16, or final visit = 45 (SD 15.4) mg/day **Co-intervention** <u>Optional individual therapy session</u> During the first four weeks of the study, subjects had the option of one individual therapy session. This non-mandatory session was aimed at improving study retention and medication compliance; 67% (N = 28) of participants opted to attend.
Control arm	**Placebo** Matching placebo was delivered as for Paroxetine Mean dose at week 16, or final visit = 53 (SD 15.5) mg/day **Co-intervention** Same as for Experimental arm.
Outcomes	**Substance use [6]** Quantity and Frequency of Drinking measurments: drinks per drinking days; proportion of days abstinent, drinks per week, proportion of heavy drinking days, proportion of drinking days over a week (TLFB), self-reported, measured at baseline and weekly, baseline uses time frame last 30 days, weekly measurements use the horizon of the last week. Drinking to cope* (DTC), self-reported, administered at baseline, 8 weeks, and 16 weeks. Alcohol dependence (ADS), self-reported Treatment eagerness (SOCRATES), self-reported **Mental health [5]**

Results

Primary outcomes:

Anxiety (LSAS), self-reported

Secondary outcomes:

Anxiety – Fear (LSAS-F), self-reported

Anxiety – Anxiety (LSAS-A), self-reported

Social anxiety (CGI-S, CGI-F), clinician reported

Social Phobia (SPIN), self-reported

Quality of life

Not assessed

Function

Not assessed

Mortality

Not assessed

Compliance

Record how compliance was defined and measured; include when and other details that may be important. Results will come later.

Adverse effects

Method for collecting information about adverse effects

Substance use [6]

	Paroxetine		Placebo	
TLFB	**Baseline N = 20**	**Endpoint N = 19**	**Baseline N = 22**	**Endpoint N = 19**
Drinks per drinking day, M (SEM)	5.32 (0.59)	5.88 (1.02)	6.51 (0.87)	7.00 (1.48)
Proportion days abstinent, M (SEM)	0.61 (0.04)	0.66 (0.07)	0.54 (0.06)	0.65 (0.07)
Proportion of heavy drinking days, M (SEM)	0.47 (0.07)	0.54 (0.11)	0.58 (0.08)	0.55 (0.13)
Drinks per drinking day, M (SEM)	5.32 (0.59)	5.88 (1.02)	6.51 (0.87)	7.00 (1.48)

Comments

"There was no overall group mean difference on any of the (TLFB) measures (i.e., no main effect of group, all p-values > 0.23), no change over time (i.e., no main effect of time, all p-values > 0.15), nor any interaction of group with time (all p-values > 0.23) for any of the drinking variables"

	Paroxetine		Placebo	
DTC	**Baseline N = 20**	**Endpoint N = 19**	**Baseline N = 22**	**Endpoint N = 19**
Percent of the time (0–100) you drink before social situations to feel more comfortable: M (SEM)	43 (6.3)	18 (5.6)	55 (6.4)	42 (7.1)
Percent of the time (0–100) you drink during social situations to feel more comfortable, M (SEM))	81 (3.6)	48 (6.3)	85 (3.1)	61 (6.9)
Percent of each group who reported avoiding social situations if they could not drink prior to going: % (n)	50% (10)	25%	63% (14)	45%
Percent of each group who reported avoiding social situations if they could not drink during the event: % (n)	70% (14)	35%	86% (19)	68%

Comments

Results also presented for week 8. Data not extracted

For this and all other analyses, missing data were treated as missing; no imputation procedures were employed. 90% of participants provided end of trial data (week 16).

Drinks per week reported graphically (figure 2). Data not extracted.

Proportion DTC reported graphically (figure 3). Data not extracted.

Mental health [5]

	Paroxetine ITT, n = 20		**Placebo ITT, n = 22**		**Relationship between treatment group and time**
Primary Outcomes	**Endpoint**	**Difference**	**Endpoint**	**Difference**	
LSAS*: M (SE or SD)	43.5 (NR)	53% (SE = 6.6)	60.9 (NR)	32% (SE = 6.2)	Group x week: F (15,39) = 3.79, p = 0.0004
Secondary Outcomes	**Endpoint**	**Difference**	**Endpoint**	**Difference**	
Responders**, %	55%		27%		Group x week: $X^2(5) = 13.7$, p = 0.017
LSAS-F¤, % (n)		-52%		-30%	
LSAS-A¤: M (SE or SD)		-55%		-35%	
SPIN total¤: M (SE or SD)		-46% (SE = 7)		-31% (SE = 7)	t(40) = 1.49, p = 0.15

* Endpoint mean scores were estimated based on graphical presentation of the data (Figure 1); variance was reported as SE, not estimated. Note that the error bars in figure 1 appear to all be identical.
** Treatment responders as defined by a CGI improvement score of 1 or 2.

Relationship between treatment effect on LSAS and time [5]
Mixed method analysis: F(15, 39) = 3.79, p = 0.0004
The "analysis revealed a highly significant group x week interaction"

Relationship between treatment effect on CGI-I and time [5]
Mixed method analysis: $X^2(5) = 13.7$, p = 0.017
"the effect of paroxetine on improving social anxiety was evident in the analyses of the CGI improvement scores"

Comments
The authors also assessed the phase relationship, data not extracted
Relationship between drinking and social anxiety [6]
Regression analysis:
Placebo: B = 0.13 ± .061, t(40) = 2.06, p = 0.045
Paroxetine: B = -0.01 ± .015, t(40) = 0.10, p = 0.92
"These results suggest that in participants with alcohol problems and untreated social anxiety (placebo group), drinking during the trial was linked to social anxiety severity; in participants whose social anxiety was alleviated (paroxetine group), drinking was uncoupled from social anxiety severity."

Compliance [5]

Compliant	**Paroxetine n = 20**	**Placebo n = 22**
Capsule counts: % (n)	90%	86%
Urinalysis: % (n)	N = 19 79%	N = 17 82%

Adverse effects [5]

	Paroxetine n = 20	**Placebo n = 22**

	Anorgasmia/ delayed ejaculation: : % (n)	55% (11)	18% (4)
	Myoclonus: % (n)	35% (7)	5% (1)
	Tremors: % (n)	45% (9)	14% (3)
	SAE	”No serious adverse event occurred”	
	Loss to follow up Reported graphically [6] (Figure 1) Endpoint, 16 weeks (estimated from graph): Paroxetine: 5% (n = 1) Placebo 15% (n = 3)		
Comments	Note that there is also a pilot study related to this one: [7]		
Risk of bias	Måttlig		

ADS = Alcohol Dependence Severity scale; CGI = Clinical Global Impression; subscales social anxiety (-S) and fear (-F); **DSM** = Diagnostic and Statistical Manual of Mental Disorders, roman numerals indicate version number; **DTC** = a study-specific questionnaire used to collect information about the client’s self-reported frequency of drinking to to feel more comfortable prior to and during social situations (see article for full description); **LSAS** = Liebowitz Social Anxiety Scale, 0 to 144; subscales for fear (-F) and avoidance (-A); **M** = mean; **MDD** = major depressive disorder; **NR** = not reported; **RCT** = randomized controlled trial; **SAE** = serious adverse effect; **SEM** = standard error of the mean; **SCID** = Structured Clinical Interview for DSM, roman numerals indicate DSM version number; **SD** = standard deviation; **SOCRATES** = The Stages of Change Readiness and Treatment Eagerness Scale; **SPIN** = Social Phobia Inventory; **SSRI** = selective serotonin reuptake inhibitor; **TLFB** = Time-Line Follow-Back, self-reported substance use.

Brown et al. 2015

Study	**Brown, 2015 [8]**
Study design	RCT (double blind)
Intervention	**Pharmacotherapy: citicoline** Co-interventions: mood stabilizers & CBT
Trial registration	NCT00619723
Country	USA
Setting	Outpatient
Aims	The primary aim of the present study was to determine whether citicoline reduces cocaine use in outpatients with bipolar I disorder and current cocaine dependence and active cocaine use.

Participants

Cocaine dependence & bipolar disorder

Outpatients with bipolar I disorder (depressed or mixed-mood state) and cocaine dependence.

Baseline characteristics

	Citicoline	Placebo
N=	61	61
Women: n (%)	16 (26.2%)	24 (39.3%)
Age: mean (SD)	41.1 (9.1)	43.6 (8.3)
Other current SUD*		
Alcohol: n (%)	36 (59.0%)	38 (62.3%)
Cannabis: n (%)	33 (54.1%)	23 (37.7%)
Mental health status		
HAM-D: mean (SD)	17.9 (5.6)	18.0 (6.3)
YMRS: mean (SD)	10.2 (5.9)	10.1 (6.1)
IDS-SR: mean (SD)	33.8 (23.6)	29.4 (27.1)
Concomitant medications		
Number of: mean (SD)	2.6 (1.4)	2.3 (1.3)

*More baseline SUD reported in study

Comments

Data presented only for participants who completed the baseline assessment and at least one additional assessment, number randomized = 130

Inclusion criteria

Adult outpatients with bipolar I disorder (depressed or mixed mood state, based on DSM-IV criteria using the SCID), current cocaine dependence with self-reported cocaine use within 7 days before baseline, a cocaine-positive urine screen at baseline, a baseline HAM-D score <35 and a baseline YMRS score <35 (to exclude those with severe mood symptoms), and current treatment with a mood stabilizer at a stable dosage for at least 14 days.

Exclusion criteria

Vulnerable populations (e.g., inmates, pregnant women), patients who were medically unstable, patients who were receiving intensive outpatient treatment for substance abuse, individuals whose current symptoms included psychotic features, individuals at high risk of suicide and individuals whose drug of choice was not cocaine.

Recruitment & screening

	Potential participants were identified through physician referral and through flyers and brochures at clinics that treat the population needed for this study The first participant was enrolled on May 1, 2008, and the final assessment was conducted on March 14, 2012; the trial was stopped when the predetermined enrolment goal was achieved. **Remuneration** Study subjects were paid for their participation. In addition, to minimize missing data, participants were given bonus vouchers for food and non-alcoholic beverages or for use in certain stores on an escalating payment scale for attending appointments and providing urine samples (payment was unrelated to urine screen results). The payments were reset to baseline if an appointment was missed.
Comparison	**Citicoline vs. placebo**
	Duration of treatment 12 weeks **Follow ups** Measurements during treatment: weekly or thrice weekly
Experimental arm	**Citicoline, adjunct** Citicoline was initiated at 500mg/day and increased to 1000mg/day at week 2, 1500mg/ day at week 4, and 2000mg/day at week 6. **Co-interventions:** <u>Maintenance pharmacotherapy</u> Current treatment with a mood stabilizer (lithium, divalproex/valproic acid, lamotrigine, carbamazepine, quetiapine, risperidone, olanzapine, aripiprazole, or ziprasidone) at a stable dosage for at least 14 days. Changes in concomitant medications were managed through the use of a treatment algorithm developed for the study: changes were considered when they coincided with changes in outcome scores (HAM-D, YMRS) <u>CBT</u> All participants received manual-based CBT (two sessions a week for 4 weeks followed by weekly sessions, for a total of 16 sessions) specifically designed for persons with bipolar disorder and substance abuse, delivered by an experienced therapist.
Control arm	**Placebo** Matching placebo delivered as for active substrate. **Co-interventions**

Outcomes

Same as for Experimental arm.

Substance use

Primary outcome:

Cocaine use (urine), collected thrice weekly, collapsed into a weekly score

Mental health

Secondary outcomes:

Depression (HAM-D), weekly

Depressive symptoms (IDS-SR), self-reported, weekly

Manic symptoms (YMRS), weekly

Quality of life

Not assessed

Function

Not assessed

Mortality

Not assessed

Compliance

Adherence with study medication was assessed with the Medication Event Monitoring System (metered medication bottle caps) and pill counts.

Adverse effects

No method specified

Results

Substance use

	Between groups analysis (mITT*, n = 122)	
Primary outcome	**F-value**	**p-value**
Urine drug screen positive for cocaine**	F(1,1351) = 5.2	P = 0.022

* modified ITT, participants who completed the baseline assessment and at least one additional assessment were included in the primary analysis, number randomized = 130.

*Random regression for binary outcome. Missing data were imputed as cocaine positive.

Mental health

Secondary outcomes	Between groups analysis (mITT*, n = 122) F-value	p-value
HAM-D*	F(1,106) = 0.0	P = 0.830
IDS-SR	F(1,111) = 1.5	P = 0.216
YMRS	F(1,105) = 0.0	P = 0.976

* modified ITT, participants who completed the baseline assessment and at least one additional assessment were included in the primary analysis, number randomized = 130

** Random regression analysis for continuous data.

Compliance

	Citicoline n = 61	Placebo n = 61	Significance
Average drug adherence: %	82.3%	79.2%	NS

Comments

Study drug adherence is defined as the total number of times the medication bottle was opened (as monitored with the Medication Event Monitoring System cap) divided by the number of times it should have been opened.

Adverse effects

No between group differences were observed on the Somatic Symptom Scale. A total of 13 serious adverse events were recorded during the study, five in the citicoline group and eight in the placebo group. Side effects did not differ significantly between the citicoline and placebo groups.

Loss to follow up

Results of a log-rank test indicated no significant between-group difference in study survival. Completion rates were 71% for the citicoline group and 57% for the placebo group. Treatment retention did not differ significantly between the citicoline and placebo groups.

During the time they were in the study, 59.0% of the citicoline group and 49.2% of the placebo group had at least one urine drug screen for every study week; urine screens were missing for more than half of the study weeks for 16.4% of the citicoline group and 19.7% of the placebo group.

	Comments Adherence/compliance to CBT is not reported.
Risk of bias	Moderate

CBT = cognitive behavioral therapy; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, roman numerals indicate version number; **HAM-D** = Hamilton Rating Scale for Depression; **IDS-SR** = Inventory of Depressive Symptomatology–Self-Report; **mITT** = modified intention to treat; **NR** = not reported; **RCT** = randomized controlled trial; **SCID** = Structured Clinical Interview for DSM; **SD** = standard deviation; **SUD** = substance use disorder; **YMRS** = Young Mania Rating Scale.

Brown et al. 2012

Study	**Brown, 2012 [9]**
Study design	RCT (double blind)
Intervention	**Pharmacotherapy: lamotrigine** Co-interventions: concomitant medications, if any, were maintained.
Trial registration	NCT00280293
Country	USA
Setting	Outpatient
Aims	The aims of the study were to determine the impact of lamotrigine therapy on cocaine use (primary aim) and cocaine craving, as well as manic and depressive symptoms (secondary aims).
Participants	**Cocaine dependence & bipolar disorder** Adult outpatients with bipolar I, II, NOS or cyclothymic disorders, and current cocaine dependence. **Baseline characteristics**

	Treatment	**Comparison**
N*=	55	57
Women: n (%)	23 (41.8)	22 (38.6)
Age: M (SD)	45.1 (7.3)	43.5 (10.0)
Education in years: M (SD)	13.5 (2.2)	13.5 (2.4)
Mental health status		
Bipolar I: n (%)	30 (54.5)	29 (50.9)
Bipolar II: n (%)	21 (38.2)	21 (36.8)
Bipolar NOS: n (%)	4 (7.3)	7 (12.3)
Depressed mood state: n (%)	49 (89.1)	52 (91.2)
Mixed mood state: n (%)	6 (10.9)	5 (8.8)

	Comorbidities (current SUD) Alcohol dependence: n (%) 28 (50.9) 33 (57.9) Cannabis dependence: n (%) 9 (16.4) 10 (17.5) Amphetamine dependence: n (%) 3 (5.5) 4 (7.0) Opioid dependence: n (%) 3 (5.5) 6 (10.5) Concomitant medications Lithium: n 1 6 Antidepressants: n 10 10 Antipsychotics: n 2 2 Sedative/hypnotic/anxiolytics: n 5 4 Comments More comorbidities reported in Table 1: Baseline demographic characteristics of Lamotrigine and Placebo Groups Data presented only for participants who completed the baseline assessment and at least one additional assessment, number randomized = 120 **Inclusion criteria** Men or women aged 18–70 years, diagnosis of bipolar I, II, or NOS disorders currently depressed or mixed mood as determined by SCID-IV-CV current cocaine dependence with self-reported cocaine use within 14 days before randomization, English or Spanish speaking, and baseline Hamilton rating scale for depression (HRSD <=17). **Exclusion criteria** Currently taking an enzyme inducing or inhibiting anticonvulsant (e.g., valproic acid, carbamazepine), currently experiencing severe psychotic features that require antipsychotic therapy, and that do not appear to be secondary to cocaine use, active suicidal ideation or ≥2 attempts in past 12 months or any attempt in the last month, highly unstable medical condition, change in concomitant psychiatric medications (e.g., initiated antipsychotic) or in other substance abuse treatment within 7 days before study entry, and vulnerable populations (e.g., pregnant or nursing women, incarcerated, or cognitively impaired individuals). Potential participants dependent on substances in addition to cocaine were not excluded. **Recruitment & screening** 120 individuals recruited from local referral sources and newspaper advertisements. **Remuneration** Participants were paid for participation (amount NR).
Comparison	**Lamotrigine vs Placebo**

	Duration of treatment 10 weeks **Follow ups** Measurements during treatment, weekly Endpoint / time of last treatment
Experimental arm	**Lamotrigine** Lamotrigine therapy was initiated at 25 mg/day and increased to 200 mg/day using a slow upward titration over 5 weeks. After that time additional increases in 100 mg/day increments to a maximum of 400 mg/day were made if the medication was well tolerated. The mean exit dose of lamotrigine was 221.8±148.0mg **Co-interventions:** <u>Pharmacological, maintenance treatment</u> Existing medication, if any, was maintained. Concomitant medications were managed with an algorithm that, if necessary, allowed changes in other psychiatric medications.
Control arm	**Placebo** Matching placebo, details of administration NR Pills dispensed were equivalent to 192.1±146.8 mg in the placebo group. **Co-interventions:** <u>Pharmacological, maintenance treatment</u> Assumed to be as for lamotrigine group.
Outcomes	**Substance use** Percent of days of cocaine use per week (TLFB), weekly Mean amount spent on cocaine per day (TLFB), weekly Cocaine use (urine drug screen), weekly **Mental health** Depression (HRSD17), who measured (ie. self-reported), weekly Depressive symptoms (QIDS-SR), self-reported, weekly Manic symptoms (YMRS), weekly **Quality of life**

Results

Not assessed

Function

Not assessed

Mortality

Not assessed

Compliance

Adherence was based on pills dispensed and returned.

Adverse effects

Side effects (PRD-III), bi-weekly

Substance use

	Between treatment groups Initial effect, weeks 0–1 (mITT, n = 122)		**Between treatment groups By week effect, weeks 1–10** (mITT, n = 122)	
Primary outcome	**F-value**	**p-value**	**F-value**	**p-value**
Cocaine use (probability of +UDS)*: M (SD)	F (1, 113) = 1.1	0.30	F (1, 80)=0.0	0.99
Secondary outcomes				
Percent days used cocaine: M (SD)	F(1, 147)=2.5	0.12	F(1, 96)=1.1	0.31
Dollar amount spent on cocaine: M (SD)**	F(1, 93)=11.2	0.01	F(1, 62)=3.9	0.05

*Baseline covariates: bipolar type, sedative/hypnotic use, days of alcohol use.

**Baseline covariates: bipolar type, sedative/hypnotic use, cocaine use, Stroop color word scores, CCQ score.

Comments

Declining effects random regression model used for analyses. All participants completing baseline and at least 1 postbaseline assessment (N=112/120) were used in the mITT analysis.

Data not extracted: post hoc analysis of cocaine use including mood as a time varying covariate, CCQ

Mental health

Between treatment groups Initial effect, weeks 0–1 (mITT, n = 122)	**Between treatment groups By week effect, weeks 1–10** (mITT, n = 122)

Secondary outcomes	F-value	p-value	F-value	p-value
HRSD*: M (SD)	F (1, 04)=0.6	0.44	F (1, 79) = 0.3	0.57
QIDS-SR: M (SD)**	t (106)=0.0	0.97	t (77) = 0.1	0.89
YMRS*: M (SD)**	F (1, 174) = 0.3	0.56	F (1, 190) = 0.5	0.47

* Baseline covariates: bipolar type.

** Baseline covariates: bipolar type, anxiety disorder diagnosis.

*** Baseline covariates: bipolar type, age, gender, income, previous psychological treatment.

Comments

Declining effects random regression model. All participants completing baseline and at least 1 postbaseline assessment (N=112/120) were used in the mITT analysis.

Data not extracted: subgroup analysis of patients with baseline HRSD scores >24.

Compliance

Pill count estimate of adherence: 92% with lamotrigine and 93% with placebo.

However, at 8% of appointments with lamotrigine and 7% with placebo, participants did not return the unused pills. In addition, participants were no shows for 9% of appointments with lamotrigine and 12% for placebo. These missing data were not included in the pill count adherence estimate.

Adverse effects

	Between treatment groups Initial effect, weeks 0–1 (mITT, n = 122)		**Between treatment groups By week effect, weeks 1–10** (mITT, n = 122)	
	F-value	**p-value**	**F-value**	**p-value**
PRD-III score*: M (SD)	F (1, 93) = 0.5	0.49	F (1, 71) = 1.3	0.26

* Baseline covariates: bipolar type, RAVLT total score.

Comments

	Side effects were similar in the two groups. 2 adverse events were considered study-related and included drying and peeling of the skin, and increased sweating (both reported by the same patient on two different visits (lamotrigine group)). A total of 15 additional adverse events were classified as unexpected and unrelated to the study. **Loss to follow up** 47.5% (n=57) 63 / 120 participants completed the study. Reasons for discontinuation included: 26 lost to follow-up, 5 moved, 3 withdrew consent, 3 unrelated medical reasons, 1 severe treatment nonadherence, 2 suicidal ideation and 2 suicide attempt, 2 inpatient admissions for unrelated medical conditions, 1 rash that was determined to not be related to lamotrigine, 1 related to a probation violation, 1 due to incarceration, and 2 for other reasons.
Risk of bias	Low

CCQ = cocaine craving questionnaire; **HRSD17** = 17-item Hamilton Rating Scale for Depression; **M** = mean; RCT = randomized controlled trial; **mITT** = modified intention to treat; **NOS** = not otherwise specified; **NR** = not reported; **PRD-III**: Psychobiology of Recovery in Depression III—Somatic Symptom Scale (side effects); **QIDS-S** = quick inventory of depressive symptomatology-SR; **RAVLT** = Rey auditory verbal learning test; **SCID-IV-CV** = Structured Clinical Interview for DSM – clinician version, Diagnostic and Statistical Manual of Mental Disorders version IV (DSM-IV); **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **UDS** = urine drug screen; **YMRS** = Young Mania Rating Scale.

Brown et al. 2008

Study	**Brown, 2008 [10]**
Study design	RCT, double blind
Intervention	**Pharmacotherapy: Quetiapine** Co-interventions: NR
Trial registration	NCT00223249
Country	USA
Setting	Outpatient
Aims	The primary aim was to assess alcohol use between groups, with changes in mood and tolerability as secondary aims.
Participants	**AUD & Bipolar disorder** Outpatients with bipolar disorder and alcohol use disorders. **Baseline characteristics** **Quetiapine** **Placebo**

	N=	52	50
	Men: n (%)	35 (67.3)	29 (58.0)
	Age: M (SD)	39.2 (10.4)	37.5 (9.1)
	Alcohol use diagnosis		
	Dependence: n (%)	50 (96.2)	49 (98.0)
	Abuse: n (%)	2 (3.8)	1 (2.0)
	Bipolar diagnosis		
	Bipolar I disorder: n (%)	27 (51.9)	23 (46.0)
	Bipolar II disorder: n (%)	25 (48.1)	27 (54.0)

Comments

Data presented only for participants who completed the baseline assessment and at least one additional assessment, number randomized = 115

Inclusion criteria

Bipolar I or II disorders confirmed by the Mini-International Neuropsychiatric Interview (MINI), current alcohol abuse or dependence with use within 14 days of random assignment, age 18 to 55 years, and no changes in concomitant psychiatric medications within 7 days of random assignment.

Exclusion criteria

Exclusion criteria included history of cataracts or likely cataracts on ocular examination, history of hepatic cirrhosis or aspartate aminotransferase or alanine aminotransferase levels greater than 3 times normal, current active suicidal or homicidal ideation, current antipsychotic treatment, pregnancy or nursing, or contraindications to quetiapine therapy.

Recruitment & screening

115 patients were enrolled from the community. The study was conducted from November 2002 to September 2005.

Remuneration

NR

Comparison

Quetiapine vs. Placebo

Duration of treatment

12 weeks

Follow ups

	Endpoint / time of last treatment
Experimental arm	**Quetiapine**
	Quetiapine was titrated using the following schedule: baseline to week 1: 25 mg b.i.d., week 1 to 2: 50 mg b.i.d., week 2 to 4: 100 mg b.i.d., week 4 to 6: 200 mg b.i.d., week 6 to exit: 300 mg b.i.d.
	Maintenance pharmacotherapy
	NR
Control arm	**Placebo**
	Matching placebo delivered as for active substrate.
	Maintenance pharmacotherapy
	NR
Outcomes	**Substance use**
	Primary outcomes:
	Drinking days per week (TLFB), week 1, 2 and then every two weeks
	Drinks per week (TLFB), week 1, 2 and then every two weeks
	Heavy drinking days per week (TLFB), week 1, 2 and then every two weeks
	Mental health
	Secondary outcomes:
	Mood (HAM-D), baseline, week 1, 2 and then every two weeks
	Mood (YMRS), baseline, week 1, 2 and then every two weeks
	Quality of life
	Not assessed
	Function
	Not assessed
	Mortality
	Not assessed
	Compliance
	Not measured
	Adverse effects
	Antipsychotic side effects (AIMS), week 1, 2 and then every two weeks

Results

Antipsychotic side effects (SAS), week 1, 2 and then every two weeks

Antipsychotic side effects (BAS), week 1, 2 and then every two weeks

Substance use

	Quetiapine (mITT, n = 52)		Placebo (mITT, n = 50)		
Primary outcomes	**Baseline**	**Endpoint**	**Baseline**	**Endpoint**	**Significance***
Drinking days/wk, mean (SD)	3.3 (2.2)	2.1 (2.1)	3.0 (1.6)	1.7 (2.1)	F = 0.03, df = 1,110; p = 0.86
DPW, median	15	6	17	3	F = 0.01, df = 1,118; p = 0.92
HDD/wk, mean (SD)	2.4 (2.3)	1.2 (1.7)	2.1 (1.6)	1.0 (1.6)	F = 0.02, df = 1,129; p = 0.88

* Declining-effects random-regression analysis (week 1 to 12). Baseline level of the outcome measured was used as a covariate. LOCF was used for missing data.

Comments

Data presented only for participants who completed the baseline assessment and at least one additional assessment, number randomized = 115

Mental health

	Quetiapine (mITT, n = 52)		Placebo (mITT, n = 50)		
Secondary outcomes	**Baseline**	**Endpoint**	**Baseline**	**Endpoint**	**Significance***
HAM-D, mean (SD)	19.8 (6.9)	11.1 (7.4)	20.0 (5.9)	12.6 (7.7)	F = 4.2, df = 1,234; p = 0.04
YMRS, mean(SD)**	9.5 (7.0)	5.0 (3.8)	12.3 (5.8)	6.9 (5.8)	F = 0.02, df = 1,126; p = 0.88

* Declining-effects random-regression analysis (week 1 to 12). Baseline level of the outcome measured was used as a covariate. LOCF was used for missing data. **p = 0.03 for between-group difference in baseline scores.

Comments

Data presented only for participants who completed the baseline assessment and at least one additional assessment, number randomized = 115

Adverse effects

	Quetiapine (mITT, n = 52)	Placebo (mITT, n = 50)	Significance*
AIMS: M (SD)	1.2 (14.0)	–2.9 (24.6)	p = 0.30
BAS: M (SD)	–1.3 (2.2)	–1.7 (2.0)	p = 0.38
SAS: M (SD)	3.9 (19.2)	1.7 (31.5)	p = 0.67

	* 2-sided, independent sample t test. Side effects in 5% or more of quetiapine or placebo groups, respectively, included sedation (24% vs. 16%), dizziness (22% vs. 0%), dry mouth (18% vs. 6%), fatigue (8% vs. 4%), and indigestion (6% vs. 0%) Comments Data presented only for participants who completed the baseline assessment and at least one additional assessment, number randomized = 115 **Loss to follow up** NR
Risk of bias	Moderate

BAS = Barnes Akathisia Rating Scale; **HAMD** = Hamilton Rating Scale for Depression; **HDD** = heavy drinking day; **HRSD17** = 17-item Hamilton Rating Scale for Depression; **mITT** = modified intention to treat; **NR** = not reported; **QIDS-SR** = quick inventory of depressive symptomatology-SR; **RCT** = randomized controlled trial; SAS = Simpson-Angus Scale; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **YMRS** = Young Mania Rating Scale.

Brunette et al. 2020.

Study	**Brunette, 2020 [11]**
Study design	RCT (double blind, multi-site)
Intervention	**Pharmacotherapy: Samidorphan (SAM)** Co-interventions: Olanzapine (OLZ), supportive counselling when needed
Trial registration	NCT02161718
Country	USA, Bulgaria, and Poland
Setting	Outpatient
Aims	To evaluate the efficacy, safety, and tolerability of OLZ/SAM, administered as 2 tablets, compared with olanzapine and matched placebo tablets (olanzapine) in a phase 2, randomized, double-blind study in patients with schizophrenia and comorbid AUD.
Participants	**AUD & schizophrenia** Outpatients with schizophrenia, AUD, and a recent acute exacerbation (within 6 months). **Baseline characteristics**

	OLZ/SAM	**Olanzapine**
N=	112	117
Male: n (%)	89 (79.5)	91 (77.8)
Age: M (SD)	46.4 (10.6)	45.1 (10.2)
Substance use status		

	DPD: M (SD)	3.7 (3.5)	3.0 (2.2)
	DDD: M (SD)	5.3 (3.9)	4.7 (2.8)
	% HDDs: n (%)	33.6 (33.0)	27.0 (26.8)
	Schizophrenia severity		
	PANSS total score: M (SD)	64.9 (7.9)	64.4 (7.7)
	CGI-S scale score: M (SD)	3.4 (0.7)	3.5 (0.6)
	Past 12-mo psychiatric hospitalizations: M (SD)	0.6 (0.9)	0.8 (1.3)

Comments

mITT analyses included 229 of 234 randomized participants.

Inclusion criteria

Men and women aged 18–65 years with a diagnosis of schizophrenia according to DSM-IV-TR criteria who met prespecified symptom severity criteria and a diagnosis of AUD according to the DSM-5 and who had 10 or more drinking and 2 or more heavy-drinking days in the past month, and recent (≤ 6 mo) exacerbation of schizophrenia symptoms.

Exclusion criteria

Intolerance to olanzapine and a positive test for opioids, DSM-5 diagnosis of other substance use disorders. Benzodiazepines (except prior to visit 8 when medically indicated) and all alcohol treatment–related medications,
were prohibited during the study.

Recruitment & screening

The study was conducted between June 2014 and March 2017. 549 patients were screened, 300 patients received open-label olanzapine treatment for 4 weeks, 255 received OLZ/SAM treatment for 2 weeks, 234 were randomized. Of these, 5 did not receive study drug due to loss to follow-up and 229 were included in the ITT analysis.

Remuneration

NR

Comparison

Pharmacotherapy: Samidorphan + olanzapine (OLZ+SAM) vs. placebo + olanzapine (OLZ + placebo)

Duration of treatment

36-60 weeks

Follow ups

Measurements during treatment, every 4 weeks

Experimental arm	Mid-treatment, weeks 24 Endpoint / time of last treatment (36-60 weeks) **OLZ/SAM** Daily OLZ/SAM for a double-blind treatment phase lasting a minimum of 36 weeks and a maximum of 60 weeks, with an additional 3-week safety follow-up with open-label olanzapine. Open label lead in of Olanzapine and samidorphan 6-week lead-in phase involving open label olanzapine once daily for 4 weeks (dose determined by the investigator) to ensure that the subjects were able to tolerate olanzapine. Then 2 weeks of both open-label olanzapine (fixed dose) and samidorphan tablets. **Co-interventions** Supportive counselling, psychosocial Supportive counselling was provided as per investigator's judgment at specified monthly visits. Counselling focused on: (1) disease education, (2) encouragement of treatment adherence, and (3) crisis intervention.
Control arm	**OLZ/placebo** Daily olanzapine and matched placebo for a double-blind treatment phase lasting a minimum of 36 weeks and a maximum of 60 weeks, with an additional 3-week safety follow-up with open-label olanzapine. Open label lead in of Olanzapine and samidorphan As for OLZ/SAM arm check this **Co-interventions** Supportive counselling, psychosocial As for OLZ/SAM arm
Outcomes	**Substance use** Primaly outcomes Exacerbation of schizophrenia symptoms, according to protocol [12]: NR Secondary outcomes Percentage of HDD (TLFB), every 4 weeks Proportion of patients with a ≥ 1 level decrease in World Health Organization (WHO) drinking risk level from baseline to week 24 (abstinence (0 g); low risk (men 1–40 g, women 1–20 g); medium risk (men 41–60 g, women 21–40 g); high risk (men 61–100 g, women 41–60 g); and very high risk (men ≥ 101 g, women ≥ 61 g)), Baseline and week 24 **Mental health (overall health)**

	Primary outcome: Time to the first event of exacerbation of disease symptoms (EEDS), defined as any of eight events: (1) hospitalization due to worsening psychiatric symptoms, alcohol intoxication, or alcohol withdrawal (2) worsening in PANSS total score (determined by a ≥ 25% or ≥ 15-point increase from randomization) (3) confirmed worsening in PANSS item score (P1, P2, P3, P6, P7, or G8) from baseline (4) deliberate self-injury, aggressive behavior, or showing signs of clinically significant suicidal or homicidal ideation (5) administration of rescue medication or increased olanzapine dose due to worsening symptoms (6) an emergency-room visit (7) discontinuation for lack of efficacy, loss to follow-up, or withdrawal by the patient (8) arrest or incarceration. Assessments every 4 weeks Secondary outcomes: Rate and number of EEDS Schizophrenia symptoms (PANSS), every 4 weeks Schizophrenia symptoms (CGI-S), every 4 weeks **Compliance** Compliance with study medication was monitored through pill counts at medication dispensing visits every 2 weeks. **Quality of life** Not assessed **Function** Not assessed **Mortality** **N**ot assessed **Adverse effects** Safety (AE) Suicide assessment (C-SSRS) vital signs, electrocardiogram, and laboratory assessments
Results	**Substance use** **OLZ/SAM** **Olanzapine** **OLZ/SAM vs Olanzapine**

	(mITT, n = 112)	(mITT, n = 117)		(mITT, n = 229)	
	Week 24	**Week 24**	**OR**	**95% CI**	**p-value**
WHO drinking risk improvement*	40.5%	37.9%	0.99	0.56–1.73	0.963
absence of any HDDs*	10.8%	13.8%	0.82	0.36–1.90	0.649
Baseline to week 36	**Difference**	**Difference**			
	(n=61)	(n=66)			
%HDD: M (SD)	−21.2 (26.6)	−15.0 (28.3)			
Baseline to week 60	**Difference**	**Difference**			
	(n=31)	(n=32)			
%HDD: M (SD)	−16.9 (22.9)	−13.2 (31.5)			

* Proportion of subjects with a ≥ 1 level decrease in WHO drinking risk. Analysed with logistic regression.

Comments

mITT population was defined as all randomized patients who received at least 1 dose of OLZ/SAM or olanzapine during the double-blind treatment period.

Mental health

OLZ/SAM vs Olanzapine

(mITT, n = 229)

Primary outcome	**HR**	**95% CI**	**p-value**
Time to first EEDS*	0.91	0.53–1.56	0.746
Secondary outcome	**HR**	**95% CI**	**p-value**
Time to recurrent EEDS**	0.77	0.43–1.37	0.372

	OLZ/SAM	**Olanzapine**			
Randomization to week 36***	**Difference**	**Difference**	**LS mean difference**	**p-value**	**Cohen d**
	(ITT, n = 112)	(ITT, n = 112)			
PANSS total scores: LS M (SE)	−5.4 (1.01)	−3.4 (0.99)		0.175	
Baseline to week 36****	**Difference**	**Difference**	**LS mean difference**	**p-value**	**Cohen d**
	(n=61)	(n=67)			
PANSS total scores: LS M (SE)	−6.9 (1.3)	−3.3 (1.2)	–3.6 (1.8)	0.043	0.27
CGI-S scores: LS M (SE)	−0.52 (0.08)	−0.24 (0.08)	–0.29 (0.11)	0.013	0.34
Baseline to week 60****	**Difference**	**Difference**	**LS mean difference**	**p-value**	**Cohen d**
	(n=30)	(n=32)			
PANSS total scores: LS M (SE)	−8.9 (1.5)	−3.6 (1.5)	–5.3 (2.2)	0.016	0.32
CGI-S scores: LS M (SE)	−0.68 (0.11)	−0.39 (0.11)	–0.29 (0.15)	0.065	0.25

* Log rank test for treatment comparison, and the Cox proportional-hazards model was used to estimate the hazard ratio, adjusting for relevant covariates. **Andersen-Gill mean/rate intensity model. *** ANCOVA with LOCF imputation for missing data in the ITT population. **** Post hoc analyses conducted by MMRM.

Comments

mITT population was defined as all randomized patients who received at least 1 dose of OLZ/SAM or olanzapine during the double-blind treatment period.

Compliance

NR

Comments

Compliance was measured but results are not reported.

Adverse effects

	OLZ/SAM	**Olanzapine**
	n = 112	**n = 117**
Any treatment-emergent AE: n (%)	64 (57.1)	69 (59.0)
Treatment-related AE: n (%)	36 (32.1)	32 (27.4)
AE leading to treatment discontinuation: n (%)	10 (8.9)	13 (11.1)
Serious AE: n (%)	7 (6.3)	12 (10.3)
Death: n (%)	1 (0.9)	1 (0.9)

Comments

The most commonly reported AEs were weight gain, nasopharyngitis, and exacerbation of schizophrenia symptoms. Most AEs were mild or moderate in severity and rates of AEs leading to discontinuation were similar between treatment groups. More AEs reported in the study, data not extracted.

Loss to follow up

Endpoint: OLZ/SAM 59 (52.7%), Olanzapine 59 (50.4%)

Risk of bias

Low

AE = adverse events; **ANCOVA** = analysis of covariance; **AUD** = alcohol use disorder; **CI** = confidence interval; **C-SSRS** = Columbia–Suicide Severity Rating Scale; **DSM-5** = Diagnostic and Statistical Manual of Mental Disorders – 5th edition; **DSM-IV-TR** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition - Text Revision; **LOCF** = last observation carried forward; **M** = mean; **mITT** = modified intention to treat; **MMRM** = mixed model with repeated measurements; **SD** = standard deviation.

Brown et al. 2014

Study	Brown, 2014 [13]
Study design	RCT (double blind)
Intervention	**Pharmacotherapy: Quetiapine** Co-interventions: mood stabilizer treatments maintained, CBT
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	To clarify whether quetiapine may be effective in reducing alcohol consumption in patients with BPD and alcohol dependence.
Participants	**AUD & Bipolar disorder** Outpatients with bipolar I or II disorders, depressed or mixed mood state, and current alcohol dependence. N = 90 (88 in ITT analysis) **Baseline characteristics**

	Quetiapine	Placebo
N=	44	44
Women: % (n)	38.6% (17)	43.2% (19)
Age: M (SD)	43.3 (8.2)	39.7 (10.1)
Education, yrs: mean (SD)	13.6 (2.5)	13.3 (2.4)
Substance use status		
Drinks per drinking day: M (SD)	6.0 (3.4)	6.5 (3.4)
Percent drinking days: M (SD)	74.2 (27.3)	74.6 (26.1)
Percent heavy drinking days: M (SD)	53.0 (30.9)	60.0 (30.1)
Mental health status		
Depressed mood state: % (n)	86.4% (38)	90.9% (40)
Depressed mixed mood state: % (n)	13.6% (6)	9.1% (4)
Concomitant medications		
Lithium: % (n)	67.5% (27)	68.3% (28)
Anticonvulsants: % (n)	32.5% (13)	31.7% (13)
Antidepressants: % (n)	27.5% (11)	14.6% (6)
Sedatives/hypnotics*	20.0% (8)	4.9% (2)

*$p > 0.05$

Study	Brown, 2014 [13]
	Inclusion criteria Men and women 18 to 65 years old with a diagnosis of bipolar I or II disorder, depressed or mixed phase, current alcohol dependence with alcohol use of at least 15 drinks in the 7 days prior to baseline. Structured Clinical Interview for DSM-IV clinician version was used to establish diagnoses. **Exclusion criteria** A baseline YMRS score ≥35 or HRSD17 score ≥35, current clinically significant psychotic features, CIWA-Ar score of >8, history of hepatic cirrhosis or baseline liver enzymes >3X upper limit of normal or other clinically significant findings on physical or laboratory examination, vulnerable persons (severe cognitive impairment, inmates, pregnant, or nursing women), antipsychotic therapy within 14 days prior to randomization, current carbamazepine or benzodiazepine therapy, current treatment with medications shown to reduce alcohol consumption in large randomized, controlled trials (naltrexone, acamprosate, disulfiram, or topiramate), initiation of antidepressants or mood stabilizers or psychotherapy within past 14 days, high risk for suicide defined as any suicide attempts in the past 3 months or current suicidal ideation with plan and intent, intensive outpatient treatment for substance abuse (12-step programs or weekly psychotherapy that started at least 14 days prior to randomization were allowed), current treatment with ketoconazole, itraconazole, erythromycin, or nefazodone, severe or life-threatening medical condition or diabetes, or history of cataracts or suspected cataracts on ophthalmic exam. **Recruitment & screening** Possible participants were identified through physician referral and through flyers and brochures at clinics for this study. **Remuneration** Participants were paid for their participation.
Comparison	**Quetiapine vs. Placebo**
	Duration of treatment 12 weeks
	Follow ups Endpoint / time of last treatment

Study	Brown, 2014 [13]
Experimental arm	**Quetiapine** Sustained release quetiapine was initiated at 50 mg/at bedtime (QHS) at baseline, increased to 100 mg/QHS at week 1, 200 mg/d at week 2, 400 mg/QHS at week 3, and 600 mg/QHS at week 4. Slower titration or doses reductions were allowed, if needed, using clinician judgment, due to side effects. Pharmacological component All participants were currently taking a mood stabilizer defined as lithium, divalproex/valproic acid, oxcarbazepine, or lamotrigine at a stable dose for ≥14 days before the start of the study. Psychosocial component All participants received manual-driven CBT designed for persons with BPD and substance abuse.
Control group	**Placebo** Matching placebo delivered as for active substrate. Pharmacological component As for quetiapine group Psychosocial component As for quetiapine group
Outcomes	**Substance use** Primary outcomes: Drinks per day (TLFB), assessed weekly Secondary outcomes: Percent days of alcohol use (TLFB), assessed weekly Mean drinks per drinking day (TLFB), assessed weekly Percent heavy drinking days per week (TLFB), assessed weekly Drinks per heavy drinking day (TLFB), assessed weekly **Mental health** Primary or secondary?? Depression (HRSD17), measured weekly Manic symptoms (YMRS), measured weekly Depressive symptoms (IDS-SR30), self-reported, measured weekly

Study: Brown, 2014 [13]

Quality of life

Not assessed

Function

Not assessed

Mortality

Compliance

The percent of pills taken per week (pills taken between visits/pills that should have been taken between visits)

Adverse effects

Blood test (AST, ALT, GGT, and PRD-III) were measured at baseline and weeks 6 and 12

Antipsychotic side effects (AIMS)

Antipsychotic side effects (SAS)

Antipsychotic side effects (BAS)

Results

Substance use

	Between treatment groups	
Primary outcomes	**F-value**	**p-value**
Drinks per day	F(1, 78) = 0.1	0.75
Secondary outcomes	**F-value**	**p-value**
Percent days of alcohol use	F(1, 81) = 1.3	0.27
Mean drinks per drinking day	F(1, 152) = 0.2	0.63
Percent heavy drinking days per week	F(1, 72) = 0.3	0.60
Drinks per heavy drinking day	F(1, 159) = 0.1	0.73

Declining-effects random-regression analysis using covariates: baseline drinks per day, bipolar type, race-African American vs. non-African American. All participants completing baseline and at least 1 post-baseline assessment (N=88/90) were used in the ITT analysis. Data on non-completers were analyzed up to the point of study discontinuation.

Study

Brown, 2014 [13]

Mental health

	Between groups	
	F-value	**p-value**
HRSD17	F(1, 69) = 2.5	0.12
IDS-SR30	F(1, 70) = 3.3	0.07
YMRS	F(1, 73) = 0.0	0.88

Declining-effects random-regression analysis (covariates: baseline drinks per day, bipolar type, race-African American vs. non-African American). All participants completing baseline and at least 1 postbaseline assessment (N=88/90) were used in the ITT analysis. Data on non-completers were analyzed up to the point of study discontinuation.

Compliance

N = 63 of total ITT sample (88) were ≥90% compliant. Adherence between treatment group was similar (F = 2.9, p = 0.098).

Adverse effects

	Between groups		**Difference (week 6)** Quetiapine	**Difference (week 6)** Placebo
	F-value	**p-value**	**Mean (SE)**	**Mean (SE)**
Weight, lbs	F(1, 14) = 6.2	p = 0.03	2.9 (SE 1.4)	-2.0 (SE 1.4)
Akathisia (BARS)	F(1, 48) = 4.3	p = 0.04	0.40 (SE 0.3) points	-0.52 (SE 0.3) points

Comments

Overall side effect burden (PRD-III total score), glucose, cholesterol, AIMS, SAS did not differ significantly between groups. All SAE (5 in quetiapine and 3 in placebo group) were deemed unrelated to the study.

Loss to follow up

Endpoint: Quetiapine 36.4%, Placebo 47.9%

Treatment retention was similar in the 2 treatment groups (log-rank test p = 0.33)

Comments

Loss to follow up data extracted from Kaplan-Meier plot

Risk of bias

Moderate

AIMS= Abnormal Involuntary Movement Scale; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **BAS** = Barnes Akathisia Rating Scale; **BPD** = Bipolar disorder; **CBT** = cognitive behavioral therapy; **GGT** = gamma-glutamyltransferase; **HRSD17** = 17-item Hamilton Rating Scale for Depression; **IDS-SR30** = 30-item Inventory of Depressive Symptomatology–Self-Report; **ITT** = intent to treat; **NR** = not reported; **PRD-III =** Psychobiology of Recovery in Depression III—Somatic Symptom Scale (side effects); **RCT** = randomized controlled trial; **SAS** = Simpson-Angus Scale; **TLFB** = Time-Line Follow-Back, self-reported substance use (time to outcomes); **YMRS** = Young Mania Rating Scale.

Carpenter et al. 2004

Study	**Carpenter, 2004 [14]**
Study design	RCT, double-blind
Intervention	**Pharmacotherapy: Sertraline** Co-interventions: MMT
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	To determine whether sertraline would yield greater improvement than placebo in depression outcome and in substance use outcome in methadone-maintained opiate dependent patients with a current depressive disorder. <u>Comment</u> Authors also aim to explore whether aspects of patients' environments at study entry moderate the effect of sertraline on mood and substance use outcome. Data related to this second aim not extracted.
Participants	**Opioid use disorder (OUD) & depressive disorder** Methadone-maintained opiate dependent patients with a current depressive disorder

Study

Carpenter, 2004 [14]

Baseline characteristics

	Sertraline n = 47	Placebo n = 48
Women: % (n)	46.8% (22)	33.3% (16)
Age: M (SD)	38.9 (9.3)	40.8 (7.3)
Education, years: M (SD)	12.0 (1.9)	11.7 (2.1)
Housing situation	NR	NR
Employment status	NR	NR
Substance use status		
Proportion of days heroin or cocaine use was reported in past 30 days: M (SD)	0.20 (0.30)	0.32 (0.39)
Proportion of days any drug or alcohol use was reported in past 30 days: M (SD)	0.33 (0.37)	0.44 (0.41)
Methadone dose (mg): M (SD)	80.4 (31.4)	79.5 (28.7)
No. of previous drug treatments: M (SD)	5.0 (3.7)	4.5 (3.3)
Mental health status		
Major depression:n (%)	23 (48.9%)	27 (56.2%)
Dysthymia: n (%)	4 (8.5%)	5 (10.4%)
Both: n (%)	20 (42.6%)	16 (33.3%)
HAM-D score: M (SD)	21.1 (4.4)	21.1 (5.0)

No significant baseline differences.

Inclusion criteria

Required to meet DSM-III-R (1987) criteria for current Major Depression or Dysthymia Disorders; the depressive disorders had to be either primary (antedated the earliest lifetime substance abuse), persistent during 6 months of abstinence in the past, or at least 3 months duration in the current episode; the depressive disorder must have persisted for at least a month during stable methadone treatment; current enrolment in a methadone maintenance program with methadone doses of 60 mg or greater per day and the use of illicit drugs or alcohol at least once per week for the month prior to study participation

Exclusion criteria

Meeting DSM-III-R criteria for past mania, having a seizure disorder, having a history of allergic reactions to sertraline, having unstable physical disorders (e.g., hypertension), and/or currently using other prescribed psychotropic medications.

Study	Carpenter, 2004 [14]
	Recruitment & screening At two university-affiliated, community-based methadone maintenance programs. Participants identified as possibly depressed or depressed were referred to the study team for further evaluation. Those who obtained medical clearance and met inclusion criteria were entered into a single blind placebo phase for 7–10 days. If depression response, defined as a 50% or greater reduction in HAMD scores, participant was removed from the trial and followed clinically. Eligible and entering placebo lead-in period: n = 106; randomized: n = 95 **Remuneration** NR
Comparison	**Sertraline vs placebo** Duration of treatment 12 weeks **Follow ups** Measurements during treatment: at baseline + weekly Endpoint: week 12 or the last week in the study for early withdrawals
Experimental arm	**Sertraline** Given in a “fixed-flexible” dose schedule with the aim of achieving the maximum tolerated dose for each participant. Began with 25 mg daily for the first week and increased by 25 mg every week (50 mg increments above 100 mg) until the maximum recommended dose of 200 mg or side effects prevented further increases. Dispensed weekly at the methadone clinic. **Co-interventions** Pharmacological Methadone treatment was administered by the regular clinic staff according to state and federal guidelines and was not influenced by the research protocol. All participants continued meeting with their assigned counsellor and were subject to the clinics’ rules and regulations.
Control arm	**Placebo** Given according to the same protocol as the treatment group **Co-interventions** Pharmacological Same as for Experimental arm.

Study | **Carpenter, 2004 [14]**

Outcomes

Substance use

Proportion of days that heroin or cocaine use was reported (SUI), self-reported (urine confirmed), weekly

Proportion of days any drug or alcohol use was reported (SUI), self-reported (urine confirmed), weekly

Drug abuse responder (a 50% reduction in baseline substance use measures), at endpoint

Mental health

Depression (interview version of HAMD): weekly

Depression responder (a 50% reduction in baseline HAMD score), at endpoint

Quality of life

Not assessed

Function

Not assessed

Mortality

Not assessed

Compliance

Definition NR, measured weekly by sertraline serum level

Adverse effects

Method for collecting information NR

Results

Substance use

	Sertraline (ITT, n = 47) Endpoint	Placebo (ITT, n = 48) Endpoint	Test of difference
Drug abuse responder (50% reduction in baseline SU measures), n (%)	19 (40%)	20 (42%)	$\chi 2(1) = 0.01$; $P < 0.90$
Proportion of days that heroin or cocaine use was reported, mean (SD)	0.14 (0.21)	0.20 (0.28)	$t(93) = 0.98$; $P < 0.33$
Proportion of days any drug or alcohol use was reported, mean (SD)	0.23 (0.27)	0.33 (0.36)	$t(93) = 1.53$; $P < 0.13$

Comments

End point values used in the analyses were the average of the last four observations.

In random regression analyses, treatment did not significantly account for differences in the rate of change in heroin or cocaine use ($t(93) = 0.82$; $P = 0.42$) or any drug or alcohol use ($t(93) = 0.86$; $P = 0.39$) when entered in the regression models alone.

Study

Carpenter, 2004 [14]

Mental health

	Sertraline (ITT, n = 47) Endpoint	Placebo (ITT, n = 48) Endpoint	Test of difference
Depression responder (50% reduction in baseline HAMD scores), n (%)	15 (32%)	16 (33%)	$\chi 2$ (1) = 0.02; P < 1.00
HAMD total score, mean (SD)	14.5 (5.4)	14.9 (5.8)	t(93) = 0.88; P < 0.38

Comments

End point values used in the analyses were the average of the last four observations.

Treatment did not significantly account for differences in the rate of change in depression when entered in the regression model alone (t(93) = −0.57; P =0.57).

Compliance

Compliant	Sertraline n = 47	Placebo n = 48
Discontinuation due to non-compliance*: n (%)	5 (11%)	2 (4%)
Completed at least 4 weeks: n (%)	44 (93%)	46 (96%)
Completed 12 weeks: n (%)	32 (68%)	39 (81%)
Treatment completion: weeks (SD):	10.2 (3.3)	10.9 (2.7)

* Compliance not defined, may be related to methadone clinic rules: all participants were subject to the clinics' rules and regulations.

Comments

The wide range of serum levels during the study suggests medication compliance was not uniform across all patients.

Study	Carpenter, 2004 [14]
	Adverse effects

	Sertraline n = 47	Placebo n = 48
None: n (%)	9 (19%)	11 (23%)
Nausea/stomach discomfort: n (%)	14 (30%)	21 (44%)
Headache: n (%)	13 (28%)	7 (15%)
Jitteriness: n (%)	10 (21%)	7 (15%)
Constipation: n (%)	7 (15%)	4 (8%)
Dry mouth: n (%)	3 (6%)	1 (2%)
Fatigue: n (%)	8 (17%)	9 (19%)
Weight gain: n (%)	5 (11%)	3 (6%)
Insomnia: n (%)	3 (6%)	0 (0%)
Diarrhea: n (%)	7 (15%)	4 (8%)
Heartburn: n (%)	1 (2%)	1 (2%)
Libido loss: n (%)	5 (11%)	2 (5%)
Memory problems: n (%)	4 (9%)	1 (2%)
Dizziness: n (%)	2 (4%)	2 (5%)
Aches: n (%)	3 (6%)	1 (2%)
Blurred vision: n (%)	0 (0%)	1 (2%)

	Comments:
	No SAE reported. No significant differences between groups on reported side effects
	Loss to follow up
	Endpoint: 95-71 = 24 (25%) loss;15/47 in sertraline group and 9/48 in placebo group, ns
Risk of bias	Low

HAM-D = Hamilton Rating Scale for Depression; **MMT** = methadone maintenance therapy; **NR** = not reported (not relevant); **RCT** = randomized controlled ; trial; **SAE** = serious adverse effect; **SUI** = Substance use weekly inventory.

Cornelius et al. 1997

Study	Cornelius, 1997 [15]
Study design	RCT, double blind
Intervention	**Pharmacotherapy: Fluoxetine**
	Cointerventions: weekly supportive psychotherapy
Trial registration	NR
Country	USA

Setting

Inpatient and outpatient. The first two weeks, patients were treated at the hospital (inpatient) and thereafter as outpatients.

Aims

Efficacy of fluoxetine in reducing the depressive symptoms and the alcohol consumption in patients who display both major depression and alcohol dependence.

Participants

AUD & depression

Psychiatric hospital inpatients diagnosed as having comorbid major depressive disorder and alcohol dependence (DSM III-R).

Baseline characteristics

	Fluoxetine	Placebo
N=	25	26
Women: %	48.0	50.0
Age: M (SD)	35.7 (10.4)	34.0 (10.0)
Employed: %	36.0	26.9
Substance use status		
No. of days drinking, past 90 days: M (SD)	54.5 (29.2)	45.2 (28.9)
No. of days drinking to drunkenness, past 90 days: M (SD)	40.1 (27.7)	32.0 (26.4)
Mental health status		
HAM-D-24 at presentation: M (SD)	33.2	33.0
HAM-D-24 after detoxification and washout: M (SD)	19.2 (8.2)	17.9 (8.1)
BDI at presentation: M (SD)	29.6 (12.4)	24.8 (12.4)
BDI after detoxification and washout*: M (SD)	19.7 (13.4)	12.3 (7.5)
Current suicide ideation: %	92.0	88.5

*Significant difference

Inclusion criteria

Patients 18 to 65 years of age admitted to inpatient services. Only patients meeting the diagnostic criteria for current diagnoses of both major depressive disorder and alcohol dependence were included in the study. Following a 2- to 3-day detoxification with minor tranquilizers and a subsequent 1-week washout period, the continued presence of the comorbid

	diagnoses was confirmed using the Structured Clinical Interview for DSM-III-R. The depressive diagnosis was required to be primary diagnosis, defined by DSM-III-R as being "the condition that was chiefly responsible for occasioning the evaluation." **Exclusion criteria** Diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia, or nonalcohol substance dependence. Abuse of other substances was not an exclusionary criterion, provided that alcohol was clearly the main substance of abuse. Patients with hyperthyroidism or hypothyroidism, clinically significant liver disease (liver function tests ≥ 3x normal), notable cardiac or renal impairment, pregnancy, mental retardation, or clinically evident cognitive impairment were excluded. Patients who had received antipsychotic or antidepressant medication in the month before admission to the hospital were excluded. **Recruitment & screening** All patients were recruited from consecutive admissions on the inpatient services of a large, comprehensive, urban university psychiatric hospital. Patients were recruited into the study without regard to sex, race, or ethnicity. A total of 147 patients were screened. **Remuneration** NR
Comparison	**Fluoxetine vs. placebo** (adjunct to psychotherapy) **Duration of treatment** 12 weeks **Follow ups** Measurements during treatment, weekly Endpoint / time of last treatment
Experimental arm	**Fluoxetine** All subjects were initially given 1 capsule 20 mg fluoxetine, which could be increased to 2 capsules after 2 weeks if substantial residual depressive symptoms persisted. **Co-interventions** Usual care, psychotherapy

Contorl arm	All patients also received "usual care" for dual-diagnosis patients at our facility, consisting of weekly supportive psychotherapy sessions and weekly meetings with an attending psychiatrist with expertise in evaluating and treating dual-disorder patients. <u>Psychosocial, optional</u> Attendance at Alcoholics Anonymous also was encouraged for all patients. **Placebo** Matching placebo delivered as for active substrate. **Co-interventions** <u>Usual care, psychotherapy</u> Same as for Experimental arm. <u>Psychosocial, optional</u> Same as for Experimental arm.
Outcomes	**Substance use** Cumulative drinks during 12-week trial (TLFB), weekly Cumulative no of drinking days during trial (TLFB), weekly Drinks per drinking day during trial, DDD (TLFB), weekly Cumulative no of heavy drinking days during trial, HDD (TLFB), weekly No. of weeks until first drink (TLFB), weekly No. of weeks until first heavy drinking (TLFB), weekly No. of patients abstinent throughout entire trial (TLFB), weekly Drinking behaviour (ASI), weekly **Mental health** Depression (HAM-D-24), observer-rated, weekly Depression (BDI), self-reported, weekly Functioning (GAS), weekly **Quality of life** Not assessed **Function** Not assessed

Results

Mortality

Not assessed

Compliance

Verification of compliance with medication was assessed by weekly pill counts and by plasma levels of fluoxetine and norfluoxetine at weeks 2, 4, and 12.

Adverse effects

Method not stated.

Substance use

	Fluoxetine (ITT, n = 25) Endpoint	Placebo (ITT, n = 26) Endpoint	Test statistic	p-value
Cumulative drinks during trial*: M (SD)	70.2 (100.7)	215.5 (248.5)	F=5.12	<0.03
Cumulative no. of drinking days during trial*: M (SD)	10.6 (15.6)	20.3 (18.3)	F=4.26	<0.05
Drinks per drinking day during trial*: M (SD)	2.4 (2.9)	5.4 (5.5)	F=4.13	<0.05
Culmulative no. of days of heavy drinking during trial*: M (SD)	4.8 (7.0)	16.0 (18.0)	F=4.51	0.04
No. of weeks until first drink*: M (SD)	5.5 (4.5)	3.9 (4.0)	F=3.14	0.08
No. of weeks until first heavy drinking*: M (SD)	8.0 (4.8)	4.7 (4.2)	F=6.03	<0.02
No. of patients abstinent throughout entire trial: n (%)**	7 (28.0%)	4 (15.4%)	χ^2=1.20	0.27

ITT analysis with LOCF for missing data.* ANCOVA, baseline depression and drinking as covariates. **Chi square test, corrected for continuity.

Mental health

	Fluoxetine (ITT, n = 25) Endpoint	Placebo (ITT, n = 26) Endpoint	Test statistic	p-value
Change in HAM-D-24: M (SD)	-6.0 (9.6)	-2.0 (13.3)	F=4.17	<0.05
Change in BDI: M (SD)	-6.5 (12.8)	-0.9 (12.1)	F=1.90	0.17
Change in GAS: M (SD)	16.8 (14.5)	5.2 (17.0)	F=8.73	0.005

ITT analysis with LOCF for missing data. *ANCOVA, baseline depression and drinking as covariates. **Chi square test, corrected for continuity.

Compliance

	Compliant	**Fluoxetine** (ITT, n = 25)	**Placebo** (ITT, n = 26)		
		Endpoint	**Endpoint**	**Test statistic**	**p-value**
	Alcoholics Anonymous attendance sessions: M (SD)	14.7 (17.0)	15.3 (19.8)	F=0.01	0.92
	Psychotherapy attendance, sessions: M (SD)	9.9 (2.8)	8.9 (3.1)	F=1.53	0.22
	Comments Compliance to pharmacotherapy by pill count NR. Substantial blood levels of fluoxetine were observed in more than 99% of blood specimens of patients assigned to fluoxetine. **Adverse effects** None of the patients in either treatment group made a suicide attempt during the course of the pharmacotherapy trial, nor did they experience other adverse events. Also, no patients were discontinued from the study because of medication side effects. Fluoxetine was well tolerated by the patients in this study. **Loss to follow up** Endpoint: 5 (10%)				
Risk of bias	Moderate				

RCT = randomized controlled trial; **ASI** = Addiction Severity Index; **BDI** = Beck Depression Inventory; **DDD** = drinks per drinking day; **DSM** = Diagnostic and Statistical Manual of Mental Disorders, roman numerals indicate version number; **GAS** = Global Assessment Scale; **HAMD** = Hamilton Rating Scale for Depression; **HDD** = heavy drinking day; **M** = mean; **NR** = not reported (not relevant); **SD** = standard deviation; **HAM-D** = Time-Line Follow-Back, self-reported substance use (time to outcomes).

Gao et al. 2017

Study	**Gao, 2017 [16]**
Study design	RCT, double-blinded (post hoc analysis)
Intervention	**Pharmacotherapy: Quetiapine-XR** As monotherapy or adjunctive therapy to a mood stabilizer
Trial registration	NCT00671853
Country	Ohio, USA
Setting	Outpatient, university hospital

Aims

The aim of this post hoc analysis is to assess the efficacy and safety of quetiapine-XR relative to placebo in patients with bipolar I or II depression and GAD with or without a recent ALC/CAN.

Participants

Bipolar I or II depression & GAD & alcohol or cannabis dependence

Baseline characteristics*

	quetiapine-XR	**Placebo**
N**=	46	44
With recent ALC/CAN: N=	22	21
Women: % (n)	45.5% (10)	38.1% (8)
Age: M (SD)	35.7 (12.2)	35.9 (11)
Education level	NR	NR
Housing situation	NR	NR
Employment status	NR	NR
Substance use status		
Actively drinking at the week before randomization***: % (n)	23% (5)	48% (10)
Actively using cannabis the week before randomization***: % (n)	41% (9)	29% (6)
Mental health status		
HAMD-17, total score: M (SD)	24.3 (4.3)	26.4 (5.3)
HAMA, total score: M (SD)	26 (4.6)	25.2 (6)
QIDS-SR-16, total score: M (SD)	21.2 (7.7)	22.8 (6.5)
CGI-BP-S, total score: M (SD)	4.5 (0.5)	4.7 (0.6)
Bipolar I disorder: % (n)	90.9% (20)	90.5% (19)
Current manic / hypomanic episode duration: M (SD)	427.5 (860.5)	214.6 (411.6)
Mean episodes in last 12 months		
- Mania/mixed/hypomania: M (SD)	6 (7.4)	8.3 (12.1)
- Depression: M (SD)	7.4 (8.5)	8.9 (11.8)
- Total: M (SD)	13.4 (13.7)	17.2 (23.7)
Comorbidities		
Lifetime other anxiety disorder: % (n)	90.9% (20)	90.5% (19)
Current other anxiety disorder: % (n)	86.4% (19)	81% (17)
Lifetime psychosis: % (n)	31.8% (7)	38.1% (8)

Past suicide attempt: % (n)	36.4% (8)	33.3% (7)
Past hospitalization: % (n)	50% (11)	23.8% (5)

* Data is provided for ALC/CAN group separately, data for groups without recent ALC/CAN not extracted

** 100 were originally randomized according to Gao 2014 [17].

*** Based on the available data for 35 participants; the substance use status for 8 people in this subgroup is unknown.

Inclusion criteria

Males and females from 18 to 65 years of age who met DSM-IV criteria for bipolar I or II disorder, currently depressed with a HAMD-17 total score ≥18 at screening and baseline visits, and current GAD with a HARS total score ≥18 at screening and baseline visits were eligible.

All Axis I disorders were ascertained using a modified MINI.

Participants were required to be in good physical health.

Comment

SUD was not an inclusion criteria in the original study. Only data relevant to the "recent ALC/CAN" subgroup is extracted.

Exclusion criteria

(1) severe medical or neurologic problems; (2) severe personality disorder; (3) current suicidal risk judged by a physician; (4) known history of intolerance or hypersensitivity to any of the medications involved in the study; (5) treatment with quetiapine ≥ 100 mg/d in the 6 months prior to randomization; (6) known lack of response to quetiapine in a dosage of ≥ 100 mg/d for 4 weeks at any time, as judged by the investigator; (7) dependence on an opiate, phencyclidine, and/or barbiturate; (8) concurrent obsessive-compulsive disorder; (9) use of any cytochrome P450 3A4 inhibitors or cytochrome P450 inducers in 14 days; (10) administration of a depot antipsychotic injection within 1 dosing interval (for the depot) before randomization; (11) unable to wean off benzodiazepines or other medication; (12) female patients who were pregnant, planning to be pregnant, or breastfeeding; and (13) Young Mania Rating Scale (YMRS) total score ≥ 12.

Those who could not tolerate 150 mg/d were discontinued from the study.

Participants who were unable to discontinue prohibited concomitant medication were discontinued from the study.

Recruitment & screening

Pre-screening: An Extensive Clinical Interview (Similar to SCID-IV-P) was performed to confirm the diagnosis of bipolar disorder and GAD and to determine if the inclusion and exclusion criteria were met.

Screening (N = 120*)

Axis I disorders were ascertained using a modified MINI. Substance use disorder was confirmed using SCID-IV-P

	The subgroup recent ALC/CAN was defined as patients who had a diagnosis of substance dependence and continued to meet abuse or dependence criteria for a substance(s) in the past 6 months at the initial assessment or those who had a diagnosis of substance abuse and continued abusing a substance in the last 3 months. Substance use disorder was confirmed with SCID-IV-P. The severity of alcohol and cannabis use was assessed a week prior to randomization and after randomization (TLFB) Randomization (N = 100*) Randomization balanced for bipolar I vs II, gender, +/- recent ALC/CAN * According to Gao 2014 [17]. **Remuneration** NR
Comparison	**Quetiapine-XR vs placebo** **Duration of treatment** 8 weeks **Follow-ups** Assessments were performed at weeks 0, 1, 2, 4, 6, and 8.
Experimental arm	**Quetiapine-XR** The study medications were started at 50 mg for day 1 and day 2, increased to 150 mg at day 3 and day 4, and finally increased to 300 mg/d at day 5 and onward. For those who could not tolerate 300 mg/d, a 50-mg decrement per week was allowed to a minimum of 150 mg/d. **Co-interventions:** <u>Mood stabilization</u> Current treatment with the mood stabilizers lithium, valproic acid, and/or lamotrigine were permitted after stable dosing was maintained for a minimal 2-week period. 91.3% (42/46) did not have any additional pharmacologic treatment* 4.3% (2/46) received lithium* 4.3% (2/46) received lamotrigine* * Regarding the whole group, according to Gao 2014 [17]. <u>Sleep aids</u>

Control arm	Rescue medication for sleep such as zolpidem (Ambien 5–10 mg/d or Ambien-CR 6.25–12.5 mg/d) was permitted during the washout period and the double-blind phase Other All other medications were discontinued at least 5 half-lives prior to randomization. **Placebo** Same as for Experimental arm. **Co-interventions** Same as for Experimental arm. Mood stabilization 84.4% (38/45) did not have any additional pharmacologic treatment* 6.7% (3/45) received Valproate/divalproex* 6.7% (3/45) received lamotrigine* 2.2% (1/45) received some combination of lithium, valproate, and or lamotrigine * Regarding the whole group, according to Gao 2014 [17].
Outcomes	**Substance use** Changes in number of drinks per week, (TLFB), self-reported, at weeks 0, 1, 2, 4, 6, and 8 Changes in number of heavy drinking days per week, (TLFB), self-reported, at weeks 0, 1, 2, 4, 6, and 8 Changes in number of drinking days per week, (TLFB), self-reported, at weeks 0, 1, 2, 4, 6, and 8 Changes in number of joints of cannabis per week, (TLFB), self-reported, at weeks 0, 1, 2, 4, 6, and 8 Changes in number cannabis smoking days per week, (TLFB), self-reported, at weeks 0, 1, 2, 4, 6, and 8 **Mental health** Change in depression, baseline to EOS (HDRS-17, total score), at weeks 0, 1, 2, 4, 6, and 8 Mean change in anxiety, baseline to EOS (HAMA), who measured (ie. self-reported), at weeks 0, 1, 2, 4, 6, and 8 Mean change in bipolar disorder Severity, baseline to EOS (CGI-BP-S), clinician measured, at weeks 0, 1, 2, 4, 6, and 8 Mean change in depression, baseline to EOS (QIDS-SR-16), self-reported, at weeks 0, 1, 2, 4, 6, and 8 Responders, depression (≥50% improvement in HAMD-17 total score), baseline to EOS Remission, depression (HAMD-17 total score ≤7), baseline to EOS **Quality of life** Mean change in QoL, baseline to EOS (Q-LES-Q), self-reported, at weeks 0, 1, 2, 4, 6, and 8

Results

Function

Not assessed

Mortality

Not assessed

Compliance

Not assessed

Adverse effects

Incidence of AE based on the following monitored symptoms:

Extrapyramidal symptoms (SAS)

Akathisia (BARS)

Frequency, intensity, and burden of side effects (FIBSER)

Signs of mania (YMRS)

Clinical laboratory assessments and physical examinations were performed at baseline and repeated at the end point.

For those with current SUD, monthly liver function tests were obtained if clinically indicated

Substance use

	Quetiapine-XR with recent ALC/CAN		Placebo-XR with recent ALC/CAN		p value between groups
	N	M (SD)	N	M (SD)	
Number of drinks/week:					
Baseline	16	7.6 (13.0)	19	13.7 (21.8)	
Average (post randomization)	16	2.7 (4.2)	20	10.0 (14.1)	
Change	15	−5.2 (10.6)	18	−3.8 (10.9)	0.71
Number of heavy drinking days/week:					
Baseline	16	1.0 (2.2)	19	19 (1.5)	
Average (post randomization)	16	0.1 (0.3)	20	20 (1.0)	
Change	15	−0.9 (2.3)	18	18 (−0.3)	0.32
Number of drinking days/week:					

	Baseline	16	1.9 (2.7)	19	2.1 (2.7)	
	Average (post randomization)	16	1.0 (1.8)	20	1.8 (1.9)	
	Change	15	−1.0 (2.2)	18	−0.1 (1.4)	0.17
	Number of joints/week:					
	Baseline	16	15.6 (20.3)	18	6.2 (11.0)	
	Average (post randomization)	16	10.7 (14.8)	20	5.4 (7.5)	
	Change	15	−4.8 (8.6)	17	−0.4 (4.9)	0.09
	Number of smoked days/week:					
	Baseline	16	4.0 (3.5)	18	2.3 (3.2)	
	Average (post randomization)	16	3.1 (3.5)	20	2.7 (3.3)	
	Change	15	−0.5 (1.7)	17	−0.03 (2.4)	0.55

Comments

The authors used mITT, however fewer patients had baseline alcohol (n=38) or cannabis (n=34) data than for the other outcomes in this study.

Mental health

	Quetiapine-XR with recent ALC/CAN (mITT, n =22)			**Placebo-XR with recent ALC/CAN** (mITT, n = 21)		
	Baseline	**EOS**	**Change**	**Baseline**	**EOS**	**Change**
HAMD-17: M (SD)	24.3 (4.3)	14.8 (6.6)	−9.5 (5.8)	26.4 (5.3)	18.4 (10.2)	−8.0 (9.7)
HAMA: M (SD)	26 (4.6)	15.4 (7.8)	−10.6 (6.9)	25.2 (6)	17.8 (11)	−7.4 (10.4)
QIDS-SR-16: M (SD)	21.2 (7.7)	12.4 (8.4)	−8.8 (7.8)	22.1 (6.7)	20.2 (8.2)	−1.8 (7.4)
CGI-BP-S: M (SD)	4.5 (0.5)	3 (1)	−1.5 (1.1)	4.7 (0.6)	3.8 (1.3)	−0.9 (1.3)
Response, % (n)		31.8% (7)			28.6% (6)	
Remission, % (n)		18.2% (4)			19.1% (4)	

Comments

Outcomes assessed using mITT with LOCF

Results also presented from a mixed-effects model of repeated measures, assuming a first-order autoregressive variance-covariance structure in table 3, data not extracted

Adverse effects

Occurrences of adverse events experienced by ≥5% of patients in any group	Quetiapine-XR Recent ALC/CAN n = 22	Placebo Recent ALC/CAN n = 21
Dizziness: % (n)	6.3% (4)	9.1% (3)
Dry mouth: % (n)	23.4% (15)	9.1% (3)
Fatigue: % (n)	10.9% (7)	15.2% (5)
Sedation: % (n)	14.1% (9)	6.1% (2)
Total occurences	64	33

Comments

Safety data were analysed using ANOVA, mITT and LOCF

Loss to follow up

At study completion, recent ALC/CAN subgroup

Quetiapine-XR: 63.64% (14/22)

Placebo: 42.9% (9 of 21)

Note: Whole group data	Quetiapine-XR (whole group) n = 50 (analysed 46)	Placebo (whole group) n = 50 (analysed 45)
Completed study: N	26	18
Lack of efficacy: N	3	7
Side effects: N	8	1
Withdrawal of consent: N	1	5
Poor medication adherence: N	1	0

	Poor visit adherence: N	8	8
	Non-adherence to study procedures: N	0	3
	New/return to substance abuse/dependence: N	0	1
	Lost to follow-up: N	3	5
	Other: N	0	2
	Comments Reasons for not completing study reported in Gao 2014 [17], whole group, not only ALC/CAN subgroup. Note that reasons for non-completion include lack of efficacy, poor medication adherence, poor visit attendance, non-adherence to study procedures, and new or return of active substance abuse.		
General Comments	The study was conducted from January 2007 to November 2011. Results from that trial were also published in: Gao 2008 [18] (excluded due to wrong study design) Gao 2014 [17] (excluded due to wrong population) "The primary outcome and major secondary outcomes were published in 2014 (Gao et al. 2014)."		
Risk of bias	Moderate		

ALC/CAN = recent alcohol and/or cannabis use disorder; **BARS** = Barnes Akathisia Scale; **CGI-BP-S** = Clinical Global Impression for Bipolar Disorder-Severity; **EOS** = end of study; **FIBSER** = Frequency, Intensity, and Burden of Side Effects Rating scale; **GAD** = generalized anxiety disorder; **HAMA** = Hamilton Anxiety Rating Scale; **HDRS-17** = Hamilton Depression Rating Scale, 17 items; **LOCF** =last observation carried forward; **MINI** = Mini-International Neuropsychiatric Interview; **mITT** = modified intent to treat, in this study data was analysed if the participant took 1 dose of study medication and had at least 1 post-baseline assessment; **QIDS-SR-16** = Quick Inventory for Depression−16 item; QoL = quality of life; Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q); **RCT** = randomized controlled trial; **SAS** = Simpson Angus Scale; **SCID-IV-P** = Structured Clinical Interview for DSM-IV, Patient Edition; **SD** = standard deviation; **SUD** = substance use disorder; **TLFB** = Timeline Follow Back; **XR** = extended release.

Green et al. 2015

Study	**Green, 2015 [19]**
Study design	RCT, open-label, single blinded, multi-center
Intervention	**Pharmacotherapy: Risperidone oral vs. long-acting injectable (LAI)** Co-interventions: continued pre-existing treatments with psychotropic medications
Trial registration	NCT00130923
Country	USA

Study | **Green, 2015 [19]**

Setting

Outpatients at community mental health and Veterans Affairs clinics at four sites (New Hampshire, South Carolina, Florida and Missouri)

Aims

The 6-month study was initiated to compare the effects of these 2 forms of risperidone on alcohol drinking and related measures in dual diagnosis patients, with the primary hypothesis that patients using LAI risperidone will have less alcohol use as measured by heavy drinking days than patients taking oral risperidone

Participants

AUD & schizophrenia

Populations consisted of 95 patients with diagnosis of schizophrenia and alcohol use disorder according to DSM-IV-TR.

The study participants were primarily men with moderate symptoms whose average age was 41.7 years. Most study participants had alcohol dependence (rather than abuse) and reported, on average, 2 heavy drinking days per week and minimal drug use.

Baseline characteristics

	Total	Oral Risperidone	LAI Risperidone
N=	95	46	49
Men: n (%)	73 (76.8)	36 (78.3)	37 (75.5)
Age: M (SD)	41.73 ± 10.7	41.72 ± 11.5	41.73 ± 10.1
Education, yrs: M (SD)	11.0 ± 1.7	11.2 ± 1.4	10.9 ± 2.0
Ever employed: n (%)	92 (96.8)	45 (97.8)	47 (95.9)
Substance use status			
Alcohol dependence (vs abuse), n (%)	80 (84.2)	41 (89.1)	39 (79.6)
Drinks/wk: M (SD)	23.99 ± 23.1	24.4 ± 22.7	23.6 ± 24.5
Drinking days/wk: M (SD)	3.6 ± 1.8	3.7 ± 1.8	3.6 ± 1.9
Heavy drinking days/wk: M (SD)	2.0 ± 2.3	2.2 ± 2.1	1.8 ± 1.9
Days cannabis use/wk: M (SD)	1.1 ± 2.0	1.1 ± 2.1	1.1 ± 1.9
Days other drug use/wk: M (SD)	0.3 ± 0.8	0.3 ± 0.6	0.4 ± 0.9
Mental health status			
Diagnosis schizophrenia (vs schizoaffective disorder): n (%)	46 (48.4)	23 (50.0)	23 (46.9)
Lifetime hospitalizations: M (SD)	7.5 ± 15.9	6.9 ± 14.9	8.1 ± 16.9

Study	Green, 2015 [19]
Comparison	**Inclusion criteria** Adults (18-65 year) with schizophrenia or schizoaffective disorder and current alcohol use disorder (abuse or dependence) as assessed using the Structured Clinical Interview for DSM-IV-TR Axis I disorders, Research version, Patient Edition (SCID-I/P), with use of alcohol on at least 4 days during the 4 weeks prior to randomization (based on the timeline Follow-Back procedure). Other current substance use disorders were allowed. Participants were required to be psychiatrically stable and taking antipsychotic medication without a change of psychotropic medications for the past 30 days. **Exclusion criteria** (1) being treated with clozapine, 2 or more concurrent antipsychotics, or any LAI antipsychotic; (2) being treated with agents that may curtail substance use (eg, disulfiram, naltrexone, valproic acid, topiramate, acamprosate, opiate replacement therapy, or benzodiazepines); (3) currently pregnant or unwilling to use an acceptable form of birth control; (4) currently residing in a residential program designed to treat substance use disorders; or (5) intolerant of or allergic to oral or LAI risperidone. **Recruitment & screening** Participants were recruited from adults (18-65 year) at community mental health and Veteran Affairs clinics at 4 sites. 150 patients consented to participate and 95 met study criteria. **Remuneration** Patients were given a 25 USD gift card at the completion of each study visit. **Long-acting injectable (LAI) vs. oral risperidone** **Duration of treatment** 6 months **Follow ups** Measurements during treatment Endpoint = 24 weeks or time of last treatment <u>Comments</u> Analyses were conducted using weeks 5 to 23 to ensure that steady risperidone blood levels were reached.

Study	Green, 2015 [19]
Experimental arm	**LAI-isperidone** Study participants who were randomized to the LAI risperidone group were started on a dose of 25 mg given intreamuscular every 2 weeks. The dose was titrated up to a target dose of 37.5 mg IM, with injections given every 2 weeks. Most people reached 37.5 mg at the second injection, and some increased or decreased thereafter depending upon tolerability, reaching their final dose by 6 weeks. **Pretreatment, discontinuation of antipsychotic medication** Antipsychotics were gradually lowered and discontinued over the first 6 weeks of the study. **Co-interventions** Psychotropic pharmacotherapy, maintenance Concomitant psychotropic medications were maintained without changes, whenever possible. While use of any antipsychotic medication in addition to study risperidone (oral or long-acting) was avoided, olanzapine was allowed on a short-term basis for symptom exacerbation during the switch period, e.g., during the initial 6 weeks of the study. Psychosocial component At the second study visit, participants viewed a 30-minute alcohol education videotape, were given a list of local self-help groups and were encouraged to continue with psychosocial treatment at their clinic as before.
Comparison arm	**Oral risperidone** Participants who were randomized to take oral risperidone were titrated over 2 weeks up to a target dose of 4 mg/d. **Pretreatment, discontinuation of antipsychotic medication** Antipsychotics not taking oral risperidone at study start were gradually lowered and discontinued over the first 6 weeks of the study. **Co-interventions** Psychotropic pharmacotherapy, maintenance Same as for LAI risperidone group Psychosocial component Same as for LAI risperidone group

Study Outcomes	Green, 2015 [19]
	Substance use Primary outcomes: Days of heavy drinking (TLFB), interview, every 2 weeks Secondary outcomes: Number of drinks per week (TLFB), interview, every 2 weeks Substance use (Urine drug screens), every 2 weeks Substance use (breathalyzer), every 2 weeks Substance use (Alcohol Use Scale), clinician rating, baseline, 3 months, and 6 months **Mental health** Psychopathology (PANSS; 30 items), clinician rating, monthly Symptom severity (CGI), clinician rating, monthly **Quality of life** Not assessed **Function** Functioning (GAF), clinician rating, monthly **Mortality** **N**ot assessed **Compliance** Plasma concentrations of risperidone (and 9-hydroxy [OH] risperidone) were obtained at 8, 16, and 24 weeks. Medication adherence was assessed by weekly pill count or documentation of injections. **Adverse effects** Neurologic side effects (SAS), clinician rated, monthly Neurologic side effects (AIMS), clinician rated, monthly Neurologic side effects (BARS), clinician rated, monthly Study investigators conducted a clinical assessment of medication effectiveness, side effects, and vital signs every 2 weeks for the first 2 months and then every 4 weeks.

Study	Green, 2015 [19]
Results	**Substance use**

	Between groups analysis (ITT=95)*	
Primary outcomes:	**Statistics**	**P-value**
Heavy drinking days/wk	NR	NS
Secondary outcomes:	**Statistics**	**P-value**
Number of drinking days/wk	t_{87}= 2.42	P = 0.018
Drinks per week	NR	NS
Global Alcohol Use Scale	NR	NS

* For the intent-to-treat analyses, data were censored (1) for the rest of the study if a subject was given clozapine or received a medication thought to decrease alcohol use or (2) for every week that a subject was in the hospital or otherwise incarcerated for more than 4 days during that week. Data not extracted: Raw data (?) in Figure 1 on HDD week by week.

Comments

Analyses were conducted using longitudinal random-effects models on data from weeks 5 to 23 to ensure that steady blood levels were reached in the LAI group and to avoid end of study effects on drinking behavior.

Study	Green, 2015 [19]

Mental health and Function

	Between groups analyses	
	Statistics	**P-value**
Total PANSS	NR	NS
CGI	NR	NS
GAF	NR	NS
Rate of Psychiatric symptom exacerbation*	NR	NS

***** Psychiatric symptom exacerbation occurred in 36 participants (37.9%): 20 (21.1%) were hospitalized, 16 (16.8%) were not. Rates did not differ between groups.

Comments

Analyses used longitudinal random-effects models that controlled for baseline scores.

Although the correlation between heavy drinking and symptoms in the LAI group was significant, it was weak and not clinically relevant: a 1-point increase in symptom score was associated with an increase of 0.018 heavy drinking days per week (t199 = 2.43, P = 0.016).

Comments

Study Compliance

Green, 2015 [19]

	Oral risperidone (ITT, n = 46)	LAI Risperidone (ITT, n = 49)
Weeks on study medication: M (SD)	17.1 (8.1)	17.6 (7.9)
Medication dose: M (SD)	4.3 (1.5)	33.8 (9.0)
Patients ending medication early: n (%)	21 (46)	14 (29)
Good adherence*: n (%)	28 (61)	43 (88)
Counseling sessions per week: M (SD)	0.6 (1.2)	0.6 (0.8)
Alcoholics Anonymous sessions per week: M (SD)	0.4 (1.3)	0.2 (0.6)

* Medication adherence (defined as taking medication at least 75% of the days in the treatment period):
Significantly worse among participants assigned to oral risperidone (61% vs 88%; $\chi 2\ 1 = 9.08$, P = 0.003).
Risperidone and plasma metabolite concentrations:
Between-group differences reached significance for 9-OH risperidone at every time point (weeks 8, 16, 24) and for risperidone at week 8.
Sixty-eight patients (71.6% of the randomized sample) remained in the study for 6 months; 36 (38% of the randomized sample) stopped assigned medication at some point during follow-up. Eight participants (2 on LAI, 6 on oral) switched to a different antipsychotic medication but completed the study. Moreover, 3 participants took other prohibited medication (1 on LAI, 2 on oral). Study retention and length of time on study medication did not differ between the oral and the injectable groups. Participants engaged in a minimal amount of psychosocial treatment during the study period, which did not differ between the groups.

Adverse effects, % (N)

	Total n = 95	Between groups analysis
AE, any: % (n)	79% (75)	NS
AE, possibly or probably related to study medication: % (n)	47.4% (45)	NS
SAS		NS
AIMS		NS
BARS		NS

The frequency of side effects did not differ between the oral and the LAI risperidone groups.

Study	Green, 2015 [19]
Comments	Longitudinal random-effects models were used to investigate potential differential treatment effects over time on alcohol use. Explanatory (efficacy) analyses were carried out to evaluate differences between groups using data (complete or partial) obtained while subjects were still taking their assigned medication; intent-to-treat analyses were secondary.
Loss to follow up: N (%)	**Oral risperidone (ITT, n = 46)** / **LAI Risperidone (ITT, n = 49)** **Retained 6 months, n (%)**: 32 (69.6) / 36 (73.5) *Kvarstannande och inte egentligt bortfall*
Comments	If the prescribing psychiatrist stopped the study medication because of lack of efficacy or side effects, he/she prescribed the subject an alternate antipsychotic medication based on clinical judgment, with input from both the patient's clinical treatment team and the patient. Whenever possible, subjects who stopped their study medication were followed for the full 6-month study period. There are data that can be extracted from graph, but unclear how useful any of the data is.
Risk of bias	Low

AIMS = Abnormal Involuntary Movement Scale; **BARS** = Barnes Akathisia Rating Scale; **CGI** = Clinical Global Impression; **GAF** = Global Assessment of Functioning; **LAI** = Long-acting injectable; **M** = mean; **NR** = not reported (not relevant); **PANSS** = Positive and Negative Syndrome Scale; **RCT** = randomized controlled trial; **SAS** = Simpson-Angus Scale; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use (time to outcomes).

Gual et al. 2003

Study	Gual, 2003 [20]
Study design	RCT, double-blind, placebo-controlled, parallel group
Intervention	**Pharmacotherapy: Sertraline** Co-interventions: NR, possibly enrolled in an alcohol detoxification program
Trial registration	The protocol was submitted to, and approved by, the Ethics Committee of the Hospital Clinic of Barcelona
Country	Spain
Setting	Outpatient
Aims	To evaluate the efficacy of sertraline at achieving stable abstinence, at ameliorating depressive symptoms and at improving quality of life in recently detoxified alcohol- dependent patients.
Participants	**AUD & Depression**

Study	Gual, 2003 [20]

Participants had recently undergone an acute alcohol detoxification and subsequently remained abstinent at least 2 weeks.

Baseline characteristics

	Sertraline		Placebo	
Total: n = 83	n = 44		n =39	
Sex:	**Men**	**Women**	**Men**	**Women**
% (n)	52.3% (23)	47.7% (21)	53.9% (21)	46.1% (18)
	Mean (SD)	**Median (range)**	**Mean (SD)**	**Median (range)**
Age:	46.1 (9.2)	44.4 (29.1 to 69.6)	47.3 (9.9)	46.9 (31.7 to 68.9)
Substance use status	**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Median (range)**
Duration of Alcoholism (years)	13.7 (8.2)	15.0 (0.5 to 30.0)	18.7 (9.4)	14.5 (0.1 to 38.0)
Mental health status	**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Median (range)**
Duration of Depression (years)	3.3 (4.73)	0.9 (0.1 to 15.0)	3.3 (5.0)	1.0 (0.1 to 21.0)
MADRS Score	22.7 (6.9)	21 (10 to 36)	22.4 (8.0)	21 (5 to 43)
HAM-D Scale Score	13.9 (5.6)	14 (3 to 30)	12.8 (4.0)	14 (5 to 20)
Quality of life	**Mean (SD)**	**Median (range)**	**Mean (SD)**	**Median (range)**
SF36-PCS	48.6 (9.6)	49.0 (19.4 to 70.5)	47.0 (11.0)	49.9 (24.3 to 66.6)
SF36-MCS	36.9 (13.1)	38.5 (7.9 to 56.3)	41.9 (10.1)	43.4 (19.1 to 59.1)

Comments

The authors report that the two groups were comparable with all parameters evaluated.

Meeting diagnostic criteria for major depression: n = 81 (97.6 %)

Meeting diagnostic criteria for dysthymia: n = 2 (2.4 %)

MADRS scores consistent with severe depression: n = 28 (34%)

The quality-of-life scores were low compared to normative data on both the physical and mental component subscales.

Inclusion criteria

They must be at least 18 years old, and fullfill DSM-IV and ICD-10 diagnostic criteria for alcohol dependence and for major depression or dysthymia or both, and they must have remained abstinent for at least 2 weeks following detoxification, and had to have a negative drug and alcohol urine screen at inclusion.

Exclusion criteria

(1) Women who were pregnant, breast-feeding or who were of childbearing potential and were not using reliable contraceptive methods or who wished to become pregnant during the study or within a month after the study. (2) Patients with a primary psychiatric disorder apart

Study	Gual, 2003 [20]
	from alcohol dependence and depressive symptoms. (3) Patients with moderate or severe liver disease including active cirrhosis or acute hepatitis. (4) Patients showing a high suicide risk. (5) Patients whom the investigator considered would require therapy with additional psychotropic drugs, electroconvulsive therapy (ECT) or intensive psychotherapy during the study. (6) Patients with a history of convulsive disorders, cerebral organic disease or laxative misuse within the 6 months prior to receiving the test drug. (7) Patients who had received therapy with depot neuroleptics during the 6 months prior to their inclusion in the study. (8) Patients requiring therapy with reserpine, methyldopa, guanetidine or clonidine, or who might require general anaesthesia or drugs that interact with sertraline or any serotonergic drug during the study. (9) Patients with a history of failure on sertraline or any other serotonin reuptake selective inhibitor, either alone or combined with another therapy, for treating the current depressive episode. (10) Patients in whom sertraline therapy was contraindicated. (11) Patients with the following diseases: severe allergies or multiple adverse reactions to drugs, unstable thyroid disease, severe organic diseases, or patients who had suffered severe infections or major surgery one month before their inclusion in the study. (12) Patients considered being insufficiently motivated for the therapy or with other emotional or intellectual problems that might limit the patient's ability to comply with the protocol requirements. (13) Patients who had been involved in other clinical studies within the 6 months prior to the onset of this study or who were involved in such studies simultaneously with this study. (14) Patients who had not undergone a sufficient wash-out period since the administration of previous psychotropic medication. (15) Patients who insisted on giving blood while participating in the study and/or a month after the end of the study. (16) Patients with a prothrombin time out of normal range. **Recruitment & screening** Patients were recruited into the study from those outpatients attending the Alcohol Unit therapeutic programme, and having recently undergone an acute alcohol detoxification. 1758 patients were compatible with entry criteria. 88 were screened. Patients with characteristics known to be determinants of poor outcome were not invited to participate (e.g. patients with associated substance abuse, poor motivation or other psychiatric problems) 83 randomized **Remuneration** NR
Comparison	**Sertraline vs. placebo** **Duration of treatment**

Study	Gual, 2003 [20]
Experimental arm	24 weeks **Follow-ups** Measurements were obtained from study visits scheduled at study weeks: 2, 4, 8, 12, 18 and 24 **Adjunct sertraline (50 to 150 mg / day)** The sertraline dose was initially 50 mg/day and could be titrated up to 150 mg/day over the first 8 weeks at the investigator's discretion. The final doses achieved were not described. The mean (SD) time on sertraline was 141.0 (9.7) days. **Co-interventions** Therapeutic program Not described. It is possible that patients recruited from "Alcohol Unit therapeutic program" after acute alcohol detoxification remained in the program during the trial. Pharmacotherapy Participants could be prescribed benzodiazepines to treat alcohol withdrawal. Disulfiram, acamprosate, and antidepressants other than citalopram were not permitted during the trial.
Control arm	**Placebo (vitamin C), adjunct** Matching packets containing placebo were provided for all possible sertraline dose progressions, so that titration could be performed double-blind. The mean (SD) time on placebo was 143.8 (10.3) days. **Co-interventions** Same as for Experimental arm.
Outcomes	**Substance use** Primary outcomes: Rate of relapse[a], self-reported using a daily diary, collected at study visits (weeks 2, 4, 8, 12, 18 and 24). Secondary outcomes: Rate of treatment failure[b], self-reported using a daily diary, collected at study visits. Abstinence[c] duration, self-reported using a daily diary, collected at study visits. Time to first relapse, self-reported using a daily diary, collected at study visits.

Study	Gual, 2003 [20]
	a- Number of participants who relapsed. Relapse is defined as the intake of an average of 50 g alcohol per day for at least 3 days per week or the single intake of 100 g alcohol in a single dose. b- Failure defined as the occurrence of at least three relapses, as defined above, during the course of the study. c- Abstinence defined as the number of days when less than 50g of alcohol was consumed **Mental health** Primary outcomes: Depressive symptoms: MADRS responder rate defined as ≥ 50% reduction in baseline MADRS score (MADRS, 1979), clinician administered at baseline and study visits. Secondary outcomes: Depressive symptoms: Overall MADRS score (MADRS, 1979), clinician administered at baseline and study visits. Depressive symptoms: Overall HAM-D score (HAM-D, 17-item), clinician administered at baseline and week 24. **Quality of life** Quality of life - PCS (SF-36, Spanish version), clinician administered at baseline and week 24 study visit. Quality of life - MCS (SF-36, Spanish version), clinician administered at baseline and week 24 study visit. **Function** See QoL (SF-36-PCS) above **Mortality** **N**ot assessed **Compliance** NR **Adverse effects** Adverse events, spontaneously reported by the patient or observed by the investigator, were recorded at each study visit, and vital signs measured. All AE were classified according to the WHO–ART system.
Results	**Substance use**

	Sertraline n = 44	**Placebo** n = 39	**p**
Primary outcomes			
Number who relapsed: % (n)	31.8 (14)	23.1 (9)	0.37
Secondary outcomes			

Study | **Gual, 2003 [20]**

Mean time to relapse, days: mean (SD)	153.0 (7.9)	160.6 (8.8)	0.43
Mean cumulative abstinence duration, days: mean (SD)	136.5 (9.7)	140.6 (10.3)	0.86
Cumulative abstinence (% of study duration)	84.9	85.5	0.98

Comments

Median time to relapse > 150 days

For alcohol consumption data, patients with missing assessments at last observation were treated as non-abstinent.

Mental health

Primary outcome

	Intervention (ITT, n = 44)	**Placebo** (ITT, n = 39)
MDRS responders, % (n)	44% (19)	39% (15)

Secondary outcomes

	Intervention (ITT, n = 44)		**Placebo** (ITT, n = 39)	
	Baseline	**Endpoint**	**Baseline**	**Endpoint**
MDRS overall score, M (SD)[a]	22.8 (6.9)	20.9 (8.6)	22.5 (7.9)	14.2 (9.7)
HAM-D overall score, M (SD)[a]	14.1 (5.7)	5.4 (4.5)	13.0 (4.0)	7.5 (5.2)

a- Data presented graphically in figure 1, data extracted with PlotDigitizer. Measures of error not specified in caption or text, we have assumed the figure illustrates mean score and standard deviation.

Comments

In the text the authors state that there was “a significant amelioration of depressive symptoms in both treatment groups as determined by scores on the MADRS and HAM-D scales. There were marginally better outcome in the sertraline group on all measures, but this was not statistically significant.”

Missing data were handled using LOCF.

A subgroup analysis available for the outcome MDRS responders, data not extracted (See figure 2).

Adverse effects

	Setraline n = 44	**Placebo n = 35**	**Global n = 79[a]**
Headache: % (n)	27.3 (12)	28.2 (11)	27.7 (23)
Influenza-like symptoms: % (n)	13.6 (6)	15.4 (6)	14.5 (12)
Dizziness: % (n)	11.4 (5)	12.8 (5)	12 (10)

Study	Gual, 2003 [20]

Dyspepsia: % (n)	13.6 (6)	5.1 (2)	9.6 (8)
Diarrhoea: % (n)	9.1 (4)	7.7 (3)	8.4 (7)
Nausea: % (n)	9.1 (4)	7.7 (3)	8.4 (7)
Procedure (medical/surgical/health service): % (n)	11.4 (5)	5.1 (2)	8.4 (7)
Paresthesia: % (n)	2.3 (1)	10.3 (4)	6 (5)
Back pain: % (n)	6.8 (3)	5.1 (2)	6 (5)
Coughing: % (n)	6.8 (3)	5.1 (2)	6 (5)

a- Data was assessed for all patients having taken study medication.

Loss to follow up

Reasons for premature withdrawal:

	Placebo	**Sertraline**	**Total**
Participants randomized, n	39	44	83
Completed treatment, n (%)	22 (56.4%)	24 (54.6%)	46 (55.4%)
Loss to follow-up, n			11
Protocol violations, n			9
Adverse events, n			6
Withdrawn prior to end of treatment, n (%)	17 (43.6%)	20 (45.4%)	37 (44.6%)

Comments

The authors state that there were no differences in rates of premature study discontinuation or in protocol violations between the two treatment groups.

Comments	Recruitment began in 2007 and finished in 2011 due to exhausting research funds. Targeted sample size was n=220.
Risk of bias	Moderate

AE = adverse effects; **ANOVA** = analysis of variance; **AUD** = alcohol use disorder; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, 4th edition; **HAM-D** = Hamilton Rating Scale for Depression, 17 item; **ICD-10** = International Classification of Diseases, 10th edition; **ITT** = intention to treat; **LOCF** = last observation carried forward; **M** = mean; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **NR** = not reported; **RCT** = randomized controlled trial; **SD** = standard deviation; **SF-36–MCS** = short form health survey, mental composite score; SF-36–PCS = short form health survey, physical composite score; **TLFB** = Time Line Follow Back, self-reported substance abuse; **WHO–ART** = WHO Adverse Reaction Terminology, a dictionary meant to support rational coding of adverse reactions.

Foa et al. 2013

Study: Foa, 2013 [21]

Study design: RCT (single-blind), 4-arm

Intervention: **Pharmacotherapy: Naltrexone**

Co-interventions: PET and supportive counselling

Trial registration: NCT00006489

Country: USA

Setting: Outpatient

Aims: To compare the efficacy of an evidence-based treatment (naltrexone) for alcohol dependence, an evidence-based treatment (PET) for PTSD, and supportive counselling.

Participants: **AUD & PTSD**

Participants with PTSD and alcohol dependence according to DSM-IV

Baseline characteristics

	Group I PET+ naltrexone	Group II PET + placebo	Group III SC + naltrexone	Group IV SC + placebo
n	**40**	**40**	**42**	**43**
Women:n (%)	13 (32.5)	13 (32.5)	16 (38.1)	15 (34.9)
Age: M (95% CI))	40.1 (36.7 to 43.5)	44.7 (41.8 to 47.7)	44.9 (41.8 to 47.9)	41.2 (38.6 to 43.9)
Substance use status				
PDD: M (95% CI)	71.2 (62.5 to 79.9)	78.6 (71.4 to 85.6)	75.4 (67.1 to 83.5)	74.1 (66.4 to 81.8)
Mental health status				
PSS-I: M (95% CI)), % of days	30.3 (27.7 to 32.9)	27.7 (24.7 to 30.8)	27.1 (24.7 to 30.8)	27.5 (25.4 to 29.6)

NS baseline differences.

Inclusion criteria

	(1) current PTSD and alcohol dependence according to DSM-IV, (2) clinically significant trauma-related symptoms, as indicated by a score of at least 15 on the PSS-I; and (3) heavy drinking in the past 30 days, defined as an average of more than 12 standard alcohol drinks per week with at least 1 day of 4 or more drinks determined by the TFBI interview **Exclusion criteria** (1) current substance dependence other than nicotine or cannabis; (2) current psychotic disorder (eg, schizophrenia, bipolar disorder); (3) clinically significant suicidal or homicidal ideation; (4) opiate use in the month prior to study entry; (5) medical illnesses that could interfere with treatment (eg, AIDS, active hepatitis); or (6) pregnancy or nursing **Recruitment & screening** Participants were treatment-seeking individuals recruited through advertisements and professional referrals; numbers screened via telephone = 657, numbers randomized = 165; prior to beginning treatment, participants completed outpatient medical detoxification (≥3 consecutive days of abstinence from alcohol) measured via self-report and breath testing for alcohol; oxazepam was administered as needed to manage symptoms of alcohol withdrawal **Remuneration** NR
Comparisons	**Group I: Naltrexone + PET + SC** **Group II: Placebo + PET + SC** **Group III: Naltrexone + SC** **Group IV: Placebo + SC**
	Duration of treatment 24 weeks **Follow ups** During treatment: weekly until week 12, thereafter biweekly until week 24 Endpoint: week 24 Follow up: weeks 38 (3 months) and 52 (6 months)
Group I	**Naltrexone + PET + SC** <u>Naltrexone</u> With a target dose of 100 mg/day, starting with 50 mg/day for a minimum of 3 days and titrating up within 1 week**.** <u>Prolonged exposure therapy, PET</u>

	PET consisted of 12 weekly 90-minute sessions followed by 6 biweekly sessions and included repeated imaginal exposure and processing the memory, and homework including repeated in vivo exposure to safe situations he/she avoided because of trauma-related distress. Supportive counselling, SC Based on the BRENDA-model, which combines medication management with compliance enhancement techniques based on motivational interviewing. All participants received eighteen 30- to 45-minute sessions of SC, administered by a study nurse. Sessions also included dispensing medication, monitoring compliance, assessing and providing education about alcoholism, and offering support and advice concerning drinking. Visits were weekly during the first 3 months and biweekly during the remaining 3 months.
Group II	**Placebo + PET + SC** Placebo NR Prolonged exposure therapy, PET As for group I Supportive counselling, SC As for group I
Group III	**Naltrexone + SC** Naltrexone As for group I Supportive counselling, SC As for group I
Group IV	**Placebo + SC** Placebo NR Supportive counselling, SC As for group I
Outcomes	**Substance use** Percentage of days drinking alcohol, (TLFB), interview weekly until week 12, thereafter biweekly until week 24, and at week 52 **Mental health** PTSD severity (PSS-I), clinician-rated interview at weeks 0, 4, 8, 12, 16, 20, 24, 38 and 52

Results

Quality of life

Not assessed

Function

Not assessed

Mortality

Not assessed

Compliance

Treatment adherence for prolonged exposure therapy was monitored by 3 doctoral-level clinicians. Of the total prolonged exposure therapy sessions provided, 15% were randomly selected to assess treatment adherence. Adherence to medication and supportive counselling was defined as ≥80% adherence to medication and attendance to supportive counselling.

Adverse effects

Method for collecting information about AE NR.

Substance use

	Group I ITT, n = 40			Group II ITT, n = 40			Group III ITT, n = 42			Group IV ITT, n = 43		
Week	**0**	**24**	**52**	**0**	**24**	**52**	**0**	**24**	**52**	**0**	**24**	**52**
Percent drinking days, mean (95% CI)	71.2 (62.5 to 79.9)	7.3 (1.9 to 12.7)	8.8 (3.3 to 14.3)	78.6 (71.4 to 85.6)	13.4 (5.5 to 21.1)	18.9 (8.8 to 29.1)	75.4 (67.1 to 83.5)	3.5 (0.1 to 6.8)	21.5 (10.6 to 32.4)	74.1 (66.4 to 81.8)	13.2 (7.3 to 19.2)	27.3 (14.7 to 40.0)

Analyses based on hierarchical linear and nonlinear modelling which does not exclude any data (replacement or imputation for missing values is unnecessary).

Comments

At posttreatment, a significant main effect of naltrexone emerged (mean difference = 7.93%, P = .008, d = 0.42) such that patients receiving naltrexone had lower percent drinking days (mean, 5.38%; 95% CI, 2.23% to 8.54%) than patients receiving placebo (mean, 13.29%; 95% CI, 8.45% to 18.12%). At posttreatment, the main effect of prolonged exposure therapy (P = .51) and the interaction of naltrexone × prolonged exposure therapy (P = .53) were not statistically significant. During the 6 months following treatment discontinuation, a significant prolonged exposure therapy × time interaction emerged (P = .01, d = 0.41) such that patients receiving prolonged exposure therapy had a mean change in percent drinking days during follow-up of 3.6% (95% CI, −2.2% to 9.5%), which was not significant, whereas patients not receiving prolonged exposure therapy exhibited a mean increase in percent drinking days during

follow-up of 15.9% (95% CI, 8.8% to 23.1%). The interactions of naltrexone × time (P = .98) and prolonged exposure therapy × naltrexone × time (P = .39) were not statistically significant during follow-up.

Mental health

	Group I ITT, n = 40			Group II ITT, n = 40			Group III ITT, n = 42			Group IV ITT, n = 43		
Week	**0**	**24**	**52**	**0**	**24**	**52**	**0**	**24**	**52**	**0**	**24**	**52**
PSS-I, mean (95% CI)	30.3 (27.7 to 32.9)	12.2 (8.2 to 16.1)	7.9 (4.1 to 11.8)	27.7 (24.7 to 30.8)	13.3 (9.3 to 17.3)	10.8 (6.3 to 15.2)	27.1 (24.7 to 30.8)	15.3 (12.2 to 18.3)	10.9 (7.2 to 14.6)	27.5 (25.4 to 29.6)	15.5 (12.4 to 18.6)	11.1 (8.2 to 14.1)

Analyses based on hierarchical linear and nonlinear modelling which does not exclude any data (replacement or imputation for missing values is unnecessary).

Comments

The main effect of prolonged exposure therapy at posttreatment was not significant (mean difference = 2.63, P = .15, d = 0.23). At posttreatment, the main effects of naltrexone (P = .70) and the interaction of prolonged exposure therapy × naltrexone (P = .80) were also not significant. The interactions of prolonged exposure therapy × time (P = .55), naltrexone × time (P = .66), and prolonged exposure therapy × naltrexone × time (P = .63) were not statistically significant for the follow-up period.

Compliance

	Group I N = 40	Group II N = 40	Group III N = 42	Group IV N = 43
Completed exposure therapy sessions: M (SD)	6.18 (3.86)	6.48 (3.49)	-	-
≥80% adherence to medication and attendance to supportive counselling: N (%)	34 (85%)	34 (85%)	36 (85.7%)	37 (86%)

Differences between groups were not statistically significant (P = 0.99).

Adverse effects

NR per group.

The authors state:" Twelve participants were removed from the study because of serious adverse events (serious suicidal ideation, n = 7; serious medical illness, n = 3; psychotic symptoms, n = 1; death, n = 1; however, none of these events was determined to be related to the study)."

Loss to follow up

Endpoint

53 (32.1%) dropped out overall (n = 165)

Not significantly different between groups (p = 0.67; $\chi^{2\,3}$ = 1.55)

	Group I: 35% Group II: 38% Group III: 31% Group IV: 26% 6-month follow-up Group I: 18 (45%) Group II: 18 (45%) Group III: 23 (55%) Group IV: 13 (30%)
Risk of bias	Moderate

AUD = alcohol use disorder; **PET** = prolonged exposure therapy; **PSS-I** = PTSD Symptom Severity Interview; **PTSD** = posttraumatic stress disorder; **SC** = supportive counselling; **TLFB** = Time-Line Follow-Back, self-reported substance use (time to outcomes).

Han et al. 2013

Study	**Han, 2013 [22]**
Study design	RCT (potential blinding poorly described)
Intervention	**Pharmacotherapy: Aripiprazole** Co-interventions: escitalopram, short education, medications to reduce side effects
Trial registration	NR
Country	Republic of Korea
Setting	Outpatient
Aims	Hypothesized that augmentation therapy of escitalopram with aripiprazole would improve depressive symptoms as well as reduce craving for alcohol and cue-induced brain activity in patients with alcohol dependence compared with treatment with escitalopram alone (craving and brain activity outcomes not extracted by SBU)
Participants	**AUD & MDD** Patients with co-morbid alcohol dependence and major depressive disorder; before and after detoxification, assessed and diagnosed based on the Structured Clinical Interview for DSM-IV **Baseline characteristics** **Aripiprazole + escitalopram** **Escitalopram only** n **17** **18**

	Women: n (%)	7 (41)	5 (28)
	Age: M±SD	39.1±8.8	40.0±6.4
	Education, years: M±SD	11.7±1.6	11.6±3.1
	Substance use status		
	MAST: M±SD	27.2±12.0	25.6±13.5
	Mental health status		
	CGI-S: M±SD	4.5±0.7	4.2±0.8
	BDI: M±SD	32.0±13.1	29.5±10.0

Comment

Baseline assessments were done after a 5-10 day detoxification period. NS baseline differences.

Inclusion criteria

(1) first onset comorbid major depression and alcohol dependence or recurrent psychotropic medication naïve patients with MDD and alcohol dependence; (2) Michigan alcohol screening test (MAST) score >19 for alcohol problems; (3) Beck Depression Inventory (BDI) > 19; (4) impaired behaviors or distress due to maladaptive patterns which are consistent with DSM-IV criteria for MDD.

Exclusion criteria

(1) patients with history or current episode of other Axis I psychiatric diseases; (2) patients with other substance abuse history (except for tobacco); (3) patients with medical illness; (4) patients with claustrophobia

Recruitment & screening

Screening for eligible participants among patients evaluated at the Department of Psychiatry of Chung Ang University Medical Center and Eunpyeong Hospital for co-morbid alcohol problems and MDD; numbers screened = 63, number eligible = 40; number randomized = 35; over a period of 5–10 days, all subjects were detoxified with lorazepam (1–4 mg/day), thiamine (100mg/day orally) and multiple vitamin (containing folate) injection; five patients who could not
complete detoxification were excluded from enrolment before randomization

Remuneration

NR

Comparison

Aripiprazole + escitalopram vs escitalopram

Duration of treatment

6 weeks

Follow ups

Drinking behaviour: 2, 4, 6 weeks

Depressive symptoms: 6 weeks

Experimental arm	**Aripiprazole + escitalopram** Flexible dose of aripiprazole, 5–15mg, and escitalopram, 10–20mg, daily for six weeks; aripiprazole was started at 5 mg/day during the first week and then increased to 15 mg/day; escitalopram was started at 10 mg/day during the first week and then increased to 20 mg/day **Co-interventions** Pharmacological Lorazepam, zolpidem and propranolol as necessary were used for managing tremor, anxiety and insomnia Psychosocial Three-session education regarding the nature and health consequences of alcohol dependence (conducted by a doctor and social worker) and three sessions of individual supportive psychotherapy were provided to all patients during the study period
Comparison	**Escitalopram** Only escitalopram 10–20mg daily for six weeks **Co-interventions** Pharmacological Same as for Experimental arm. Psychosocial Same as for Experimental arm.
Outcomes	**Substance use** Remaining alcohol free (questionnaires), self-report and proxy-report by family members at 6 weeks (proxy reports adopted if disagreement), verified by AST, ALT and GGT Relapse defined as either five or more standard drinks (standard dosage = 50mg/day) on a drinking occasion or drinking on more than five days per week **Mental health** Depressive symptoms (BDI score), at 6 weeks Response to antidepressant treatment was defined as reduction in follow-up BDI scores to less than 50% of initial BDI scores **Quality of life** Not assessed **Function**

Results

Not assessed

Mortality

Not assessed

Compliance

NR if/how compliance was defined and measured

Adverse effects

NR

Substance use

	Aripiprazole + escitalopram (ITT, n = 17) Endpoint	Escitalopram (ITT, n = 18) Endpoint	Test of difference
Remained alcohol free, n	15	14	$\chi 2=0.68$, p=0.66

Mental health

	Aripiprazole + escitalopram (Completers, n = 14) Baseline	Aripiprazole + escitalopram (Completers, n = 14) Endpoint	Escitalopram (Completers, n = 17) Baseline	Escitalopram (Completers, n = 17) Endpoint	Test of difference
BDI, mean±SD	32.1±13.1	16.0±14.9	29.6±2.3	16.9±8.9	F=2.3, p=0.13
CGI-S, mean±SD	4.6±0.8	2.7±1.1	4.2±0.7	2.8±0.8	F=1.1, p=0.30
Responding to antidepressant treatment, n		10		11	β =0.27, SEM=0.17, t=1.5, p=0.15

Comments

Not ITT. Analyses on completers only.

Loss to follow up:

Endpoint, N (%): 4 (11%)

Comments

Data for healthy control group not extracted

Risk of bias

Moderate

AUD = alcohol use disorder; **BDI** = Beck Depression Inventory; **CGI-S** = Clinical Global Impression – Severity; **DSM-IV**: Diagnostic and Statistical Manual of Mental Disorders, 4th edition; **ITT** = intent to treat; **MDD** = major depressive disorder; **NR** = not reported (not relevant); **RCT** = randomized controlled trial; **SD** = standard deviation.

Hernandez-Avila et al. 2004

Study	Hernandez-Avila, 2004 [23]
Study design	RCT, double-blind
Intervention	**Pharmacotherapy: Nefazodone** Co-interventions: manual based psychotherapy
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	This study examined the hypothesis that nefazodone, in conjunction with supportive psychotherapy, is superior to placebo in reducing mood, anxiety, and insomnia symptoms and alcohol consumption among alcohol-dependent subjects with comorbid major depression.
Participants	**AUD & depression** Alcohol-dependent subjects with current major depression; presence of current substance use and psychiatric disorders was determined by using the Structured Clinical Interview for DSM-IV. **Baseline characteristics** **Total n= 41** / **Nefazodone n = 21** / **Placebo n = 20** Women: % — 51 / 52.4 / 50 Age: M (SD) — 42.9 (8.6) / 43.1 (9.0) / 42.7 (8.4) Education level, — / / / High school or less: % — / 42.9 / 50 Collage education: % — / 28.6 / 40 Graduate degree: % — / 28.6 / 10 Employed, % — / 71.5 / 70 Substance use status — / / / Drinks per drinking day: M (SD) — / 8.65 (3.57) / 8.52 (4.26) Drinks per week: M (SD) — / 47.82 (28.95)) / 44.16 (21.39) Mental health status — / / / HAM-D: M (SD) — / 16.33 (2.31) / 17.35 (1.98) SAI: M (SD) — / 51.06 (9.88) / 47.95 (9.45) Comorbidities — / / / Antisocial personality disorder: n (%) — 13 (31.7) Any anxiety disorder: n (%) — 12 (29.3) Dysthymic disorder: n (%) — 11 (24) Comments

Study	Hernandez-Avila, 2004 [23]
	NS baseline differences. **Inclusion criteria** 21 to 65 years of age, able to speak and read English, met DSM-IV criteria for major depression for at least 1 week after discontinuation of heavy drinking and before randomization, scored 17 on the 17-item HAM-D with a score 1 on item 1, met criteria for a current DSM-IV diagnosis of alcohol dependence, and drank an average of 18 drinks per week for men or 14 drinks per week for women, with heavy drinking (5 drinks for men and 4 drinks for women) on at least 1 day/week during the month preceding screening **Exclusion criteria** History of major medical or psychiatric problems other than major depression or an anxiety disorder, had clinically significant baseline laboratory abnormalities or a positive pregnancy test, met current DSM-IV criteria for drug dependence other than for alcohol or nicotine, had a positive urine drug screen, were being treated with disulfiram or naltrexone, were deemed to be a serious suicide risk, or were being treated with any psychotropic drug **Recruitment & screening** Recruited by newspaper advertisement and referrals from area clinicians; number screened = 46; number randomized = 41; after baseline assessment, subjects were entered into a 1-week placebo lead-in period, followed by random assignment; information on detoxification NR **Remuneration** NR
Comparison	**Nefazodone vs placebo** **Duration of treatment** 10 weeks + 1 week placebo lead in period **Follow ups** At baseline, weekly, and at endpoint (for most outcomes)
Experimental arm	**Nefazodone** Initiated at a dose of 100 mg twice daily, titrated up to a maximum dose of 300 mg twice daily; medication was dispensed at each visit; visits weekly for the first 5 weeks and then every other week for 6 weeks **Co-interventions** Psychotherapy

Study	Hernandez-Avila, 2004 [23]
Control arm	All subjects received manual-guided supportive psychotherapy at each study visit for a total of eight sessions **Placebo** Not described **Co-interventions** Psychotherapy As the nefazodone treatment group
Outcomes	**Substance use** Drinking outcomes (TLFB), self-report in interview by blinded assessors, at baseline, weekly, and at endpoint: -Weekly drinking days -Drink/drinking day -Weekly drinks -Weekly heavy drinking days -Drinks per week -Total abstinence GGTP level, at endpoint (provided an objective measure of alcohol consumption during treatment) **Mental health** Depressive symptoms (HAM-D), at baseline, weekly, and at endpoint Anxiety symptoms (SAI), at baseline, weekly, and at endpoint **Quality of life** Not assessed **Function** Not assessed **Mortality** Not assessed **Compliance** Monitored at each visit via tablet counts **Adverse effects** At each visit, using a symptom checklist derived from the Systematic Assessment for Treatment of Emergent Events (SAFTEE)
Results	**Substance use**

Study: Hernandez-Avila, 2004 [23]

	Nefazodone (ITT, n = 21)	Placebo (ITT, n = 20)	Effect size	Test of difference
Primary outcomes	**Average over treatment period**	**Average over treatment period**	**F-statistic**	**p-value**
Weekly drinking days, mean (SD)	2.49 (2.24)	3.72 (1.84)	0.52	0.12
Drinks/drinking day, mean (SD)	3.45 (2.45)	4.47 (2.39)	0.35	0.29
Weekly drinks, mean (SD)	6.52 (7.33)	12.83 (16.48)	NR	0.11
Weekly heavy drinking days, mean (SD)	.23 (.22)	1.4 (1.57)	0.89	0.01
	Rate of improvement	**Rate of improvement**	**Cohen's d**	**p-value**
Total abstinence, n (%)	7 (33%)	3 (15%)	0.45	0.17
	Endpoint	**Endpoint**	**F-statistic**	**p-value**
GGTP concentration (units), mean (SD)	32.5 (27.5)	41.2 (32.1)	NR	0.74

Univariate ANOVA and χ2 or Fisher's exact tests were used to compare treatment groups on continuous and categorical measures, respectively. Mixed model analysis allowed individual trajectories to be estimated even when other data points are missing.

Mental health

	Nefazodone (ITT, n = 21)	Placebo (ITT, n = 20)	Effect size	Test of difference
Primary outcomes	**Average over treatment period**	**Average over treatment period**	**Cohen's d**	**p-value**
HAM-D, mean (SD)	7.05 (5.63)	7.45 (5.39)	0.07	0.82
Secondary outcomes	**Average over treatment period**	**Average over treatment period**	**Cohen's d**	
SAI, mean (SD)	34.00 (9.70)	39.93 (8.71)	0.52	0.11
	Rate of improvement	**Rate of improvement**		

Univariate ANOVA and χ2 or Fisher's exact tests were used to compare treatment groups on continuous and categorical measures, respectively. Mixed model analysis allowed individual trajectories to be estimated even when other data points are missing.

Compliance

Number of capsules ingested/day did not differ between groups [nefazodone, 4.6 (SD, 1.6); placebo, 4.1 (SD, 1.3); p = 0.33]

Adverse effects

Nefazodone-treated subjects experienced more AE over time than those taking placebo (t = 2.0; df = 202; p = 0.05); nefazodone-treated subjects reported non-significantly more gastrointestinal side effects such as nausea, vomiting, and diarrhea [F(1,31) = 3.21; p = 0.08] and neuropsychiatric side effects such as blurred vision, dizziness, and lightheadedness [F(1,31) = 2.91; p = 0.09] than did placebo-treated subjects

Loss to follow up

Endpoint: 41 – 28 = 13 (32%); nefazodone 38%, placebo 25%

Risk of bias: Moderate

AUD = alcohol use disorder; **HAM-D** = Hamilton Rating Scale for Depression; **NR** = not reported (not relevant); **RCT** = randomized controlled trial; **SAI** = Spielberger State Anxiety Inventory; **TLFB** = Time-Line Follow-Back, self-reported substance use (time to outcomes).

Hien et al. 2015

Study	Hien, 2015 [24]
Study design	RCT
Intervention	Seeking Safety with either sertraline or placebo
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	The present study was designed to test the following hypothesis: the combination treatment of Seeking Safety and sertraline would be significantly more efficacious than Seeking Safety and placebo in reducing PTSD and AUD symptoms. An additional exploratory analysis was conducted to examine whether response to treatment was moderated by AUD onset (early vs. late).

Study | **Hien, 2015 [24]**

Participants

Category of population – Individuals with co-occurring posttraumatic stress disorder (PTSD) and alcohol use disorder (AUD)

Baseline characteristics

AUD/SUD diagnoses were considered current if diagnostic criteria were met in the prior 6 months.

Characteristic	Seeking Safety + Sertraline (n = 32)		Seeking Safety + Placebo (n = 37)	
	M	SD	M	SD
Age (years)	42,2	9,8	42,5	8,5
Education (years)	13,7	3,1	13,0	2,0
Age at PTSD onset	28,1	14,4	22,8	13,5
CAPS severity, total	65,8	19,4	59,0	19,2
DDD*	6,8	5,1	6,9	4,7
HDD*	3,3	2,2	2,9	2,4
Prior AUD treatment episodes	1,1	1,9	1,6	4,3

PTSD = posttraumatic stress disorder; DDD = drinks per drinking day; HDD = heavy drinking day (5+ drinks for men, 4+ for women); CAPS = Clinician Administered PTSD Scale; AUD = alcohol use disorder (abuse or dependence); SUD = substance use disorder (abuse or dependence).

* in past 7 days

No differences were found between treatment conditions with regard to alcohol use frequency/severity, PTSD severity, other SUD comorbidities, or demographic characteristics.

Baseline characteristics

Characteristic	**Seeking Safety + Sertraline (n = 32)**		**Seeking Safety + Placebo (n = 37)**	
	n	%	n	%
Women	26	81,3	30	81,1
Race/ethnicity				
African American	16	50,0	25	67,6
Caucasian	10	31,3	6	16,2
Latino	3	9,4	4	10,8
Other	3	9,4	2	5,4
Marital status				
Married	9	28,1	5	13,5
Single	17	53,1	25	67,6

Study	Hien, 2015 [24]				
	Divorced/separated	6	18,8	7	18,9
	Employment				
	Employed	23	71,9	30	81,1
	Unemployed	8	25,0	4	10,8
	Student/retired/disabled	1	3,1	3	8,1
	Past 7-days abstinence rate	3	9,7	4	10,8
	Alcohol dependence	28	87,5	33	89,2
	Alcohol abuse	3	9,4	0	0
	Early onset AUD	13	40,6	16	48,5
	Drug dependence				
	Cannabis	5	15,6	3	8,1
	Cocaine	8	25,0	13	35,1
	Comorbid AUD & SUD	16	50,0	22	59,5
	Lifetime traumatic experience				
	Child physical	14	43,3	18	48,5
	Adult physical	16	50,0	16	42,4
	Child sexual	12	36,7	15	41,2
	Adult sexual	12	36,7	13	35,3
	Accident	19	60,0	27	73,5
	Exposed to violent death	14	43,3	10	26,5
	Current major depression	20	62,5	22	59,5
Inclusion criteria	Inclusion criteria were: 1. Diagnostic and Statistical Manual of Mental Disorders criteria for full PTSD or subthreshold PTSD. 2. DSM-IV-TR criteria for current alcohol dependence or alcohol abuse. Individuals who did not meet criteria for alcohol abuse or dependence were eligible if they reported at least one episode of alcohol misuse (defined as either hazardous alcohol use or binge) during the prior 90 days.				
Exclusion criteria	Exclusion criteria were: 1. advanced stage medical disease as indicated by global physical deterioration and incapacitation, 2. organic mental syndrome, 3. diagnosis of bipolar I or psychotic-spectrum disorders, 4. any disorder which might have made antidepressant treatment hazardous,				

Study	Hien, 2015 [24]
	5. current pregnancy or lactation, 6. history of seizures (not related to alcohol withdrawal), 7. current use or prescription of psychotropic medications by another physician, 8. history of allergic reaction to sertraline, 9. current active suicidal or homicidal ideation, intent, or behavior, 10. age over 65 or under 18, and 11. refusal to be audio and videotaped. Individuals with other SUDs or current major depressive disorder were not excluded
Recruitment & screening	Participants were recruited through newspaper and radio advertisements, flyers, and referrals from outpatient mental health centers. Individuals were screened through a brief telephone interview and then completed a baseline interview where alcohol use, PTSD, and demographic data were collected.
Remuneration	Participants were compensated $30 for the completion of baseline, end-of-treatment, and follow-up assessments. They received $15 at each treatment session with the return of their pill-bottles and completion of weekly assessments.
Interventions	Seeking Safety + sertraline
Duration of treatment	12 weeks
Follow ups	During the intervention phase of the study, participants met weekly with a research assistant for the collection of a urine sample, alcohol breathalyzer test, and self-report assessments of PTSD symptoms, alcohol and drug use, and any adverse events. After the study treatment phase, assessment interviews were conducted by blind independent assessors at end-of treatment, 6- and 12-months posttreatment.
Name of intervention	**Seeking Safety** Seeking Safety (integrated cognitive behavioral therapy) was abbreviated from 25 to 12 core sessions to better fit within a feasible timeframe for community-based outpatient treatment programs. Treatment sessions were delivered in a 60-minute weekly individual format by eight experienced research therapists with rigorous training in the Seeking Safety protocol. **Medication** Matching capsules contained sertraline as well as riboflavin to assess medication adherence. Compliance was also monitored by pill count. Participants receiving sertraline started on 50 mg daily and titrated up to 200 mg daily over a 2-

Study	Hien, 2015 [24]
	week period. Participants continued on their full sertraline dose until the end of the trial and were tapered after unblinding. Other component After baseline assessment and medical clearance, all eligible participants began a one-week, single-blind placebo lead-in phase, during which they met with a trained clinician for a 30–45 minute motivational enhancement session (MET). There was no requirement for abstinence during the lead in phase.
Name of comparison	**Seeking Safety + placebo** Seeking Safety (see above). **Medication** Matching capsules contained placebo as well as riboflavin to assess medication adherence. Compliance was also monitored by pill count. Other component See above
Outcomes	**Substance use** Primary outcomes: Average number of drinks per drinking day in the past 7 days (DDD), number of heavy drinking days in the past 7 days (HDD; five or more drinks per day for men and four or more drinks per day for women are considered heavy drinking days), and self-reported abstinence from alcohol in the prior 7 days and negative breathalyzer tests at follow-up assessments. TLFB was used to assess alcohol use patterns before the start of treatment, weekly during the trial, and at each follow-up timepoint. The SCID-I, a semi-structured interview, was administered at baseline and follow-up points to assess current AUD/SUD diagnoses, age of AUD/SUD onset, and the presence of any other current or past mood disorder. An alcohol breathalyzer test was administered at all study visits in order to measure participants' blood alcohol concentration. **Mental health** Primary outcomes: The main outcome variable for PTSD was CAPS total score, administered at baseline and all follow-up assessments.

Study	Hien, 2015 [24]
Results	The CAPS is a structured, clinical interview for assessing the frequency and intensity of DSM-IV-TR PTSD symptoms, impairments in social and occupational functioning, diagnosis, and overall symptom severity. **Quality of life - NR** **Function - NR** **Mortality - NR** **Compliance** Attended at least half of treatment (six or more therapy sessions and six or more medication visits). Adherence to medication measured by riboflavin levels in weekly urine collection. Compliance was also monitored by pill count. **Adverse effects** Method for collecting information about adverse effects **Substance use**

Drinking HDD	Seeking Safety + sertraline (n = 32)			Seeking Safety + placebo n = 37			Treatment Group Effect (SS+sertraline vs. SS+placebo)		
	n	M	SD	n	M	SD	IRR	95% CI	p
							1,60	0,61, 4,23	.34
Baseline	32	3,13	2,17	37	2,89	2,35			
End of treatment	22	1,05	1,79	25	0,48	1,69			
6-month	22	0,86	1,46	28	0,75	1,53			
12-month	20	0,30	0,47	21	0,24	0,44			

Drinking DDD	Seeking Safety + sertraline (n = 32)			Seeking Safety + placebo n = 37			Treatment Group Effect (SS+sertraline vs. SS+placebo)		
	n	M	SD	n	M	SD	IRR	95% CI	p
							1,38	0,63, 3,04	.42
Baseline	32	7,03	5,00	37	6,89	4,69			
End of treatment	22	2,45	3,00	25	1,40	2,52			
6-month	22	2,41	3,06	28	3,14	4,84			

Study	Hien, 2015 [24]

12-month 20 2,55 3,01 21 2,62 4,63

Drinking Abstinence	Seeking Safety + sertraline (n=32) n	%	Seeking Safety + placebo n = 37 n	%	OR	95% CI	p
					1,54	0,62, 3,83	.35
Baseline	32	9,40	37	10,80			
End of treatment	22	45,50	25	60,00			
6-month	22	54,50	28	46,40			
12-month	20	40	21	57,10			

PTSD = Post-traumatic stress disorder; CAPS = Clinician Administered PTSD Scale; DDD = drinks drinking days; HDD = heavy drinking days; IRR = incidence rate ratio; OR = odds ratio; CI = confidence interval. Drinking outcomes are for previous 7 days. PTSD outcomes were probed at each timepoint after trend-level time-by-treatment interaction. Drinking outcomes were modeled for main treatment effects after no interactions were observed.

Mental health

Outcome	Seeking Safety + sertraline (n = 32)			Seeking Safety + placebo n = 37			Treatment Group Effect (SS+sertraline vs. SS+placebo)		
CAPS total	n	M	SD	n	M	SD	Estimate	95% CI	p
Baseline	32	65,50	20,03	37	59,50	18,97	-	-	-
End of treatment	24	36,25	28,23	25	41,88	29,30	-16,15	-31,18, – 1,13	.04
6-month	21	30,09	20,70	28	37,46	25,88	-13,81	-26,88, -0,74	.04
12-month	21	24,90	19,95	22	31,82	24,44	-12,72	-25,40, – 0,03	.05

Comments

Effect sizes were calculated following guidelines for models employing GEEs and can be characterized as large for end-of-treatment, and medium for 6- and 12-month follow-ups.

Not all participants attended all three follow-up assessments and preliminary data analyses indicated that across each of the dependent variables there was not sufficient evidence to conclude that data was not missing completely at random.

Compliance

Compliant	Seeking Safety + sertraline n = 32	Seeking Safety + placebo n = 37

Study	Hien, 2015 [24]			
	Attendance rates of Seeking Safety sessions	M = 6.7, SD = 4.0	M = 6.0, SD = 4.3	t(67) = 0.71; p = .48
	Attended at least half of treatment (six or more therapy sessions and six or more medication visits)	59,4 %	56,8 %	χ2 (1) = 0.05; p = .83
	Rates of riboflavin detection	46 %	40 %	χ2 (1) = 0.77, p = .44
Adverse effects	NR			
Comments	Three participants were removed due to serious medical illness. These incidents were reported to the study's institutional review boards and none were determined to be study related.			
Loss to follow up	**Lost to follow up % (n)**	**Seeking Safety + sertraline n = 32**	**Seeking Safety + placebo n = 37**	
	End of treatment	12,5 (4)	10,8 (4)	
	6-month	18,7 (6)	2,7 (1)	
	12-month	21,8 (7)	18,9 (7)	
	Included in primary analysis	90,6 (29)	86,5 (32)	
Risk of bias	Måttlig			

AUD = alcohol use disorder; **DDD** = drinks per drinking day; **HDD** = heavy drinking day (heavy defined as ≥ 4 drinks for women and ≥ 5 drinks for men, drink size may need to be defined per article as grams of alcohol where possible*); **NR** = not reported (not relevant); **PTSD** = posttraumatic stress disorder; **RCT** = randomized controlled trial; **SCID** = Structured Clinical Interview for DSM, roman numerals indicate **DSM** version number; **SD** = standard deviation; **SUD** = substance use disorder; **TLFB** = Time-Line Follow-Back, self-reported substance use (time to outcomes).

Hollander et al. 2005

Author	Hollander, 2005 [25]
Study design	RCT (double-blind)
Intervention	Pharmacotherapy: sustained-release lithium carbonate
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	To investigate the efficacy and tolerability of sustained-release lithium carbonate in the treatment of pathological gamblers with bipolar spectrum disorders.

Author	Hollander, 2005 [25]
Participants	**Gambling & bipolar disorder** Adult outpatients with DSM-IV diagnoses of pathological gambling and bipolar spectrum disorder. N = 40 (29 included in analysis)

Baseline characteristics

	Lithium	Placebo
N=	12	17
Women: (n)	6	11
Age: M (SD, range)	40 (8.39)	47.7 (8.08)
Education (n)		
Some high school	0	1
High school graduate	3	9
Some college	5	2
College graduate	4	4
Graduate degree	0	1
Gambling status		
Duration of pathological gambling, yrs: M (SD)	19.17 (8.63)	21.59 (9.28)
Y-BOCS, total score: M (SD)	26.58 (5.76)	25.06 (6.74)
CGI: M (SD)	5.42 (0.79)	5.29 (0.85)
SOGS: M (SD)	13.50 (2.65)	11.56 (3.31)
CARS-M, total score: M (SD)	10.33 (3.85)	10.00 (5.06)
Bipolar diagnosis		
Bipolar II: n	1	5
Cyclothymia: n	9	11
Bipolar NOS: n	1	0
Mental health status		
HAM-D: M (SD)	10.75 (3.91)	10.65 (4.09)
HAM-A: M (SD)	11.08 (4.32)	11.71 (7.23)
Comorbidities: Lifetime SUD		

Author	Hollander, 2005 [25]
	Alcohol: n 6 6 Cannabis: n 4 3 Cocaine: n 2 5 Opioids: n 0 3 Test of differences on demographic or clinical characteristics at baseline NR.
Inclusion criteria	Men and women, ages 18–65, with DSM-IV diagnoses of pathological gambling and bipolar spectrum disorder (bipolar II, bipolar disorder not otherwise specified, or cyclothymia). None of the subjects had ever previously received treatment with mood stabilizers and thus were treatment naive to lithium. Women of childbearing potential or who were less than 2 years postmenopausal were required to use a medically acceptable method of birth control and to have a negative serum pregnancy test before study entry.
Exclusion criteria	Major medical illness; bipolar I subjects; primary diagnosis of schizophrenia, other psychotic disorders, current substance abuse (except nicotine), or other organic mental disorders; patients at serious suicidal risk or those who displayed significant self-injurious behavior; abnormal ECG, liver function, thyroid function, or hematological findings; positive urine drug screens; focal neurological abnormalities.
Recruitment & screening	Recruitment by advertisements in local newspapers. The subjects were interviewed with a self-report Mood Disorder Questionnaire. For subjects who scored 7 or more on the Mood Disorder Questionnaire, diagnoses of pathological gambling were confirmed with the Structured Clinical Interview for DSM-IV and the South Oaks Gambling Screen. 88 subjects were screened, 40 were enrolled and randomly assigned. All subjects were at least 2 weeks free of psychotropic medications (5 weeks for fluoxetine) before entering the study.
Remuneration	NR
Interventions	**Sustained-release lithium vs. placebo**
Duration of treatment	10 weeks
Follow ups	Measurements during treatment: week 0, 1, 2, 3, 4, 6, 8, and 10 Endpoint: week 10
	Sustained-release lithium Administered during the first 2 weeks, according to a fixed titration schedule and the subjects' tolerance. The dosing regimen began with one tablet (300 oral mg in the evening) for the first 4 days, two tablets (300 mg in the morning and 300 mg at 3:00 p.m.) for the next 4 days, and three tablets (300 mg in the morning and 600 mg in the evening) for the

Author	Hollander, 2005 [25]
Outcomes	next 6 days. An unblinded person from the laboratory reported serum lithium levels of <0.6 or >1.2 meq/liter to the clinician so that the dose of the study drug could be adjusted appropriately. During the last 4 weeks of the trial, the dose was maintained at a constant level. No other psychoactive medications were allowed during the study. **Placebo** Matching placebo delivered as for active arm. **Gambling** Primary outcomes: Gambling (Y-BOCS, pathological gambling section), week 0, 1, 2, 3, 4, 6, 8, and 10 Gambling (CGI, pathological gambling improvement scale), week 0, 1, 2, 3, 4, 6, 8, and 10 Secondary outcomes: Gambling severity (pathological gambling Behavioral Self-Report Scale), self-reported, week 0, 1, 2, 3, 4, 6, 8, and 10 **Mental health** Depressive symptoms (HAM-D17), week 0, 1, 2, 3, 4, 6, 8, and 10 Affective instability (CARS-M), clinician rated, week 0, 1, 2, 3, 4, 6, 8, and 10 Anxiety symptoms (HAM-A), week 0, 1, 2, 3, 4, 6, 8, and 10 Impulsivity severity (BIS), week 0, 1, 2, 3, 4, 6, 8, and 10 **Compliance** A pill count of unused tablets was made at each visit (week 0, 1, 2, 3, 4, 6, 8, and 10) to help assess and reinforce compliance. Patients who missed more than 3 days of medication in any given treatment week or more than 10 days of medication during the entire treatment duration were dropped from the study. **Adverse effects** Clinician and self-ratings and adverse events were recorded by means of patients' spontaneous reports of adverse events. At baseline (week 0) and at the end of weeks 1, 2, 3, 4, 6, 8, and 10.

Author	Hollander, 2005 [25]					
Results	**Gambling**					
		Lithium ITT, n = 18 **Endpoint**	**Placebo** (ITT, n = 22 **Endpoint**	**Between groups analysis Endpoint**	**p-value**	**Between groups analysis 1-10 weeks**	**p-value**
	Primary outcomes						
	Y-BOCS, total score*			F(1, 39)=7.03	p<0.02	F(1,37)=4.57	p<0.04
	CGI*			F(1, 38)=7.37	p=0.01	F(1,36)=7.81	p=0.008
	Responder (≥35% reduction on Y-BOCS score and "much/very much" improved on CGI*	11 (69%)	5 (31%)	$X^2(1)=6.08$	p<0.02		
	Secondary outcomes	Completers n = 12	Completers n = 17				
	Pathological gambling Behavioral Self-Report Scale, change in money lost per week (dollar): M (SD)	170.33 (197.24)	317.94 (541.29)	F(1,28)=1.11	NS		
	Pathological gambling Behavioral Self-Report Scale, change in gambling episodes per week: M (SD)	6.17 (6.18)	3.41 (5.01)	F(1,28)=2.18	NS		
	Pathological gambling Behavioral Self-	86.25 (96.69)	149.35 (227.70)	F(1,28)=2.56	NS		

Author	Hollander, 2005 [25]

Report Scale, change in time spent per episode (minutes): M (SD)

Data NR NS

Comments

*ITT-analyses with LOCF, main effect of treatment

Mental health

	Lithium (completers, n = 12)	Placebo (completers, n = 17)	Between groups analysis		Betwee analysis
Secondary outcomes	**Endpoint**	**Endpoint**	**Endpoint**	**p-value**	**1-10 we**
HAM-D			Data NR	NS	
HAM-A			Data NR	NS	
CARS-M, change score: M (SD)	6.58 (3.99)	3.88 (2.98)	F(1,28) = 4.82	<0.04	
BIS among responders, reduction in nonplanning impulsivity	t=2.75, df=9, p<0.02	t=0.93, df=3, p=0.42	NR		NR
BIS among responders, reduction in cognitive impulsivity	t=–1.07, df=9, p=0.31	t=–0.25, df=3, p=0.82	NR		NR
BIS among responders, reduction in motoric impulsivity	t=–0.41, df=9, p=0.69	t=0.76, df=3, p=0.50	NR		NR

Comments

* Notes

Compliance

	Lithium n = 12	**Placebo n = 17**
Nonadherence to protocol: n (%)	0 (0%)	2 (12%)

Adverse effects

	Lithium n = 12	**Placebo n = 12**
Dry mouth: n	2	1

Author	Hollander, 2005 [25]		
	Nausea: n	1	0
	Diarrhea: n	1	1
	Sedation: n	2	1
	Polyurea: n	1	0
	Weight gain: n	0	1
	Tremor: n	0	2
Comments	By authors: There were no clinically meaningful differences in side effects between the lithium and placebo groups over the 10-week trial		
Loss to follow up	Endpoint: Lithium 6 (33%), placebo 5 (23%), p=0.50, Fisher's exact test.		
Comments			
Risk of bias	Low		

BIS = Barratt Impulsiveness Scale; **CARS-M** = Clinician-Administered Rating Scale for Mania; **CGI** = Clinical Global Impression; **DSM-IV-TR**: Diagnostic and Statistical Manual of Mental Disorders, 4th revision (text revision); **HAM-D** = Hamilton Rating Scale for Depression; **LOCF** = last observation carried forward; **NR** = not reported (not relevant); **RCT** = randomized controlled trial; **SOGS** = South Oaks Gambling Screen; **Y-BOCS** = Yale-Brown Obsessive Compulsive Scale.

Kleber et al. 1983

Author	**Kleber, 1983 [26]**
Study design	double-blind placebo-controlled clinical trial
Intervention	Imipramine, as adjunct to methadone maintenance program
Trial registration	NR
Country	Connecticut, USA
Setting	Outpatient
Aims	To evaluate the efficacy of imipramine as treatment for depression in methadone-maintained patients with opioid dependence.
Participants	**Opioid dependence, depression** The subjects were 46 patients with opioid dependence who had received methadone for a minimum of three months in one of two clinics in Connecticut. Patients met criteria for MDD according to DSM-II.
Baseline characteristics	**Total** / **Treatment** / **Comparison** N= 46 / 23 / 23 Women: % (n) 42% (19) Age: M (SD, range) 29 (NR) High school education or lower 78% Housing situation NR Unskilled or semiskilled occupation group 100% Comorbidities NR
Inclusion criteria	Subjects had received methadone for at least 3 months. They were also experiencing an episode of depression according to DSM-II criteria lasting at least two weeks and a current Raskin Depression Scale15 score of 7 or greater. (Although DSM-III was not available when the study was done, review of the charts indicated the patients would have met DSM-III MDD)
Exclusion criteria	Exclusion criteria included a diagnosis such as heart disease or liver disease.
Recruitment & screening	All patients who had received methadone for at least 3 months as part of a methadone maintenance program delivered by either of two dispensary clinics were screened for depression using a brief, self-reported screening instrument (the Center for Epidemiological Studies Depression Scale). A psychiatrist evaluated subjects with elevated symptoms (score > 15) who were interested in participating in the trial to establish whether they met depression inclusion criteria.
Remuneration	NR

Author	Kleber, 1983 [26]
Interventions	**Imipramine HCl vs placebo**
Duration of treatment	8 weeks
Follow ups	Measurements were made at baseline, weekly, and at the time of last treatment visit (max 8 weeks)
	Imipramine HCl Imipramine hydrochloride was administered once daily in flexible doses in multiples of 75 mg which was the contents of each tablet (the initial dose was 75 mg, which was raised to 150 or 225 mg after subsequent weekly evaluations in relation to treatment response and/or side effects). The average dose at the end of the study was 139.4 mg Authors remark that many subjects dropped out of treatment before higher doses could be given. Methadone maintenance program Mandatory group therapy, 90-minute, 1x / week co-led by a psychiatric nurse and a counselor Optional individual counseling by same staff as in group therapy, as-needed (authors do not mention methadone) **Placebo** Inert placebo was administered similarly (to imipramine HCl) The pills taken would have equalled a "dose" of 149.7 mg Methadone maintenance program Same as for imipramine HCl
Outcomes	**Substance use** Illicit drug use (urine analysis), clinician rated, number of positive tests, weekly **Mental health** Symptoms of depression (HAMD, range 0 to 64), clinician rated, weekly Symptoms of depression (Raskin Depression Scale, range 0 to 15), clinician rated, weekly Symptoms of depression (BDI, range 0 to 39), self-reported, weekly General psychologic symptoms (Symptom Check list, range 0 to 360), self-reported, weekly Global improvement rating scale (range 1 to 5), self-rated, weekly Global improvement rating, psychiatrist, at week 8 **Quality of life** Not assessed

Author

Kleber, 1983 [26]

Results

Function

Social functioning (Social adjustment scale report, range 0 to 4) self-rated, weekly

Mortality

Not assessed

Compliance

Medication compliance not assessed

Adverse effects

Measured with a side effects scale evaluating 32 potential medication-related symptoms, self-reported, weekly

Substance use

	Intervention (mITT*)	Imipramine-HCl (mITT*)	Between group differences**
Illicit drug use	**Endpoint**	**Endpoint**	**Significance of difference**
	n= 22	n= 22	
Proportion of urine specimens tested that contained illicit substances per number of days in the study, mean* **	0.03	0.02	NS

Comments

* mITT refers to modified ITT: To be included in the efficacy data analysis, subjects were required to have completed at least one week of study treatment and to have taken the medications prescribed during the week; 44 of 46 randomized were assessed, 22 per treatment group. Analyses used the last measure obtained as the endpoint value for early terminators (assumes no further improvement).

** Assessed using analysis of covariance, controlling for levels of initial ratings.

*** No measure of variance reported

Mental health

	Imipramine-HCl (mITT*)		Placebo (mITT*)		Between group differences**
Primary outcomes	**Baseline**	**Endpoint**	**Baseline**	**Endpoint**	**Significance of difference**
	n=23	n= 22	n=23	n= 22	
Symptoms of depression (HAMD scores), mean* **	20.1	10.1	19.5	11.2	NS
Symptoms of depression (self-rated global improvement), mean* **	-	2.9	-	3.1	NS
Symptoms of depression (BDI scores), mean* **	15.1	10.2	13.3	10.4	NS

Author	Kleber, 1983 [26]
	Symptoms of depression (RDS scores), mean* ** 8.7 5.8 8.2 5.9 NS **General psychologic symptoms (Symptom Check list scores), mean*** ** 226.0 173.6 221.1 176.7 NS
Comments	* mITT refers to modified ITT: To be included in the efficacy data analysis, subjects were required to have completed at least one week of study treatment and to have taken the medications prescribed during the week; 44 of 46 randomized were assessed, 22 per treatment group. Analyses used the last measure obtained as the endpoint value for early terminators (assumes no further improvement). ** Assessed using analysis of covariance, controlling for levels of initial ratings. *** No measure of variance reported Psychiatrist rated global improvement reflects only those participants who attended the final follow-up, therefore the data was not extracted.
Adverse effects	**Function** Social functioning: data not extracted. Analysis appears to be per protocol. Subjects in the imipramine group reported significantly (P<.05) higher symptom levels for 2 of the 32 side effects monitored: visible tremor and dry mouth There was no between group differences for the other 30 symptoms monitored.
Comments	No subjects cited medication side effects as a reason for drop out.
Loss to follow up, retention to treatment	Completed 8 weeks of therapy: I: 57% (n=13) C: 48% (n=11) Met with psychiatrist for final assessment*: I: 61% (n=14) C: 65% (n=15) Length of treatment, mean days: I: 38.5 C: 39.1 (max number of days = 56) “Timing of attrition was comparable in the two groups” Withdrawals: I: 43% C: 52% Reasons for withdrawal: I: 22% voluntary withdrawals, 21% were symptomatic failures** C: 43% voluntary withdrawals, 9% were symptomatic failures**
Comments	* Some participants appear to have remained in contact with the study clinicians despite having terminated treatment before the end of the trial.

Author	Kleber, 1983 [26]
General comments	** Symptomatic failures included those whose psychological symptoms were too severe to continue study treatment or those who were discharged from methadone maintenance due to disciplinary reasons related to relapse or illicit drug use. Retention to treatment and reasons for withdrawal included under loss to follow up
Risk of bias	Moderate Randomization and blinding not described High loss to follow up, uneven between groups, often very early so last measure carried forward may have effected results No protocol

BDI = Beck Depression Inventory; **DSM =** Diagnostic and Statistical Manual of Mental Disorders, roman numerals indicate version number; **HAMD**= Hamilton Depression Rating Scale; **MDD** = major depressive disorder; **NR** = not reported (not relevant); **RDS** = Raskin Depression Scale.

Konstenius et al. 2014

Study	Konstenius, 2014 [27]
Study design	RCT (double-blind)
Intervention	**Pharmacotherapy: methylphenidate (MPH)** Co-intervention: psychotherapy
Trial registration	ISRCTN77940178
Country	Sweden
Setting	First 2 weeks inpatient (at three prisons), outpatient after release; the study was carried out in the Stockholm region
Aims	To test the efficacy and safety of osmotic release oral system (OROS) MPH in doses up to 180 mg/day to treat ADHD and prevent any drug relapse in individuals with a co-diagnosis of ADHD and amphetamine dependence.
Participants	**Amphetamine dependence & ADHD** Male criminal offenders with ADHD and amphetamine dependence according to DSM-IV criteria **Baseline characteristics**

	MPH	Placebo
n	**27**	**27**
Men: n (%)	27 (100%)	27 (100%)
Age: M (SD)	41 (7.5)	42 (11.7)
Education, years: M (SD)	9.6 (2.2)	9.6 (1.9)

Study	Konstenius, 2014 [27]

Homeless: n (%)	11 (41%)	10 (37%)
Substance use status		
Amphetamine use by injection, n (%)	24 (89%	25 (93%)
Amphetamine use (years) life-time, mean (SD) years	20.6 (10.2)	18.3 (12.7)
Mental health status		
OQ45 score mean (SD)	111.5 (3.7)	114.8 (3.6)
ADHD measures: n (%)		
Inattentive subtype	4 (15%)	3 (11%)
Hyperactive subtype	3 (11%)	5 (19%)
Combined subtype	20 (74%)	19 (70%)
Co-morbidity (SCID):		
Axis I diagnosis, n (%)	21 (96%)	16 (76%)
Axis II diagnosis, n (%)	19 (70%)	15 (56%)

Comments

There were no significant differences on demographic or clinical characteristics at baseline.

Inclusion criteria

Met the diagnostic criteria for ADHD according to the DSM-IV and the DSM-IV diagnostic criteria for amphetamine dependence during the last 12 months prior to the current incarceration, and had used amphetamines on a minimum of 12 occasions during the last 12 weeks preceding the incarceration

Exclusion criteria

(i) DSM-IV diagnosis of any other substance dependence except nicotine, currently or during the 12 months prior to incarceration, (ii) a major psychiatric disorder (e.g. schizophrenia, severe depression), (iii) current antipsychotic medication, (iv) current use of benzodiazepine, (v) traces of any of the following substances in urine: amphetamine, benzodiazepine, cannabis, cocaine, dextropropoxyphene and opiates, (vi) serious somatic disease (e.g. moderate to severe hypertension >150/95 mm Hg, hyperthyroidism) and (vii) known hypersensitivity to methylphenidate.

Recruitment & screening

Participants were recruited from medium security prisons in Sweden; numbers initially assessed for eligibility = 168; numbers screened = 156; numbers assessed for ADHD = 83; numbers randomized = 54; patients were required to abstain from any illicit substances during the 2 weeks preceding the inclusion, verified by patient self-reports and supervised urine toxicology

Remuneration

Study	Konstenius, 2014 [27]
	The participants received no financial compensation.
Comparison	**Methylphenidate (MPH) vs placebo** **Duration of treatment** 24 weeks **Follow ups** Measurements during treatment: Varying between outcomes, from once or twice weekly, to every four weeks, or at baseline, weeks 12 and 24 Endpoint / time of last treatment: At 24 weeks
Experimental arm	**Methylphenidate (MPH)** Medication started 14 days before release from prison and continued for 24 weeks; start dose was 18 mg MPH titrated over a period of 19 days (with 36 mg increments every 3 days), to a maximum dose of 180 mg/day, or as tolerated; to enhance compliance, the subjects were picked up by a prepaid taxi at the prison gate on the day of their release and taken to the out-patient clinic, where they received study medication for 2–4 days and were asked to provide a supervised urine specimen; participants visited the clinic twice weekly for study medication and supervised urine sampling **Co-intervention** CBT, psychotherapy Once weekly, for the first 12 weeks, the participants attended individual manual-based cognitive–behavioural therapy sessions targeting relapse
Control arm	**Placebo** Administered as the for the treatment group **Co-intervention** CBT, psychotherapy As the treatment group
Outcomes	**Substance use** Primary outcome: Relapse to any drug use, amphetamine and other drugs (the proportion of urine samples negative for drugs of abuse), twice weekly Secondary outcomes: Time (days) to relapse, (first positive urine)

Study

Konstenius, 2014 [27]

Results

Mental health

Secondary outcomes:

Change in self-reported ADHD symptoms (CAARS:SV), once weekly for the first 6 weeks, and once every 4 weeks thereafter

ADHD symptom severity and improvement (seven-point CGI), clinician-rated, at baseline, 12 and 24 weeks

Psychiatric symptoms (OQ45), at baseline, 12 and 24 weeks

Quality of life

Not assessed

Function

Not assessed

Mortality

Not assessed

Compliance

For the MPH group, compliance was verified by analysing MPH in the urines at the end of the trial

Retention to treatment (number of days to last visit at the clinic; proportion visiting the clinic at week 24)

Adverse effects

Weekly, using a standardized form

Substance use

	MPH (ITT, n = 27)	Placebo (ITT, n = 27)	Effect size	Test of difference
Primary outcomes	**Md over the study time**	**Md over the study time**	**r**	**p-value**
Proportion of drug-negative urines (any drugs), Md	23%	16%	0.27	0.047
Secondary outcomes				
Proportion of amphetamine-negative urines, Md	23%	14%	0.32	0.019
Proportion of other drug-negative urines, Md	44%	29%	0.29	0.032
Time (days) to first positive urine, any drug, Md	29	15	0.39	0.004
Time (days) to first positive urine, amphetamine, Md	25	16	0.42	0.002

For repeated measures, missing data were completed using the LOCF method. Missing samples or refusal to provide a sample were recorded as positive.

Mental health

	MPH (ITT, n = 27)	Placebo (ITT, n = 27)	Test of difference
Secondary outcomes	**Endpoint**	**Endpoint**	**p-value**

Study	Konstenius, 2014 [27]

CAARS-score, mean*	23.90	30.14	0.002
			0.011
Decreased symptoms of inattention or hyperactivity by at least 30% (CAARS): n (%)	17 (65%)	7 (27%)	0.012
Clinician-rated CGI-S	Data NR	Data NR	NS
Other psychiatric symptoms	Data NR	Data NR	NS

*Extracted from Figure 2: Change in self-rated ADHD symptoms (95% CI = −13.78 to −1.91, p = 0.011), not consistent with value reported in text for all ADHD symptoms (95% CI = −14.18 to −3.28, df = 50, p = 0.002)

Comments

In text: Compared to the placebo group, the MPH group showed significantly greater improvement in CAARS:SV:

- all ADHD symptoms: 95% CI = −14.18 to −3.28, df = 50, p = 0.002
- inattention: 95% CI = −7.0 to −1.59, df = 50, p = 0.026
- hyperactivity: 95% CI = −6.95 to −1.59, df = 50, p = 0.002

Compliance

Compliant	MPH n = 27	Placebo n = 27	Test of difference
% MPH-positive urine samples: M (SD)	0.83 (0.25)	NR	NR
Completed the titration period: n (%)	21 (79%)	16 (59%)	NR
Retention to treatment, days: Md	51	18	HR 0.38, 95% CI 0.174 to 0.647, p = 0.001, r = 0.44
Retention to treatment: Clinic visit at week 24: %	29%	7.4%	NR

Adverse effects

Most frequent AE of 23 reported:	MPH n = 27	Placebo n = 27
Headache: n	6	2
Abdominal discomfort: n	6	1
Sleep problems: n	6	2
Loss of apetite: n	7	0
Depressed mood: n	3	4
Increased blood preassure: n	2	4
Sweating: n	5	1

Comments

Authors state that AE were generally mild to moderate.

Loss to follow up

Endpoint: Did not complete trial MPH, N = 17 (63%), placebo, N = 23 (85%)

Study	Konstenius, 2014 [27]
Risk of bias	Low

CAARS:SV = Conners' adult ADHD self-rating scale; **CBT** = cognitive behavioral therapy; **CI** = confidence interval **DSM-IV-TR**: Diagnostic and Statistical Manual of Mental Disorders, 4th revision (text revision); **LOCF** = last observation carried forward; **MD** = median; **MPH** = methylphenidate; **NR** = not reported (not relevant); **OQ45** = Outcome Questionnaire 45; **RCT** = randomized controlled trial.

Kranzler et al. 2006

Study	Kranzler, 2006 [28]
Study design	RCT, double-blind, multi-center
Intervention	**Pharmacotherapy: Sertraline** Co-interventions: supportive therapy for abstinence and compliance support
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	To evaluate (stratified by HAM-D score below or above 17 at randomization) the safety and efficacy of sertraline in patients with co-occurring MDD and AD in a typical outpatient setting where, after only a brief period of abstinence, antidepressants are often prescribed to depressed alcohol dependent patients.
Participants	**AD & MDD** **Baseline characteristics**

	HAM-D ≥17 Sertraline	HAM-D ≥17 Placebo	HAM-D ≤16 Sertraline	HAM-D ≤16 Placebo
n	**89**	**100**	**70**	**69**
Women: %	34%	36%	34%	42%
Age: M (SD)	41.7 (9.4)*	44.0 (8.0)*	41.8 (9.4)	42.9 (9.2)
Education level: attended college	74.2%	69.0%	71.4%	78.3%
Substance use status				
No. DSM-IV AD symptoms: M (SD)	5.6 (0.9)	5.5 (0.9)	4.6 (1.2)	4.5 (1.0)
Drinks per week: M (SD)	45.9 (32.2)*	63.1 (44.4)*	54.4 (40.5)	46.8 (27.9)
Mental health status				

Study	Kranzler, 2006 [28]

No. DSM-IV MDD symptoms: M (SD)	6.7 (1.0)	6.8 (1.2)	5.3 (1.3)	5.4 (1.1)
HAM-D17, total score: M (SD)	20.3 (2.8)	20.9 (4.0)	12.6 (2.8)	12.5 (2.9)
CGI depression score: M (SD)	4.3 (0.7)*	4.5 (0.8)*	3.7 (0.5)	3.7 (0.6)

* Significant baseline differences.

Inclusion criteria

Outpatients, 21 to 65 years old, with a modified DSM-IV diagnosis of MDD (i.e., all met DSM-IV criteria for MDD, except that symptoms could have occurred during a period of heavy alcohol use) and a current DSM-IV diagnosis of AD; at screening, all patients had a total score of ≥17 on the 17-item HAM-D; drunk an average of ≥18 drinks weekly for men or ≥14 drinks weekly for women; at least one heavy drinking day per week (i.e., ≥5 drinks on one occasion for men and ≥4 drinks on one occasion for women) during the month before screening.

During the placebo lead-in period, patients had to report at least 4 days with no heavy drinking to allow alcohol-induced depressive symptoms to diminish; however, no more than 16 days of abstinence could elapse before randomization

Exclusion criteria

Pregnant or nursing or women of childbearing potential not using an effective method of contraception; clinically significant co-occurring psychiatric or medical diagnoses, including dependence on any psychoactive substance other than alcohol or nicotine during the preceding year; current treatment with disulfiram, naltrexone, or psychotropic medication; serum aminotransferase levels or other measures of hepatic function that were greater than 250% of normal; patients with significant suicidal risk

Recruitment & screening

From the community using announcements and advertisements and from the pool of patients seeking alcohol treatment at the 13 participating sites; numbers screened = NR; numbers randomized = 345

After screening, eligible patients were placed on a single-blind placebo lead-in for 7 to 14 days, during which baseline assessments were administered (the duration varied with the individual's capacity to sustain non-hazardous drinking); Randomization was stratified, based on whether initially elevated scores on the 17-item HAM-D declined with cessation of heavy drinking

Remuneration

NR

Comparisons

Sertraline vs placebo

Duration of treatment

Study	Kranzler, 2006 [28]
	10 weeks **Follow ups** Measurements during study visits at weeks 1,2,3,4,6,8 and 10 Endpoint: week 10 Follow-up: NR
Experimental arm	**Sertraline** Medication was dispensed in bottles with MEMS caps, which contain an electronic monitoring device that records the date and time of bottle cap openings; the starting dose was 50 mg, a dose level that was maintained until the end of week 1; if no dose-limiting side effects, the dose was increased at weekly intervals by 50 mg to a maximum of 200 mg daily; if the maximum dose was not achieved by week 4, it could be increased during the final 6 weeks of the study to the maximum dose; decreases in the dose because of AE were possible throughout the study period; responders who wished to continue treatment beyond the end of week 10 were continued double-blind on the same medication for an additional 14-week period; patients who did not continue in the extension study were tapered off medication by reducing the daily dose by one capsule every 2 to 3 days until completely discontinued; patients were instructed to abstain from alcohol and psychoactive substances (except nicotine) during the study **Co-interventions** <u>Supportive therapy</u> General support for abstinence, promotion of compliance, and monitoring of medication side effects at each study visit.
Control arm	**Placebo** Dispensed as in the treatment group; following the same protocol as the treatment group, with a starting dose of one tablet, increased weekly by one tablet to a maximum of 4 tablets daily; instruction to abstain from alcohol and psychoactive substances (except nicotine) during the study **Other component** (supportive therapy) Same as for Experimental arm.
Outcomes	**Substance use** Percent days abstinent (TLFB), at weeks 1, 2, 3, 4, 6, 8, and 10 Standard drinks per week (TLFB), at weeks 1, 2, 3, 4, 6, 8, and 10 No. of AD symptoms (DSM-IV AD checklist), at weeks 2, 4, 8, and 10

Study

Kranzler, 2006 [28]

Mental health

Depressive symptoms (HAM-D), at weeks 1, 2, 3, 4, 6, 8, and 10

Symptom severity (CGI), at weeks 1, 2, 3, 4, 6, 8, and 10

No. of MDD symptoms (DSM-IV MDD checklist), at weeks 2, 4, 8, and 10

Depressive symptoms (BDI), at weeks 4 and 10

Quality of life

Not assessed

Function

Not assessed

Mortality

Not assessed

Compliance

Used computerized medication containers to monitor medication adherence; a urine drug screen was performed at week 2 visit to assess compliance with abstinence from psychoactive substances

Adverse effects

Method for collecting information about adverse effects unclear

Results

Substance use

	HAM-D ≥17 Sertraline N = 89	HAM-D ≥17 Placebo N = 100	HAM-D ≥17 Test of difference,	HAM-D ≤16 Sertraline N = 70	HAM-D ≤16 Placebo N = 69	HAM-D ≤16 Test of difference	HAM-D ≥17 Test of difference, across the 10-week study	HAM-D ≤16 Test of difference, across the 10-week study
	At week 10	**At week 10**	**p-value**	**At week 10**	**At week 10**	**p-value**		
Percent of days abstinent from alcohol: M (SD)*	75,1% (3,8%)	78.2 %	ns	80.6% (3.8%)	81.2 %	ns		

Study	Kranzler, 2006 [28]					
		(3.5%)	(3.6%)			
	Difference between sertraline and placebo in percent of days abstinent: M (95% CI)			-3.5% (-10.7 to 3.7), p = 0.34	-3.2 (-11.0 to 4.8), p = 0.43	
	Difference between sertraline and placebo in standard drinks per week: M (SD)			ns (data NR)	ns (data NR)	

*Extracted by SBU from Figure 2.

Comments

All analyses used a mITT approach. 17 people were lost to follow up before any post-baseline measures were taken and were not included in analyses. Weekly comparisons included only subjects for whom data was available for that visit. End of study analyses used LOCF analysis. Analysis of covariance adjusted for baseline values and for treatment center.

Standard drinks per week (TLFB): NR

No. of AD symptoms (DSM-IV AD checklist): NR

Mental health

	HAM-D ≥17 Sertraline N = 89	**HAM-D ≥17 Placebo N = 100**	**HAM-D ≥17 Test of difference,**	**HAM-D ≤16 Sertraline N = 70**	**HAM-D ≤16 Placebo N = 69**	**HAM-D ≤16 Test of difference**
	Across the 10-week study	**Across the 10-week study**	**p-value**	**Across the 10-week study**	**Across the 10-week study**	**p-value**
Change in HAM-D score: M (SD)	-10.8 (6.5)	-9.6 (7.8)	0.14	-6.0 (5.4)	-7.2 (5.7)	0.15
50% reduction in HAM-D score: % (N)	64% (57)	47% (47)	0.022	58% (41)	77% (53)	0.018
Change in BDI score: M (SD)	NR	NR	0.69	NR	NR	0.55
	Week 10	**Week 10**		**Week 10**	**Week 10**	
Endpoint HAM-D: M (SD)*	7.1 (5.8)	8.6 (6.5)		5.4 (3.9)	4.5 (3.9)	

*Extracted from Figure 1.

Comments

All analyses used a mITT approach. 17 people were lost to follow up before any post-baseline measures were taken and were not included in analyses. Weekly comparisons included only subjects for whom data was available for that visit. End of study analyses used LOCF analysis.

Study | **Kranzler, 2006 [28]**

Symptom severity (CGI): NR

No. of MDD symptoms (DSM-IV MDD checklist): NR

Compliance

	HAM-D ≥17 Sertraline N = 89	HAM-D ≥17 Placebo N = 100	HAM-D ≤16 Sertraline N = 70	HAM-D ≤16 Placebo N = 69
Medication-adherent (≥80% of doses taken): %	74.4	73.8	75.7	76.5
Duration of double-blind treatment, days: M (SD)	62.4 (27.5)	66.6 (22.9)	64.2 (25.8)	69.9 (22.8)

Comments

mITT: 17 people were lost to follow up before any post-baseline measures were taken and were not included in analyses.

Adverse effects

Worsening of clinical condition because of…	Sertraline N = 89+70	Placebo N = 100+69
Alcoholic relapse: n	7	2
Depression: n	1	1
Suicidal ideation or attempt: n	1	3
Chest pain: n	0	1
Blood in the stool: n	1	0
Syncope: n	0	1

Comments

A significantly greater number of sertraline-treated patients (n = 20) than placebo-treated patients (n = 10) discontinued treatment because of adverse events (x2 1 = 3.84, P < 0.05).

Loss to follow up

	HAM-D ≥17 Sertraline N = 89	HAM-D ≥17 Placebo N = 100	HAM-D ≤16 Sertraline N = 70	HAM-D ≤16 Placebo N = 69
Not completing the study: % (N)	42% (37)	44% (44)	44% (31)	22% (15)

Study	Kranzler, 2006 [28]
Risk of bias	Comments mITT: 17 people were lost to follow up before any post-baseline measures were taken and were not included in analyses. Moderate

AD = alcohol dependence; **BDI** = Beck Depression Inventory; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, version four; **HAM-D** = Hamilton Rating Scale for Depression; **CGI** = Clinical Global Impression; **LOCF** = last observation carried forward; **M** = mean; **MDD** = major depressive disorder; **mITT** = modified intention to treat; **NR** = not reported; **RCT** = randomized controlled trial; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report.

Levin 2015

Study	Levin, 2015 [29]
Study design	RCT, double-blind, 3-arm, placebo-controlled
Intervention	**Pharmacotherapy: XR-mixed amphetamine salts** Co-interventions: CBT/RP
Trial registration	NCT00553319
Country	USA
Setting	Outpatients
Aims	To examine whether treatment of co-occurring ADHD and cocaine use disorder with extended-release mixed amphetamine salts is effective at both improving ADHD symptoms and reducing cocaine use. It was hypothesized that extended-release mixed amphetamine salts would decrease ADHD symptoms and cocaine use in a dose related fashion with greatest to least reductions with decreasing dose (80 mg > 60 mg > placebo).
Participants	**CUD & ADHD**

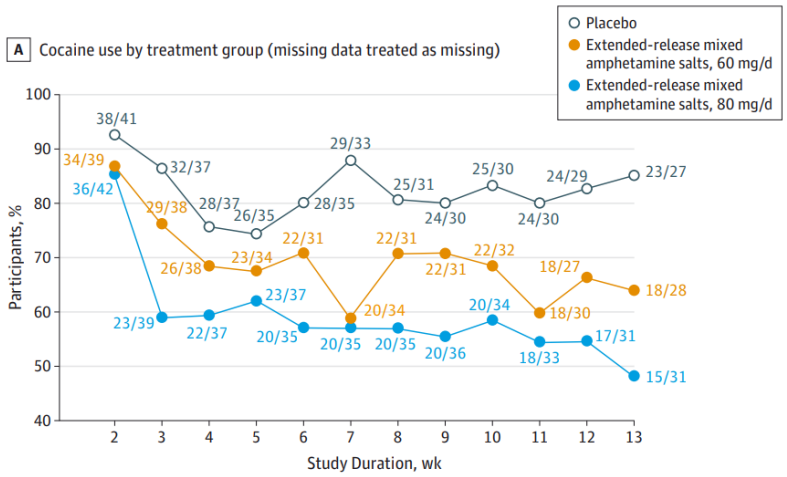
Baseline characteristics

Characteristic	Placebo	Extended-Release Mixed Amphetamine Salts		
		60 mg	80 mg	P Value
	(n = 43)	(n = 40)	(n = 43)	
Female, No. (%)	5 (11.6)	7 (17.5)	8 (18.6)	0.68
Age, mean (SD), y	39.26 (7.42)	43.90 (7.45)	38.37 (8.56)	0.004
Education, mean (SD), y	13.49 (2.26)	13.92 (2.46)[a]	13.67 (2.81)	0.74
Marital status, N (%)				
Currently married	5 (12.2)[b]	9 (22.5)	7 (16.3)	0.48

Study	Levin, 2015 [29]				
	Not currently married	36 (87.8)[b]	31 (77.5)	36 (83.7)	
	Current employment, N (%)				
	Full-time	14 (34.1)[b]	10 (25.6)[a]	17 (39.5)	
	Part-time	4 (9.8)[b]	4 (10.3)[a]	5 (11.6)	0.71
	Unemployed	23 (56.1)[b]	25 (64.1)[a]	21 (48.8)	
	Cocaine use (TLFB) for 28 d before, M (SD)	11.28 (7.47)	12.40 (7.76)	11.33 (6.96)	0.74
	Cocaine-positive urine screen at wk. 1 N (%)	39 (92.9)[c]	35 (87.5)	37 (86.0)	0.60
	Alcohol dependence, N (%)				
	Current	12 (27.9)	8 (20.0)	8 (18.6)	0.54
	Lifetime	23 (53.5)	21 (52.5)	21 (48.8)	0.90
	Cannabis dependence, N (%)				
	Current	6 (14.0)	4 (10.0)	3 (7.0)	0.57
	Lifetime	14 (32.6)	12 (30.0)	12 (27.9)	0.90
	AISRS score, M (SD)	34.67 (9.83)	35.85 (11.65)	36.09 (11.04)	0.81
	CAARS observer T-score, M (SD)				
	ADHD total	69.19 (13.83)	74.60 (13.37)	71.06 (13.15)	0.18
	Hyperactive	68.72 (14.43)	73.26 (14.01)	70.40 (14.36)	0.35
	Inattentive	65.84 (13.43)	70.64 (12.44)	67.58 (13.79)	0.25
	a Based on n = 39 owing to missing data. b Based on n = 41 owing to missing data. c Based on n = 42 owing to missing data.				
	Inclusion criteria Age 18 to 60 years, medically and psychiatrically stable, and meeting DSM-IV-TR diagnosis for current cocaine dependence and adult ADHD.				
	Exclusion criteria Exclusion criteria were the following: past mania, schizophrenia, or any psychotic disorder other than transient psychosis due to drug abuse; current treatment, an unstable psychiatric or medical condition such as uncontrolled hypertension, or coronary vascular disease as indicated by history or suspected by abnormal electrocardiographic results, cardiac symptoms, fainting, open-heart surgery, and/or arrhythmia; and legally mandated to substance abuse treatment.				
	Recruitment & screening				

Study	Levin, 2015 [29]
	Patients seeking treatment for CUD were recruited by local advertising for treatment research or clinical referrals. Screening (prior to week 0) included a comprehensive psychiatric and medical evaluation, the Structured Clinical Interview for DSM-IV Axis I Disorders, and Conners' Adult ADHD Diagnostic Interview for DSM-IV. Screening of 1614 individuals yielded 126 participants meeting eligibility criteria who were randomized. Common reasons for nonrandomization included dropout prior to study entry or medical exclusions. Participants were enrolled at the Substance Treatment and Research Service of Columbia University/New York State Psychiatric Institute or at the Ambulatory Research Center, Department of Psychiatry, University of Minnesota.
	Remuneration Individuals were reimbursed for travel and given progressive vouchers for attendance at the clinic and following study procedures.
Comparisons	**XR-Mixed amphetamine salts (80 mg) vs. XR-Mixed amphetamine salts (60 mg) vs. placebo**
	Duration of treatment 14 weeks First week: placebo lead-in preceded randomization. Second week: titration up to desired dose of study medications Week 14: tapered down study medications
	Follow ups Patients were scheduled to attend the clinic 3 times a week. Urine samples were obtained at each visit and tested for cocaine.
Experimental arm I	**XR-Mixed amphetamine salts (80 mg)** Medication was packaged in capsules that were to be taken daily. Participants unable to tolerate the maximum doses had their doses reduced based on clinical assessment.
	Co-interventions Psychosocial All participants received CBT/RP treatment weekly from experienced Masters- or PhD-level therapists.
Experimental arm II	**XR-Mixed amphetamine salts (60 mg)** Same as for Experimental arm I.
	Co-interventions Psychosocial

Study	Levin, 2015 [29]
	Same as for Experimental arms.
Control arm	**Placebo** Placebo were given identical capsules containing approximately 100 mg of riboflavin to be taken daily
	Co-interventions Psychosocial Same as for Experimental arm.
Outcomes	**Substance use** Primary outcome: Cocaine use, scored as positive, negative, missing (TLFB, self-reported; urinalysis*), collected weekly A cocaine-abstinent week was defined as: (1) at least 2 urine drug screens collected and all collected urine samples (either 2 or 3) were cocaine negative; and (2) all self-reported cocaine use for the week was negative. A cocaine-positive week was defined as at least 1 positive result on the urine screen or positive self-report. Weeks with insufficient data to determine use were designated as missing. * For any day with both a qualitative urine screen or quantitative laboratory assessment collected, the quantitative assessment was used, with a benzoylecgonine level of 300 ng/mL or less considered negative.
	Mental health Primary outcome: Responders, ADHD symptoms (AISRS), baseline to week 12 or last observation, response = 30% reduction in AISRS score Secondary outcome: ADHD symptom improvement (CGI), change from baseline to week 14 or last observation. Change in ADHD symptoms (AISRSI), change from baseline to week 14 or last observation. Change in ADHD symptoms (CAARS), change from baseline to week 14 or last observation.
	Quality of life Not assessed
	Function Not assessed
	Mortality

Study	Levin, 2015 [29]
	Not assessed
	Compliance Adherence was measured from urine quantification of amphetamines and urine riboflavin fluorescence.
	Adverse effects Side effects were assessed weekly by the study psychiatrist using a modified SAFTEE. Vital signs were obtained at each study visit. Participants with blood pressure higher than 140/90 mm Hg or heart rate higher than 100 beats/min for 2 weeks or with single readings of blood pressure higher than 160/110 mm Hg or heart rate higher than 110 beats/min were discontinued from study medication.
Results	**Substance use** Figure 2. Proportion of Participants With Cocaine Use by Randomized Treatment Group From Randomization (Week 2) Through End of Treatment Maintenance (Week 13)  Comments The highest dose of extended-release mixed amphetamine salts (80 mg) produced the greatest reduction in proportion of cocaine-positive weeks (determined through urine screens) throughout the study (Figure 2), regardless of whether missing weeks were coded positive or missing. There was a significant main effect of treatment, with higher cocaine abstinence in the 80-mg group over placebo

Study	Levin, 2015 [29]

(OR = 5.46; 95% CI, 2.25-13.27; P < .001) and in the 60-mg group over placebo (OR = 2.92; 95% CI, 1.15-7.42; P = .02). This was not different between the 80-mg and 60-mg groups (OR = 1.87; 95% CI, 0.86-4.05; P = .11). There was also a main effect of study week (P = .01) but no treatment-by-week interaction (P = .35), consistent with the similar spacing between groups across weeks in Figure 2. Pooled 60-mg and 80-mg groups vs placebo showed an OR of 4.08 (95% CI, 1.79-9.32; P < .001).

The proportions with abstinence in the last 3 weeks were 30.2% (13 of 43) for the 80-mg group, 17.5% (7 of 40) for the 60-mg group, and 7.0% (3 of 43) for the placebo group, with ORs of 11.87 (95% CI, 2.25-62.62; P = .004) for the 80-mg group vs placebo and 5.85 (95% CI, 1.04-33.04; P = .04) for the 60-mg group vs placebo. Abstinence in the last 3 weeks was no different between the 80-mg and 60-mg groups (OR = 0.49; 95% CI, 0.16-1.53; P = .22). Pooled 60-mg and 80-mg groups vs placebo showed an OR of 8.74 (95% CI, 1.78-42.97; P = .008).

Mental health

Scale	Placebo n = 43	60 mg[a] n = 40	80 mg[a] n = 43	P-value Placebo vs. 60 & 80 mg	Placebo vs. 60 mg	Placebo vs. 80 mg	60 vs. 80 mg
AISRS							
Score at last wk., M (SD)[b]	25.78 (13.94)[c]	15.34 (12.93)[d]	20.61 (14.22)[c]				
Responders, baseline to last measure, N (%)	17 (39.5)	30 (75.0)	25 (58.1)	0.003	<0.001	0.07	0.09
Change in score, last measure to baseline, M (SD)[e]	8.59 (12.24)[c]	20.53 (13.18)[d]	15.63 (10.93)[c]	<0.001	<.001	.01	0.04
CGI							
Improvement, with score of ≤2, N (%)	5 (11.6)	16 (40.0)	15 (34.9)	0.002	0.003	0.006	0.86
Score change, M (SD)[e]	0.80 (1.23)[c]	1.66 (1.17)[d]	1.24 (1.11)[c]	0.001	<0.001	0.03	0.20
CAARS							
Total score at last week, M (SD)	63.23 (15.77)[f]	55.03 (15.56)[g]	57.62 (14.70)[h]				
Total score change, last wk. to baseline, M (SD)[e]	5.01 (12.84)[f]	19.64 (16.33)[g]	12.79 (13.53)[h]	<0.001	<0.001	0.02	0.07
Hyperactivity score at last week, M (SD)	62.73 (17.12)[f]	55.54 (16.83)[g]	57.90 (13.42)[h]				
Hyperactive score change, last wk. to baseline, M (SD)[e]	5.42 (14.92)[f]	17.58 (14.71)[g]	11.26 (12.47)[h]	0.002	<0.001	0.06	0.08
Total score at last week, M (SD)	60.65 (14.21)[f]	53.11 (13.04)[g]	55.28 (14.44)[h]				
Inattentive score change, last wk. to baseline, M (SD)[e]	4.03 (11.66)[f]	17.75 (16.19)[g]	12.18 (14.05)[h]	<0.001	<0.001	0.02	0.15

a- 60 mg and 80 mg indicate the doses of XR-mixed amphetamine salts per day.

b- mITT, When missing scores are omitted: 9.49 (3.92) weeks for placebo, 10.18 (3.48) for 60-mg extended-release mixed amphetamine salts, and 10.47 (3.25) weeks for 80-mg extended-release mixed amphetamine salts.

Study	Levin, 2015 [29]

c- Based on n = 41 owing to missing data.
d- Based on n = 38 owing to missing data.
e- Calculated as the value at week 0 minus the value at the last week.
f- Based on n = 40 owing to missing data.
g- Based on n = 37 owing to missing data.
Comments
Statistical tests are adjusted for baseline cocaine use and for the week 0 measure of the ADHD scale.

Compliance

	80-mg group (n = 43)	**60-mg group** (n=40)	**Placebo** (n=43)	
Number of CBT sessions, mean (SD)	9.1 (3.8)	9.5 (4.0)	8.1 (4.4)	p = 0.27

Participants completed a mean (SD) of 8.9 (4.1) of 12 CBT sessions with no differences across groups.
Medication adherence (self-reported pills taken) = mean 98.8%
Median rates were not significantly different across groups (Kruskal-Wallis test, df = 2; p = 0.63).

Adverse effects

Discontinuation due to AE*
80-mg group (n = 43): 12.2 %
60-mg group (n=40): 17.5 %
Placebo (n=43): 10 %
$\chi 2\ 2 = 1.038$; p = 0.60
* AE = intolerable AE or blood pressure or heart rate above strict study parameters Moderate to severe adverse events included insomnia and anxiety.
Adverse symptoms
Dry mouth was the only adverse event that occurred significantly more frequently in the groups receiving extended-release mixed amphetamine salts (p = 0.01).
SAE:

Study	Levin, 2015 [29]			
	Two participants had serious adverse events requiring hospitalization: rape and pneumothorax. Both participants were receiving placebo and neither serious adverse event was deemed study related. Comments Adverse effects and adverse events were compared between groups using Fisher exact test.			
	Loss to follow up			
		80-mg group n = 43	**60-mg group n = 40**	**Placebo n = 43**
	Retention to week 13, % (n)	79,1 % (34)	75,0 % (30)	67.4 % (29) p= 0.51
	Discontinued before week 13, n (%)	20.9% (9)	25% (10)	32.5% (14)
	Reasons for discontinuation	5 lost to follow-up 2 non-compliant 1 sought treatment elsewhere 1 other life event	9 lost to follow-up 1 sought treatment elsewhere	10 lost to follow-up 1 sought treatment elsewhere 1 other life event 1 incarcerated
Comments	Baseline ADHD scores reflected moderate ADHD symptoms.			
Risk of bias	Moderate			

ADHD = attention-deficit/hyperactivity disorder; **AE** = adverse events; **AISRS** = Adult ADHD Investigator Symptom Rating Scale; **CAARS** = Conners' Adult ADHD Rating Scale; **CBT/RP** = Cognitive Behavioral Therapy/ Relapse Prevention Treatment; **CGI** = Clinical Global Impression scale, scores of 1 = very much improved; 2 = much improved; **CUD** = cocaine use disorder; **DSM-IV-TR** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition - Text Revision; **NR** = not reported; **RCT** = randomized controlled trial; **SAE** = serious adverse events; **SAFTEE** = Systematic Assessment for Treatment and Emergent Events; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **XR** = extended release.

Levin et al. 2013

Study	Levin, 2013 [30]
Study design	RCT double-blind, placebo-controlled
Intervention	**Pharmacotherapy: venlafaxine-XR** Co-interventions: CBT/RP
Trial registration	NCT00131456
Country	USA
Setting	Outpatients

Study | **Levin, 2013 [30]**

Aims

Evaluate whether venlafaxine-extended release (VEN-XR) is an effective treatment for cannabis dependence with concurrent depressive disorders. It was hypothesized that VEN-XR would both reduce depressive symptoms and increase marijuana abstinence compared to placebo.

Participants

Cannabis dependence & depression

Treatment seeking adults (n = 103) with DSM-IV cannabis dependence and major depressive disorder or dysthymia.

The majority enrolled had "moderate to moderately severe" depression based on the Hamilton Scale scores and were heavy users of cannabis.

Baseline characteristics

	Placebo	VEN-XR	p-value
N=	52	51	
Age (years), M (SD)	35.9 (9.3)	34.2 (10.8)	0.40
Male, % (n)	78.9% (41)	68.6% (35)	0.24
Education			
≤ High school, % (n)	23.5% (12)	33.3% (17)	
Some College, % (n)	56.9% (29)	54.9% (28)	0.46
College & Graduate School, % (n)	19.6% (10)	11.8% (6)	
Employed full-time, % (n)	37.3% (19)	43.1% (22)	0.49
Unemployed/Others, % (n)	62.8% (32)	56.9% (29)	
Currently married	17.7% (9)	19.6% (10)	0.80
Substance use			
Marijuana use days per month, M (SD)	27.5 (6.5)	27.4 (4.5)	0.91
Grams Marijuana used per using day, M (SD)	2.4 (2.9)	2.7 (2.8)	0.63
Joints of Marijuana used per week, M (SD)	36.3 (40.6)	38.2 (36.6)	0.81
Years of regular Marijuana use, M (SD)	16.0 (9.0)	15.1 (10.6)	0.63
Mental health			
High depression (>20 HAM-D score), % (n)	36.5% (19)	33.3% (17)	0.73
High Marijuana use (>21 joints/week), % (n)	55.8% (29)	64.7% (33)	0.35
Baseline HAMD-21 Score, M (SD)	19.0 (4.6)	17.9 (4.2)	0.21
Baseline HAMD-17 Score, M (SD)	17.3 (4.0)	16.3 (3.7)	0.19
Baseline Creatinine-Corrected Urine (ng/mg), M (SD)	926 (1165)	1139 (1530)	0.43

Inclusion criteria

Study	Levin, 2013 [30]
	Inclusion required that participants 1) were between the ages of 18-60, 2) met DSM-IV-TR criteria for current cannabis dependence and reported that marijuana was their primary drug of abuse, 3) met DSM-IV criteria for current Major Depression or Dysthymic Disorder and received a total score of ≥ 12 on the HAMD, 4) had a depressive syndrome of at least 3 months duration in the current episode. **Exclusion criteria** 1) met DSM-IV criteria for past mania, schizophrenia, or any psychotic disorder other than transient psychosis due to drug abuse; 2) were physiologically dependent on any substances (other than nicotine) that would require a medical intervention/detoxification; 3) had significant risk for suicide; 4) had a history of a seizure disorder; 5) had an unstable medical condition; 6) had a history of allergic reaction to venlafaxine; 7) failed to respond to a previous adequate trial of venlafaxine of at least 300 mg for ≥ 6-week period; 8) were currently being prescribed psychotropic medication, except for acute treatment of insomnia; and 9) females who were nursing, pregnant and/or unwilling to use an effective method of birth control. **Recruitment & screening** Treatment seekers for problems related to marijuana use were recruited by local advertising or clinical referrals. The medical screening included a history and physical exam, an electrocardiogram, and laboratory testing. The psychiatric evaluation included the SCID-IV for Axis I disorders. 1009 treatment seekers were assessed for eligibility, 886 were excluded and 123 entered the trial. 20 discontinued prior to randomization. **Remuneration** Participants were compensated $5-$20 for transportation costs per visit. To better assess medication compliance, participants earned an additional $10 per week if they returned their pill bottles and any remaining medication.
Comparisons	**Venlafaxine-XR vs placebo** **Duration of treatment** 12 weeks + 1 week placebo lead-in before randomization **Follow ups** Patients were asked to come to the clinic twice a week. Once a week patients met with a psychiatrist to administer clinical ratings of mood and marijuana use, assess side effects and clinical status, and adjust medication dosage as needed Endpoint: time of last treatment - week 12 End-of-study was defined as week 12, or the last measurement.
Experimental arm	**Venlafaxine-XR**

Study	Levin, 2013 [30]
	Participants were instructed to take the medication once per day in the morning. The medication was titrated to the target dose of 225 mg/day (or the maximum tolerated dose) over the first 3 weeks after randomization. After the fourth week post-randomization, patients with persistent depression who were not rated as having a CGI -Depression score of 1 (“very much improved’) and who were tolerating 225 mg/day had their dose increased to a maximum of 375 mg/day. Dose reductions were also allowed if 225 mg/day was not tolerated. **Co-interventions** Psychosocial All participants received weekly CBT/RP. Patients were encouraged to set a quit date at the onset of treatment, however, if a patient set a goal of reducing their use, therapy focused on this goal, and abstinence sampling was revisited during the study using motivational interviewing principles. The core therapy modules focused on the reduction and cessation of marijuana use by developing the skills necessary to manage thoughts and cravings for marijuana, implementing drug refusal skills, and managing environmental contexts that could increase the probability of relapse. In addition, modules were included to address the relationship between cognition and negative affect, developing strategies for managing negative mood, altering depressionogenic thinking patterns, and increasing the frequency of pleasant activities.
Control arm	**Placebo** Same dosage, mode and frequency of delivery as for Venlafaxine-XR **Co-interventions** Psycosocial Same as for Experimental arm.
Outcomes	**Substance use** Primary outcomes: Abstinence response, defined as at least two consecutive urine-confirmed abstinent weeks Urine-confirmed abstinence = negative for both • Self-reported marijuana use for the week (TLFB), collected at weekly visits • THC levels (quantitative urinalysis), collected at weekly visits, negative urinalysis defined as THC <100 mg/ml normalized for creatinine.

Study	Levin, 2013 [30]
	Secondary outcomes: THC urine level (measured once a week, longitudinal continuous) **Mental health** Primary outcomes: Response – depression • at least a 50% reduction in the HAMD total score between randomization and end-of-study • a HAMD total score of less than 8 at end-of-study Mood outcome was evaluated with the HAMD every two weeks. For secondary analysis purposes, the HAMD scores were used as continuous longitudinal data measured once a week. **Quality of life** Not assessed **Function** Not assessed **Mortality** **N**ot assessed **Compliance** Secondary outcomes: % pills taken; study medication was provided to participants on a weekly basis. Each week, participants were asked to return all bottles and unused medication. The study staff documented any unused or missed medication. Blood levels of VEN-XR CBT attendance **Adverse effects** Secondary outcomes: Side effects were assessed weekly (Modified SAFTEE) by the study psychiatrist
Results	**Substance use** **VEN-XR** **PBO** ITT, n = 51 ITT, n = 52 **Primary outcomes**

Study	Levin, 2013 [30]

At least two consecutive abstinent weeks[a]	11.8 % (n=6)	36.5% (n=19)	Unadjusted by baseline: X_1^2=7.87, p-value<0.01 Adjusted by baseline: X_1^2=7.46, p-value<0.01
Self-reported use in grams (week 12) mean	7.18	4.51	$F_{1,340}$=0.99, p-value=0.32
Secondary outcomes			
THC urine levels (week 12) mean nl/mg	1403	439	$F_{1,372}$=9.06, p-value <0.01

a- Patients who achieved the two consecutive abstinent weeks were classified as abstinent whether or not they subsequently dropped out of the study. Patients who dropped out of the study without achieving two continuous weeks of abstinence were classified as not abstinent.

Comments

In the logistic regression model, abstinence was significantly affected by:

1) Treatment group: higher likelihood of abstinence for placebo compared to VEN-XR. A patient receiving placebo had 4.51 (95% CI: 1.53, 13.3) times the odds of achieving two weeks continuous abstinence than a patient receiving VEN-XR with comparable baseline urine THC levels.

2) Baseline urine THC level: higher baseline THC urine level is associated with lower odds of achieving abstinence (see Table 2).

Data not extracted for secondary outcomes: effect of time on longitudinal outcomes and time by treatment interaction

Mental health

	VEN-XR	**PBO**	
	ITT, n = 51	ITT, n = 52	
Primary outcomes			
50% reduction of HAMD at end of study	62.7 % (n=32)	69.2 % (n=36)	Unadjusted by baseline: X_1^2=0.48, p-value=0.49 Adjusted by baseline: X_1^2=0.44, p-value=0.51
< 8 on the HAMD at end of study	51.0 % (=26)	57.7 % (n=30)	Unadjusted by baseline: X_1^2=0.47, p-value=0.49 Adjusted by baseline: X_1^2=0.95, p-value=0.33
Secondary outcomes			
HAMD over time	6.61	5.65	Adjusted by baseline: $F_{1,456}$=0.76, p-value=0.38

Compliance

	Overall	**VEN-XR n = 51**	**Placebo n = 52**	**significance**
% pills taken (pill count): mean	88.9%	87.5%	90.3%	T100=0.93, p-value=0.35
% CBT sessions attended: mean	79.2%	76.0%	82.3%	T101=1.5, p-value=0.14
No medication detected in blood test		10% (9/90)		

* 7 of those 9 tests (77.8%) were for the 5 subjects who never tested positive for VEN-XR

Study	Levin, 2013 [30]
	Comments Five participants in the VEN-XR group never tested positive for VEN-XR, indicating clear non-compliance. **Adverse effects** **VEN-XR n = 51** / **Placebo n = 52** / **p-value** Anxiety: % (n) 11.8% (6) / 1.9 % (1) / 0.060 Diarrhea: % (n) 5.8 % (3) / 7.8 % (4) / 0.717 Dizziness: % (n) 3.8 % (2) / 15.7 % (8) / 0.052 Fatigue: % (n) 11.8 % (6) / 1.9 % (1) / 0.060 GI Upset: % (n) 11.8 % (6) / 3.8 % (2) / 0.160 Headache: % (n) 3.9 5 (2) / 7.7 % (4) / 0.678 Insomnia: % (n) 13.7 % (7) / 7.7 % (4) / 0.358 Loss of libido: % (n) 11.8 % (6) / 0.0 % (0) / **0.013** Muscle Aches: % (n) 3.9 5 (2) / 7.7 % (4) / 0.678 Nausea: % (n) 11.8 % (6) / 7.7 % (4) / 0.526 Syncopy or lightheaded 3.9 % (2) / 7.7 % (4) / 0.678 **Loss to follow up** **VEN-XR n = 51** / **Placebo n = 52** **Completed 12 weeks intervention: % (n)** 60.8 % (31) / 63.5 % (33) **Discontinued intervention: % (n)** 39.2 % (20) / 36.5 % (19) **Loss to follow up: % (n)** 13.7 % (7) / 9.6 % (5)
Risk of bias	Low

AARS = ADHD Rating Scale; **CBT/RP** = Cognitive Behavioral Therapy/ Relapse Prevention Treatment; **CGI** = Clinical Global Impression scale, scores of 1 = very much improved; 2 = much improved; **DSM-IV-TR** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition – text revision; **HAMD** = Hamilton Depression Inventory; **ITT** = intention to treat; **M** = mean; **NR** = not reported; **RCT** = randomized controlled trial; **SAFTEE** = Systematic Assessment for Treatment and Emergent Eve; **SCID-IV=** Structured Clinical Interview for DSM; **SD** = standard deviation; **TAADDS** = Targeted Adult Attention Deficit Disorder Scale; **THC** = tetrahydrocannabinol; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **VEN-XR** = venlafaxine-extended release; **XR** = extended release.

Levin et al. 2007

Study	Levin, 2007 [31]
Study design	RCT, double-blind, placebo-controlled

Study	Levin, 2007 [31]
Intervention	Pharmacotherapy: MPH Co-intervention: CBT/RP
Trial registration	NR
Country	USA
Setting	Outpatient, New York City metropolitan area
Aims	To compare the efficacy of sustained-release methylphenidate (MPH) to placebo in treating ADHD symptoms in current cocaine dependent treatment seekers.
Participants	**Cocaine dependency and Adult ADHD**

Baseline characteristics

	Placebo	MPH	χ2 or F, p	d.f.	n
N=	53	53			106
Men: n (%)	44 (83%)	44 (83%)	.00, 1.00	1	106
Age: M (SD)	37 (6)	37 (7)	.39, .98	104	106
Education (years), M (SD)	14 (2.4)	14 (2.5)	−.64, .52	102	104
Currently married, n (%)	14 (26%)	11 (21%)	.58		
Currently employed (full time), n (%)	38 (72%)	22 (50%)	5.34,	2	97
Current substance use disorder[a]					
Alcohol, n (%)	24 (45%)	19 (36%)	.98, .32	1	106
Marijuana, n (%)	15 (28%)	21 (40%)	1.51, .22	1	106
Opiate, n (%)	1 (2%)	0 (0%)	1.01, .32	1	106
Cocaine, n (%)	81 (37)	83 (23)	0.27, 0.76	2, 92	
Cocaine (heavy users), n (%)	32 (60%)	31 (59%)	0.04, 0.84	1	106
CGI Cocaine Severity, M (SD)	5.13 (1.02)	5.11 (.89)	0.10, 0.92	104	106
Days used (last 30 days), M (SD)	13 (8)	14 (9)	−0.68, 0.50	104	106
Pattern drug use of cocaine users (n)	21	13			
Use (in days) over last 30 days, M (SD)	12 (11)	14 (10)	0.35, 0.71	2, 49	
Psychiatric disorders					
Lifetime anxiety/affective, n (%)	11 (21%)	10 (19%)	0.06, 0.81	1	106
Current anxiety/affective, n (%)	26 (49%)	22 (42%)	0.61, 0.44	1	106
ADHD					
WURS, M (SD)	51.98 (19.15)	30.40 (9.78)	−0.04, 0.97	103	106

Study	Levin, 2007 [31]
	AARS, M (SD) 33.47 (10.39) 33.00 (11.40) 1.57, 0.12 104 106 TAADDS total, M (SD) 19.49 (3.94) 19.17 (3.51) 0.44, 0.66 104 106 CGI ADHD severity, M (SD) 5.19 (1.00) 5.30 (.75) −0.66, 0.51 104 106 a- Abuse or dependence
	Inclusion criteria Study inclusion required participants between the ages of 18–60 to meet DSM-IV criteria for cocaine dependence and persistent adult ADHD. ADHD diagnosis was established with SCID-IV and the Kid-SCID modified for use in adult ADHD. Patterns of lifetime drug use and recent use over the 30 days prior to evaluation were assessed with RDU.
	Exclusion criteria (1) met DSM IV criteria for current psychiatric disorders (other than ADHD or substance abuse) which required psychiatric intervention, (2) were physiologically dependent on opioids, sedatives or alcohol such that medical attention was required during periods of abstinence or significant reductions in use, (3) exhibited suicidal or homicidal behavior within the past 2 years, (4) were prescribed any psychotropic medication, (5) had an unstable medical condition that would make participation hazardous (i.e. uncontrolled diabetes), (6) had a known sensitivity to MPH, (7) were nursing and/or pregnant and (8) were unable to give full and informed consent.
	Recruitment & screening All participants were seeking outpatient treatment for problems related to cocaine use and were recruited by local advertising or by referrals in the New York City metropolitan area. A total of 1125 cocaine-dependent treatment seekers began screening for the trial. 124 individuals met inclusion/exclusion criteria and entered the study. 106 participants completing the placebo lead-in and randomized to either group.
	Remuneration Participants were compensated $3.00 in cash for transportation costs at each of the three weekly visits.
Comparisons	**XR-methylphenidate vs. placebo**
	Duration of treatment 14 weeks Including a 1-week placebo lead-in phase, and a 2-week dose titration phase followed by 11 weeks at a stable dose.

Study	Levin, 2007 [31]
	Follow ups All clinical assessments of drug use and ADHD symptoms were conducted on a weekly basis. Endpoint: week 14
Experimental arm	XR-MPH The dosing was initiated at 10 mg/day of standard formulation MPH and increased up to 20 mg two times a day (40 mg/day). If tolerated, the sustained-release formulation replaced the standard formulation and was administered as two 20 mg doses. The dose was then increased to the maximal dose of 60 mg/day, depending on patient tolerance of MPH. Patients who could not tolerate a dose of at least 40 mg/day of MPH were discontinued off the medication but were continued in the trial.
	Co-interventions Psychosocial Individual structured manual-based CBT/RP was delivered weekly.
Control arm	**Placebo** Four capsules per day were prescribed. Each capsule contained 1 mg folic acid and 25 mg of riboflavin
	Co-interventions Psychosocial Same as intervention group.
Outcomes	**Substance use** Primary outcomes Proportion of cocaine positive weeks Abstinence, categorical response measure of (i.e., 2 weeks of continuous abstinence) Drug use measured with self-report questionnaire completed at every visit, and urine toxicology results. In addition, to assess drug use over the course of the study, the number of cocaine positive urine specimens collected per week (up to 3) over the total number of urines submitted per week were examined.
	Mental health Primary outcome % responders – ADHD symptoms (AARS, continuous, range 0–54), weekly

Study	Levin, 2007 [31]
	Responder defined as someone who had a ≥30% reduction in total AARS, comparing the last observation to baseline. Secondary outcomes ADHD symptoms, (TADDS total score, continuous, range 0–28), weekly ADHD improvement (CGI) weekly, last rating compared to baseline. Responder _ ADHD symptoms (composite) - 30% reduction in self-reported ADHD symptoms and CGI < 3
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Riboflavin, 3x per week Self-reported
	Adverse effects Side effects were rated on a scale of 0–3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Only side effects rated moderate or severe were included in the analysis
Results	**Substance use** **Primary outcomes** / **MPH Difference** / **Placebo Difference** **Weeks with positive urines for cocaine**: 73 % / 70 % / t = −0.40, d.f. = 101, p = 0.69 **% of individuals achieving 2 weeks of continuous abstinence**: 15 % (n=8) / 17 % (n=9) / χ2 = 0.16, d.f. = 1, p = 0.69 **CGI cocaine improvement score < 3**: 49 % (n=26) / 60 % (n=32) / χ2 = 1.37, d.f. = 1, p = 0.24 (Last observed value) Secondary analysis

Study	Levin, 2007 [31]

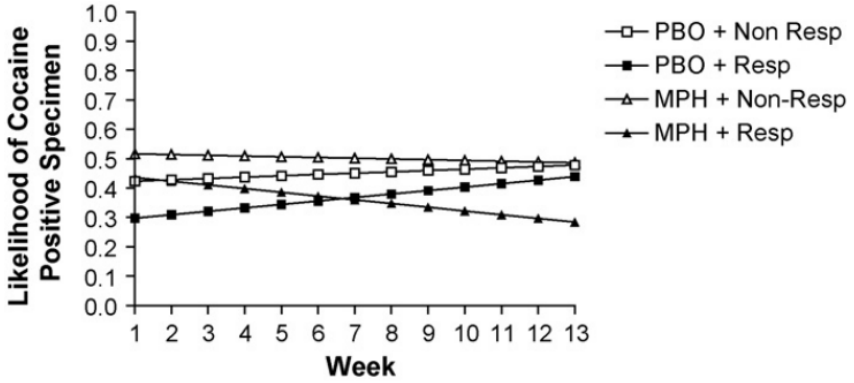


Fig. 4. Predicted probability of cocaine positive urine samples per week obtained from fitting the data using GEE comparing responders and non-responders on the TAADDS for the PBO and MPH groups.

Comments

There was a significant main effect of the TAADDS score (Z = 2.97, p =0.003) and the baseline cocaine use covariate (Z = 7.51, p < 0.0001), as well as a significant treatment by time interaction (Z = 2.29, p = 0.02).

There was no improvement in cocaine use for participants in the placebo group, regardless of ADHD response. However, in the MPH group, the likelihood of submitting a cocaine positive urine decreased by 36% over time for ADHD-responders compared to under 10% for ADHD non-responders.

Mental health

	XR-MPH (ITT, n = 53) **Difference**	Placebo (ITT, n = 53) **Difference**	
Primary			
Response, at least 30% reduction from baseline (AARS)	47 % (n=25)	55 % (n=29)	χ2 = 0.60, d.f. = 1, p = 0.44
Improvement (CGI), mean	34 % (n=18)	30 % (n=16)	χ2 = 0.17, d.f. = 1, p = 0.68]
Secondary			
Responder, CGI and 30% reduction	30 % (n=16)	28 % (n=15)	χ2 = 0.05, d.f. = 1, p = 0.83
TAADDS	40 % (n=21)	28 % (n=15)	χ2 = 1.51, d.f. = 1, p = 0.22

Study	Levin, 2007 [31]

Compliance

The mean proportion of self-reported doses taken did not differ significantly between the groups, with each group taking about 93% of their doses (t = −0.27, d.f. = 102, p = 0.79).

For those patients for whom riboflavin data were available (placebo n = 48, XR-MPH n = 43), the proportion of positive fluorescence results indicated that compliance did not differ between groups [placebo = 0.82 (0.17), XR-MPH = 0.84 (0.16); t = −0.58, d.f. = 89, p = 0.56].

Adverse effects

	Placebo n = 53	XR-MPH n = 53
Headache:	2 %	8 %
Gastrointestinal upset:	4 %	8 %
Diarrhea:	9 %	2 %
Insomnia:	2 %	9 %

Comments

In the MPH group, one individual was removed from the protocol because of worsening of pre-existing mood lability, another individual was removed because of increased anxiety, one person was dropped because of side effects, two left the trial to enroll in drug detoxification programs, and two individuals were incarcerated.

In both groups, most participants who dropped from the trial did so because they failed to attend clinic appointments and would not return phone calls or they specifically stated that they were no longer interested in receiving treatment.

Lost to follow-up

	Placebo n = 53	XR-MPH n = 53
Completed at least 4 weeks: % (n)	83 % (44)	85 % (45)
Completed the entire 14-week trial: % (n)	45 % (24)	43 % (23)
Discontinued intervention:	29	30
Reasons for discontinuation	22 withdrew[a]	19 withdrew[a]
	3 non-compliant[b]	4 non-compliant[b]
	3 worsening pre-existing depressive symptoms	1 worsening pre-existing mood liability
	1 side effects	1 increased anxiety
		1 side effects
		2 sought treatment elsewhere

Study	Levin, 2007 [31]
	2 incarcerated a- participants specifically stated that they were no longer interested in receiving treatment b- participants who they failed to attend clinic appointments and would not return phone calls
Risk of bias	Moderate

ADHD = attention-deficit/hyperactivity disorder; **CBT/RP** = cognitive behavioral therapy for relapse prevention; **CGI** = Clinical Global Improvement scale; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition; **ITT** = intention to treat; **KidSCID-IV**= Structured Clinical Interview for DSM-IV adapted for children and adolescents; **M** = mean; **MPH** = methylphenidate; **NR** = not reported; **RCT** = randomized controlled trial; **RDU** = recent drug use; **SCID-IV**= Structured Clinical Interview for DSM-IV; **SD** = standard deviation; **TAADDS** = Targeted Adult Attention Deficit Disorder Rating Scale; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **XR** = extended release

Levin et al. 2006

Study	Levin, 2006 [32]
Study design	RCT, double-blind, placebo-controlled, three-arms
Intervention	**Pharmacotherapy: XR-bupropion (BPR), XR-methylphenidate (MPH)** Co-intervention: weekly individual CBT/RP, methadone maintenance
Trial reg.	NR
Country	USA
Setting	Outpatient
Aims	1) Compare the efficacy of sustained-release methylphenidate or sustained release bupropion to placebo in treating adult ADHD symptoms. 2) Determine if active medication treatment reduced cocaine use among those methadone maintenance patients with both adult ADHD and cocaine dependence/abuse.
Participants	**Opiate dependence and adult ADHD** 98 methadone-maintained patients, predominately male (57%) All participants met DSM-IV criteria for adult ADHD and opiate dependence/abuse.

Study	Levin, 2006 [32]

Baseline characteristics

	Placebo	MPH	BPR	χ2 or F, p	d.f
N=	33	32	33		
Men: n (%)	18 (55%)	19 (59%)	19 (66%)	0.16, 0.92	2
Age: M (SD)	39 (8)	40 (6)	38 (8)	0.52, 0.59	2, 95
Education (years)	12 (3)	12 (3)	12 (2)	0.37, 0.69	2, 95
Currently married	3 (9%)	7 (21%)	8 (24%)	2.92, 0.23	2
Currently employed[b]	13 (43%)	18 (58%)	25 (89%)	13.60, 0.001	2
Current substance use disorder					
Alcohol	5 (15%)	7 (22%)	5 (15%)	0.68, 0.71	2
Marijuana	5 (15%)	5 (16%)	8 (24%)	1.15, 0.56	2
Cocaine	21 (64%)	13 (41%)	18 (54%)	3.50, 0.17	2
Opiate	20 (61%)	15 (47%)	17 (51%)	1.28, 0.53	2
Meth. dose (mg)	81 (37)	83 (23)	87 (37)	0.27, 0.76	2,92
Pattern drug use of cocaine users (n)	21	13	18		
Use (in days)-last 30 days	12 (11)	14 (10)	14 (11)	0.35, 0.71	2, 49
Psychiatric disorders - Current					
Affective	6 (18%)	5 (16%)	6 (18%)	0.098, 0.95	2
Anxiety	7 (21%)	4 (12%)	6 (18%)	0.884, 0.64	2
Lifetime Affective	11 (33%)	11 (34%)	9 (27%)	0.44, 0.8	2
Lifetime Anxiety	1 (3%)	4 (12%)	1 (3%)	0.28, 98[c]	
ADHD					
WURS	61.21 (21.90)	58.60 (18.74)	60.40 (19.10)	0.14, 0.86	2,95
AARS	34.61 (11.70)	33.00 (11.40)	33.24 (11.10)	0.20, 0.82	2,95
ADHD CGI severity	5.3 (0.70)	5.2 (0.82)	5.0 (0.92)	1.66, 0.19	2,95
WRAADS	20.18 (3.84)	19.22 (3.55)	19.76 (4.20)	0.50, 0.61	2,95

[a] Data obtained during screening for trial prior to initiation of any study procedures. Values in the table are N (%) for categorical variables or mean (SD) for continuous variables.

[b] Defined as fulltime or part-time employment, student or in military service.

[c] Subjects either abuse or are dependent.

Study	Levin, 2006 [32]
	[d] Fisher exact test showing p-value, n.
	Inclusion criteria Study inclusion required participants to meet DSM-IV criteria for opiate dependence and adult ADHD, to be between the age of 18 and 60, and on the same dose of methadone for at least 3 weeks.
	Exclusion criteria Participants were excluded if they: (1) met DSM-IV criteria for current psychiatric disorders (other than ADHD or substance abuse) which required psychiatric intervention or had a history of an eating disorder. (2) were physiologically dependent on either sedatives or alcohol, such that medical attention was required during periods of abstinence or significant reduction in amount of use. (3) exhibited suicidal or homicidal behavior within the past 2 years. (4) were taking any prescription psychotropic medications other than methadone. (5) had an unstable medical condition that would make participation hazardous. (6) had a known sensitivity to MPH or BPR. (7) were nursing and/or pregnant. (8) could not read or understand the self-report assessment forms unaided and/or were so severely impaired they could not comply with the requirements of the study and were therefore unable to give full and informed consent.
	Recruitment & screening Most participants were recruited at five community-based methadone programs in the New York City area. A total of 2715 methadone patients were screened, and of those, 526 reported ADHD-like symptoms and agreed to a screening interview. 115 individuals met inclusion/exclusion criteria and entered the study. 98 participants completed the placebo lead-in and were randomized to one of three treatment arms.
	Remuneration At each of the three weekly visits, participants were compensated $3.00 in cash for transportation costs.
Comparison	**MPH-XR vs. bupropion (BPR) vs. placebo**

Study	Levin, 2006 [32]
	Duration of treatment 12 weeks Included a 2-week placebo lead-in phase, a 2-week dose titration period followed by 8 weeks at a stable dose.
	Follow ups All clinical assessments of drug use and ADHD symptoms were conducted on a weekly basis. Endpoint / time of last treatment: Week 10 (10 weeks of treatment)
Active arm I	**I. MPH-XR** All patients received two capsules and two tablets twice per day. Following 2 weeks of placebo lead-in, participants were randomized into one of the three arms. During the titration phase, the standard formulation of MPH was administered twice a day, starting at 10 mg/day. This dose was increased by 10 mg/day, up to 40 mg/day. At this time, the XR formulation replaced the standard formulation and was administered as two 20 mg doses. The dose was then increased to the maximal dose of 80 mg/day, depending on patient tolerance of MPH. Patients who could not tolerate a dose of at least 40 mg/day of MPH were discontinued.
	Co-interventions Psychosocial All participants attended weekly individual CBT/RP, focused on relapse prevention and adjusted for individuals with ADHD
Active arm II	**II. Bupropion-XR (BPR-XR)** All patients received two capsules and two tablets twice per day. Following 2 weeks of placebo lead-in, participants were randomized into one of the three arms. BPR-XR was started at 100 mg/day and increased by 100 mg by the end of the first week of the titration phase. If tolerated, by the end of the second week patients received the maximum dose of 400 mg/day. Patients who could not tolerate a dose of at least 200 mg/day of BPR-XR were discontinued.
	Co-interventions Psychosocial As in arm I: MPH-XR
Control arm	**III. Placebo** As in arm I: MPH-XR

Study	Levin, 2006 [32]
	Folic acid in the form of a 1 mg tablet was added to all placebo capsules to improve the blind.
	Co-interventions Psychosocial As in arm I: MPH-XR
Outcomes	**Substance use** Drug use assessments included a *self-report* and *urine toxicology* completed at every visit. The proportion of positive weeks using any drugs was examined. A week was considered positive for drug use if the self-report indicated any drug use in that week, and/or (1) no urine samples were collected, (2) only one (out of a possible three) urine sample was collected (regardless of toxicology result), or (3) any urine sample out of two or three samples collected tested positive for any drug. Note that cocaine use was specifically measured in the subgroup with cocaine addiction.
	Mental health Primary outcomes: Weekly AARS scores were used as the primary ADHD outcome measure. Two outcome measures based on AARS were compared: (1) the proportion of participants in each treatment arm reporting a 30% reduction or more in the AARS from baseline, and (2) the proportion of participants in each treatment group reporting a 30% reduction or more in the AARS and a CGI ADHD rating of less than 3 at the end of study. Syptom improvement, ADHD (CGI). On a weekly basis, the research psychiatrist rated the severity of the ADHD symptoms on the CGI, as well as any improvement in ADHD symptoms relative to baseline. Secondary outcomes: Total WRAADDS score each week.
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance

Study: Levin, 2006 [32]

Compliance was measured by self-reported medication compliance.

Urinalysis (uv detection of riboflavin), samples collected 3x per week. Riboflavin was added to all capsules that the last 49 randomized participants received.

Adverse effects

Side effects were rated on a scale of 0–3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Only side effects rated moderate or severe were included in the analysis.

Results

Substance use

	Placebo (ITT, n = 33)	MPH (ITT, n = 32)	BPR (ITT, n = 33)	*F* or χ2, p	d.f.
Proportion of positive weeks for any drug[b]	0,91 (0,09)	0,94 (0,08)	0,93 (0,08)	0.79 (0.46)	2, 92
Percent with 2 or more abstinent weeks	15% (5)	9% (3)	6% (2)	1.48 (0.48)	2
Cocaine use (subgroup w/ cocaine addiction)	**Placebo ITT (*n*=21)**	**MPH ITT (*n*=13)**	**BPR ITT (n=18)**	**F or χ2, p**	**d.f.**
Proportion of positive weeks for Cocaine[b]	0,86 (0,28)	0,86 (0,25)	0,91 (0,23)	0.17 (0.84)	2, 47
Percent with 2 or more abstinent weeks	14% (3)	15% (2)	11% (2)	0.11 (0.95)	2

[a] Values are mean (S.D.) or percent (N)

[b] No data was available during the treatment phase for four subjects (out of 98) for the any drug use measure, and data on two subjects (out of 52) was missing for the cocaine using subgroup.

Mental health

	Placebo (ITT, n = 33)	MPH (ITT, n = 32)	BPR (ITT, n = 33)	X^2, *p*	d.f.
	Endpoint	Endpoint	Endpoint	Endpoint	
AARS[b]	46% (15)	34% (11)	49% (16)	1.46 (0.48)	2
CGI[c]	39% (13)	19% (6)	30% (10)	3.34 (0.19)	2
AARS+CGI[d]	21% (7)	9% (3)	15% (5)	1.76 (0.42)	2

[a] Values in the table are percent (N)

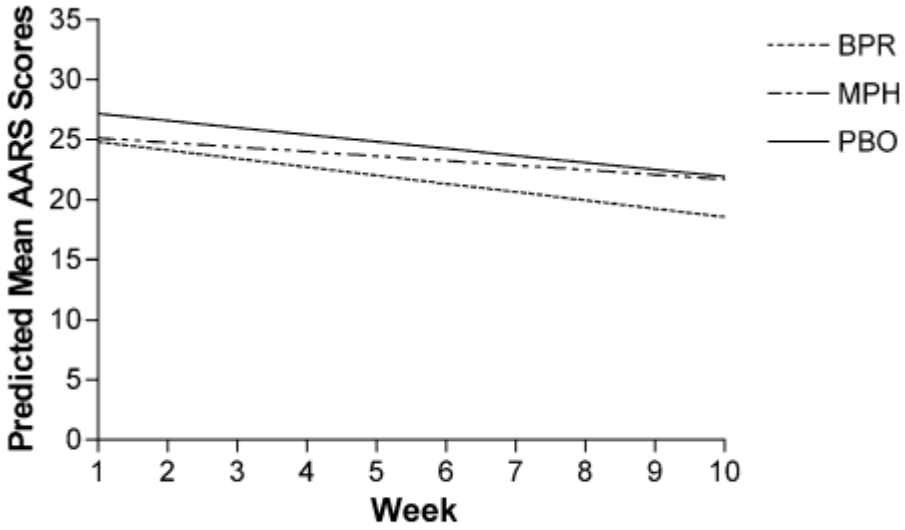
[b] Responders are those participants that report >30% drop in AARS scores **at end of study compared to baseline**.

[c] Responders are those participants that achieve a CGI ADHD improvement rating <3 at end of study.

[d] Responders are those participants that report >30% drop in AARS scores and a CGI ADHD rating <3 at end of study.

Comments

A substantial proportion of patients met the standard response criterion of at least a 30% reduction in the AARS (placebo 46%, MPH 34%, BPR 49%), or the alternate criterion of a CGI ADHD improvement score of 1 or 2 (placebo 39%, MPH 19%, BPR 30%). Using the

Study	Levin, 2006 [32]
	combined outcome measure of at least a 30% reduction in AARS and a CGI ADHD rating of less than 3 at end of study, the placebo response rate was substantially lower than the AARS measure alone (21% versus 46%) but there remained no significant group differences (placebo 21%, MPH 9%, BPR 15%). Odds ratios and 95% confidence intervals were obtained from fitting a logistic regression with the dichotomous outcome based on a 30% reduction in the AARS as the dependent measure and treatment assignment as the predictor. The odds of achieving a 30% reduction in AARS were greater in the BPR group than in the placebo group but not significantly (odds ratio = 1.28, 95% CI = 0.48 to 3.37), while the odds were lower for the MPH group compared to placebo group, again, not significantly (odds ratio = 0.53, 95% CI = 0.19–1.50). Using the combined AARS and CGI outcome measure, the odds of treatment response were lower in both active arms than in the placebo arm, but not significantly (odds ratio BPR versus placebo = 0.66, 95% CI = 0.19–2.35; odds ratio MPH versus placebo = 0.38, 95% CI = 0.09–1.64).
Linear analyses	**Outcome** AARS  Fig. 2. Mean AARS scores over 10-week treatment phase.

Study	Levin, 2006 [32]
	The figure plots the predicted mean response over time for the three treatment arms. On average, AARS severity reduced by 21% for the placebo group, compared to 24% of the BPR group and 12% for the MPH group, with no statistically significant differences among the groups. These findings were paralleled in the analysis of the WRAADDS total scores, which also showed significant time and baseline covariate effects but no treatment effects. Secondary analyses were conducted to explore whether baseline level of ADHD severity influenced response rates. When the participants were analyzed based on ADHD severity at baseline (using a median split with a cutoff of 32 on the AARS), no significant differences were observed across the groups for those with low baseline ADHD severity and those with high baseline severity, confirming no baseline by treatment interaction.
	Analysis of other outcome measures Other outcome measures were assessed for the three treatment arms. These included: **adherence** to methadone maintenance and severity of various problem areas (e.g., social, legal, family) as assessed by the Addiction Severity Index. None of the three treatment arms were shown to be superior based on these outcome measures (data not presented). All three groups self-reported being adherent to their methadone maintenance over 96% of the days while in the trial. This was confirmed with over 98% of their urine samples testing positive for methadone.
	Compliance The mean proportion of self-reported missed doses did not differ between the three groups, with each group missing about 5% of their doses. For the patients for whom riboflavin data were available (n = 49), the proportion of positive fluorescence results indicated that compliance did not differ across groups (placebo = 0.83, MPH = 0.77, BPR = 0.91)
	Adverse effects A variety of side effects were reported across all three groups but there were no significant group differences. A total of three patients were removed from the trial because of reported side effects.
	Loss to follow up Endpoint: N 29 (30 %) 24 % (8 out of 33) in the placebo group, 34 % (11 out of 32) in the MPH group, and 30 % (10 out of 33) in the BPR group were lost to follow up.

Study	Levin, 2006 [32]
Risk of bias	Low

BPR = Bupropion; **CBT/ RP**= cognitive behavioural therapy, relapse prevention; **CGI** = Clinical Global Improvement scale; **CI** = confidence interval; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition; **M** = mean; **MPH** = methylphenidate; **NR** = not reported; **RCT** = randomized controlled trial; RP = relapse prevention; **SD** = standard deviation; **XR** = extended release.

Malcolm et al. 1992

Study	Malcolm, 1992 [33]
Study design	RCT, double-blind
Intervention	**Pharmacotherapy: buspirone** Co-interventions: minimal, AA
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	First, to confirm the efficacy of buspirone in the treatment of clinically significant anxiety in adult, alcohol dependent males and second, to extend previously published studies to include the impact of that treatment on time-to-event alcohol relapse measures, volume of alcohol consumed, alcohol craving, and psychosocial functioning of those individuals.
Participants	**AUD & anxiety disorder** Highly anxious veterans who recently completed inpatient detoxification for alcoholism. Subjects met DSM-III-R criteria for GAD and/or other non-panic forms of anxiety disorders and alcohol dependence.
	Baseline characteristics **Buspirone** / **Placebo** n: **33** / **34** Women: n (%): 0 (0%) / 0 (0%) Age: M (SE) range: 44.3 (1.6) 26-58 / 41.7 (1.3) 28-64 Substance use status Years drinking: M (SD): 27 (10) / 26 (9) Years drinking to intoxication: M (SD): 17 (11) / 19 (10) Previous inpatient detoxifications, 0-1: %: 79% / 85% Previous inpatient detoxifications, ≥2: %: 21% / 15% Mental health status Previous treatment for emotional problems (yes): n (%): 19 (58%) / 19 (56%) Ever hospitalized for emotional problems (yes): n (%): 7 (21%) / 6 (18%)

Study	Malcolm, 1992 [33]
	Previously treated with psychiatric drugs (yes) n (%) 19 (58%) 20 (59%) NS baseline differences.
	Inclusion criteria Included an Axis I diagnosis of alcohol dependence and GAD as defined by DSM-III-R criteria based on the SCID interview for DSM-III-R; a consistently high HAM-A score >18 (0-12 mild; 13-20 moderate; 20 and above severe) at screening 2 weeks prior to the start of the study and again at the start of the study; subjects with GAD plus other types of nonpanic anxiety were permitted into the study; MMS score of ≥26 indicated no significant cognitive impairment
	Exclusion criteria Used CNS-acting medications for at least 7 days prior to the start of the study medication or used alcohol or illicit drugs for at least 14 days prior to the start of the study medication; severe liver disease or other significant medical problems; had used benzodiazepines or other sedative hypnotics for 7 or more days in the month prior to hospital admission; a current diagnosis of psychoactive drug abuse or dependence (other than alcohol), current major depressive episode, dementia, delirium, schizophrenia, mania, or panic disorder with or without agoraphobia as defined by DSM-III-R, using SCID interviews; had an AMA discharge from an alcohol treatment center within 1 year of screening or more than 2 inpatient enrollments for detoxification in the previous 12 months
	Recruitment & screening Male veterans (age 21-65) admitted for detoxification to the Veterans Administration Medical Center Alcohol Dependence Treatment Unit during 1987 to 1989 were screened for participation in the study; the subjects were enrolled during the 3rd week of their 28-day hospital stay and continued in the study on an outpatient basis for up to 26 weeks; numbers screened = 892; numbers randomized = 67
	Remuneration NR
Comparison	**Buspirone vs placebo**
	Duration of treatment 6 months
	Follow ups Measurements during treatment: weekly the first 12 weeks, thereafter every 2 weeks Endpoint: at week 26
Experimental arm	**Buspirone**

Study	Malcolm, 1992 [33]
	Initially one tablet three times per day (daily dose of 15 mg). At the end of 1 week, increased with one additional tablet every 2 days until a maximum dosage of four tablets three times per day (60 mg buspirone) by the end of the 2nd week. Subjects were then seen as outpatients once per week for the next 12 weeks and thereafter every 2 weeks until the end of the study (week 26).
	Co-interventions Pharmaceutical Subjects were not to take any investigational drug och any psychotropic medication with the exception of diphenhydramine for allergies or insomnia. All subjects were additionally prescribed to take riboflavin (50 mg three times daily) at the same time as their study medication. Subjects were told not to take vitamins other than those provided by the investigators. Psychosocial No additional psychotherapy or counseling was offered subjects by the research staff. Instead, all subjects were seen by the VA aftercare social worker as a routine part of their inpatient treatment. Optional psychosocial As with all patients leaving the twenty-eight-day treatment program, these patients were strongly encouraged to attend 90 meetings in 90 days of AA.
Control arm	**Placebo** Followed the same protocol (number of tablets) as the treatment group
	Co-interventions Pharmaceutical Same as for experimental arm. Psychosocial Same as for experimental arm. Optional psychosocial Same as for experimental arm.
Outcomes	**Substance use** Time to first drink (TLFB), patient-rated at each visit patient-rated at each visit Time to 5 consecutive drinking days (TLFB), patient-rated at each visit

Study	Malcolm, 1992 [33]
	Time to first intoxication (TLFB), patient-rated at each visit Number of standard drinks per drinking day (TLFB), patient-rated at each visit Proxy information on patient's abstinence or drinking behavior (FVR), interview in person or by telephone. Composite scores for medical-, alcohol-, drug-, legal-, family-, and psychosocial severity (ASI subscales), observer-rated at each visit Drug use (urine screen), 5 times over the study
	Mental health Anxiety (HAM-A,), observer-rated at each visit Anxiety (State-Trait Anxiety Scale), patient-rated at each visit Anxiety (Speilberger State Anxiety Scale), observer-rated at each visit Response defined as participants who demonstrated, at 12 weeks and beyond, HAM-A score <18 and HAM-A score reduction ≥30% from baseline.
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Subjects were instructed to return any unused study medication at each outpatient visit and a medication count was undertaken by the research pharmacist (results NR). Riboflavin was measured in urine as an ancillary measure of compliance of medication ingestion in both groups.
	Adverse effects Interview about incidence and severity of adverse reactions at each visit.
Results	**Substance use**

Survival outcomes[a]	Buspirone n=33	Placebo n = 34	Test of difference p-value
Time to first drink: months: Md	2.1	4.2	Log rank p = 0.57
Time to 5 consecutive drinking days, months: Md	NE	NE	Log rank p = 0.99
Time to first intoxication (≥5 standard drinks on one occasion), months: Md	4.0	4.2	Log rank p = 0.78

Study	Malcolm, 1992 [33]

	Endpoint	Endpoint	p-value
Drinks and drinkers[b]	**n=20****	**n = 18**	
Number of standard drinks per 28-Day period, M	152.0	171.7	0.7759
Number of drinkers	12	13	-
Number of nondrinkers	13	16	-
ASI scores[c]	**n=29**	**n = 34**	**p-value**
ASI subscale scores at week 12	NR	NR	NS
ASI subscale scores at week 26	NR	NR	NS
Subjects with detected drug use over the study (urine screen): n	3	2	NR

a- Time-to-event survival analysis included all randomized participants. The survival distribution function was computed using product-limit estimates. Data was extracted from the text. Additional information may be available from survival curves illustrated in figure 2; data not extracted.

b- The analyses for drinks and drinkers did not include non-drinkers and is otherwise based mITT data set (extender), e.g., only on the participants completing at least 2 weeks on study medication, 4 participants in the busiprone group did not meet this criterion. Missing data was handled using LOCF, however data collected more than fourteen days after the discontinuation of study medication was not included in the efficacy analyses. Median values provided; not extracted. No measure of variance is reported.

c- The analyses of ASI scores is mITT (extender data set), e.g., only participants who completed 2 or more weeks on medication, 4 participants in the busiprone group did not meet this criterion. Test of differences based on t-test and/or Wilcoxon rank sum test for non-parametric data. Analyzing data based on both visit data set and extender data sets indicated no significant differences on any of the subtests.

Comments

The visit data set uses only data for participants who completed the study; data not extracted.

Mental health

	Buspirone (n=29*) 12 weeks and beyond	Placebo (n = 34) 12 weeks and beyond	Test of difference p-value
Anxiety responders (HAM-A <18 plus ≥30% reduction in HAM-A from baseline): %	62%	56%	NS*

Analysis is mITT (extender data set), e.g., only participants who completed 2 or more weeks on medication, 4 participants in the busiprone group did not meet this criterion.

Comments

Similar analyses were made using change scores from baseline on the Speilberger State Anxiety Scale. Again, no statistical differences were found for either extender or visits data sets (data NR).

Study	Malcolm, 1992 [33]
	The visit data set uses only data for participants who completed the study; data not extracted.
	Compliance **Compliant** — **Buspirone n = 29**: **Riboflavin level in the urine, µg/ml: M (SD)** 4.6 (1.7); **Placebo n = 34**: 5.3 (4.0)
	Adverse effects **Buspirone n = 29** / **Placebo n = 34** **Reported at least one AE during the study: n (%)** 22 (67%) / 24 (71%) **Dizziness: %)** 45% / 0%
	Loss to follow up Endpoint: buspirone 33-10 = 23 (70%), placebo 34-10 = 24 (71%) Median number of weeks in the study was 9.1 weeks for the buspirone group and 12.8 weeks for the placebo group (NS).
Comments	All participants but one had inpatient treatment before study enrolment.
Risk of bias	Moderate

AA = Alcoholics Anonymous; **ASI** = Addiction Severity Index; **AUD** = alcohol use disorder; **CNS** = central nervous system; **DSM-III-R** = Diagnostic and Statistical Manual of Mental Disorders – 3rd edition, revised; **FVR** = Family visit report; **GAD** = generalized anxiety disorder; **HAM-A** = Hamilton Rating Scale for Anxiety; **LOCF** = last observation carried forward; **M** = mean; **Md** = median; **mITT** =modified intention to treat, in this case participants completing ≥ 2 weeks on study medication; **NE** = data not extracted; **NR** = not reported; **NS** = not significant; **RCT** = randomized controlled trial; **SCID** = Structured Clinical Interview for DSM; **SD** = standard deviation; **SE** = standard error; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **VA** = Veterans Administration.

McDowell et al. 2005

Study	McDowell, 2005 [34]
Study design	RCT, double-blind
Intervention	**Pharmacotherapy: Desipramine** Co-interventions: CBT/RP
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	The aim of this study was to test the hypothesis that desipramine would be an effective treatment in cocaine abusers with current depressive disorders.

Study	McDowell, 2005 [34]
Participants	**Cocaine dependence & depressive disorders** Outpatients meeting DSM-III-R criteria for cocaine dependence and major depression or dysthymia (by SCID interview).
	Baseline characteristics No significant baseline differences; the difference on dollar value of cocaine consumed per day approached statistical significance (p = 0.09)
	Inclusion criteria Meet DSM-III-R criteria for both cocaine dependence and current major depression or dysthymia, with at least one of the following features: (1) the depression was chronologically primary, antedating the onset of substance abuse on a lifetime basis; (2) the depression was chronologically secondary but persisted or emerged during a past episode of at least 6 months abstinence; (3) the depression was of at least 3 months duration in the current episode
	Exclusion criteria A history of bipolar disorder or psychotic illness other than brief psychotic symptoms attributable to cocaine intoxication; at risk for suicidal behavior; medically unstable; had a medical problem for which treatment with a tricyclic antidepressant was contraindicated

	Desipramine	Placebo
N=111	**55**	**56**
Women: n (%)	14 (25)	14 (25)
Age: M (SD)	36.04 (6.57)	35.75 (7.34)
Education, years: M (SD)	13.84 (2.16)	13.73 (2.14)
Employed: n (%)	45 (82)	51 (91)
Substance use status		
Days per week using cocaine: M (SD)	2.22 (2.26)	1.76 (1.91)
USD value of cocaine used per day: M (SD)	56.45 (85.60)	34.82 (38.68)
Proportion with any use at baseline: n (%)		
Alcohol	43 (78)	39 (70)
Cannabis	12 (22)	17 (30)
Benzodiazepines	2 (4)	0 (0)
Opiates	0 (0)	1 (2)
Mental health status		
Current major depression: n (%)	38 (69)	40 (71)
Current dysthymia: n (%)	26 (47)	27 (48)
HAM-D: M (SD)	15.85 (3.56)	16.27 (5.51)

Study	McDowell, 2005 [34]
	(e.g. history of seizures, cardiac conduction disease); diagnosis of current dependence on other substances (not nicotine, alcohol, or cannabis); in the case of concurrent alcohol or cannabis dependence, it was required that cocaine be the predominant clinical problem
	Recruitment & screening Adults (aged 18–65) seeking treatment for cocaine abuse were recruited by word of mouth and advertisement to a research clinic; prospective participants were screened with a physical and laboratory evaluation, and diagnostic evaluation was carried out; eligible patients were placed on single-blind placebo for 1 week in order to remove noncompliant patients prior to randomization, as well as those with an initial placebo response (having a CGI depression improvement score of 2 or, i.e. “much” or “very much improved”, and no drug use or craving); numbers screened = NR; numbers eligible (entering single blind placebo phase) = 127; numbers randomized = 111
	Remuneration NR
Comparison	**Desipramine vs. placebo**
	Duration of treatment 12 weeks
	Follow ups Measurements during treatment: weekly or biweekly Endpoint: at 12 weeks
Experimental arm	**Desipramine** 50 mg tablets packaged in unmarked gelatin capsules with lactose filler and titrated on a fixed-flexible schedule; doses began at 50 mg per day and were increased by 50 mg every 4 days up to 300 mg per day or the maximum tolerated dose; visits at the clinic twice a week for the duration of the 12-week study
	Co-interventions <u>Psychosocial</u> All patients received weekly individual manual-guided CBT/RP and MI at the onset of treatment, administered by a masters or doctoral level clinician
Comparison	**Placebo** Placebo consisted of identical appearing gelatin capsules containing only filler; titration and visits as in treatment group

Study	McDowell, 2005 [34]
	Co-interventions Psychosocial As for experimental arm
Outcomes	**Substance use** Primary outcomes: Global cocaine response (clinician's rating designed to reflect at least 75% reduction in cocaine use), at week 12, or the last week of study attendance for dropouts. Proportion of patients with at least three consecutive weeks of urine-confirmed abstinence (composite of self-report of no cocaine use and a supervised urine negative for cocaine metabolite), assessed weekly and calculated at end of study Secondary outcomes: Frequency (in days per week) of cocaine use (modified TLFB), weekly self-report USD value of cocaine consumed per day of use (estimation), weekly self-report
	Mental health Primary outcomes: Global depression response (composite outcome, clinician's rating based on all available data, consistent with a CGI improvement score of 2 "much improved" or 1 "very much improved"), at week 12 Proportion of patients with at least 50% reduction in HAM-D, at week 12 Secondary outcomes: Depression severity score (CGI), assessed by the study psychiatrist, weekly Depression (HAM-D), assessed by the study psychiatrist, biweekly
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance

Study | **McDowell, 2005 [34]**

Retention in the study: number and proportion completing the 12-week trial

Retention in the study: number and proportion completing at least 4 weeks of the trial

Compliance to medication: Serum desipramine levels (blood test), at weeks 6 and 12 (part way thorough the trial, a blood draw at 3 weeks was added)

Adverse effects

Method for collecting information about adverse effects NR

Results

Substance use

	Desipramine (ITT, n = 55)	Placebo (ITT, n = 56)	Difference (95% CI)	p-value
Primary outcomes	**Endpoint**	**Endpoint**		
Cocaine response, clinician's global rating, proportion (n)	0.45 (25)	0.38 (21)	0.08 (−0.10 to 0.26)	0.40
Abstinent for at least three consecutive weeks, proportion (n)	0.20 (11)	0.20 (11)	0.00 (−0.14 to 0.15)	0.96
Secondary outcomes	**Endpoint**	**Endpoint**	**Difference (95% CI)**	**p-value**
Days per week using cocaine*, M (SD)	1.25 (1.31)	1.19 (1.33)	−0.06 (−0.56 to 0.44)	0.82
USD value of cocaine used per day of use*, M (SD)	27.27 (30.21)	25.47 (25.49)	−1.80 (−12.29 to 8.69)	0.74

* Scores from the last 4 weeks before the endpoint were averaged to arrive at a summary score

Comments

Results for the outcomes days per week using cocaine, dollar value, och urine cocaine metabolite based on mixed effects models are presented in table 4; data not extracted.

Mental health

	Desipramine (ITT, n = 55)	Placebo (ITT, n = 56)	Difference (95% CI)	p-value
Primary outcomes	**Endpoint**	**Endpoint**		
Global depression response*, proportion (n)	0.51 (28)	0.32 (18)	0.19 (0.01 to 0.37)	0.05
Depression response, at least 50% reduction in HAM-D score*, proportion (n)	0.56 (31)	0.30 (17)	0.26 (0.08 to 0.44)	0.01
Secondary outcomes	**Endpoint**	**Endpoint**	**Difference (95% CI)**	**p-value**
CGI depression severity score, M (SD)	2.78 (1.42)	3.43 (1.52)	0.65 (0.10 to 1.20)	0.02
HAM-D total score, M (SD)	8.93 (6.72)	11.28 (7.40)	2.35 (−0.30 to 5.00)	0.08

* Using the last observation for patients completing less than 12 weeks

Comments

Study	McDowell, 2005 [34]
	Sub-group analyses comparing patients who experienced a substantial mood improvement (meeting the depression response criteria) to patients whose mood did not respond also reported, data not extracted by SBU.
	Compliance **Compliant** / **Desipramine n = 55** / **Placebo n = 56** / **Test of difference** **Retention, completed the 12-week trial: n (%)** 25 (45%) 22 (39%) NS **Retention, completed at least 4 weeks of the trial: n (%)** 43 (78%) 42 (75%) NS **To medication, mean of maximum serum desipramine levels, ng/ml: M (SD)** 251 (277) - NA **Proportion of maximum serum levels below minimum therapeutic level (125 ng/ml)** 41% - NA
	Adverse effects **Desipramine n = 55** / **Placebo n = 56** **SAE, suicide attempt: n** - 1 **SAE, severe diarrhea requiring hospitalization: n** - 1 **SAE, episodes of syncope: n** 2 - Comments By authors: Desipramine was associated with more dropouts due to side effects and medical adverse events (16% in desipramine group, 2% in placebo group), while placebo was associated with more dropouts due to psychiatric worsening (2% in desipramine group, 13% in placebo group).
	Loss to follow up Endpoint, N (%): desipramine 30 (55%); placebo 34 (61%)
Risk of bias	Moderate

CBT/RP = Cognitive behavioural therapy, focus on relapse prevention; **CGI** = Clinical Global Impression; **CI** = confidence interval; **DSM-III-R** = Diagnostic and Statistical Manual of Mental Disorders – 3rd edition, revised; **HAM-D** = Hamilton depression scale; **ITT** = intention to treat; **M** = mean; **MI** = motivational interviewing; **NA** = not applicable; **NR** = not reported; **NS** = not significant; **RCT** = randomized controlled trial; **SAE** = serious adverse effects; **SCID** = Structured Clinical Interview for DSM; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **USD** = US American dollar.

McGrath et al. 1996

Study	McGrath, 1996 [35]
Study design	RCT, placebo-controlled
Intervention	**Pharmacological: Imipramine HCl**

Study	McGrath, 1996 [35]
	Co-interventions: individual RP counselling
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	Our study enrolled alcohol-abusing subjects who gave a history of clear primary depression in a placebo-controlled antidepressant trial using a vigorous antidepressant treatment regimen to address three main questions: (1) Does primary depression identified in actively drinking alcoholics respond to tricyclic antidepressants? (2) Is a tricyclic antidepressant safe to administer to actively drinking alcoholic outpatients without physical dependency on alcohol? (3) Do patients whose depression responds to an antidepressant and concurrent alcohol counselling decrease their drinking?
Participants	**AUD & depression** Actively drinking people with AUD (dependence or abuse) with depression Subjects were between the ages of 18 and 65 years, met the DSM-III-R criteria for either current alcohol dependence or abuse and for current major depression, dysthymia, or depressive disorder not otherwise specified. According to DSM III-R criteria, patients largely were alcohol dependent with histories of early-onset chronic depressive illness of moderate severity and atypical subtype. The relatively low HAM-D scores for both groups may be a result of the large proportion of subjects meeting criteria for atypical depression. They had high prevalence's of panic disorder and past dysthymia and modest histories of dependence on other substances. Their drinking was moderately heavy with a moderate severity of alcoholism on the Michigan Alcoholism Screening Test (mean [±SD] score, 13.8±6.5).
	Baseline characteristics* **Imipramine** / **Placebo** / **Test statistic** / **P** N= 36 / 33 Women: % 48.5 / 53.3 / x^2=0.12 / 0.72 Age years: M (SD) 37.4 (6.7) / 40,6 (9.1) / F=1.64 / 0.11 White % 83.3 / 78.8 / x^2=2.66 / 0.45 Currently married % 30.6 / 9.1 / x^2=4.34 / 0.04 Education, year M (SD) 14.5 (2.3) / 14.5 (3.2) / F=0.02 / 0.99 Employed % 42.9 / 59.4 / x^2=1.22 / 0.27

Study	McGrath, 1996 [35]				
	Alcohol dependence	94.4	96.9		1
	Major depression	72.2	71.0	0.00	
	Bipolar depression NOS	11.1	12.2		1
	Atypical depression[a]	70.4	72.4	0.00	0.50
	Past dysthymia	48.1	44.8	0.00	1
		M (SD)	**M (SD)**		
	HAMD 21 item	15.4 (5.2)	14.3 (5.2)	0.85	.34
	HSCL-90, summary	20.0 (4.9)	21.6 (5.6)	0.46	0.65
	Age onset alcohol disorder	28.6 (15.2)	25.7 (9.2)	0.94	0.33
	Proportion days drinking[b]	63.8 (33.5)	68.0 (31.8)	0.65	0.52
	Proportion days drinking heavily (>6 oz/d) % (2)	38.3 (34.4)	51.5 (39.3)	1.48	0.14
	Drinks per drinking day, mean (3)	9.1 (6.5)	11.4 (13.7)	0.90	0.37
	All diagnoses definite plus probable by DSM-III-R unless otherwise indicated. a- Atypical depression, definite and probable, by Columbia criteria b- Drinking measures from the TLFB for the week before beginning the study c- Two-tailed Fischer's exact test employed for expected call frequencies 5 or less. <u>Comments</u> Although groups were comparable on almost all measures, significantly more subjects randomized to imipramine were currently married.				
	Inclusion criteria Depressive disorder was required to be primary, defined as either having had its onset prior to the onset of alcohol abuse or having continued during at least 6 months of sobriety. Subjects with secondary depressive disorders were excluded from our study.				
	Exclusion criteria Subjects were excluded because of a history of mania, psychosis, seizure disorder, severe current physical dependence on alcohol requiring inpatient detoxification, abstinence of 2 weeks' duration at baseline, or for current serious and unstable physical illnesses. Also excluded were subjects meeting criteria for dependence on another substance, apart from nicotine, within the last 6 months and women not using adequate contraception. A history of current abuse of other substances was not exclusionary, provided that alcohol was clearly the main substance of abuse.				

Study	McGrath, 1996 [35]
	Recruitment & screening Subjects were recruited to a university-based depression research clinic through advertisements and referrals. The DSM III-R diagnoses were made by a research psychiatrist using the structured clinical interview for DSM IÍI-R, patient version. Physical evaluation consisted of medical history, physical examination, electrocardiogram, chemistry screening, urinalysis, and urine screen for drugs of abuse. Of approximately 480 telephone inquiries from potential subjects, 123 who were interested and possibly eligible were screened in person. Twenty-three (19%) subjects did not meet inclusion criteria for either alcohol abuse or a depressive disorder or both, eight (6%) were excluded because of a physical illness, and seven (6%) were uninterested in study participation. Of the remaining 85 patients who began the single-blind placebo washout week, 11 (13%) responded to placebo with much improved depression, five (6%) were excluded because they were abstinent at both baseline and randomization visits, and 69 (81%) were randomized, with 36 to imipramine and 33 to placebo. <u>Pre-screening</u> Patients were given single-blind placebo for 1 week. Patients whose depression was not rated "much improved" or "very much improved" on the improvement item of the CGI for depression were randomized
	Remuneration NR
Comparison	**Imipramine vs. placebo**
	Duration of treatment 12 weeks An adequate trial of imipramine was prospectively defined as 4 weeks medication with a minimum dose of at least 150 mg of imipramine-HCl for 2 consecutive weeks or the equivalent number of placebo capsules.
	Follow ups Patients were seen weekly and assessed for depression and alcohol consumption using the TLFB the CGI, and HAMD. Plasma levels of imipramine and desipramine were measured at weeks 6 and 12. Attendance at AA was rated for the previous 7 days as percentage of days attending of 7 days. Saliva samples were screened for alcohol at each visit using an enzymatic dipstick method. Urine samples for alcohol and drugs of abuse were obtained at baseline and end of treatment.
Experimental arm	**Imipramine-HCl**

Study	McGrath, 1996 [35]
	Patients randomized to imipramine HCl began at 50 mg and increased by 50 mg every 3 to 5 days until a maximum dose of 300 mg was reached, there was significant improvement, or side effects became dose limiting. Medication was given as a tablet in a single evening dose.
	Co-interventions Psychosocial Patients were seen weekly for individual RP counselling sessions. The focus of the counselling was identifying individual high-risk situations for drinking and developing cognitive and behavioral coping strategies to avoid alcohol use in those situations. Attendance at AA was strongly encouraged.
Control arm	**Placebo** Same as for Imipramine-HCl, identical tablets.
	Co-interventions Psychosocial Same as for Imipramine-HCl.
Outcomes	**Substance use** Patients were seen weekly and assessed for alcohol consumption using the TLFB and the CGI (criterion much improved or better). Saliva samples were screened for alcohol at each visit using an enzymatic dipstick method. Urine samples for alcohol and drugs of abuse were obtained at baseline and end of treatment. Patients who were abstinent or whose amount of alcohol use declined by at least 50%, supported by any available significant other report, were considered responders if they also met the response criterion for depression.
	Mental health Patients were seen weekly and assessed for depression using the CGI criterion of much improved or better and the Hamilton Depression Scale. Plasma levels of imipramine and desipramine were measured at weeks 6 and 12.
	Quality of life Not assessed
	Function Not assessed

Study	McGrath, 1996 [35]
	Mortality Not assessed
	Compliance 56 patients (81% of those randomized) met criteria for adequate medication treatment. 35 patients (51%) of those randomized completed the entire 12 weeks of the trial. 13 patients dropped out after randomization: 9 (13%) because of side effects from imipramine and 4 who were receiving placebo; 3 (4%) placebo treated patients dropped out because of noncompliance; and 1 (1%) because of elective hospitalization for alcohol detoxification (2 [1]=1.1 ; P, not significant). Attendance at AA was rated for the previous 7 days as percentage of days attending of 7 days. Patients receiving active imipramine attended a comparable number of counseling sessions (mean±SD, 7.8±5.0) as those receiving placebo (mean±SD, 6.9±3.0; t [63] =0.9; P, not significant).
	Adverse effects 9 patients (13%) dropped out because of side effects from imipramine and 4 who were receiving placebo.
Results	**Substance use**

Treatment outcome at end point for completers and ITT - Substance use

	Imipramine (n=27)	**Placebo** (n=29)	**x² or F***	**P****	**Imipramine** ITT (n=36)	**Placebo** ITT (n=33)	**x² or F***	**P****
Global response rate %	52	21	4.6	<0.05	42	18	3.4	<.05
Abstinent last week %	44	22	1.1	NS				
Abstinent last 4 week %	31	21	1.1	NS				
Proportion days drinking[2] %					28.3	30.8	.09	NS
Proportion days drinking heavily (>6 oz/d) %					13.5	9.0	1.02	NS
Drinks per drinking day, mean					3.7	4.1	1.0	NS

* $x^{2,}$ df=1

** One tailed≥

Study	McGrath, 1996 [35]

[1] Hamilton Depression (HAM-D) Scale score decreased from baseline by 50% or more.
[2] During the final week in the study

SUBGROUP ANALYSIS

Table 3. Drinking Outcome Measures by Depression Response and by Drug for Study Completers*

Outcome Variable Mean (SD)	Depression Responders IMI	Depression Responders PBO	Depression Nonresponders IMI	Depression Nonresponders PBO	Depression Response F	Depression Response P	Drug Effect F	Drug Effect P	Interaction F	Interaction P
Mean drinks per drinking day (n=56)	1.5 (2.5)	4.0 (5.1)	6.4 (5.6)	4.1 (3.6)	4.8	<.05	.01	NS	4.5	<.05
No. (%) of days drinking (n=56)	17 (30)	25 (35)	42 (33)	33 (32)	4.2	<.05	.00	NS	1.2	NS
No. (%) of days drinking heavily (≥6 oz, n=56)	1 (4)	5 (6)	29 (30)	11 (19)	11.1	<.01	2.3	NS	4.4	<.05
No. (%) of days drinking lightly (≤6 oz, n=56)	25 (38)	21 (33)	19 (34)	31 (35)	0.1	NS	0.3	NS	0.8	NS
No. (%) of days AA attendance (n=33)	3 (6)	8 (11)	20 (33)	16 (30)	2.4	NS	0.1	NS	0.8	NS

*IMI indicates imipramine hydrochloride; PBO, placebo; and NS, not significant.

Comments	* Global response was rated on the CGI scale where patients rated much improved or very much improved on both depression and on alcohol ratings were considered to be responders.

Results
Mental health

Treatment outcome at end point for completers and ITT - Mental health

	Imipramine (n =27)	Placebo (n =29)	x² or F*	P**	Imipramine ITT (n=36)	Placebo ITT (n=33)	x² or F*	P**
Global response rate %	52	21	4,6	<.05	42	18	3.4	<.05
HAM-D 21 item, mean (SD)	9,4 (7,7)	12,4 (9,7)	0,6	<.03	10.3 (7.2)	12.7 (6.9)	2.69	.05
HAM-D decreased ≥50 %[1]	48	31	1,1	NS				
HAM-D decreased ≥50 % and final HAM-D scale ≤6	37	28	0,1	NS				

Study	McGrath, 1996 [35]
	* $x^{2,}$ df=1 ** One tailed≥ [1] Hamilton Depression (HAM-D) Scale score decreased from baseline by 50% or more. [2] During the final week in the study
Compliance	56 patients (81% of those randomized) met criteria for adequate medication treatment. 35 (51%) of those randomized completed the entire 12 weeks of the trial.
Adverse effects	The most common side effect resulting in discontinuation was severe sedation experienced by four patients; other side effects included dizziness, constipation, gastrointestinal distress, urinary retention, and a single case of drug rash. No patient discontinued medication because of a clear adverse interaction between imipramine and alcohol and no seizures or hepatotoxicity occurred.
Loss to follow up	13 patients dropped out after randomization: nine (13%) because of side effects from imipramine and four who were receiving placebo; three (4%) placebo treated patients dropped out because of noncompliance. and one (1%) because of elective hospitalization for alcohol detoxification (2 [1]=1.1 ; P, not significant).
Risk of bias	Måttlig

AA = Alcoholics Anonymous; **AE** = adverse events; **AUD** = alcohol use disorder; **BAI** = Beck Anxiety Inventory; **BDI** = Beck Depression Inventory; **CGI** = Clinical Global Impression; **DSM-III-R** = Diagnostic and Statistical Manual of Mental Disorders – 3rd edition, revised; **HAM-A** = Hamilton Rating Scale for Anxiety; **HAMD** = Hamilton depression scale; **HCl** = hydrochloride; **HSCL-90** = Hopkins Symptom Checklist, 90-item self-rated version; **ITT** = intention to treat; **LOCF** = last observation carried forward; **M** = mean; **NOS** = not otherwise specified
NR = not reported; **RCT** = randomized controlled trial; **RP** = relapse prevention; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report.

McRae et al. 2004

Study	McRae, 2004 [36]
Study design	RCT, double-blind, pilot study
Intervention	**Pharmacotherapy: busiprone** Co-interventions: methadone maintenance treatment
Trial registration	NR
Country	USA
Setting	Outpatient

<table>
<tr><th>Study</th><th>McRae, 2004 [36]</th></tr>
<tr><td>Aims</td><td>To evaluate the efficacy of buspirone for the treatment of anxiety in opioid-dependent subjects receiving methadone maintenance treatment. We hypothesized that buspirone treatment would reduce anxiety symptoms, and that a reduction in anxiety symptoms would result in decreased substance use among buspirone-treated subjects as compared to placebo.</td></tr>
<tr><td>Participants</td><td>OUD & anxiety disorder
Opioid-dependent patients with anxiety symptoms receiving methadone-maintenance treatment
78% of subjects met DSM-IV criteria for at least one anxiety disorder; the largest percentage (47%) met criteria for GAD.</td></tr>
<tr><td></td><td>Baseline characteristics
<table>
<tr><th></th><th>Buspirone</th><th>Placebo</th></tr>
<tr><td>n</td><td>19</td><td>17</td></tr>
<tr><td>Women: %</td><td>42%</td><td>47%</td></tr>
<tr><td>Age: M (SD)</td><td>37.0 (9.3)</td><td>36.6 (9.6)</td></tr>
<tr><td>Education, years: M (SD)</td><td>12.6 (2.2)</td><td>12.7 (2.4)</td></tr>
<tr><td>Employed: %</td><td>53%</td><td>76%</td></tr>
<tr><td><u>Substance use status</u></td><td></td><td></td></tr>
<tr><td>Methadone dose,mg: M (SD)</td><td>102.9 (50.7)</td><td>85.3 (40.0)</td></tr>
<tr><td>Percentage days abstinent prior 3 months: M (SD)</td><td>73.5 (30.5)</td><td>83.4 (27.1)</td></tr>
<tr><td><u>Mental health status</u></td><td></td><td></td></tr>
<tr><td>HAM-A: M (SD)</td><td>21.7 (4.1)</td><td>22.4 (3.9)</td></tr>
<tr><td>HAM-D: M (SD)</td><td>18.6 (5.2)</td><td>15.4 (5.9)</td></tr>
<tr><td>BAI: M (SD)</td><td>26 (12.8)</td><td>18.1 (11.9)</td></tr>
<tr><td>BDI: M (SD)</td><td>22.6 (9.5)</td><td>17.9 (11.62)</td></tr>
</table>
NS baseline differences.</td></tr>
<tr><td></td><td>Inclusion criteria
At least 18 years old; meet DSM-IV criteria for opioid dependence; have a score of ≥18 on HAM-A; been in methadone maintenance treatment for a minimum of four weeks and on a stable methadone dose for a minimum of two weeks</td></tr>
<tr><td></td><td>Exclusion criteria
Currently met DSM-IV dependence criteria for another psychoactive substance (excluding caffeine or nicotine); had a primary Axis I disorder other than an anxiety disorder; lack of stable housing; women who were pregnant, nursing, or refused to use adequate birth control; major medical illnesses that might interfere with the conduct of the study</td></tr>
<tr><td></td><td>Recruitment & screening</td></tr>
</table>

Study	McRae, 2004 [36]
	Screened clinic charts for clients on a stable methadone dose at two outpatient methadone maintenance treatment facilities; numbers screened = 297; numbers eligible = 62; numbers randomized = 36; information on detoxification period before randomization NR
	Remuneration NR
Comparison	**Buspirone vs placebo**
	Duration of treatment 12 weeks
	Follow ups Measurements during treatment: weekly (TLFB), or more seldom (see Outcomes for details) Endpoint: week 12
Experimental arm	**Buspirone** Provided in opaque capsules, packed with cornstarch and containing either 5 or 15 mg of buspirone with 25 mg of riboflavin; if a subject was taking a multivitamin containing riboflavin, a vitamin preparation without riboflavin was given in place of the regular supplement; initial dosage of 5 mg buspirone twice daily; flexible dosing titration; medication was increased by 5 mg twice daily every three to four days to a maximum total daily dose of 60 mg unless side effects limited dosage increase or therapeutic efficacy was achieved; the maximum dose was generally reached by the end of the second week of treatment
	Co-interventions Methadone maintenance treatment Details NR
Control arm	**Placebo** Placebo capsules were matched for colour and appearance and contained 25 mg riboflavin; dosage followed the same protocol as the treatment group
	Co-interventions Methadone maintenance treatment Details NR
Outcomes	**Substance use**

Study	McRae, 2004 [36]
	Secondary outcome (primary assessment) Time until drug use (TLFB), self-reported at baseline and weekly during treatment (until week 12) Secondary outcome (secondary assessment) Time until drug use (urine drug screen), weekly for opioids (other than methadone), cocaine, marijuana, and stimulants; at baseline, weeks 5 and 10 for benzodiazepines
	Mental health Primary outcomes Anxiety (HAM-A), clinician-administered at baseline and weeks 1, 2, 3, 4, 6, 8, and 12 Anxiety (BAI), clinician-administered at baseline and weeks 4, 8, and 12 Depression (HAM-D), clinician-administered at baseline and weeks 4, 8, and 12 Depression (BDI), clinician-administered at baseline and weeks 4, 8, and 12
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Assessed by pill count (having taken at least 90% of the directed dosage), subject self-report, and urine riboflavin levels (at least one positive riboflavin test at either week 5 or 10; missing riboflavin data was considered a negative test result). Treatment retention reported as number (percentage) of subjects completing the 12-week study.
	Adverse effects Method for collecting information about AE NR
Results	**Substance use**

	Buspirone (ITT, n = 19)	Placebo (ITT, n = 17)	Test of difference, p-value
Primary assessment			
Time to substance use (TLFB), median days	23	9	0.134
Secondary assessment			

Study	McRae, 2004 [36]

Time to substance use (urine drug screen for any drug), worst case scenario	Data NR	Data NR	0.8144
Time to substance use (urine drug screen for any drug), LOCF*	Data NE	Data NE	0.0853
		R	

* Median value is presented in figure 4; data not extracted.

Comments

Primary survival analyses were based on ITT-principle. Two methods applied to missing data: (1) worst case scenario, where a missed weekly urine test was considered positive for substance use, and (2) LOCF.

Data for secondary analysis on compliant subjects not extracted.

Mental health

	Buspirone (ITT, n = 19)	Placebo (ITT, n = 17)	Test of difference, (time x treatment)
Primary outcomes	**Endpoint**	**Endpoint**	**p-value**
HAM-A, mean	9.2	13.8	0.6241
HAM-D, mean	9.2	11.3	0.7107
BAI, mean	7.8	13.4	0.2262
BDI, mean	8.4	11.4	0.1560

Endpoint values extracted by SBU from Figure 1

Comments

Primary HLM analyses were based on ITT-principle; p-values reflect the regression coefficient for interactions between time and treatment effect; baseline scores were used as a covariate.

Data for secondary analysis on compliant subjects not extracted.

Compliance

Compliant	Buspirone ITT, n = 19	Placebo ITT, n = 17
Pill count: %	92.3%	94.3%
At least one riboflavin-positive urine sample: n (%)	10 (53%)	9 (53%)
Treatment retention (completers): n (%)	8 (42%)	11 (65%)

Adverse effects

	Buspirone ITT, n = 19	Placebo ITT, n = 17
Any AE, reporting subjects: n (%)	11 (58%)	6 (35%)
Headache; %	21%	18%

Study	McRae, 2004 [36]		
	Nausea and/or vomiting: %	16%	18%
	Increased dreaming: %	10%	6%
	Dizziness: %	10%	0%
	Drowsiness: %	5%	0%
	Loss to follow up		
	Endpoint, n (%): total 17 (47%); buspirone 11 (58%); placebo 6 (35%)		
Risk of bias	Moderate		

AE = adverse events; **BAI** = Beck Anxiety Inventory; **BDI** = Beck Depression Inventory; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition; **HAM-A** = Hamilton Rating Scale for Anxiety; **HAM-D** = Hamilton Rating Scale for Depression; **ITT** = intention to treat; **LOCF** = last observation carried forward; **M** = mean; **NR** = not reported; **OUD** = opioid use disorder; **RCT** = randomized controlled trial; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report.

Moak et al. 2003

Study	Moak, 2003 [37]
Study design	RCT, double-blind
Intervention	**Pharmacotherapy: sertraline** Co-intervention: CBT/RP
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	To determine the efficacy of the SSRI sertraline when added to CBT in the treatment of individuals with depression and alcoholism.
Participants	**AUD & depression** Currently depressed (either primary or substance-induced), actively drinking alcohol-dependent individuals; the subject population consisted of early-stage alcoholics who were appropriate for outpatient treatment
	Baseline characteristics

	Sertraline	**Placebo**
n	**38**	**44**
Women: n (%)	15 (39%)	17 (39%)
Age: M (SD)	41 (11)	42 (10)
Education, years: M (SD)	15 (2)	15 (2)
Substance use status		
Drinking days during placebo lead-in period: M	0.7	0.5

Study	Moak, 2003 [37]
	Drinks per drinking day during placebo lead-in period: M 0.9 0.9 Persons drinking during placebo lead-in period: n 14 14 Drinks per drinking day 90 days before study entry: M (SD) 11.3 (5.2) 10.5 (4.5) Heavy drinking days (≥5 drinks) per week 90 days before study entry: M (SD) 5.0 (1.7) 4.9 (2.0) Alcohol dependence scale: M (SD) 17.7 (8.4) 17.7 (6.9) Mental health status HAM-D: M (SD) 19.4 (2.6) 18.8 (2.4) BDI: M (SD) 24.1 (8.4) 22.0 (9.7) The authors report no significant differences between treatment groups for any of the baseline measures.
	Inclusion criteria Meet current DSM III -R criteria for either major depressive episode or dysthymic disorder; either primary (independent) major depressive episode or dysthymic disorder or a clear family history of affective disorder without comorbid substance abuse in a first degree relative (parent, sibling, or child); a score of at least 17 on the HAM-D (21 item) both at screening and at the end of 1 week of single-blind placebo; meet criteria for current alcohol dependence or abuse and have drunk a minimum of 40 standard drinks during the month before study entry; mild to moderate alcohol dependence, which was operationally defined as not having more than 1 past inpatient alcohol detoxification; women of childbearing potential were required to use a reliable form of birth control; been off the detoxification medication for at least 48 hours prior to being started on single-blind placebo; subjects who were receiving serotonergic medications, including SSRIs, had to be completely off these medications for at least 4 weeks before study entry; other psychoactive medications, including tricyclic antidepressants, had to be discontinued for at least 2 weeks.
	Exclusion criteria Any current psychoactive substance dependence other than nicotine; psychoactive substance abuse in the month before study entry other than marijuana; current panic disorder or posttraumatic stress disorder; and lifetime history of bipolar affective or psychotic disorder; evidence of treatment-resistant depression, defined as 2 or more past adequate, unsuccessful treatment episodes for depression; subjects with any significant current suicidal ideation or plan, homicidal ideation, unstable medical illness, or history of a seizure disorder were referred for standard clinical treatment.
	Recruitment & screening Subjects were treatment-seeking individuals who responded to newspaper advertisements or who were referred from clinical sources (in- and outpatient); numbers screened by telephone = 240; numbers in-person screened (including assessment of need for outpatient detoxification) = 185; numbers randomized = 82; 7-day single-blind placebo period before randomization, when subjects were encouraged to remain sober

Study	Moak, 2003 [37]
	Remuneration NR
Comparison	**Sertraline vs placebo**
	Duration of treatment 12 weeks
	Follow ups Measurements during treatment: weekly Endpoint: 12 weeks Follow-up (posttreatment): at weeks 16 and 26 (to be reported in separate publication)
Experimental arm	**Sertraline** Daily dosage of 4 tablets (50-mg) with a 100-mg riboflavin tablet; started on 50 mg daily and titrated up to 200 mg daily over a 2-week period; at the end of the study, the dosage was titrated back down to 50 mg over a 7-day period and then stopped prior to the week 12 visit; a study physician saw all subjects weekly for the first 6 weeks, thereafter every other week and prescribed a reduced dosage if side effects warranted a reduction (reduced with 50 mg increments at a time) until the side-effect was either relieved or could be tolerated
	Co-interventions CBT All subjects received weekly individual modified alcohol relapse prevention CBT (8 core sessions, 4 elective) with the first session delivered during the single-blind week to provide the subject with some initial tools to maintain abstinence and to establish contact with the therapist. AA Four subjects attended AA meetings during the study
Control arm	**Placebo** Followed the same protocol as the treatment group
	Co-interventions CBT Followed the same protocol as the treatment group

Study	Moak, 2003 [37]
	AA Seven subjects attended AA meetings during the study
Outcomes	**Substance use** Time to first HDD defined as ≥5 std drinks in 1 day (TLFB), administered weekly Time to first drink (TLFB). administered weekly DDD while in study (TLFB), administered weekly Percent days abstinent while in study (TLFB), administered weekly Alcohol use (the blood marker CDT), at baseline, and weeks 4, 8 and 12
	Mental health Depression (HAM-D), administered weekly Depression (BDI), administered weekly
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Subjects were asked each week for a urine sample for riboflavin; medication compliance was defined as having a urine riboflavin level of at least 1500 ng/mL in at least 75% of urine samples
	Adverse effects Method for collecting information about adverse effects NR
Results	**Substance use**

	Sertraline (ITT, n = 38) Over the 12-week study	Placebo (ITT, n = 44) Over the 12-week study	Test of difference p-value
Time to first HDD (≥5 std drinks in 1 day)*	-	-	NS
Time to first drink*	-	-	NS
Drinks per drinking day while in study: M (SE)**	2.3 (0.5)	3.5 (0.5)	0.027

Study | **Moak, 2003 [37]**

Percent days abstinent while in study: M (SE)**	81.1 (4.4)	80.6 (3.8)	NS
CDT levels	NR	NR	NS***

* Results presented graphically in figure 1; no measure of significance represented. Data cannot be extracted as the graphs presented for time to first HDD and time to first drink are identical. The authors report in the text that the between group differences are not statistically significant for either outcome.

** Results also presented by gender in table 3, data not extracted.

*** The authors report that there was "no effect of treatment group" on this outcome.

Comments

Models for all outcome measures were fit adjusting for baseline measures, gender, CBT attendance (8 weeks or more vs. less than 8 weeks), and AA attendance during the study (yes/no); controlling for baseline alcohol intake, alcoholism severity as measured by the Alcohol Dependence Scale or baseline HAM-D score did not change the results of the Kaplan -Meier survival analysis.

Mental health

	Sertraline (ITT, n = 38) Endpoint	**Placebo (ITT, n = 44) Endpoint**	**Test of difference p-value**
HAM-D*: M (SD)	7.8 (7.0)	8.8 (6.3)	NR
Non-responders (HAM-D score ≥50% of baseline)*: % (n)	14% (5)	30% (13)	0.13
BDI*: M (SD)	8.3 (8.4)	10.4 (11.4)	NR

* Results also presented by gender in table 3, data not extracted.

Comments

Models for all outcome measures were fit adjusting for baseline measures, gender, CBT attendance (8 weeks or more vs. less than 8 weeks), and AA attendance during the study (yes/no); using *drinking in the week before measurement of depression* as a time-dependent covariate in a repeated measures ANCOVA did not change the results.

Compliance

Compliant	**Sertraline n = 38**	**Placebo n = 44**	**Test of difference, p-value**
Subjects completing study: n (%)	31 (84%)	28 (67%)	0.08
Subjects with >75% medication compliance: n (%)	30 (79%)	34 (77%)	0.95
Study weeks completed: M (SD)	10.2 (3.7)	8.8 (4.2)	0.12
CBT sessions (completers only): M (SD)	10.5 (1.6)	10.8 (2.1)	0.45

Adverse effects

	Sertraline	**Placebo**

Study	Moak, 2003 [37]		
		n = 38	**n = 44**
	SAE: hospitalized due to deterioration of alcohol problem/emergence of another substance use problem: n	1	1
	SAE: hospitalized due to increased depression and suicidal ideation: n	2	0
	Loss to follow up Endpoint: Total* 28% (23), sertraline 18% (7), placebo 36% (16) * Based on data presented in Table 2 (59 of 82 completed study), however in the text the authors write that 57 people completed the study; loss to follow up would then be 30% (25).		
Risk of bias	Moderate		

AA = Alcoholics Anonymous; **ANCOVA** = analysis of covariance; **AUD** = alcohol use disorder; **BDI** = Beck Depression Inventory; **CBT/ RP**= cognitive behavioural therapy, relapse prevention; **DSM-III-R** = Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, Revised; **HAM-D** = Hamilton depression scale; **M** = mean; **NR** = not reported; **NS** = not significant; **RCT** = randomized controlled trial; **SD** = standard deviation.

Muhonen et al. 2008

Study	Muhonen, 2008 [38, 39]
Study design	RCT, double blind
Intervention	**Pharmacotherapy: Memantine vs Escitalopram** Co-interventions: need based individual counselling
Trial registration	NCT00368862
Country	Finland
Setting	Outpatient
Aims	The aim of this study was to compare effects of NMDA receptor antagonist memantine to escitalopram on alcohol consumption, in a natural sample of treatment-seeking alcohol-dependent patients (both actively drinking and recovering) with comorbid MDD [38], and to assess the effect of memantine relative to escitalopram in the treatment of MDD in these patients [39].
Participants	**AUD & Depression** Treatment-seeking for AUD, current episode of MDD

Study	Muhonen, 2008 [38, 39]

Baseline characteristics

	Memantine n = 40	Escitalopram n = 40
Men: % (n)	23 (57.5)	21 (52.5)
Age: M (SD, range)	47.5 (8.3)	47.9 (8.3)
Substance use status		
First alcohol intoxication, age: M (SD)	15.3 (3.8)	15.4 (2.3)
Onset of regular use of alcohol, age: M (SD)	20.7 (6.7)	20.5 (6.3)
Onset of alcohol abuse, age: M (SD)	29.5 (8.1)	28.3 (8.3)
Onset of alcohol dependence, age: M (SD)	30.6 (8.3)	29.1 (8.5)
AUDIT: M (SD)	27.4 (1.1)	28.4 (1.0)
No abstinence before study initiation: n (%)	17 (43.6)	17 (42.5)*
Alcohol problems among relatives: n (%)	31 (79.5)*	30 (76.9)*
Mental health status		
MADRS: M (SD)	25.8 (4.4)	26.8 (4.1)
First depressive episode, age: M (SD)	27.8 (12.3)	24.2 (13.0)
Total number of depressive episodes: M (SD)	10.0 (7.1)	9.6 (9.0)

There were no significant differences between the groups of any baseline socio-demographic background measures.

*missing information in one patient

Inclusion criteria

Patients were interviewed by a psychiatrist using SCID and were required to meet the criteria for both alcohol dependence and MDD according to DSM-IV-TR. In addition, the eligible patients had to be currently in a depressive episode lasting for more than two weeks.

Exclusion criteria

Other substance use dependence, schizophrenia or other psychotic disorder and bipolar I and II disorder, acute risk of suicide, pregnancy or breastfeeding, a severe untreated somatic problem or a serious liver dysfunction, and mental disability.

Recruitment & screening

Men and women who were voluntarily seeking outpatient treatment for alcohol problems at 3 Helsinki municipal Alcohol-clinics were screened. Helsinki, Finland, is a city of a half-million inhabitants, and municipal A-clinics provide various non-profit medical and psychosocial options yearly for 6000 people with alcohol problems. Eighty-nine patients were initially screened. Study enrolment began on December 20, 2004, and the last patient completed the study on May 25, 2006.

Remuneration

Study	Muhonen, 2008 [38, 39]
	The patients were not paid or reimbursed for participation.
Comparison	**Memantine vs. Escitalopram**
	Duration of treatment 26 weeks
	Follow ups Data collection at the clinic at weeks 1, 2, 4, 12 ± 2, and 26 ± 2
Intervention I	**Memantine** 20 mg/day of active medicine with a starting dose of 5 mg which and was increased at weekly intervals by 5 mg/day to 20 mg/day. After 4 weeks, the study physician was allowed to decrease the dose if a patient could not tolerate the medication.
	Co-interventions Pharmacological Other medications prescribed by participants' physicians were allowed, with the exception of other antidepressants. Psychosocial Psychological counselling (not manualized) at the clinic was given as needed. There were no additional psychosocial interventions by the study physician for alcohol consumption or other treatment goals.
Intervention II	**Escitalopram** 20 mg/day of active medicine with a starting dose of 5 mg which and was increased at weekly intervals by 5 mg/day to 20 mg/day. After 4 weeks, the study physician was allowed to decrease the dose if a patient could not tolerate the medication.
	Co-interventions Pharmacological Same as for memantine group. Psychosocial Same as for memantine group.
Outcomes	**Substance use** Drinking (personal everyday drinking diary), self-reported, recorded at weeks 0, 4, 12, and 26 [38] Alcohol (AUDIT), self-reported, weeks 0, 12 and 26 [38] Alcohol consumption (AUDIT-QF), interview, weeks 0, 12 and 26 [38]

Study	Muhonen, 2008 [38, 39]
	The number of heavy drinking days (AUDIT-3), interview, weeks 0, 12 and 26 [38]
	Mental health Primary outcomes: Depression (MADRS), interview, weeks 0, 4, 12, and 26 [39] Anxiety (HAM-A), interview, weeks 0, 4, 12, and 26 [39] Secondary outcomes: Depression (BDI-II), self-reported, weeks 0, 4, 12, and 26 [39] Anxiety (BAI), self-reported, weeks 0, 4, 12, and 26 [39]
	Quality of life Quality of Life (VAS), self-reported, weeks 0, 4, 12, and 26 [39]
	Function Cognitive test (CERAD), interview, weeks 0 and 26 [39] Cognitive test (MMSE), interview, weeks 0 and 26 [39] Social and Occupational Functioning (SOFAS), interview, weeks 0, 4, 12, and 26 [39]
	Mortality Not assessed
	Compliance The study medication intake was measured with the pill count from the returned blisterpacks, at weeks 0, 4, 12, and 26.
	Adverse effects Clinical laboratory tests (MCV, AST, ALT, CDT, and GGT) were taken at the beginning of the study and were repeated at weeks 4, 12, and 26, to ensure the safety of the medication. Any possible adverse events were elicited by the study physician at each visit and recorded by the study participant to the diary for adverse events adverse events.
Results	**Substance use** [38]

	Memantine (ITT, n = 40)			Escitalopram (ITT, n = 40)			Between group difference
	Baseline	Endpoint	Difference	Baseline	Endpoint	Difference	
AUDIT*, mean (SD)	27.4 (7.1)	14.3 (9.9)	NR, ***	28.4 (6.4)	17.6 (10.4)	NR, ***	F [2.77] = 1.19, p = 0.31

Study	Muhonen, 2008 [38, 39]							
	AUDIT QF*, mean (SD)	6.2 (1.7)	4.1 (2.5)	NR, ***	6.1 (1.7)	4.3 (2.3)	NR, ***	F [2.77] = 1.58, p = 0.21
	HDD (AUDIT-3)*, mean (SD)	2.9 (1.1)	1.8 (1.3)	NR, ***	3.1 (1.0)	2.4 (1.3)	NR, ***	F [2.77] = 1.37, p = 0.27
	The number of abstinent days per week*, mean (SD)	NA	NR	NA	NA	NR	NA	F [2.74] = 0.07, p = 0.93
	Alcohol intake (grams/day)*, mean (SD)	NA	15.0 (2.6)	NA	NA	21.1 (3.6)	NA	F [1.74] = 1.94, p = 0.17
	Self-experienced decrease of alcohol intake, %**	NA	68.9%	NA	NA	62.1%	NA	NR
	* Repeated measures ANOVA, ** Logistic regression, *** Statistically significant difference. Other analyses found in paper: Multiple Linear Regression analyses on predictors of treatment response.							
	Comments							
	Data in graph on number on abstinent days per week not extracted.							
	Mental health [39]							
	Primary outcomes	**Baseline**	**Memantine (ITT, n = 40) Endpoint**	**Difference**	**Baseline**	**Escitalopram (ITT, n = 40) Endpoint**	**Difference**	**Between group difference**
	MADRS*, mean (SD)	25.8 (4.4)	12.7 (7.0)	NR, ***	26.8 (4.1)	11.5 (6.6)	NR, ***	(F = 1.13, df = 3, p = 0.94)
	HAM-A*, mean (SD)	17.1 (4.7)	7.8 (4.3)	NR, ***	18.1 (4.4)	7.9 (5.5)	NR, ***	(F = 0.38, df = 3, p = 0.4)
	Secondary outcomes	**Baseline**	**Endpoint**	**Difference**	**Baseline**	**Endpoint**	**Difference**	**Between group difference**
	BDI, mean* (SD)	27.7 (8.4)	15.3 (11.1)	NR, ***	27.6 (6.8)	14.3 (11.8)	NR, ***	F = 0.92, df = 4, p = 0.68
	Self-experienced decrease of depression, % (n)**	NA	75.9 % (22/29)	NA	NA	72.4 % (21/29)	NA	NR
	BAI*, mean (SD)	21.5 (11.7)	12.6 (10.2)	NR, ***	20.2 ± 9.3	13.6 (14.9)	NR, ***	(F = 1.31, df = 4, p = 0.27)
	* Repeated measures ANOVA, ** Logistic regression, *** Statistically significant difference							
	Quality of life [39]							

Study | **Muhonen, 2008 [38, 39]**

	Memantine (ITT, n = 40)			Escitalopram (ITT, n = 40)			Between group difference
	Baseline	Endpoint	Difference	Baseline	Endpoint	Difference	
VAS*, mean (SD)	39.7 (19.3)	54.6 (20.8)	NR, **	40.5 (16.5)	56.6 (23.2)	NR, **	F = 0.25, df = 3, p = 0.9

* Repeated measurements ANOVA, ** Statistically significant difference

Function [39]

	Memantine (ITT, n = 40)			Escitalopram (ITT, n = 40)			Between group difference
	Baseline	Endpoint	Difference	Baseline	Endpoint	Difference	
MMSE*, mean (SD)	28.1 (1.4)	27.9 (1.5)	NR, NS	28.0 (1.7)	27.4 (1.5)	NR, NS	NR
SOFAS*, mean (SD)	52.7 (9.2)	67.2 (11.7)	NR, **	53.2 (9.9)	63.8 (11.4)	NR, **	F = 1.7, df = 3, p = 0.86

* Repeated measurements ANOVA, ** Statistically significant difference

Compliance

At least 80% compliance based on tablet counts. The average daily consumption of medication (mean ± SD) did not differ between the 2 medication groups: during the first 12 weeks, 17.4 ± 2.8 mg for memantine and 16.9 ± 3.6 mg for escitalopram, and for weeks 13 to 26, 17.4 ± 3.2 mg for memantine and 15.9 ± 4.4 mg for escitalopram.

Adverse effects

	Memantine n = 40	Escitalopram n = 40
Insomnia: % (n)	9 (23.1)	6 (15.8)
Sexual dysfunction: % (n)	8 (20.5)	9 (23.7)
Gastrointestinal problems: % (n)	10 (25.6)	10 (26.3)
Dizziness: % (n)	11 (28.2)	7 (18.4)
Increased sweating: % (n)	4 (10.3)	8 (21.1)
Somnolence: % (n)	14 (35.9)	13 (34.2)
Headache: % (n)	14 (35.9)	11 (28.9)
Aggressiveness: % (n)	4 (10.3)	2 (5.3)
Instability in mood: % (n)	11 (28.2)	9 (23.7)
Dry mouth: % (n)	1 (2.6)	4 (10.6)
Discontinued treatment due to AE: N	4	3
SAE	2	1

There was no significant difference in the incidence of AE between the 2 treatment groups.

SAE

Study	Muhonen, 2008 [38, 39]
	Serious adverse events included: 1 suicide attempt in the memantine group and 2 sudden deaths (1 due to hyperglycemia in the memantine group and 1 due to intoxication with street drugs in the escitalopram group). The mortality is equal with the average mortality in this group of patients in Finland. These events were considered by the study coordinator (H.A.) not to be related to the study treatment on the basis of clinical evaluation and forensic autopsy reports for each case.
	Loss to follow up Endpoint: Memantine: 11/40 (27.5 %), Escitalopram: 11/40 (27.5 %)
Risk of bias	Moderate

AA = Alcoholics Anonymous; **AE** = adverse events; **ALT** = alanine aminotransferase; **AST** = aspartate aminotransferase; **AUD** = alcohol use disorder; **AUDIT** = Alcohol Use Disorders Identification Test; **BAI** = Beck Anxiety Inventory = **BDI-II** = Beck Depression Inventory II; **CDT** = carbohydrate-deficient transferrin; **DSM-IV-TR** = Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revised; **GGT** = gamma-glutamyltransferase; **HAM-A** = Hamilton Rating Scale for Anxiety; **ITT** = intention to treat; **M** = mean; **MADRS** = Montgomery– Åsberg Depression Rating Scale; **MDD** = major depressive disorder; **NR** = not reported; **RCT** = randomized controlled trial; **SAE** = serious adverse events; **SCID** = Structured Clinical Interview for DSM-IV; **SD** = standard deviation; **VAS** = visual analogue scale.

Nejtek et al. 2008

Study	Nejtek, 2008 [40]
Study design	RCT, double blind, multi-center
Intervention	**Pharmacotherapy: Risperidone** Co-interventions: concommittent pharmacological and psychosocial were permitted
Trial registration	NCT00227123
Country	USA
Setting	Outpatients
Aims	The primary objective was to compare the efficacy and tolerability of quetiapine and risperidone in the treatment of mood symptoms, drug cravings, and drug use in outpatients with concurrent DSM-IV–defined bipolar I or II disorder and cocaine or methamphetamine dependence.
Participants	**SUD (cocaine or metamfetamine dependence) & Bipolar I or II**
	Baseline characteristics

	Quetiapine	Risperidone
N=	48	46
Women: % (n)	52% (25)	54% (25)

Study	Nejtek, 2008 [40]		
	Age: M (SD)	36.8 (6.7)	34.7 (6.7)
	Education, years: M (SD)	13.3 (1.4)	13.0 (1.1)
	Housing situation*	**n% (n)**	**n% (n)**
	Independent living	17% (8)	11% (5)
	Family/significant other	35% (17)	34% (15)
	Residential treatment	42% (20)	55% (24)
	Shelter	6% (3)	0% (0)
	Employment status*	**n% (n)**	**n% (n)**
	Full-time employment	4% (2)	7% (3)
	Part-time employment	8% (4)	9% (4)
	Unemployed	88% (42)	84% (37)
	Mental health status	**Quetiapine**	**Risperidone**
	Bipolar I disorder: n% (n)	79% (38)	89% (41)
	Bipolar I disorder with psychotic features: n% (n)	12.5% (6)	4.3% (2)
	Bipolar II disorder: n% (n)	21% (10)	11% (5)
	Duration of bipolar illness, years: M (SD)	**24.7 (8.3)**	**23.3 (7.6)**
	Baseline mood state	**n% (n)**	**n% (n)**
	Mania	8% (4)	4% (2)
	Hypomania	19% (9)	22% (10)
	Depressed	50% (24)	41% (19)
	Mixed	23% (11)	33% (15)
	Baseline clinical measures	**M (SD)**	**M (SD)**
	YMRS	16.8 (4.9)	18.2 (4.3)
	IDS-C-30	24.8 (9.6)	26.8 (8.4)
	Secondary (current) Axis I diagnosis)	**n% (n)**	**n% (n)**
	Obsessive-compulsive disorder	25% (12)	15% (7)
	Posttraumatic stress disorder	33% (16)	39% (18)
	Concomitant psychiatric medications	**n% (n)**	**n% (n)**
	None	48% (23)	61% (28)
	Mood stabilizer	8% (4)	4% (2)
	Mood stabilizer + antidepressant	13% (6)	15% (7)
	Antidepressant	29% (14)	20% (9)
	Other mood	2% (1)	0% (0)

Study	Nejtek, 2008 [40]
	ANOVA was used to compare medication groups for continuous variables, and χ2 tests were used to analyze categorical variables. There were no significant between-group differences in baseline sociodemographic characteristics, diagnoses, mood states, or drug use history. * Percentages for risperidone group based on N = 44, as this information was missing for 2 cases.
	Inclusion criteria English-speaking men and women (20–50 years old) of all ethnic origins; (2) were outpatients with a current DSM-IV diagnosis of bipolar I disorder with or without psychotic features or bipolar II disorder; (3) had current DSM-IV cocaine or methamphetamine dependence; (4) were currently experiencing hypomanic, manic, or mixed state episodes with a YMRS score of ≥ 9; (5) were currently craving stimulants with a craving score of ≥ 20 on the 10-item, self-reported SCQ-10; and (6) had a high school diploma, graduation equivalency diploma, or Shipley IQ test score of ≥ 85. SCID-IV-CV was used to determine current and lifetime Axis I diagnoses and history of illness. The SCID-IV-CV life chart was utilized to document a chronological timeline for age of mood symptom onset preceding the onset of substance abuse or dependence.
	Exclusion criteria (1) were inpatients or anyone with a high risk of suicide (i.e., active suicidal ideation with a proposed plan, history of any suicide attempt within the last 6 months); (2) had a DSM-IV diagnosis of substance-induced mood disorder; (3) were pregnant or breast-feeding; (4) had a history of special education, mental retardation, or dementia; (5) had HIV/AIDS, reactive hepatitis, hepatic cirrhosis or any active liver disease, a personal or familial history of diabetes, or a personal history of heart disease (i.e., congenital heart abnormalities, congestive heart failure, chronic atrial fibrillation, rheumatic heart disease, or heart attack); (6) had central nervous system diseases (e.g., multiple sclerosis, severe head trauma, or seizures); (7) had contraindications or allergic reactions to study medications; (8) were currently participating in any other research program; (9) had a positive urine screen for glucose or ketones; (10) were currently receiving any antipsychotic medications or more than 2 psychotropic medications; (11) were currently receiving benzodiazepines, sedatives, or stimulants; (12) had any other current substance dependence; (13) had cataracts or glaucoma; and/or (14) had electrocardiogram (ECG) evidence of QT prolongation.
	Recruitment & screening Participants were recruited from psychiatrist referrals and through flyers placed in local community mental health outpatient clinics and drug treatment facilities.

Study	Nejtek, 2008 [40]
	Of 651 volunteers screened for study participation, 124 were enrolled, 96 were randomly assigned, and 94 received study medication
	Remuneration Study patients received compensation (i.e., a $40 gift card) after successful completion of 4 study weeks.
Comparison	**Quetiapine vs. risperidone**
	Duration of treatment 20 weeks
	Follow ups Weekly Endpoint / time of last treatment
Experimental arm	**Quetiapine** Weekly dosing of quetiapine was 50 mg/day for the first week, 100 mg/day for the second week, and up to 600 mg/day by the 12th week. Study doctors could adjust each subsequent weekly dose by titrating up or down in increments of 50 mg/day, as clinically needed. 48% (n = 23) received quetiapine as a monotherapy Dosage: Mean at study exit (SD) = 303.6 (151.9) mg/day Mean of the max (SD) = 309.5 (150.7) mg/day Median during study (SD) = 215.5 (125.9) mg/day
	Co-interventions 52% (n = 25) received quetiapine as an adjunctive therapy <u>Pharmacological</u> Psychotropic medications: Patients who entered the study with no more than 2 allowable psychotropics (i.e., antidepressant or mood stabilizer) were permitted to continue those medications concomitantly with the study drug. Dose adjustments of concomitant psychotropics were proscribed. No other psychotropic medications could be added after study entry. Medications to treat hypertension; acute care antibiotics; non-narcotic over-the-counter cold or allergy medications. Concomitant psychiatric medications are indicated in baseline characteristics were permitted.

Study	Nejtek, 2008 [40]
	Psychosocial Behavioral treatments for drug use (e.g., residential treatment, intensive outpatient classes, drug aftercare classes, and Narcotics or Alcoholics Anonymous meetings) were permitted.
	Risperidone Weekly dosing of risperidone was 0.5 mg/day for the first week, 1 mg/day for the second week, and up to 6 mg/day by the 12th week. Study doctors could adjust each subsequent weekly dose by titrating up or down in increments of 0.5 mg/day, as clinically needed. 61% (n = 28) received risperidone as a monotherapy. Dosage: Mean at study exit (SD) = 3.1 (1.2) mg/day Mean of the max (SD) = 3.2 (1.2) mg/day Median for individuals during study (SD) = 2.3 (1.0) mg/day
	Co-interventions 39% (n = 18) received risperidone as an adjunctive therapy Pharmacological Same as for quetiapine. Psychosocial Same as for quetiapine.
Outcomes	**Substance use** Primary outcomes: Drug craving scores (SCQ-10) Drug use (urinalysis) tested weekly for presence of cocaine, methamphetamine, phencyclidine, cannabis, opiates, and benzodiazepine. percentage of actual drug screens that were positive for cocaine or methamphetamine was used to examine the overall drug use for each subject during the trial (i.e., number of positive screen divided by the number of weeks in the study).
	Mental health Primary outcomes: Mood (YMRS & IDS-C-30), clinician rated, weekly

Study	Nejtek, 2008 [40]
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Patients received study medication dispensed in a 7-day "med-minder," and they were instructed to bring it with them at each subsequent visit so that medication adherence could be monitored
	Adverse effects Somatic complaints and adverse events were evaluated weekly using PRD-III at study visits. Also weight, blood pressure, eyes and heart rhythm were regularly checked.
Results	**Substance use**

Substance use	**Total population**	**Quetiapine**	**Risperidone**	**Treatment effect**
Urinalysis	**M (SD)**	**M (SD)**	**M (SD)**	**ANOVA**
N*=	80	42	38	-
% positive screens for primary drug of choice*	27% (38)	32% (40)	22% (33)	F = 1.67, df = 1,78; p = 0.20
% positive screens for primary drug of choice, projecting positive screens**	NR	63% (35)	60% (32)	F = 0.17, df = 1,78; p = 0.68
	% (n)	**% (n)**	**% (n)**	
Abstained from cocaine or methamphetamin	51% (41)	NR	NR	
Ever tested positive for primary drug of choice	49% (39)	NR	NR	
Ever tested positive for cannabis	20% (16)	NR	NR	
opiates	6% (5)	NR	NR	
phencyclidine	2.5% (2)	NR	NR	
benzodiazepine	0	NR	NR	

Study | **Nejtek, 2008 [40]**

* Modified ITT. All calculations are based on those who attended ≥ 1 study visit: N = 80, 38 in risperidone group and 42 in quetiapine group.Note that 96 were randomized.

** Based on the number of positive screens for the drug of choice / number of weeks in the study.

*** Based on the number of positive screens for the evaluable population / 20 weeks. Missing screens are counted as positive. Follow-up contact with these non-completing study participants or their families, friends, or drug treatment providers confirmed a return to drug use.

Comments

Craving is not relevant to the study questions, therefore SCQ-10 data was not extracted.

Mental health

Primary outcomes	Score change**: M (SD)	Correlation Score change / study week	Type III tests of fixed effects* Study week	Study week x medication
YMRS (total scores)	7.3 (5.8)	r = 0.44 p < 0.0005	F = 13.21, df = 19,530.2 p < 0.0005	F = 1.12, df = 19,530.0 p = 0.32
IDS-C-30 (total scores)	7.3 (14.1)	r = 0.26 p = 0.02	F = 8.35, df = 19,519.8 p < 0.0005	F = 1.19, df = 19,519.8 p = 0.26

* Linear mixed model analysis used fixed-effects terms for medication group (quetiapine or risperidone), study week (1–20), and group-by-study-week. Study patients were treated as a random effect variable. Restricted maximum likelihood estimation was used, and autoregressive covariance structures were specified.

** Mean positive change from baseline to last measure (lower scores = positive change)

	Week 3		Week 6		Kaplan-Meier survival
Rate of clinical improvement	Quetiapine (N = 42)	Risperidone (N = 38)	Quetiapine (N = 42)	Risperidone (N = 38)	log rank [Mantel-Cox]
Outcome	% (N)	% (N)	% (N)	% (N)	by medication group
YMRS (total scores ≤ 9)	40% (17)	24% (9)	62% (26)	61% (23)	$\chi^2 = 0.16$, df = 1 p = 0.69
IDS-C-30 (total scores ≤ 14)	24% (10)	9 (24%)	19 (40%)	19 (50%)	$\chi^2 = 0.46$, df = 1 p = 0.50

Comments

<table>
<tr><th>Study</th><th>Nejtek, 2008 [40]</th></tr>
<tr><td></td><td>Estimates of marginal means are presented graphically for YMRS and IDS-C-30 total scores per week in figure 2 and 3, respectively. Data not extracted.
Subgroup analysis (study medication as monotherapy vs. adjunctive therapy): ”Similar reductions in manic and depression symptoms were observed in both medication groups”
Regression analysis showed that
Change in YMRS explains less than 2.7% of the variance in overall drug use in study population (regression analysis, t tests of the b-weights, t = –1.5, p = 0.14).
Change in IDS-C-30 explains less than 0.4% of the variance in overall drug use in study population (regression analysis, t tests of the b-weights, t = 0.6, p = 0.57)</td></tr>
<tr><td></td><td>Compliance
Adherence by pill count not clearly reported.
There were no missing urine drug screens during active participation; thus, we collected a urine sample at every study visit from every participant.
Attendence to weekly follow up visits not reported.</td></tr>
<tr><td>Adverse effects</td><td>
<table>
<tr><th></th><th></th><th colspan="2">Type III tests of fixed effects*</th></tr>
<tr><th>AE</th><th>Score change**: M (SD)</th><th>Study week</th><th>Study week x medication</th></tr>
<tr><td>PRD-III (total scores)</td><td>7.6 (3.7)
Range 0 to 46</td><td>F = 3.53, df = 19,509.2; p < 0.0005</td><td>F = 1.44, df = 19,509.2; p = 0.10</td></tr>
</table>
* Linear mixed model analysis used fixed-effects terms for medication group (quetiapine or risperidone), study week (1–20), and group-by-study-week. Study patients were treated as a random effect variable. Restricted maximum likelihood estimation was used, and autoregressive covariance structures were specified.
** Mean change from baseline to last measure
<u>SAE</u>
3 SAE occurred (mouth twitching, cocaine induced psychotic episode, suicide attempt) — all were considered unrelated to the study medication. See Table 2 for a full list of adverse events, data not extracted.
<u>Comments</u>
Estimates of marginal means are presented graphically for PRD-III total scores per week in figure 5. Data not extracted.</td></tr>
</table>

Study	Nejtek, 2008 [40]
	Subgroup analysis (study medication as monotherapy vs. adjunctive therapy): both medication (p < .0005) and study-medication-by-studyweek (p = 0.005) were significant. ”This result suggests that somatic symptoms are more pronounced for participants receiving adjunctive study medication than for those receiving study medication as monotherapy.”
	Loss to follow up Randomly assigned: 96 Recieved study medication: 94 defined by authors to be the ITT population. Attended ≥ 1 follow up: 85% (80/94); Quetiapine: 88% (42/48), Risperidone: 82% (38/46) (used by authors for most analyses) Loss to follow* up at week 1: 15% (14/94); Quetiapine: 12% (6/48), Risperidone: 17% (8/46) Loss to follow* up at 6 weeks: : 41% (39/94); Quetiapine: 42% (20/48), Risperidone: 41% (19/46) Loss to follow up* at 12 weeks: 70% (66/94); Quetiapine: 65% (31/48), Risperidone: 76% (35/46) Losss to follow up* at 20 weeks : 85% (80/94); Quetiapine: 83% (40/48), Risperidone: 87% (40/46) * Loss to follow-up recalculated based on number of participants retained per group from Figures 2-5 and the author’s definition of the ITT population. These numbers are not in agreement with the numbers discussed in the discussion section of the paper: “69% remained in the study for 6 weeks, and almost 50% of the entire sample completed 12 weeks.” <u>Comments</u> ”A Kaplan-Meier survival analysis found no significant differences in study attrition between the medication groups” ”Chisquare analysis showed that the reasons for discontinuation occurred with similar frequency in the 2 medication groups ($\chi 2$ = 0.90, df = 4, p = .92).”
Risk of bias	Moderate

AE = adverse events; **ANOVA** = analysis of variance; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders – 4th edition; **IDS-C-30** = Inventory of Depressive Symptomatology, Clinician-rated, 30 items; **ITT** = intention to treat; **M** = mean; **NR** = not reported; **PRD-III** = Psychobiology of Recovery in Depression- version 3, Somatic Symptom Scale (0 to 46); **RCT** = randomized controlled trial; **SAE** = serious adverse events; **SCID-IV-CV** = Structured Clinical Interview for DSM-IV Clinical Version; **SCQ-10** = Stimulant craving questionaire, 10 item, adapted from the cocaine craving questionaire; **SD** = standard deviation; **SUD** = substance use disorders; **YMRS** = Young Mania Rating Scale.

Nunes et al. 1998

Study	Nunes, 1998 [41]
Study design	RCT, double-blind
Intervention	**Pharmacotherapy: Imipramine HCl** Co-interventions: MMT
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	To test the hypothesis that antidepressant medication would result in improved mood and diminished substance abuse in patients with depressive syndromes diagnosed by clinical history who were receiving methadone treatment
Participants	**Opiate-dependent patients with depressive disorders** Opiate-dependent patients (receiving methadone hydrochloride maintenance treatment) with syndromal depression
	Baseline characteristics

	Imipramine HCl	Placebo
N*	**42/74**	**42/63**
Women: n (%)	18 (43)	14 (33)
Age: M (SD)	33.4 (6.6)	35.4 (6.4)
Education, years: M (SD)	12.0 (2.3)	12.0 (2.3)
Unemployed: (n (%)	22 (52)	18 (43)
Substance use status**		
Opiates: n (%)	17 (41)	22 (52)
Cocaine: n (%)	17 (41)	22 (52)
Freebase cocaine: n (%)	3 (7)	7 (17)
Alcohol: n (%)	17 (41)	15 (36)
Sedatives: n (%)	11 (26)	10 (24)
Cannabis: n (%)	12 (29)	9 (21)
Parenteral cocaine or herion: n (%)	14 (33)	14 (33)
Mental health status		
Major depression: n (%)	28 (67)	28 (67)
Dysthymia: n (%)	12 (29)	11 (26)
Depression not otherwise specified: n (%)	2 (5)	3 (7)
HDRS score: M (SD)	16.2 (4.0)	15.6 (3.8)

*Baseline characteristics only reported for participants completing at least 6 weeks of the study; in this subgroup, no statistically significant baseline differences were found (reported N=84, randomized N=137)

Study	Nunes, 1998 [41]
	**30 days prior to study enrolment
	Inclusion criteria Meet the criteria for a current DSM-III-R depressive disorder (major depression, dysthymia, or depression not otherwise specified) meeting at least one of the following: 1) depression was primary, i.e., it antedated the onset of regular substance use, defined as use of a substance at least 3 times/week for a month, or once a week for a month for cocaine use; 2) depression was secondary and persisted or emerged during a past period of 6 months of complete abstinence; or 3) depression was secondary and of at least 3 months' duration in the current episode; for newly admitted patients, depression had to persist for at least 1 month of stable methadone treatment
	Exclusion criteria Ever having met the criteria for schizophrenia or mania; were judged to present a clinically significant suicide risk; had medical contraindications to imipramine treatment e.g. pregnancy, cardiac construction system disease, or unstable medical condition, had a history of a seizure disorder; had failed to respond to an adequate trial of imipramine in the past; or were in treatment for depression with another practitioner
	Recruitment & screening Recruitment among newly admitted or established patients at two community-based, university-affiliated methadone maintenance clinics; numbers screened = NR, numbers eligible and admitted to a 1-week single-blind placebo period = 169; numbers randomized = 137
	Remuneration NR
Comparison	**Imipramine vs. placebo**
	Duration of treatment 12 weeks
	Follow ups Measurements during treatment: weekly Endpoint: 12 weeks
Experimental arm	**Imipramine**

Study	Nunes, 1998 [41]
	Medication (unmarked pills containing 50 mg of imipramine hydrochloride) was titrated, at a rate of 50 mg/week, toward a maximum dose of 6 pills/day (300 mg); dispensed 2-3 times a week at the clinic by a research nurse
	Co-interventions Methadone (maintenance) Administered by regular clinic staff, not influenced by the research protocol
Comparison	**Placebo** Followed the same protocol as study medication
	Co-interventions Methadone (maintenance) Same as for experimental arm.
Outcomes	**Substance use** Quantity and frequency of substance use (modeled after TLFB), clinician interview (i.e., self-reported), weekly Global response to treatment (depression and drug use) reported as a depression response and at least 75% reduction of self-reported substance use (modified CGI scale), clinician-rated at endpoint (either at 12 weeks or last week in study)
	Mental health Mood (21-item HDRS), clinician interview (i.e., self-reported), weekly Depression response, requiring substantial improvement in depression reflected by a CGI score of 2 (much improved) or 1 (very much improved), clinician-rated at endpoint (either at 12 weeks or last week in study)
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Compliance (defined as taking the medication regularly and attending treatment sessions): - Blood was drawn at weeks 4, 6 and 12 to check the level of imipramine

<table>
<tr><td>Study</td><td>Nunes, 1998 [41]</td></tr>
<tr><td></td><td>- At clinic visits (2-3 times/week), a research nurse asked about medication compliance
- A research psychiatrist also monitored compliance weekly (method NR)
Retention: reported as number (%) of participants completing an adequate trial of at least 6 weeks' duration, and numbers (%) completing all 12 weeks of the trial</td></tr>
<tr><td></td><td>Adverse effects
A research psychiatrist monitored side effects weekly (method NR)</td></tr>
<tr><td>Results</td><td>Substance use*
<table>
<tr><th></th><th>Imipramine (ITT, n = 74) Endpoint</th><th>Placebo (ITT, n = 63) Endpoint</th><th>Test of difference p-value</th></tr>
<tr><td>Global response to treatment, n (%)</td><td>26 (35%)</td><td>4 (6%)</td><td><0.001</td></tr>
<tr><td>Number of days per week using any substance, M (SD)**</td><td>1.80 (2.03)</td><td>2.97 (2.28)</td><td><0.004</td></tr>
</table>
*Only outcome analysed with ITT & LOCF were extracted by SBU. Note that the baseline data reported is only for a portion of the ITT population.
**The scores from the 4 weeks before endpoint were averaged to a single summary score. Baseline scores used as covariates in ANCOVA</td></tr>
<tr><td></td><td>Mental health*
<table>
<tr><th></th><th>Imipramine (ITT, n = 74) Endpoint</th><th>Placebo (ITT, n = 63) Endpoint</th><th>Test of difference p-value</th></tr>
<tr><td>21-item HDRS total score, M (SD)**</td><td>10.0 (6.9)</td><td>14.4 (7.0)</td><td><0.001</td></tr>
<tr><td>Depression response, n (%)</td><td>31 (42%)</td><td>13 (21%)</td><td><0.02</td></tr>
</table>
*Only outcome analysed with ITT & LOCF were extracted by SBU. Note that the baseline data reported is only for a portion of the ITT population.
**Analyses were conducted on end point scores, either at week 12 or at the last week in the study for early withdrawals.</td></tr>
<tr><td></td><td>Compliance
<table>
<tr><th>Compliant</th><th>Imipramine n = 74</th><th>Placebo n = 63</th><th>Overall n = 137</th></tr>
<tr><td>Non-compliance*: n (%)</td><td>19 (26%)</td><td>14 (22%)</td><td>33 (24%)</td></tr>
<tr><td>Retention, at least 6 weeks: n (%)</td><td>42 (57%)</td><td>42 (67%)</td><td>84 (61%)</td></tr>
<tr><td>Retention, 12 weeks: n (%)</td><td>NR</td><td>NR</td><td>38 (28%)</td></tr>
</table>
* Non-compliance includes failing to take medication regularly or stopped attending treatment sessions.</td></tr>
</table>

Study	Nunes, 1998 [41]
	Adverse effects **Participation discontinued due to AE or medical events, n (%)**: Imipramine n = 74: 12 (16%); Placebo n = 63: 3 (5%); Test of difference (p-value): <0.04
	Loss to follow up Endpoint: overall 72% drop-out (NR per study arm, see comment below regarding uneven drop-out) Prior to 6 weeks: 43% in the imipramine group; 33% in the placebo group (p<.32)
Comments	After 84 patients had been randomized, a higher rate of early attrition was noted for those receiving imipramine compared to those receiving placebo; at that point, the randomization was changed to a 2:1 imipramine-placebo ratio
Risk of bias	Moderate

AE = adverse events; **ANCOVA** = analysis of covariance; **CGI** = Clinical Global Impression; **DSM-III-R** = Diagnostic and Statistical Manual of Mental Disorders – 3rd edition – Revised; **HCl** = hydrochloride; **HDRS** = Hamilton Depression Rating Scale; **ITT** = modified intention to treat; **LOCF** = last observation carried forward; **M** = mean; **MMT** = methadone maintenance therapy; **NR** = not reported; **RCT** = randomized controlled trial; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report.

Petrakis et al. 1998

Study	Petrakis, 1998 [42]
Study design	RCT, double blind
Intervention	**Pharmacotherapy: Fluoxetine** Co-interventions: methadone maintenance
Trial registration	NR
Country	USA
Setting	Outpatient (?)
Aims	To evaluate fluoxetine's efficacy in treating depression in methadone-maintained opioid addicts
Participants	**OUD & Depression** Methadone-maintained opioid dependent patients with depression
	Baseline characteristics Fluoxetine / Placebo N= 23 / 21 Women: % (n) 39 % (9) / 33 % (7) Age: M (SD, range) 35.4 ± 6.5 / 33.3 ± 5.9

Study	Petrakis, 1998 [42]
	Substance use status Days of cocaine use*: M (SD) 4.4 (7.1) 5.4 (7.9) Days of heroin use*: M (SD) 4.6 (9.3) 5.7 (8.7) ASI composite: M (SD) 0.17 (0.10) 0.21 (0.09) Mental health status MDD: % (n) 47.1 (16) 52.9 (18) Drug-related: % (n) 18.8 (3) 44.4 (8) Independent: % (n) 81.3 (13) 55.6 (10) Dysthymia/NOS: % (n) 57.1 (4) 42.9 (3) Clinician diagnosed: % (n) 14.3 (3) 0 (0) * Over last 30 days
	Inclusion criteria Opioid dependent patients, who were maintained on methadone for at least 3 months, and who were medically healthy, and who had a current episode of a depressive disorder as assessed by SCID, DSM-III R criteria and HDRS >14 or BDI >8. Subjects met a clinical interviewer who was instructed to determine if MDD was independent of drug use or not. Three subjects (7%) were included in the based on a clinical psychiatric interview alone.
	Exclusion criteria Subjects with psychotic or bipolar disorders, as assessed by the SCID or by the psychiatric interview were excluded
	Recruitment & screening Recruitment not specifically reported. Subjects who had reduced methadone doses as a consequence of repeated infractions to the clinic's behavioral contract and who were therefore facing administrative discharge at the time of entry into the study were given an option to increase their methadone dose to the highest tolerated dose.
	Remuneration Participants in the study were not charged for treatment.
Comparison	**Fluoxetine vs. placebo**
	Duration of treatment 12 weeks
	Follow ups

Study	Petrakis, 1998 [42]
	Weekly measurements during treatment Endpoint / time of last treatment
Experimental arm	**Fluoxetine** Fluoxetine was dissolved in the liquid methadone already being orally administered. The dose was initiated at 20 mg and then, based on clinical review by the study psychiatrist, was titrated upward to 60 mg within 4 weeks, depending on tolerance of side effects. The average endpoint study medication dose was 49.5 mg (SD = 16.4).
	Co-interventions Methadone maintenance The average starting methadone dose was 67.6 mg
Control arm	**Placebo** As for fluoxetine group The methadone liquid with and without active medication had an identical appearance and taste.
	Co-interventions Methadone maintenance As for fluoxetine group
Outcomes	**Substance use** Primary outcomes: Cocaine and heroin use (ASI), self-reported, weeks 4, 8 and 12 Cocaine and heroin use (urinalysis), weekly Severity of substance use (ASI), self-reported, weeks 4, 8 and 12
	Mental health Primary outcomes: Depressive symptoms (BDI), self-reported, weekly Depressive symptoms (HDRS), clinician-reported, weekly
	Quality of life Not assessed
	Function

Study	Petrakis, 1998 [42]
	Not assessed
	Mortality Not assessed
	Compliance Urinalysis used to confirm self-reported drug use Subjects attending this clinic were required to adhere to a behavioral contract that could lead to administrative discharge. Methadone detoxification was begun after the first three infractions; each additional infraction resulted in a 5 mg reduction in methadone dose. Infractions included missing appointments, non-compliance with the rules of the general methadone clinic (such as loitering) and continuous drug positive urines.
	Adverse effects Not systematically reported.
Results	**Substance use** **Fluoxetine** n = 23 / **Placebo** n = 21 **Primary outcomes** — Baseline — Endpoint* — Baseline — Endpoint* Cocaine use, days**: M (SD) — 4.4 (7.1) — 2.3 (4.6) — 5.4 (7.9) — 4.4 (7.3) Heroin use, days**: M (SD) — 4.6 (9.3) — 1.8 (4.9) — 5.7 (8.7) — 3.1 (6.8) ASI, composite score**: M (SD) — 0.17 (0.10) — 0.11 (0.08) — 0.21 (0.09) — 0.15 (0.08) Based on random-effect regression analysis. * Values reflect data collected at week 12 or at the time of dropout. ** During preceding 30-day period Comments There was a significant decrease in heroin use during the previous 30 days from pre- to post-treatment ($z = 2.92$, $P < 0.01$) and a significant decrease in ASI composite scores ($z = 2.66$, $P < 0.01$), but no significant medication effect. Subgroup analysis reported for subjects who had been using drugs regularly, data not extracted
	Mental health **Fluoxetine** n = 23 / **Placebo** n = 21 **Primary outcomes** — Baseline — Endpoint* — Baseline — Endpoint*

Study	Petrakis, 1998 [42]
	BDI: M (SD) 17.6 (5.9) 9.6 (5.4) 12.6 (7.8) 7.9 (7.4) HDRS: M (SD) 14.0 (4.9) 8.0 (5.3) 14.9 (5.8) 7.2 (7.3) Based on random-effect regression analysis. * Values reflect data collected at week 12 or at the time of dropout. Comments Covarying for the baseline scores, there is a nonsignificant trend for time in BDI scores from pre-treatment to post-treatment. There were no significant differences in either the BDI or HDRS scores between the groups, suggesting that while there was an overall treatment effect, there was no medication effect on depressive symptoms. Subgroup analysis reported for subjects with MDD (table 3), data not extracted
	Compliance **Urinalysis** **Total, n = 299** Consistent with self-reported drug use: % (n) 85 % (253) Positive report, negative test: % (n) 11 % (33) Negative report, positive test: % (n) 4 % (13) Comments Results of urinalysis are reported in figure 1 according to the text, but the article does not appear to have a figure 1. Medication compliance NR, should be high as fluoxetine was dissolved in the methadone treatment.
	Adverse effects All three of those on fluoxetine who did not complete treatment were discontinued for medical reasons: two subjects experienced a rash and one subject reported agitation, nausea and diarrhoea.
	Loss to follow up 7 subjects did not complete treatment, 3 from fluoxetine group, 4 from placebo group Subjects completed an average of 10.9 weeks of treatment 37 subjects completed all 12 weeks of treatment There was no difference in treatment retention between the group of patients who received fluoxetine and the group that received placebo.
Comments	The first author is affiliated with West Haven Veterans Administration Medical Center, unclear whether patients were veterans or civilians.
Risk of bias	Moderate

RCT = randomized controlled trial; **NR** = not reported; **OUD** = opioid use disorder; **M** = mean; **SD** = standard deviation; **DSM-II-R** = Diagnostic and Statistical Manual of Mental Disorders – 2nd edition – revised; **SCID** = Structured Clinical Interview for DSM; **HDRS** = Hamilton Rating Scale for depression; **BDI** = Beck Depression Inventory; **MDD** = major depressive disorder; **ASI** = Addiction Severity Index.

Petrakis et al. 2016

Study	**Petrakis, 2016 [43]**
Study design	RCT, double blind
Intervention	**Pharmacotherapy: prazosin** Co-intervention: medical management therapy, continued psychiatric and pharmacological treatment via VA facility
Trial registration	NCT00532493
Country	USA
Setting	Outpatient
Aims	To test the hypothesis that prazosin would be significantly more effective than placebo in treating sleep disturbance, symptoms of PTSD, and alcohol consumption in military veterans with PTSD and comorbid AUD
Participants	**AUD & PTSD** Military veterans who met DSM-IV criteria for PTSD (CAPS score in the severe range) and AUD (heavy drinkers, intermediate level according to ADS score)
	Baseline characteristics

	Prazosin	**Placebo**
N= 96	50	46
Women: % (n)	8% (4)	4.44% (2)
Age: M (SD)	44.5 (13.2)	43.4 (12.95)
Alcohol use*	**M (SD)**	**M (SD)**
Number of drinking days	47.02 (29.87)	43.11 (27.79)
Number of heavy drinking days	41.3 (29.34)	39.51 (28.2)
Number of drinks per drinking day	17.33 (10.73)	21.9 (13.24)
Percent drinkings days	45.89 (32.6)	43.9 (31.36)
ADS,Total	18.94 (6.86)	20.2 (9.54)
PTSD status (CAPS)	**M (SD)**	**M (SD)**
Severity of PTSD	71.86 (20.32)	75.86 (14.44)
Re-experience	19.62 (8.22)	21.14 (7.23)
Hypervigilance	22.94 (7.37)	22.52 (6.15)

Study	Petrakis, 2016 [43]
	Avoidance 29.3 (9.04) 31.76 (7.08) **Comorbidities** % (n) % (n) Major depressive disorder 44.9% (22) 33.3% (15) Anxiety disorders 18.0% (9) 19.6% (9) Marijuana abuse/ dependence 12.2% (6) 11.9% (5) Cocaine abuse/ dependence 20.4% (10) 13.9% (6) * Baseline levels were based on the 90-day period prior to randomization
	Inclusion criteria Men or women, ages of 21 to 65, met DSM-IV criteria for current PTSD and AD (determined by SCID-IV), and reported at least 1 episode of heavy drinking (defined as >5 for men and >4 for women on 1 occasion) over the past 14 day. Participants needed to be medically healthy. Females must be using adequate birth control. Subjects were also required to be abstinent for 2 days prior to randomization; abstinence was determined by self-report and a negative breathalyzer reading.
	Exclusion criteria Exclusion criteria included pregnancy, unstable or current serious psychotic symptoms, suicidal or homicidal ideation, or medical problems that would contraindicate the use of prazosin. Participants could not be taking medications thought to influence alcohol consumption (such as naltrexone, disulfiram, or acamprosate), but other psychiatric medications were allowed.
	Recruitment & screening Recruitment was primarily via referrals from clinicians in the substance abuse treatment programs and the PTSD treatment programs at two VA facilities, and recruitment was augmented with advertisements at the VA facilities and in the community. Screening interview included physical and laboratory medical health examinations.
	Remuneration Indicate if participants were paid to attend, and if so, how much, and for what? participation, attendance, completion, drug free test results…
Comparison	**Prazosin vs. placebo**
	Duration of treatment 13 weeks

Study	Petrakis, 2016 [43]
	Follow ups Weekly Endpoint / time of last treatment
Experimental arm	**Prazosin** Prazosin was titrated upward during the first 2 weeks, starting at 2 mg per day, and then increased over the 2 weeks to 16 mg per day. 58% of subjects reached the 16 mg dose of prazosin within 2 weeks. The average maintenance dose of medication was 14.5 mg (SD = 3.14). Study medications were dispensed in identical looking capsules and in blister packs.
	Co-interventions <u>Medical management</u> All subjects also received medical management therapy administered by a trained research nurse, which is a manualized treatment designed to approximate a primary care approach to alcohol dependence. The treatment provides strategies to increase medication adherence and supports abstinence through education and referral to support group. <u>Continued treatment</u> Participants continued to receive psychiatric and pharmacological treatment as usual to the treatment programs they were enrolled in. 98% (N = 94) were also enrolled in other treatment programs at a VA facility: 59% in substance abuse program; 22% in a program to treat PTSD; 19% in programs to treat both PTSD and substance abuse. A portion (NR) of participants lived in “sober housing” provided through their treatment program.
	Placebo Study medications were dispensed in identical looking capsules and in blister packs.
	Co-interventions <u>Medical management</u> Same as for experimental arm. <u>Continued treatment</u>

Study	Petrakis, 2016 [43]
	Same as for experimental arm.
Outcomes	**Alcohol use** Primary outcomes: Alcohol / substance consumption (TLFB), self-reported, collected weekly Measures of consumption: percent of subjects who abstained from heavy drinking, average number of drinks per week, number of drinking days, number of heavy drinking days, consecutive days of abstinence, and number of drinks per drinking day Blood alcohol (serum GGT), assessed every 4 weeks Craving (OCDS), self-reported, collected weekly
	Mental health Primary outcomes: PTSD symptoms (CAPS-IV), self-reported, clinician administered every 4 weeks
	Quality of life Not assessed
	Function Primary outcomes: Quality of sleep (PSQI), self-reported, collected weekly Sleep (CAPS subscale*), self-reported, clinician administered weekly * 2 questions sleep related questions: distressing dreams, and difficulty falling/staying asleep
	Mortality Not assessed
	Compliance Attendance to weekly visits. Study completers = subjects for whom we had complete data at the end of the treatment period (week 12) whether they remained on medication or not. Medication compliance was monitored for each blister pack at weekly visits.
	Adverse effects

Study	Petrakis, 2016 [43]
	Side effects and common adverse symptoms (SAFTEE), self-reported, collected weekly by research nurse "Symptoms that are known to be associated with treatment with prazosin were specifically screened for on a weekly basis."
Results	**Alcohol use**

Primary outcomes

			Treatment effects (ITT, ANOVA*)
Group	**Prazosin**	**Placebo**	**Drug**
Drinking	**M (SD)**	**M (SD)**	**F, p**
Drinking days - Baseline	47.02 (29.87)	43.11 (27.79)	0.29, 0.59
- Active treatment phase	11.04 (18.86)	9.21 (16.64)	
Heavy drinking days - Baseline	41.3 (29.34)	39.51 (28.2)	0.2, 0.65
- Active treatment phase	7.16 (13.78)	6.05 (12.56)	
Drinks per drinking day - Baseline	17.33 (10.73)	21.9 (13.24)	1.36, 0.25
- Active treatment phase	4.44 (5.71)	6.91 (9.12)	
Consecutive days absitnent - Baseline	—	—	0, 0.96
- Active treatment phase	49.71 (34.74)	48.86 (31.94)	

* Analyses were performed with a 2-tailed alpha level of 0.05 Alcohol data were not normally distributed. As log transformations did not achieve normality, the data were ranked and nonparametric tests were used. Bonferroni adjustments were applied to the analysis of the alcohol data (6 drinking outcome measures; a = 0.008)

Comments:

Primary outcome blood alcohol levels (serum GGT) reported in the text: "There were no significant differences in GGT levels based on medication assignment."

Primary outcomes NR: percent of subjects who abstained from heavy drinking, average number of drinks per week, and number of drinks per drinking day.

Primary outcome craving (OCDS), not relevant to study question. Data not extracted.

Mental health

Primary outcome

			Treatment effects (ITT, ANOVA*)		
Group	**Prazosin**	**Placebo**	**Drug**	**Time****	**Drug x Time****
PTSD (CAPS-IV)	**M (SD)**	**M (SD)**	**F, p**	**F, p**	**F, p**
Total - Baseline	71.86 (24.65)	75.71 (26.36)	0.04, 0.84	54.31, 0	1.72, 0.16
- Week 12	37.94 (37.62)	37.93 (41.13)			
Re-experience - Baseline	29.3 (10.79)	31.76 (11.44)	0.19, 0.67	45.15, 0	1.68, 0.16

Study	Petrakis, 2016 [43]

- Week 12	15.57 (12.67)	14.89 (13.93)			
Avoidance - Baseline	19.62 (11.32)	20.99 (12.13)	0.02, 0.9	44.27, 0	2.21, 0.08
- Week 12	10.41 (16.76)	8.87 (18.59)			
Hyperarousal - Baseline	22.94 (9.46)	22.44 (10.04)	0.41, 0.52	25.8, 0	1.47, 0.22
- Week 12	15.65 (13.87)	14.84 (15.09)			

* Bonferroni adjustments were applied (3 subscales; a = 0.016). Analyses were performed with a 2-tailed alpha level of 0.05

** Although means and standard deviations are presented for baseline and week 12, time was calculated using data across 12 weeks.

Function (Sleep)

Primary outcome

			Treatment effects (ITT, ANOVA[a])		
Group	**Prazosin**	**Placebo**	**Drug**	**Time[b]**	**Drug x Time[b]**
Measure	**M (SD)**	**M (SD)**	**F, p**	**F, p**	**F, p**
PSQI - baseline	21.47 (0.94)	22.8 (0.97)	0.05, 0.82	14.85, 0	0.62, 0.6
- Week 12	17.05 (1.31)	16.76 (1.45)			
CAPS difficulty falling / staying asleep – baseline[c]	4.69 (0.31)	4.77 (0.32)	0.26, 0.87	9, 0	2.77, 0.03[d]
- Week 12[c]	2.5 (0.38)	2.41 (0.41)			
CAPS recurrent distressing dreams – baseline[c]c	5.92 (0.32)	5.44 (0.34)	0.02, 0.88	26.89, 0	0.3, 0.88
- Week 12	4.25 (0.46)	4.91 (0.5)			

a- Analyses were performed with a 2-tailed alpha level of 0.05

** Although means and standard deviations are presented for baseline and week 12, time was calculated using data across 12 weeks.

c- Bonferroni adjustments were applied to the analysis of the sleep data (2 CAPS questions: a = 0.025)

d- Not significant after Bonferroni correction.

Compliance

Group	**Prazosin**	**Placebo**	**Total**
Measure	**% (N)**	**% (N)**	**% (N)**
Remained on study medication for 12 weeks	40.0% (20)	47.8% (22)	56.3% (54)

<table>
<tr><td>Study</td><td>Petrakis, 2016 [43]</td></tr>
<tr><td></td><td>
<table>
<tr><th>Measure</th><th>M (SD)</th><th>M (SD)</th><th>Treatment effects (ITT, ANOVA*)</th></tr>
<tr><td>Length of treatment, days</td><td>74.9 (22.0)</td><td>70.1 (26.1)</td><td>F (1, 516.49) = 0.89, p = 0.34</td></tr>
</table>
* Analyses were performed with a 2-tailed alpha level of 0.05
<u>Comments</u>
Attendance NR
Medication compliance NR
</td></tr>
<tr><td>Adverse effects</td><td>
<table>
<tr><th></th><th>Prazosin n = 50</th><th>Placebo n = 46</th></tr>
<tr><th>Measure</th><th>% (n)</th><th>% (n)</th></tr>
<tr><td>Alcohol relapse requiring hospitalization or emergency room visit*</td><td>10% (5)</td><td>15% (7)</td></tr>
<tr><td>homicidal ideation*</td><td>0% (0)</td><td>2% (1)</td></tr>
</table>
* None of these AEs were thought to be related to study medication or participation.
</td></tr>
<tr><td>Comments</td><td>There was no difference between the medication groups on the overall rate or frequency of side effect reporting.
Analysis of individual symptoms most frequently reported with prazosin– dizziness, dizziness when standing up, and loss of balance revealed a nonsignificant medication effect for dizziness, F(1, 27.8) = 3.92, p = 0.05, after a Bonferroni adjustment, although subjects on prazosin reported this symptom more frequently than those on placebo. There were no other significant findings in the reporting of symptoms. Bonferroni adjustments were applied to the analysis of side effects (8 symptom groups; a = 0.006)</td></tr>
<tr><td>Loss to follow up</td><td>Completed study: 78.1% (75)
Lost to follow up: 22% (21)
Discontinued intervention: 22% (21)
Excluded from analysis: 0% (0)</td></tr>
<tr><td>Risk of bias</td><td>Moderate</td></tr>
</table>

ADS = Alcohol Dependence Severity scale; **ANOVA** = analysis of variance; **AUD** = alcohol use disorder; **CAPS-IV** = Clinician Administered **PTSD** Scale, based on DSM-IV; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition; **GGT** = gamma-glutamyltransferase; **ITT** = intention to treat; **M** = mean; **NR** = not reported; **OCDS** = Obsessive Compulsive Drinking Scale; **PSQI** = Pittsburgh Sleep Quality Index; **PTSD** = posttraumatic stress disorder; **RCT** = randomized controlled trial; **SAFTEE** = Systematic Assessment for Treatment Emergent Events; **SCID-IV** = Structured Clinical Interview for DSM-IV; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **VA** = veterans administration.

Petrakis et al. 2005

Study	Petrakis, 2005 [44]
Study design	RCT, 4-armed, multi-center, double blind and open-label
Intervention	**Pharmacotherapy: naltrexone, disulfiram (OL)** Co-interventions: intensive substance use program
Trial registration	NR
Country	USA
Setting	Outpatients, Veterans Administration clinics
Aims	to assess the efficacy of naltrexone and disulfiram alone and in combination in individuals with major Axis I disorders and comorbid alcohol dependence in a general clinic setting.
Participants	**AUD & Axis I** Subjects met DSM-IV criteria for a major Axis I disorder and for alcohol dependence.
	Baseline characteristics

	Total	1 Disulfiram/Naltrexone	2 Disulfiram	3Naltrexone	4 Placebo
N=	254	65	66	59	64
Women: % (n)	2.8% (7)	5.1% (3)	0% (0)	3.1% (2)	3.0% (2)
Age: M (SD, range)	47.0 (8.2)	47.7 (7.4)	46.2 (7.3)	48.2 (9.3)	45.8 (9.0)
Alcohol use status					
Years of use (lifetime): M (SD)	25.9 (9.5)	26.8 (8.6)	25.7 (10.9)	26.4 (9.6)	26.2 (9.2)
Drinking days (out of last 30): M (SD)	15.8 (12.0)	17.4 (12.3)	15.2 (12.1)	15.2 (11.7)	15.6 (11.9)
Drinks per drinking day (last 30 days): M (SD)	19.4 (12.5)	21.1 (14.3)	20.3 (11.6)	18.0 (11.3)	18.4 (12.8)
% heavy drinking days(last 30 days): M (SD)	89.8 (25.2)	91.9 (24.5)	90.4 (22.8)	90.4 (24.0)	87.0 (29.3)
Prescribed psychiatric meds					
Any: % (n)	87.6% (220)	83.1% (49)	88.9% (56)	84.4% (54)	93.8% (61)
Antidepressants: % (n)	75.3% (189)	71.2% (42)	79.4% (50)	67.2% (43)	83.1% (54)
Antianxiety: % (n)	10.8% (27)	6.8% (4)	15.9% (10)	4.7% (3)	15.4% (10)
Moodstabilizers: % (n)	34.7% (87)	28.8% (17)	36.5% (23)	32.8% (21)	40.0% (26)
Antipsychotics: % (n)	23.1% (58)	25.4% (15)	25.4% (16)	17.2% (11)	24.6% (16)
> 1 type: % (n)	44.5% (113)	39.0% (23)	49.2% (31)	31.3% (20)	55.4% (36)
Psychiatric diagnoses					
MDD: % (n)	70.1% (178)	66.1% (39)	70.3% (45)	66.2% (43)	77.3% (51)

Study	Petrakis, 2005 [44]					
	PTSD: % (n)	42.9% (109)	49.2% (29)	37.5% (24)	43.1% (28)	42.4% (28)
	Cocaine: % (n)	19.7% (50)	18.6% (11)	15.6% (10)	23.1% (15)	21.2% (14)
	Schizophrenia / schizoaffective: % (n)	7.1% (18)	15.3% (9)	6.3% (4)	4.6% (3)	3.0% (2)
	GAD/panic disorder: % (n)	22.4% (57)	22.0% (13)	21.9% (14)	20.0% (13)	25.8% (17)
	Bipolar disorder: % (n)	19.3% (49)	11.9% (7)	15.6% (10)	23.1% (15)	25.8% (17)
	Inclusion criteria Subjects met DSM-IV criteria for a major Axis I disorder and for an active alcohol dependence (abstinent ≤ 29 days) as determined by SCID-IV. Subjects were also required to be abstinent for 3 days before randomization, and the stated goal of the study was complete abstinence. Subjects on psychiatric medications had to be on a stable regimen for at least 2 weeks before randomization.					
	Exclusion criteria Exclusion criteria were unstable psychotic symptoms or serious current psychiatric symptoms, such as suicidal or homicidal ideation, or medical problems that would contraindicate the use of naltrexone and disulfiram, including liver function tests > 3 times the normal level. Exclusion after the interview also included: using opiates (n = 24), cognitive impairment (n = 23), lack of reliable transportation (n = 36), likely to move within the next 6 months (n = 15), facing possible incarceration (n = 15), not eligible for VA services (n = 9)					
	Recruitment & screening Subjects were recruited from the veterans who were treated at any of 3 clinics for military veterans. All 3 clinics have intensive substance abuse treatment programs that include an intensive rehabilitation program with aftercare and supported housing options for patients in treatment. Most subjects were already enrolled in the clinics before signing informed consent, although a few responded to advertisements and entered treatment as a result of entering into the trial. Of the 567 patients meeting initial eligibility criteria, 313 declined to participate or were deemed ineligible, and 254 were randomized.					
	Remuneration NR					

Study	Petrakis, 2005 [44]
Comparisons	**I. Naltrexone alone** **II. Placebo alone** **III. Disulfiram (OL) + naltrexone** **IV: Disulfiram (OL) and placebo** Randomization for naltrexone and placebo were double-blinded, disulfiram was open-label randomized because the drug's mechanism of action is easily detected which could have unfavourable consequences.
	Duration of treatment 12 weeks (84 days) Baseline based on measurements over last 30 days before randomization.
	Follow ups Weekly Endpoint / time of last treatment
	I. Naltrexone The delivery of 50 mg naltrexone was not described except to indicate that the medication was delivered in bottles with MEMS caps.
	Co-interventions <u>Counselling</u> All participants received weekly Clinical Management and Compliance Enhancement therapy administered by research personnel. <u>Intensive substance abuse program</u> All participants were enrolled in an intensive substance abuse program for military veterans. The programs included an intensive rehabilitation program with aftercare and supported housing options for patients in treatment. All participants continued to receive psychiatric and pharmacological treatment as usual through this program.
	II. Placebo The placebo was not described except to indicate that it was delivered in bottles with MEMS caps.
	Co-interventions <u>Counselling</u> Same as for Experimental arm I <u>Intensive substance abuse program</u>

Study	Petrakis, 2005 [44]
	Same as for Experimental arm I
	III. Disulfiram + naltrexone Participants were given two bottles of medications clearly labeled as “disulfiram” or “naltrexone study medication.” 250 mg disulfiram was dispensed in an open-label fashion from the bottle labelled “disulfiram” 50 mg naltrexone was dispensed from the bottle labelled “naltrexone study medication” No further information was provided about naltrexone.
	Co-interventions Counselling Same as for Experimental arm I Intensive substance abuse program Same as for Experimental arm I
	IV. Disulfiram + placebo Participants were given two bottles of medications clearly labeled as “disulfiram” or “naltrexone study medication.” 250 mg disulfiram was dispensed in an open-label fashion from the bottle labelled “disulfiram” The placebo was dispensed from the bottle labelled “naltrexone study medication” No further information was provided about the placebo.
	Co-interventions Counselling Same as for Experimental arm I Intensive substance abuse program Same as for Experimental arm I
Outcomes	**Alcohol and substance** Primary outcomes: Maximum consecutive days of abstinence, percent days abstinent, percent heavy drinking days, number of subjects with total abstinence (TLFB), self-reported, administered weekly by research staff Craving (OCDS), self-reported, administered weekly by research Serum levels, collected weekly by research staff.

Study: Petrakis, 2005 [44]

Mental health

Secondary outcomes:

Psychiatric symptoms (BSI), self-reported, administered biweekly by research staff

Quality of life

Not assessed

Function

Not assessed

Mortality

Not assessed

Compliance

Medication compliance was assessed using MEMS caps at each visit.

Treatment retention = number of days between the first and last medication dose taken based on the MEMS data.

Adverse effects

Side effects and common adverse symptoms (HSCL), self-reported symptom inventory, evaluated weekly by the research staff.

Results

Alcohol use, ITT, primary outcome

Group	I. Naltrexone	II. Placebo	III. Disulfiram + Naltrexone	IV. Disulfiram + Placebo	Treatment effects (ANOVA): III vs. IV or I	IV vs. I	I, III or IV vs. II
Measure	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	F, p	F, p	F, p
N=	59	64	65	66			
Consecutive abstinent days	67.2 (25.5)	61.0 (30.3)	69.2 (24.0)	70.5 (24.1)	0.01, 0.94	0.17, 0.68	4.49, 0.04*
% abstinent days	95.4 (11.8)	93.5 (14.0)	96.6 (8.7)	96.6 (10.5)	0.14, 0.71	0.36, 0.55	2.78, 0.10
% heavy drinking days	4.0 (11.4)	5.9 (12.9)	3.1 (8.1)	3.2 (10.5)	0.10, 0.76	0.20, 0.65	2.48, 0.12
Participants 100% abstinent, n	38 (64.4)	42 (65.6)	46 (70.8)	51 (77.3)	0.00, 0.95	2.55, 0.11	0.67, 0.41

* Reported in text as F (1, 246) = 4.49, p = 0.04

Comments

Drinking days per week: any med vs placebo [F (1, 246) = 5.71, p = 0.02]

Primary outcome craving (OCDS) reported in table 2. Not relevant to study question. Data not extracted.

Study | **Petrakis, 2005 [44]**

Primary outcome serum levels reported in table 2. Data not extracted.

Authors state: "Because of the high rate of abstinence, measures of quantity of alcohol consumption were of questionable significance and are therefore not reported."

Mental health, secondary outcomes

					Treatment effects over time (ITT, Random effects regression analysis)			
BSI subscales	I. Naltrexone Score	II. Placebo Score	III. Disulfiram + Naltrexone Score	IV. Disulfiram + Placebo Score	Within group z ,p	III vs. IV or I z ,p	IV vs. I z ,p	I, III or IV vs. II z ,p
Depression (pre)	1.54	1.34	1.25	1.48	-14.68, 0.00	-2.68, 0.01	1.68, 0.09	0.81, 0.42
(post)	0.93	0.65	0.61	0.89				
Anxiety (pre)	1.02	0.84	0.85	0.99	-11.97, 0.00	-0.71, 0.48	0.63, 0.53	-0.5, 0.62
(post)	0.69	0.41	0.54	0.52				
GSI (pre)	1.04	0.98	0.94	1.07	-15.72, 0.00	-1.93, 0.05	1.71, 0.09	0.29, 0.77
(post)	0.69	0.48	0.54	0.61				
Interpersonal Sensitivity (pre)	1.03	1.02	0.92	1.15	-11.85, 0.00	-0.47, 0.64	0.44, 0.66	0.28, 0.78
(post)	0.68	0.51	0.56	0.64				
Somatization (pre)	0.53	0.54	0.59	0.5	-6.47, 0.00	-1.7, 0.09	1.29, 0.20	-0.93, 0.35
(post)	0.39	0.27	0.44	0.29				
Obsessive–Compulsive (pre)	1.18	1.14	1.1	1.32	-14.5, 0	-1.56, 0.12	2.08, 0.04	-0.5, 0.62
(post)	0.82	0.49	0.69	0.74				
Phobic Anxiety (pre)	0.71	0.71	0.68	0.84	-9.61, 0	-1.37, 0.17	2.4, 0.02	0.9, 0.37
(post)	0.53	0.42	0.42	0.41				
Paranoid Ideation (pre)	0.94	0.89	0.91	0.99	-9.53, 0	-1.63, 0.1	1.23, 0.22	2.37, 0.02
(post)	0.69	0.57	0.6	0.61				

Compliance

					Treatment effects (ANOVA)		
Group	I. Naltrexone	II. Placebo	III. Disulfiram + Naltrexone	IV. Disulfiram + Placebo	III vs. IV or I	IV vs. I	I, III or IV vs. II
Days of treatment (84 days max)	M (SD)	M (SD)	M (SD)	M (SD)	F, p	F, p	F, p

Study	Petrakis, 2005 [44]

Days	73.7 (22.8)	68.2 (25.7)	61.1 (28.0)	70.2 (24.5)	7.84, 0.01*	0.60, 0.44	0.00, 0.97

Group	I. Naltrexone	II. Placebo	III. Disulfiram + Naltrexone	IV. Disulfiram + Placebo	Treatment effects (ANOVA)
% days compliant (MEMS, 84 days max)	M (SD)	M (SD)	M (SD)	M (SD)	F, p
Disulfiram	—	—	72.5 (30.4)	80.1 (27.2)	2.24, 0.14
Naltrexone	82.3 (27.4)	—	76.3 (29.8)	—	1.34, 0.25
Placebo	—	86.1 (20.0)	—	77.8 (31.4)	3.04, 0.08

* Reported in text as: F (1, 247) = 7.84, p= 0.01

Comments

The overall rate of medication compliance was 82.7% (SD = 26.1).

Adverse effects

Adverse effects

					Treatment effects (ANOVA)		
Group	I. Naltrexone	II. Placebo	III. Disulfiram + Naltrexone	IV. Disulfiram + Placebo	III vs. IV or I	IV vs. I	I, III or IV vs. II
Patients Reporting	%	%	%	%	F, p	F, p	F, p
Abdominal Pain	49.1	40.3	65.6	42.9	6.59, 0.01	0.42, 0.49	2.82, 0.10
After taste	52.6	52.6	59.4	47.6	1.45, 0.23	0.31, 0.58	5.91, 0.02
Blurred Vision	59.6	41.9	64.1	47.6	1.85, 0.18	1.77, 0.19	4.37, 0.04
Confusion	82.5	64.5	75	82.5	1.3, 0.26	0.00, 0.99	6.19, 0.01
Constipation	43.9	29	51.6	44.4	0.95, 0.33	0.004, 0.95	5.93, 0.02
Drowsy	89.5	80.6	92.2	90.5	0.2, 0.66	0.29, 0.87	4.52, 0.04
Dry Mouth	77.2	62.9	79.7	76.2	0.2, 0.66	0.02, 0.9	5.29, 0.02
Fever	22.8	32.3	34.4	41.3	0.1, 0.75	4.63, 0.03	0.004, 0.95
Irregular Heart	36.8	33.9	56.3	30.2	9.3, 0.003	0.58, 0.45	1.03, 0.31
Loss of Appetite	75.4	54.8	64.1	68.3	1.13, 0.29	0.69, 0.41	4.33, 0.04
Nausea	57.9	41.9	76.6	58.7	6.03, 0.02	0.009, 0.92	10.09, 0.002
Nervousness	98.2	79	79.7	79.4	2.63, 0.11	8.08, 0.005	1.65, 0.20
Numb Limbs	52.6	45.2	64.1	39.7	5.45, 0.02	2.05, 0.15	0.92, 0.34

Study	Petrakis, 2005 [44]						
	Pins or Needles	49.1	50	64.1	38.1	7.12, 0.008	1.48, 0.22	0.003, 0.96
	Restlessness	98.2	82.3	78.1	84.1	5.86, 0.02	4.91, 0.03	0.84, 0.36
	Tremors	57.9	38.7	53.1	50.8	0.03, 0.88	0.61, 0.44	4.33, 0.04
	Vomiting	24.6	24.2	42.2	31.7	3.88, 0.05	0.73, 0.39	1.6, 0.21
Serious adverse events	There were 14 serious adverse events in this study. Group I (N): 1 death* Group II (P): 1 death* 1 drug and alcohol overdose 1 had pneumonia requiring hospitalization Group III (D+N): 2 had cardiac events requiring hospitalization** 1 had a disulfiram–alcohol reaction requiring hospitalization Group IV (D+P): 4 had psychiatric hospitalizations (3 completed study) 1 had a cardiac event** 1 had acute axonal neuropathy requiring hospitalization * Neither of the deaths was determined to be study related ** 2 cardiac events occurred after patients had discontinued study medications for other reasons, and the other occurred in the context of heavy cocaine use.							
	Loss to follow up Randomized = 254 Completed* = 165 (65.0%) Assessed at end of study = 225 (88.6%) Loss to follow up = 89 (35%), 76 of whom completed the study Loss to follow up, without complete data set = 13 (5%)							

Study	Petrakis, 2005 [44]
	* Completed = those who took medication ≥78 of 84 possible days (MEMS)
Comments	Our search identified two related studies related to this study, both of which were judged to have a high risk of bias (CN412 & CN415)
Risk of bias	Moderate

ANOVA = analysis of variance; **AUD** = alcohol use disorder; **BSI** = Brief Symptoms Inventory; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition; **GAD** = generalized anxiety disorder; **HSCL** = Hopkins Symptom Checklist; **M** = mean; **MDD** = major depressive disorder; **MEMS** = Micro elective Events Monitoring; **NR** = not reported; **OCDS** = Obsessive Compulsive Drinking Scale; **OL** = open label; **PTSD** = post-traumatic stress disorder; **RCT** = randomized controlled trial; **SCID-IV** = Structured Clinical Interview for DSM-IV; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **VA** = veterans administration.

Petrakis et al. 2004; Ravelski et al. 2006

Study	Petrakis, 2004 [45] Ravelski, 2006 [46]
Study design	RCT, multi-center, double-blind
Intervention	Pharmacotherapy: naltrexone Co-interventions: stable treatment with neuroleptic medications
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	[45]: To evaluate the efficacy of naltrexone in alcohol dependent schizophrenic patients [46]: To examine the effect of naltrexone treatment on cognition in patients with schizophrenia and comorbid alcohol dependence. (Additional objective not relative to PICO: To assess whether changes in drinking patterns as a result of naltrexone treatment were related to changes in cognitive functioning; results for the additional objective not extracted here.)
Participants	**AUD & schizophrenia or schizoaffective disorder** Subjects, likely military veterans, met current DSM-IV criteria for schizophrenia or schizoaffective disorder and current DSM-IV criteria for alcohol dependence (n=30) or alcohol abuse (n=1) Population has mild/moderate psychosis, consistent with the clinical impression that subjects were stable on neuroleptic medications at the time of randomization. Baseline characteristics

	Total	Naltrexone	Placebo
N=	31	16	15

Study	Petrakis, 2004 [45] Ravelski, 2006 [46]			
	Men: % (n)	100% (31)	100% (16)	100% (15)
	Age: M (SD, range)	46.0 (5.7)	46.5 (5.2)	45.5 (6.4)
	Employed: % (n)	16% (5)	NR	NR
	Substance use status*			
	Drinking days: M (SD)	11.6 (8.3)	8.6 (8.5)	14.9 (7.0)
	Heavy drinking days (>5 drinks): M (SD)	9.0 (7.9)	7.3 (8.8)	10.8 (6.7)
	Total drinks: M (SD)	127.8 (126.7)	133.2 (163.8)	122.1 (74.4)
	Mental health status (PANSS)			
	General psychopathology: M (SD)	27.5 (6.6)	24.8 (4.5)	29.8 (7.4)
	Positive symptoms: M (SD)	12.7 (3.8)	11.5 (2.6)	13.75 (4.4)
	Negative symptoms: M (SD)	16.6 (6.3)	17.5 (6.9)	15.9 (6.0)
	Diagnosis			
	Schizophrenia: % (n)	58.1% (18)	56.2% (9)	60% (9)
	Schizoaffective: % (n)	41.9% (13)	43.8% (7)	40% (6)
	Medication**			
	Atypical neuroleptics: % (n)	51.6% (16)	50% (8)	53.3% (8)
	Thymoleptics: % (n)	38.7% (12)	37.5% (6)	40% (6)
	Benzodiazepines: % (n)	19.4% (6)	25.0% (4)	13.3% (2)
	Clozapine: % (n)	3% (1)		
	There were no significant differences on demographic or clinical characteristics at baseline.			
	* Average across 4 weeks of baseline			
	** Total not equal to 31 (100%) since patients may fit in one category, two categories or neither category			
	*** In Ravelski 2006, n = 30, as only subjects with alcohol dependence were included in that publication.			
	Inclusion criteria			
	Subjects met DSM-IV criteria for schizophrenia or schizoaffective disorder or for alcohol dependence or alcohol abuse as determined by SCID-IV. Subjects had been abstinent no more than 29 days.			
	Exclusion criteria			
	Exclusion criteria were unstable psychotic symptoms or serious current psychiatric symptoms, such as suicidal or homicidal ideation, or medical problems that would contraindicate the use of naltrexone.			
	Subjects with other lifetime axis I disorders, besides nicotine dependence were excluded.			
	Recruitment & screening			

Study	Petrakis, 2004 [45] Ravelski, 2006 [46]
	Subjects were recruited from the patients who were treated at clinics in New England Mental Illness and Research Education Clinical Center facilities. 78 people met initial eligibility criteria. After signing informed consent, subjects underwent an intake assessment, which included a physical examination, laboratory assessments and an interview with a psychiatrist. 17 people declined to participate or dropped out and 30 were excluded (reasons provided in text) Five people out of 31 (16%) required medically assisted detoxification prior to randomization. **Remuneration** Participants in the study were not charged for treatment. Subjects were reimbursed weekly ($10) for attending research sessions (weeks 1–11) and reimbursed $20 for the baseline assessments and $30 for the endpoint evaluations for a total of $160.
Comparison	**Naltrexone vs. placebo** **Duration of treatment** 12 weeks **Follow ups** Weekly Endpoint / time of last treatment
Experimental arm	**Naltrexone** One capsule per day for 12 weeks 50 mg naltrexone was delivered in opaque blue capsules that had been filled with ground naltrexone tablets **Co-interventions** <u>Maintenance, pharmacological</u> Participant's pharmaceutical treatment for schizophrenia was maintained. See baseline characteristics for list of which medications were being taken. <u>CBT/RP, psychotherapy</u>

Study	Petrakis, 2004 [45] Ravelski, 2006 [46]
Control arm	Participants in the study also participated in a weekly CBT/RP. This approach uses cognitive-behavioral drug relapse prevention strategies originally developed for non-mentally ill substance abusers and incorporates a skills training method originally developed to teach social and independent living skills to schizophrenics. All participants continued to receive psychiatric treatment as usual. **Placebo** One capsule per day for 12 weeks The opaque blue capsules were identical to those supplied to the naltrexone group except that they had been filled with lactose. **Co-interventions** Maintenance, pharmacological Same as for the intervention group. CBT/RP, psychotherapy Same as for the intervention group.
Outcomes	**Substance use** Primary outcomes: Drinking days (TLFB), self-reported in interview, weekly for last week Heavy drinking days (>5 drinks/day) (TLFB), self-reported in interview, weekly for last week **Mental health** Secondary outcomes: Psychiatric symptoms (PANSS), administered by the research staff at baseline and weekly **Quality of life** Not assessed **Function** Secondary outcomes: Petrakis 2004: Abnormal involuntary movement (AIMS), was measured by the staff at weeks 6 and 12 Ravelski 2006 (all assessed at baseline and week 12): Immediate recall (DS) Hopkins immediate recall (HVLT) Hopkins delayed recall (HVLT)

Study: Petrakis, 2004 [45] Ravelski, 2006 [46]

Results

Verbal memory (VF)

Attention deficits (GDS)

Mortality

Not assessed

Compliance

Medication compliance was assessed using pill counts at each visit (total number of pills taken/84 possible days)

Adverse effects

The symptoms that are known to be associated with naltrexone treatment and neuroleptic use were specifically screened for at each visit by use of AIMS and HSCL.

Substance use

	Naltrexone n = 16		Placebo n = 15		HLM random intercepts
Primary outcomes, drinking	**Baseline** Ave over 4 weeks	**Endpoint** Total over 12 weeks	**Baseline** Ave over 4 weeks	**Endpoint** Total over 12 weeks	**Drug effect during treatment**
Number of drinking days, M (SD)*	8.6 (8.5)	6.2 (8.0)	14.9 (7.0)	13.5 (15.6)	F(1, 248) = 13.4, P < 0.0001*
Number of heavy drinking days, M (SD)*	7.3 (8.8)	0.37 (1.1)	10.8 (6.7)	0.81 (1.4)	F(1, 248) = 9.32, P = 0.003
Total number of drinks, M (SD)*	133.2 (163.8)	56.7 (84.3)	122.1 (74.4)	83.1 (98.1)	NR

Baseline data extracted from table 1, endpoint data and efficacity extracted from text [45].

* Number of drinking days was used as a covariate in random regression analysis of drinking days during treatment

Comments

The mean weekly heavy drinking days is reported graphically in figure 1. Data not extracted.

Mental health

Psychosis [45]	Naltrexone n = 16		Placebo n = 15		HLM random intercepts
PANSS	**Baseline**	**Endpoint**	**Baseline**	**Endpoint**	**Effect**
General psychopathology: M (SD)	24.8 (4.5)	26.4 (5.2)	29.8 (7.4)	30.2 (8.7)	Drug: F(11, 1) = 3.37, p = 0.06 Time: F(11, 1) = 0.65, p = 0.78 Drug x time: F(11, 1) = 0.16, p = 0.35
Positive symptoms: M (SD)	11.5 (2.6)	11.1 (3.6)*	13.75 (4.4)	12.8 (4.8)	NS
Negative symptoms: M (SD)	17.5 (6.9)	15.1 (5.3)	15.9 (6.0)	17.4 (6.6)	NS

Study	Petrakis, 2004 [45] Ravelski, 2006 [46]

Baseline data extracted from table 1, endpoint data and efficacity extracted from text [45].

* Reported as 11.1 (SD=0 3.6) in text, interpreted as a typo.

Function

Cognitive functioning [46]	Naltrexone n = 15		Placebo n = 15		Significance[b]
	Baseline	Endpoint	Baseline	Endpoint	p-value
HVLT, immediate recall: M (SD)	21.1 (4.9)	18.4 (6.6)	17.4 (6.9)	18.3 (8.1)	0.33
HVLT, delayed recall: M (SD)	7.14 (2.24)	6.30 (3.12)	5.06 (3.2)	5.30 (3.47)	0.11
VF: M (SD)	11.1 (4.6)	10.8 (5.22)	12.6 (5.5)	12.2 (5.75)	0.52
GDS, vigilance: M (SD)	0.93 (0.18)	0.98 (0.02)	0.97 (0.03)	0.97 (0.03)	0.53
DS, forward: M (SD)	8.9 (2.89)	9.3 (2.62)	8.5 (3.04)	8.00 (3.11)	0.58
DS, backward: M (SD)	6.66 (3.22)	5.50 (2.71)	5.86 (2.13)	5.75 (2.80)	0.63

b- Mixed effects models, Bonferroni adjusted for multiple comparisons, alpfa level = 0.008,

Compliance

	Naltrexone N = 15	Placebo N = 15	significance
Study visit attendance:	75.3%	82.8%	NS
Pill count*:	68.4%	77.5%	NS

* Number of pills taken / potential medication days, max 84 days [45]

Adverse effects

[45]	Naltrexone n = 16	Placebo n = 15
Psychiatric hospitalization: % (n)	12.5% (2)	13.3% (2)
	Drug effect during treatment[a]	
AIMS, M (SD)	F(2, 1) = 0.87, p = 0.35	

a- The analysis used random intercepts HLM within the SPSS Mixed procedure

Comments

Overall, all subjects (100%) reported experiencing one or more symptoms potentially related to medication side effects: dry mouth, drowsiness, poor memory, headache, trouble concentrating, sweating, difficulty sitting still, frequent urination, constipation, nausea, faintness, diarrhea, decreased appetite, muscles stiffness, blurred vision, nightmares, irregular heartbeat, tremor, ringing in ears, skin rash. See table 2 for more information [45].

Study	Petrakis, 2004 [45] Ravelski, 2006 [46]
	Loss to follow up 81% (25) reached follow-up, naltrexone group: 86.7% (15); placebo group: 75.0% (12), NS different between groups.
General comments	The study was originally designed as an 8-week study and then amended to be 12 weeks, so the first two subjects completed only 8 weeks of treatment. The first two subjects completed the study without incident and therefore the study was amended to last for 12 weeks in order to be consistent with other published naltrexone trials.
Risk of bias	Moderate

AIMS = Abnormal Involuntary Movement Scale; **AUD** = alcohol use disorder; **CBT/RP** = cognitive behavioural therapy, focused on relapse prevention; **DS** = Digit Span; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition; **GDS** = Gordon Diagnostic System; **HLM** = hierarchical linear modelling; **HSCL** = Hopkins Symptom Checklist; **HVLT** = Hopkins Verbal Learning Test; **M** = mean; **NR** = not reported; **NS** = not significant; **PNASS** = Positive and Negative Symptom Scale; **RCT** = randomized controlled trial; **SCID-IV** = Structured Clinical Interview for DSM-IV; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **VF** = Verbal Fluency.

Pettinati et al. 2010

Study	Pettinati, 2010 [47]
Study design	RCT, double-blind, 4 arms
Intervention	**Pharmacotherapy: sertraline + naltrexone, sertraline, naltrexone** Co-interventions: weekly CBT
Trial registration	NCT00004554
Country	USA
Setting	Outpatient
Aims	Evaluated combining two FDA-approved medications, one for depression (sertraline) and one for alcohol dependence (naltrexone), to treat patients with both disorders. An important aim was to compare mood and drinking outcomes of this medication combination compared to placebo and treatments where each medication is prescribed.
Participants	**AUD & depression**
	Baseline characteristics

	Sertraline + naltrexone	Naltrexone	Sertraline	Placebo
N = 170	**42**	**49**	**40**	**39**
Women: n (%)	18 (42.9%)	16 (32.7%)	13 (32.5%)	17 (43.6%)

Study	Pettinati, 2010 [47]				
	Age: M (SD)	43.4 (10.2)	42.9 (8.1)	43.9 (11.5)	43.4 (8.9)
	Education, years M (SD)	14.8 (3.0)	13.8 (2.7)	13.8 (2.1)	14.5 (2.7)
	Substance use status				
	% drinking days in past 30: M (SD)	71.0% (23.6)	77.3% (22.9)	73.4% (21.7)	79.0% (21.3)
	% heavy drinking days in past 30 days, : M (SD)	63.0% (25)	72.5% (24.4)	66.9% (24.4)	69.1% (28.0)
	Drinks per drinking day in past 30 days, n: M (SD)	12.8 (9.2)	13.6 (6.9)	12.4 (5.6)	10.5 (5.9)
	Mental health status				
	HRSD score in past 30 days: M (SD)	23.7 (6.7)	22.3 (5.7)	23.4 (6.0)	22.9 (7.0)
	NS differences between the four groups at baseline.				
	Inclusion criteria Current DSM-IV major depression and alcohol dependence diagnoses; drink on average 12 or more alcoholic drinks per week and had a drink on 40% or more days in the 90 days before treatment; have 3 consecutive abstinent days just before starting medication; score 10 or higher on the HRSD (24-item) at randomization				
	Exclusion criteria Substance dependence besides alcohol or nicotine; bipolar-affective, schizophrenic, other psychotic, or organic mental disorders; regularly taking an antidepressant; needed psychiatric medications other than an antidepressant; had a significant medical disease; were pregnant or breastfeeding				
	Recruitment & screening Patients learned of the study from newspaper advertisements, local professionals, or friends and family, and after an initial telephone screening were invited for evaluation at a research-sponsored outpatient substance abuse treatment facility; numbers screened (1 week) = 355; numbers randomized = 170, stratified by gender, smoking status, HRSD scores, and drinking frequencies of the previous 90 days. No detoxification period mentioned, but an inclusion criterion was 3 consecutive abstinent days just before starting medication.				
	Remuneration NR				
Comparisons	**I. Sertraline + naltrexone**				

Study	Pettinati, 2010 [47]
	II. Naltrexone + placebo **III. Sertraline + placebo** **IV. Double placebo**
	Duration of treatment 14 weeks
	Follow ups Measurements during treatment: weekly Endpoint: at 14 weeks
Experimental arm I	**Sertraline + naltrexone** At randomization, patients took 50 mg/day of naltrexone for 4 days and then added 50 mg/day of same for 3 days to the maximum naltrexone dose of 100mg/day. In the next week, patients added 50 mg/day of sertraline and were titrated up, adding 50 mg/day every third day, to the maximum sertraline dose of 200mg/day. Study medication was dispensed weekly in blister cards. Medical clinicians could exercise flexibility in dosing patients who could not tolerate maximum daily doses. Patients continued with treatment until the 13th week, when naltrexone was reduced to 50 mg/day while maintaining sertraline at 200mg/day. In the 14th week, naltrexone was continued at 50 mg/day and sertraline was reduced to 100mg/day. Medications were completed by the last treatment day.
	Co-interventions CBT (psychiatric) Weekly, individual CBT using the National Institute on Alcohol Abuse and Alcoholism Project MATCH manual, adapted to also treat depression. Compliance data for “support meetings” indicates that some form of support meeting may also have been offered or allowed, NR.
Experimental arm II	**Naltrexone + placebo** At randomization, patients took 50 mg/day of naltrexone for 4 days and then added 50 mg/day of same for 3 days to the maximum naltrexone dose of 100mg/day. In the next week, patients added 50 mg/day of placebo and were titrated up, adding 50 mg/day of same every third day, to the maximum dose of 200mg/day. Study medication was dispensed weekly as for Experimental arm I. Flexible dosing and reduction/completion of study medication as for Experimental arm I.

Study	Pettinati, 2010 [47]
	Co-interventions CBT (psychiatric) As described for Experimental arm I.
Experimental arm II	**Sertraline + placebo** At randomization, patients took 50 mg/day of placebo for 4 days and then added 50 mg/day of same for 3 days to the maximum dose of 100mg/day. In the next week, patients added 50 mg/day of sertraline and were titrated up, adding 50 mg/day of same every third day, to the maximum sertraline dose of 200mg/day. Study medication was dispensed weekly as for Experimental arm I. Flexible dosing and reduction/completion of study medication as for Experimental arm I.
	Co-interventions CBT (psychiatric) As described for Experimental arm I.
Experimental arm IV - Control arm	**Double placebo** At randomization, patients took 50 mg/day of first placebo for 4 days and then added 50 mg/day of same for 3 days to the maximum dose of 100mg/day. In the next week, patients added 50 mg/day of second placebo and were titrated up, adding 50 mg/day of same every third day, to the maximum dose of 200mg/day. Study medication was dispensed weekly as for Experimental arm I. Flexible dosing and reduction/completion of study medication as for Experimental arm I.
	Co-interventions CBT (psychiatric) As described for Experimental arm I.
Outcomes	**Substance use** Primary outcomes: Total abstinence from alcohol (TLFB), self-reported in weekly interview Time to first heavy drinking (men: ≥5 drinks/drink day; women: ≥4 drinks/drink day) (TLFB), self-reported in weekly interview Secondary outcomes: Percentage of patients not drinking heavily (TLFB), self-reported in weekly interview

Study	Pettinati, 2010 [47]
	Time to first drinking day (TLFB), self-reported in weekly interview
	Mental health Primary outcomes: No depression at endpoint (% with HRSD ≤9 in last 3 weeks of treatment) (HRSD), weekly semi-structured interview Depressive symptoms at endpoint (HRSD), weekly semi-structured interview
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Medication adherence was defined as the percentage of prescribed pills taken while in treatment. Treatment attendance was reported as number and percentage of possible CBT sessions attended.
	Adverse effects AE recorded weekly (SATEE)

Results

Substance use

	Sertraline + naltrexone N=42	Naltrexone N=49	Sertraline N=40	Placebo N=39	Sertraline+naltrexone group vs other groups combined[a]			
Primary outcomes	**Over the 14 weeks**				**χ^2 or t**	**p-value**	**OR or Cohen´s *d***	**95%CI**
Abstinence from alcohol during treatment: % (N) number analysed[b]	53.7% (22), n=41	21.3%, n=47	27.5%, n=40	23.1%, n=39	12.9	0.001	OR 3.7	1.8 to 7.8
Time to Relapse to Heavy Drinking[c], days: M (SD, Md) number analysed[b]	63.6 (40.8, 98) n=41	45.2 (38.9, 29) n=47	39.9 (38.3, 23) n=40	41.7 (38.0, 26) n=39	3.0	0.003	d = 0.54	0.19 to 0.89
Secondary outcomes								
Percentage of patients not drinking heavily[d]: M	63.4%	Other groups combined: 34.1%			13.2	0.004	NR	NR
Time (days) to first drinking day: Md	61	Other groups combined: 15			3.5	0.001	NR	NR

Study | **Pettinati, 2010 [47]**

a- The alpha was set to 0.01 to adjust for the overall group comparisons. The alpha was fixed at 0.01 for a priori hypothesized planned subgroup contrasts, limited to comparing the two-medication group to the other three treatment groups combined.
b- Analysis of participants with data (not ITT).
c- Survival analysis, significance measured with Cox proportional hazards. Relapse occurred after 26 days for the other groups combined.
d- Secondary analysis

Mental health

					Sertraline+naltrexone group vs other groups combined[a]			
Primary outcomes	**Endpoint**	**Endpoint**	**Endpoint**	**Endpoint**	**χ^2 or t**	**p-value**	**OR or Cohen´s *d***	**95%CI**
% with HRSD ≤9 in last 3 treatment weeks: % (N), number analysed[b]	83.3% (25) n=30	68.8% (22), n=32	48.1% (13), n=27	56% (14), n=25	6.1	0.014	OR 3.6	1.2 to 10.2
HRSD rating of depression: M (SD), number analysed[b]	6.9 (6.1), n=27	8 (7.0), n=29	11.7 (7.3), n=26	10.2 (8.0), n=21	2.1	0.042	d = 0.44	0.02 to 0.87

a- The alpha was set to 0.01 to adjust for the overall group comparisons. The alpha was fixed at 0.01 for a priori hypothesized planned subgroup contrasts, limited to comparing the two-medication group to the other three treatment groups combined.
b- Analysis of participants with data (not ITT).

Comments

Change in HRSD scores over time reported graphically in figure 3, data not extracted.

Compliance

Compliant	**Sertraline+naltrexone**	**Naltrexon+placebo**	**Sertraline+placebo**	**Placebo+placebo**	**Overall**
	n = 42	**n = 49**	**n = 40**	**n = 39**	
Percentage of prescribed pills taken while in treatment: %	90.9%	84.9%	82.1%	90.5%	87%*
Number and percentage of CBT sessions attended: n (%)	NR	NR	NR	NR	8.2 (59%)*
Number of support group meetings attended: n	NR	NR	NR	NR	3.4

* reported in text, authors report no significant between group differences.

Study	Pettinati, 2010 [47]
	Adverse effects Sertraline+naltrexone n = 42 / Naltrexon+placebo n = 49 / Sertraline+placebo n = 40 / Placebo+placebo n = 39 **Discontinuations due to AE, n**: 7 / 2 / 4 / 1 Comments The authors state: The serious adverse event rate was significantly lower for sertraline + naltrexone patients (11.9%) than the other groups combined ($\chi 2 = 5.7$, df=1, $p < 0.02$; naltrexone=26.5%, sertraline=37.5%, placebo=28.2%). AE ranged from mild to very severe.
	Loss to follow up Endpoint: Overall, about 43% prematurely discontinued treatment n (%): sertraline+naltrexone = 18 (43%); naltrexone = 20 (41%); sertraline = 19 (48%); placebo = 16 (41%) Reasons for discontinuing treatment: clinical deterioration (13.5%), job or family (10.6%), adverse events (8.2%), or other (10.6%). Clinical deterioration was defined as an escalation of depression and/or drinking necessitating medication and a clinical referral. There were no differences in the number of patients by reasons across groups.
Risk of bias	Moderate

AE = adverse effects; **AUD** = alcohol use disorder (dependence); **CI** = confidence interval; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition; **HRSD** = Hamilton Rating Scale of Depression, 24 item; **ITT** = intention to treat; **M** = mean; **Md** = median; **NR** = not reported; **OR** = odds ratio; **RCT** = randomized controlled trial; **CBT** = Cognitive Behavioral Therapy; **SATEE** = Systematic Assessment for Treatment Emergent Effects; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use (time to outcomes).

Raby et al. 2014

Study	Raby, 2014 [48]
Study design	RCT, double-blind, placebo-controlled
Intervention	**Pharmacotherapy: venlafaxine** Co-interventions: CBT/RP
Trial reg.	NR
Country	USA
Setting	Outpatient
Aims	The aim was to investigate if the antidepressant venlafaxine would be an effective treatment for cocaine dependence with concurrent depressive disorders.

Study: Raby, 2014 [48]

Participants

Cocaine dependence & depression

Particpants met DSM-IIIR criteria for both cocaine dependence and current major depressive disorder or dysthymia.

Baseline characteristics

Variable	Venlafaxine	Placebo
N=	64	66
Men: (n)	72 % (46)	73 % (48)
Age: M (SD)	37 (8)	38 (8)
Education (% post HS)	60 % (37)	48 % (30)
Not married	53 % (33)	48 % (31)
Married	24 % (15)	31 % (20)
Divorced/separated	23 % (14)	20 % (13)
Employed - Full time	79 % (46)	68 % (41)
Part-time	12 % (7)	8 % (5)
Unemployed	9 % (5)	23 % (14)
Ham-D 21: total score	15.70 (4.77)	16.39 (4.99)
CGI Dep: severity score	4.42 (.90)	4.49 (.82)
Type of depression		
Primary	40 % (25)	42 % (27)
Secondary	38 % (24)	40 % (26)
Diagnosis of dysthymia	22 % (14)	18 % (12)
Diagnosis of dysthymia + major depression	10 % (6)	9 % (6)
CGI Coc: severity score	3.53 (1.52)*	4.09 (1.21)*
Days/week: using cocaine	1.57 (1.80)	1.97 (1.98)
Days/week: craving cocaine	3.98 (2.50)	4.61 (2.27)
Diagnosis of alcohol dependence	23 % (15)	21 % (14)
Diagnosis of cannabis dependence	11 % (7)	14 % (9)

*There were no significant differences between placebo and venlafaxine groups, except for CGI cocaine severity score which was modestly greater in the placebo group (4.09 ± 1.21) compared with the VEN-XR group (t = 2.3, p =0.02).

Inclusion criteria

Patients were deemed eligible only if they met DSM-IIIR criteria for both cocaine dependence and current major depressive disorder or

Study	Raby, 2014 [48]
	dysthymia, with at least one of the following characteristics: (1) 18-65 year of age; (2) the depression was chronologically primary, antedating the onset of substance abuse during a lifetime history; (3) the depression was chronologically secondary, but persisted or emerged during a past instance of abstinence lasting at least 6 months; or (4) the depression was of at least 3 months duration in the current episode.
	Exclusion criteria Patients were excluded if they had a history of bipolar disorder, psychotic illness other than brief psychotic symptoms attributable to cocaine intoxication, were judged to be at risk of suicidal behavior, were medically unstable, or had a seizure disorder. Patients dependent on nicotine, alcohol, or cannabis were not excluded, as long as cocaine dependence was the predominant clinical problem.
	Recruitment & screening One hundred and forty patients consented to participate, from the 1615 assessed for eligibility: 726 dropped out of screening; 382 entered other studies; 367 did not meet inclusion criteria; and 10 placebo responders were removed after randomization and the 1 week-lead-in phase of the trial. 130 were randomized, stratified by levels of cocaine use.
	Remuneration NR
Comparison	**Venlafaxine-XR vs. placebo**
	Duration of treatment 12 weeks + 1-week placebo lead-in phase to remove placebo responders
	Follow ups Patients were asked to come to the clinic twice a week for the 12 weeks of the trial. All outcomes were not measured at each visit.
Experimental arm	**Venlafaxine-XR** Venlafaxine was titrated on a fixed-flexible schedule, beginning at 37.5 mg for 4 days, and then twice a day for the remaining 3 days, and then increased every week by 75 mg to reach 300 mg or the maximum tolerated dosage. Venlafaxine-XR (75 mg) was packaged in unmarked gelatine capsules containing 25 mg of riboflavin.
	Co-interventions Psychosocial

Study	Raby, 2014 [48]
	CBT/RP, individual, manual-guided prevention therapy delivered weekly, that aimed to promote retention and compliance with clinical trial procedures and provide a foundation treatment to patients.
Control arm	**Placebo** Placebo was packaged in identical unmarked gelatine capsules containing 25 mg of riboflavin.
	Co-interventions Psychosocial Same as treatment group.
Outcomes	**Substance use** At week 12, or at the last week of the study participation, the treating psychiatrist rendered a global rating of cocaine response, based on whether the patient had achieved at least a 75% reduction in cocaine use compared to baseline, based on self-report and urine toxicology. Urine-confirmed abstinence (both urine and self-reports negative for cocaine) was determined weekly, and the proportion of patients achieving at least three consecutive weeks of abstinence during the trial was computed.
	Mental health Primary outcomes Global treatment response, the treating psychiatrist rendered a global rating of depression response based on all available data Depression response = >50% decrease in Ham-D scores between randomization and end of study. Mood outcome was evaluated with the Ham-D every 2 weeks, and the CGI weekly.
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Presence of riboflavin in urine (detection by UV fluorescence) Blood levels of venlafaxine were drawn at weeks 3, 6, and 12.

Study	Raby, 2014 [48]

Substance use

		Effect of medication treatment	
Cocaine use outcome	**Placebo (n = 66)**	**Venlafaxine-XR (n = 64)**	**Significance**
Cocaine responder by clinician's global rating	42% (28/66)	51% (33/64)	1.09, .30
CGI cocaine severity	3.05 (1.56)	2.91 (1.59)	.51, .61
Days per week using cocaine	1.64 (1.57)	1.49 (1.46)	.60, .55
Proportion of urines positive for cocaine	.64 (.36)	0.62 (0.35)*	.34, .738
≥3 consecutive weeks of urine confirmed abstinence	15% (10/66)	16% (10/64)	.001, .94

* Data reported 0.62 (35), interpreted as an editorial mistake.

Mental health

	Effect of medication treatment		
Mood outcome	Placebo (n = 66)	Venlafaxine (n = 64)	***X or t, p-value***
Mood responder by clinician's global rating	48% (32/66)	56% (36/64)	.67, .42
50% drop in Ham-D score	33% (22/66)	41% (26/64)	.74, .39

Comments

Linear analysis of HamD-21 and CGI presented graphically; data not extracted.

- Average Ham-D severity scores with standard deviation bars by week, from consent (week −1; baseline), randomization (week 0) to week 12 of a randomized, double-blind, placebo-controlled study of venlafaxine (up to 300 mg) versus placebo. A single-blind placebo lead-in occurs between week −1 and 0. In the mixed effect model, there was a significant effect of time, but no main or interactive effects of treatment, while post hoc t-tests indicated venlafaxine separated from placebo at week 2 (t = 2.26, p= .02) and week 4(t= 1.96, p= .05).

- Average CGI Depression Severity score with standard deviation bars by week, from consent (week −1; baseline), randomization (week 0), to week 12 of a randomized, double-blind, placebo-controlled study of venlafaxine (up to 300 mg) versus placebo. A single-blind placebo lead-in occurs between week −1 and 0. In the mixed effect model, there was a significant effect of treatment, with post hoc t-tests indicating venlafaxine separated from placebo at week 2 (t= 2.38, p= .01) and week 4 (t= 2.57, p= .01)

Compliance

Forty-one percent of all collected urine samples failed to display riboflavin fluorescence under ultraviolet light.
The presence of undetectable blood levels of medication among those randomized to venlafaxine, the wide variation in measured blood levels that do not relate to mood response, and the frequency of riboflavin-negative urine samples, suggest poor medication compliance by many patients.

Adverse effects

Study	Raby, 2014 [48]
	Placebo VEN-XR Left because of side effects of medication (n) 3 1 Withdrawn by MD for mood non-response 3 5 Removed by MD for psychiatric worsening 4 2 Removed by MD for SUD worsening 2 1 Withdrawn by MD for medical reasons - 2 Comments Side effects that occurred at a frequency greater than 1% while on venlafaxine or placebo include insomnia, headache, sexual dysfunction, nausea, lethargy, agitation, sedation, dizziness, chest pain, night sweat, diarrhea, shortness of breath, sweating, and decreased appetite. Those encountered exclusively in the venlafaxine group include diarrhea, shortness of breath, sweating, decreased appetite, weight loss, flatulence, vivid dreams, increased blood pressure, flushing, tremor and difficulty urinating. Overall, side effects did not differ significantly between groups. There were six serious adverse events, all involving patients in the venlafaxine arm. Three patients were suicidal; one patient was involved in a car accident while intoxicated; another suffered a motorcycle accident while abstinent; one patient was found to have an abdominal mass. There were no serious adverse events in the placebo group.
	Loss to follow up Placebo VEN-XR Did not complete study, drop outs: % (n) 28.8% (19) 43.7% (28) Completed at least 4 weeks of the trial % (n) 80 % (53) 70 % (51) Completed the 12 week treatment phase % (n) 49 % (32) 33 % (21) Comments Survival analysis on weeks to dropout did not reach significance (log-rank = 2.24, df = 1, p = .13), although inspection of the survival curves suggested greater dropout on venlafaxine over the later weeks of the trial. Non-compliance was the most common reason for dropout, with a non-significant trend toward more non-compliance on venlafaxine. The 77 participants who did not complete the 12 weeks of the trial did not differ in baseline demographic or clinical characteristics from those who completed the trial.
Risk of bias	Moderate

CBT/RP = Cognitive Behavioral Therapy/ Relapse Prevention Treatment; **CGI** = Clinical Global Impression scale, scores of 1 = very much improved; 2 = much improved; **DSM-IIIR** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition – revised; **DSM-IV-TR** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition – text revision; Ham-D = Hamilton Depression Inventory, 19 item; **M** = mean; **MD** = medical doctor; **NR** = not reported; **RCT** = randomized controlled trial; **SD** = standard deviation; **VEN-XR** = venlafaxine-extended release; **XR** = extended release.

Roy-Byrne et al. 2000

Study	Roy-Byrne, 2000 [49]
Study design	RCT, double-blind, placebo-controlled
Intervention	**Pharmacotherapy: nefazodone** Co-interventions: weekly group therapy for alcoholism (CBT & psychoeducation)
Trial registration	NR
Country	Washington state, USA
Setting	Outpatient clinic, University associated
Aims	We tested the efficacy of nefazodone for the treatment of comorbid alcohol dependence and depression, where alcohol-withdrawal symptoms not severe enough to warrant detoxification with benzodiazepines
Participants	**AUD & Depression** Actively drinking alcohol-dependent patients with comorbid depression
	Baseline characteristics

Demographics	Total sample (N = 64)	Nefazodone (N=32)	Placebo (N=32)
Male, n (%)	29 (45.3)	17 (53.1)	12 (37.5)
Age, years, mean (SD)	40.2 (8.2)	40.9 (8.6)	39.5 (7.9)
Education, years, mean (SD)	14.2 (2.3)	13.6 (2.4)	14.7 (2.0)
Employment, yes, n (%)	45 (70.3)	24 (75.0)	21 (65.6)
Current psychiatric diagnoses			
MD and alcohol dependence, n (%)	64 (100)	32 (100)	32 (100)
Alcohol abuse, n (%)	25 (39.1)	12 (37.5)	13 (40.6)
Dysthymia, n (%)	29 (45.3)	13 (40.6)	16 (50.0)
Panic disorder, n (%)	8 (12.5)	4 (12.5)	4 (12.5)
Agoraphobia without panic disorder, n (%)	3 (4.7)	2 (6.3)	1 (3.1)
GAD, n (%)	18 (28.2)	7 (21.9)	11 (34.4)
Social phobia, n (%)	20 (31.3)	12 (37.5)	8 (25.0)
Specific phobias, n (%)	14 (21.9)	3 (9.4)	11 (3.4)
OCD, n (%)	5 (7.8)	2 (6.3)	3 (9.4)
PTSD, n (%)	7 (10.9)	3 (9.4)	4 (12.5)
≥1 comorbid current diagnosis**, mean (SD)	49 (76.7)	22 (68.8)	27 (84.4)
Number of comorbid diagnoses**, mean (SD)	1.7 (1.4)	1.5 (1.3)	1.9 (1.4)
Baseline psychiatric symptom severity			
HAM-D, mean (SD)	23.9 (5.2)	23.1 (5.8)	24.8 (4.5)

Study	Roy-Byrne, 2000 [49]

HAM-A, mean (SD)	23.5 (8.3)	22.4 (9.5)	24.6 (6.9)
CGI, Severity of illness subscale	4.9 (0.8)	4.8 (0.8)	5.0 (0.8)
Baseline substance abuse data			
AUDIT – alcohol, mean (SD)	26.4 (6.1)	26.6 (5.5)	26.1 (6.7)
DAST, mean (SD)	7.5 (6.6)	7.3 (6.8)	7.7 (6.6)
Drinks / day in week before trial intake, mean (SD)	9.8 (10.3)	11.0 (10.5)	8.5 (10.1)

* $\chi 2$ (1) = 4.48, p = 0.03

** Not including alcohol dependence, abuse, or MD

Comments

$\chi 2$ and t-test analyses used to examine baseline values. There were no significant differences between treatment groups in any variable, except specific phobias which was more frequent in the placebo group. Data was not extracted for diagnoses that effected single or no participants.

Psychiatric symptom severity also measured with SCL-53 subscales are also reported, data not extracted.

Inclusion criteria

Subjects with concurrent major depression and alcohol dependence, as determined by SCID-III-R, who also reported a major depressive episode during a period of at least 1 month of sobriety (to decrease the likelihood of substance-induced mood disorder)

Exclusion criteria

Exclusion criteria included intravenous drug use, other drug use more than once per week, schizophrenia and bipolar disorder, active suicidal ideation with a plan, recent history of delirium tremens or alcohol-withdrawal seizures, current treatment for depression or alcoholism, serious medical problems, treatment with medications that are contraindicated in combination with nefazodone (Seldane, Hismanal, or Propulsid), pregnancy, untreated hypothyroidism or hyperthyroidism, clinically significant live dysfunction, active cardiac or renal impairment (defined as hospitalization or change in treatment plan in last 6 months), and homelessness.

Recruitment & screening

Potential subjects aged 18 to 55 years were recruited through local newspaper/radio advertisements and hospital flyers.

Initial phone screening (n=715) was followed by in person psychiatric diagnostic evaluation using SCID-III-R to establish depression and alcohol intake diagnoses.

Subjects were asked to decrease or discontinue their drinking before randomization, but only 9.5% stopped drinking.

Study	Roy-Byrne, 2000 [49]
	In total, 64 subjects were randomized to each group, N=32 per group.
	Remuneration NR
Comparison	**Nefazodone vs. placebo**
	Duration of treatment 12 weeks
	Follow-ups Data was collected at intake and at weeks 2, 4, 6, 8, and 12 EOT = 12 weeks or last
Experimental arm	**Nefazodone** Dosing was started at one capsule (100 mg) twice daily and was titrated at a rate of one additional capsule (100 mg) per week until the patients were taking two capsules in the morning and three capsules at night (500 mg total). Patients who experienced side effects were given routine instructions for alleviating those reactions, for instance to change when the medications were taken. Dose reduction was minimized unless side effects were severe, resulting in most drug-treated patients receiving the full 500-mg dose.
	Co-interventions: <u>Psychological</u> All subjects engaged in a cognitive-behavioral skills training and psychoeducational group for alcohol dependence and depression led by an experienced therapist, 12-session cycle, 1 hr per week.
Control arm	**Placebo** Same as for Experimental arm.
	Co-interventions Same as for Experimental arm.
Outcomes	**Substance use** Drug abuse screening test

Study	Roy-Byrne, 2000 [49]
	Alcohol use: average drinks per day, days abstinent, number of drinking days (TLFB), psychiatrist led, self-rated, at baseline and weeks 2, 4, 6, 8, and 12.
	Mental health Mental health (SCID-III-R), psychiatrist led, self-rated, at baseline and 12 weeks. Depression (HAM-D), psychiatrist led, self-rated, at baseline and weeks 2, 4, 6, 8, and 12. Anxiety (HAM-A), psychiatrist led, self-rated, at baseline and weeks 2, 4, 6, 8, and 12. Symptoms (SCL-53), at baseline and weeks 2, 4, 6, 8, and 12. AUD symptoms (AUDIT), at baseline and weeks 2, 4, 6, 8, and 12. Global health (CGI), psychiatrist rated, at weeks 2, 4, 6, 8, and 12 (CGI was not rated as a baseline because it is a measure of improvement, responses to other tools supported the psychiatrist's assessments) Response to treatment (CGI, HAM-D) at weeks 8 and 12. Partial response was defined as 50% decrease in HAM-D scores from baseline. Full response was defined as a HAM-D score of less than 8. A rating of 1 (very much improved) or 2 (much better) on the CGI was defined as a full response.
	Quality of life Not assessed
	Function Not assessed
	Mortality **N**ot assessed
	Compliance Pill count and blood nefazodone levels
	Adverse effects At all visits, side effects were elicited with a single open-ended question, and any reported symptom the patient believed to be a medication side effect was recorded.
Results	**Substance use** <u>Average number of drinks consumed per day</u> mITT, or endpoint analysis (N = 56), ANCOVA*

Study	Roy-Byrne, 2000 [49]
	Time effect (F[5,270] = 18.02, p < 0.001) Treatment group effect (F[1.52] = 0.09, p not significant) Time-by-treatment-group effect (F[5,270] = 1.67, p not significant) *Covariates of age and gender were used because of their relationship to drinking behavior. <u>Comment</u> The authors state "These results indicate that the average number of drinks consumed per day significantly decreased for both groups after controlling for age and gender." <u>Drinking days</u> Days drinking, mean percent: "remained between 50% and 60% over the course of the study in both groups" <u>Comments</u> Logistic regression analyses were used to determine whether abstinence or the average number of drinks consumed per week as a significant predictor of full or partial depression response at 8 or 12 weeks. Data not extracted.
	Mental health <u>HAM-D total scores</u> mITT, or endpoint analysis (N = 56), ANCOVA[a] Time effect: (F[5,269] = 30.17, p < 0.001) Treatment-group effect: (F[1,53] = 7.41, p = 0.009) effects Time-by-treatment-group effect: (F[5,269] = 0.62) <u>HAM-D response rate</u> 48.4% of the nefazodone group compared with 16% of the placebo group had a full response at week 12 (Fisher exact (one-tailed) p = 0.01)[b]. <u>Change in depression severity (</u>CGI) mITT, or endpoint analysis (N = 56), ANCOVA[a] Time effect: (F[4,215] = 3.00, p = 0.02) Treatment-group effects: (F[1,53] = 2.08, p = 0.16)

Study	Roy-Byrne, 2000 [49]

Time-by-treatment-group effects: (F[4,215] = 0.66, p not significant)
Treatment at week 12 (F[1,28] = 5.32, p < 0.03)[b].

<u>CGI response rate</u>

Response rates at week 12 (58.1% vs. 32%, Fisher exact (one-tailed) p = 0.05)[b].

a- Adjusted for the average number of drinks consumed per day.
b- Week 8 data also available, data not extracted.

Compliance

Pill count: Although patients were instructed to return unused medication, the majority failed to do this reliably, so the pill count could not be used to measure compliance.
Because of finding limitations, nefazodone levels were not measured.

Adverse effects

AE	Total sample (N = 56)	Nefazodone (N=31)	Placebo (N=25)	Between group significance
Total, mean (SD)	1.6 (1.5)	2.1 (1.5)	1.0 (1.2)	t = 2.8; df = 54, p = 0.007
Dizziness/light-headedness, n (%)	11 (19.6)	9 (29.0)	0	Fisher exact 2-tailed p=0.09
Dry mouth, n (%)	10 (17.9)	6 (19.4)	4 (16.0)	NS
Headache, n (%)	7 (12.5)	5 (16.1)	2 (8.0)	NS
Sedation, n (%)	19 (33.9)	13 (41.9)	6 (24.0)	NS
Visual trails, n (%)	10 (17.9)	10 (32.3)	0	Fisher exact 2-tailed p=0.001

<u>Comments</u>

Sample refers to participants completing at least one week of medication.
Data extracted only for the 5 most frequent AE. Some patients also experienced: anxiety, constipation, blurred vision, diarrhoea, fatigue/weakness, heart palpitations, insomnia, poor memory/concentration, nausea, sexual dysfunction, and other.

Study	Roy-Byrne, 2000 [49]
	Loss to follow up Did not complete the study: n=33; 21 placebo, 12 nefazodone Completed study: n = 31 <u>Reasons for non-completion</u> Loss to follow up*: N = 27; 18 placebo, 9 nefazodone Lack of efficacy: N = 4; 2 placebo, 2 nefazodone AE: N = 2; 1 placebo, 1 nefazodone <u>Analysis of between group differences</u> Completers (N = 31) vs. non completers (N = 33): There were no statistically significant differences in demographics, psychiatric diagnoses, depression, anxiety or global severity, substance abuse measures, or drinking behavior. Significantly more nefazodone patients (N = 20) than placebo patients (n = 11) completed the study (Fisher exact p = 0.04). Dropped out before first post-baseline measurement (N = 8) vs. rest of sample (mITT analysed sample, N = 56): There were no statistically significant differences in demographics, psychiatric diagnoses, depression, anxiety or global severity, substance abuse measures, or drinking behavior. Significantly more placebo-treated patients (N = 7) than nefazodone-treated patients (n = 11) dropped out within the first post-baseline measurement (Fisher exact p = 0.05). <u>Timing</u> Most dropouts from the placebo group occurred in the first 4 weeks (12 of 21), whereas half of the nefazodone-group dropouts occurred after 8 weeks (6 of 12).
Comments	Recruitment began in 2007 and finished in 2011 due to exhausting research funds. Targeted sample size was n=220.
Risk of bias	Moderate

AE = adverse events; **ANCOVA** = analysis of covariance; **AUD** = alcohol use disorder; **AUDIT** = Alcohol Use Disorders Identification Test; **CBT/RP** = cognitive behavioural therapy, focus ; relapse prevention; **CGI** = Clinical Global Impression scale; **DAST** = drug use screening test; **DSM-III-R** = Diagnostic and Statistical Manual of Mental Disorders, version 3, revised; **EOT** = end of trial; **GAD** = generalized anxiety disorder; **HAM-A** = Hamilton Rating Scales for anxiety; **HAM-D** = Hamilton Rating Scales for depression; **LOCF** = last observation carried forward; **MD** = major

depression; **mITT** = modified intention to treat, referred to as endpoint analysis, included only patients who were assessed at least once after baseline. LOCF was applied to mITT analyses; NR = not reported; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; RCT = randomized controlled trial; SCID-III-R = Structured Clinical Interview for DSM- III-R; SCL-53 = Symptom Checklist – 53 items; SD = standard deviation; TLFB = Time Line Follow Back, self-reported substance abuse (Sobell version).

Salloum et al. 2005

Study	**Salloum, 2005 [50]**
Study design	RCT, double-blind, placebo-controlled
Intervention	**Pharmacotherapy: valproate** Co-intervention: TAU including lithium and recovery counselling (CBT and psychoeducation)
Trial registration	NR
Country	USA
Setting	Outpatients, university hospital
Aims	To evaluate the efficacy of divalproex sodium (hereafter referred to as valproate) in decreasing alcohol use and stabilizing mood symptoms in acutely ill patients with bipolar disorder and alcohol dependence.
Participants	**AUD & bipolar I** A sample of treatment-seeking subjects meeting DSM-IV criteria for current alcohol dependence with a co-occurring acute episode of bipolar I disorder.
	Baseline characteristics

	Valproate	**Placebo**	**p-value**
N=	29	29	
Male % (n)	77% (23)	72% (21)	0.58
Age, years, mean (SD)	38 (9)	37 (9)	0.70
African American, N (%)	7 (23)	8 (28)	0.70
Married, N (%)	3 (10)	5 (17)	0.42
Employed, N (%)	19 (63)	17 (59)	0.71
With <12 y of education, N (%)	16 (53)	15 (52)	0.92
Social class V, N (%)	11 (37)	13 (45)	0.96
Recruited from inpatient treatment, N (%)	18 (60)	18 (62)	0.87
Drinking to intoxication, yes, N (%)	17.2 (8.6)	15.7 (10.3)	0.58
Drinking to intoxication, days/past 30 days, N (%)	16.3 (10.7)	12.3 (11.5)	0.19
Number of drinks per week	104 (89)	88 (99)	0.53
HRSD-25 score	21.2 (13.3)	20.3 (13.4)	0.80

Study	Salloum, 2005 [50]
	BRMS score 15.3 (10.7) 15.2 (13.0) 0.99 GAF score 38.4 (11.0) 38.1 (14.9) 0.93 Duration of bipolar disorder 15.6 (10.3) 13.0 (10.8) 0.40 Number of medical conditions 1.39 (1.29) 1.49 (1.25) 0.85 Other substances use disorders, N (%) 15 (50) 15 (52) 0.99
	Inclusion criteria Men and non-pregnant, non-nursing women aged 18 to 65 years with 4 of the 7 DSM-IV alcohol dependence criteria (only 3 are required to meet diagnostic threshold), actively drinking alcohol in the past month, concurrent acute episode of bipolar I disorder (manic, mixed, or depressed).
	Exclusion criteria (1) schizophrenia, schizoaffective disorder, any nonbipolar psychotic disorder, mental retardation, or signs of impaired cognitive functioning; (2) current DSM-IV diagnoses of opioid or cocaine dependence, or current use of intravenous drugs; (3) epilepsy, history of brain injury, or any organic brain syndrome; (4) severe cardiac, liver, kidney, endocrine, hematologic, or any other unstable medical condition; (5) persistent elevation of liver function enzyme levels greater than 3-fold above the reference range of -glutamyl transpeptidase, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase; (6) inability or unwillingness to use contraception; and (7) inability to read or understand study forms and agree to informed consent.
	Recruitment & screening Recruitment methods NR. After initial screening, a 1-week period for alcohol and other-drug detoxification was undertaken when clinically indicated. When withdrawal symptoms had cleared (Revised Clinical Institute Withdrawal Assessment for Alcohol Scale), participants were assessed with SCID-IV. After confirmation of eligibility, they randomized to treatment groups, stratified by number of past bipolar episodes, duration of alcohol use, and past response to lithium therapy.
	Remuneration NR
Comparison	**Valproate vs Placebo**
	Duration of treatment 24 weeks

Study	Salloum, 2005 [50]
	Follow ups Assessments at weeks every 2 weeks during study Endpoint / time of last treatment: 24 weeks Follow up: none
Experimental arm	**Valproate** Valproate therapy was initiated at a dosage of 750 mg/d, usually within a week of starting lithium therapy. Patients were instructed to take capsules 2x / day, 30 minutes after meals. Dosages increased as tolerated to reach a target trough serum concentration of 50 to 100 µg/mL.
	Co-interventions TAU, Lithium, pharmacological Subjects started to receive lithium as soon as it was safe to do so during the stabilization phase, which was within the first few days for most subjects. Dosage was adjusted using the level dose ratio strategy to reach a target trough serum concentration of (0.7-1.2 mEq/L). TAU, other medications Adjunctive and rescue medications were allowed temporarily, and, when possible, these therapies were discontinued. Perphenazine was permitted for treatment of psychotic symptoms. Benztropine mesylate was used to treat extrapyramidal adverse effects. Sertraline hydrochloride was permitted for treatment of unremitting depressive symptoms, Trazodone hydrochloride (25-150 mg) was permitted for persistent insomnia. Medications not allowed included other mood stabilizers such as carbamazepine and medications for alcoholism such as disulfiram or naltrexone. TAU, Dual diagnosis recovery counselling, psychosocial Counselling consisted of weekly individual sessions that integrated psychoeducation and cognitive-behavioural principles. Counselling focused on management of cravings to use alcohol or other substances, cope with negative thoughts about illness or treatment, develop structure and routine in daily living, identify warning signs of relapse/recurrence of bipolar illness, manage relapse warning signs, identify high-risk situations, and manage painful affects. Counselling emphasized use of social support systems and participation in self-help groups such as Alcoholics Anonymous, Dual Recovery Anonymous, and/or manic-depressive support groups.

Study	Salloum, 2005 [50]
Control arm	**Placebo** An equal number of identical-looking capsules were to be taken 2x / day.
	Co-interventions TAU, Lithium, pharmacological Same as for Experimental arm. TAU, other medications Same as for Experimental arm. TAU, Dual diagnosis recovery counselling, psychosocial Same as for Experimental arm.
Outcomes	**Substance use** Primary outcomes: Alcohol use (TLFB), self-reported, every 2 weeks Proportion of heavy drinking days Number of drinks per heavy drinking day Secondary outcomes: Alcohol use (TLFB), self-reported, every 2 weeks Proportion of drinking days Number of drinks per drinking day Time to relapse to heavy drinking, defined as 3 consecutive heavy drinking days Comment Other relevant measurements were taken at each visit, but they are not described as outcomes, nor are any results presented: Modified Quantitative Alcohol Inventory/Craving Scales, breath alcohol concentration, and urine drug screen for opioids, cocaine and other stimulants, marijuana, benzodiazepines, and barbiturates.
	Mental health Changes in manic symptoms (BRMS), Clinician-reported, every 2 weeks Changes in depressive symptoms (HRSD-25), Clinician-reported, every 2 weeks Remission of mania, defined as score ≤ 7 (BRMS)

Study: Salloum, 2005 [50]

Remission of depression, defined as score ≤ 7 (HRSD-25)

Quality of life

Not assessed

Function

Functioning (Global Assessment of Functioning Scale), Clinician-reported, baseline and every other week

Comment

Weekly Self-Help Activity Questionnaire was administered at each visit, but this is not described as an outcome, nor are any results presented.

Mortality

Not assessed

Compliance

Valproate and lithium serum concentration (blood test) were performed at weeks 2, 4, 8, 12, 16, 20

Frequency and pattern of medication intake (pill count), every 2 weeks

Adverse effects

AE from medication (Somatic Symptoms Checklist and Medication Adherence Form), every 2 weeks

Liver function (blood tests) at weeks 2, 4, 8, 12, 16, 20, and 24.

Results

Substance use

	Placebo	Valproate				
	mITT*, n = 25	mITT*, n = 27				
Mixed model**	**M (SD)**	**M (SD)**	**Estimate**	**t-test**	**df**	**p-value**
Proportion of heavy drinking days	0.19 (0.31)	0.09 (0.22)	0.08	2.45	25.1	0.02
Number of drinks per heavy drinking day***	10.2 (10.8)	5.59 (8.89)	2.88	2.49	31.1	0.02
Proportion of drinks per drinking days***	0.24 (0.32)	0.17 (0.27)	0.08	1.77	33.2	0.08
Number of drinks per drinking day***	8.9 (10.1)	5.14 (8.52)	2.40	2.41	29.0	0.02
Kaplan Meier survival analysis	**M (SD, median)**	**M (SD, median)**	**Log-rank test**		**df**	**p-value**
Relapse to sustained heavy drinking, days	62 (61, 44)	93 (74, 75)	3.9		1	0.048

* mITT population defined as subjects who underwent at least 1 assessment while receiving the study medication.

** The analyses were based on a mixed model with restricted maximum likelihood estimation method and unrestricted covariance matrix. Covariates were time of assessment, bipolar subtype (mixed, manic, or depressed), and treatment group. Overall means of assessments were entered into the analysis.

Study | **Salloum, 2005 [50]**

*** Medication adherence was added as a covariate in the model.

Mental health

	Placebo mITT*, n = 25	Valproate mITT*, n = 27	Estimation**	t-test	df	p-value
Mania	6.10 (7.80)	5.56 (7.73)	−0.03	−0.16	44.2	0.87
Depression	14.4 (9.72)	16.3 (10.2)	0.12	0.91	44.7	0.36

* mITT population defined as subjects who underwent at least 1 assessment while receiving the study medication.

** The analyses were based on a mixed model with restricted maximum likelihood estimation method and unrestricted covariance matrix. Covariates were time of assessment, bipolar subtype (mixed, manic, or depressed), and treatment group. Overall means of assessments were entered into the analysis.

Function

Mean functioning scores equally improved for both groups (valproate group, 57 [SD, 14]; placebo group, 57 [SD, 13]).

Compliance

	Placebo mITT*, n = 25	Valproate mITT*, n = 27	t-test	p-value
Medication adherence, M (SD)	86% (23%)	87% (22%)	t_{258}=−0.58	0.55
Participation in any psychosocial treatment, N (%)	21 (78%)	19 (76%)		
Attendance at individual and group therapy sessions, M (SD)	3.6 (4.8)	5.7 (9)	t_{50}=−1.04	p=0.30

* At least 24 individual therapy sessions were offered as part of the trial program, and other group therapies were encouraged.

Adverse effects

Symptom	Placebo n = 25	Valproate n = 27	p-value, Fisher exact test
Tremor	14 (66.7)	11 (47.8)	0.50
Dry mouth	9 (42.9)	15 (65.2)	0.22
Fatigue	10 (47.6)	7 (30.4)	0.47
Increased thirst	10 (47.6)	9 (39.1)	0.90
Nausea or vomiting	2 (9.5)	9 (39.1)	0.07
Headaches	7 (33.3)	9 (39.1)	0.91
Blurred vision	7 (33.3)	7 (30.4)	0.71
Stomach difficulties	4 (19.0)	7 (30.4)	0.62
Diarrhea	4 (19.0)	7 (30.4)	0.56
Decreased appetite	6 (28.6)	4 (19.0)	0.31

Study	Salloum, 2005 [50]

Increased appetite	5 (23.8)	6 (28.6)	>0.99
Increased urination	5 (23.8)	6 (28.6)	0.90
Nervousness	4 (19.0)	6 (28.6)	0.92
Feeling of clumsiness	5 (23.8)	5 (21.7)	>0.99
Weight gain	5 (23.8)	3 (14.3)	0.25
Constipation	6 (28.6)	4 (19.0)	0.37
Excessive perspiration	5 (23.8)	2 (9.5)	0.40

Comments

There were no serious drug-related AE. One subject (valproate group) discontinued owing to AE, and another (placebo group) discontinued owing to increased liver function test-values

Loss to follow up

	Total	Valproate	Placebo	significance
Randomized, n	59	29	30	
Dropped out before first assessment, n	7	2	5	
Dropped out before end, N (%)		15	17	
Completed trial, N (%)	38%	12 (44%)	8 (32%)	
Average days in study, M (SD)		112 (69)	102 (67)	log-rank test χ^2=0.98; p=0.32
Reasons for discontinuation		1 withdrew consent 1 treatment related AE 3 lost to follow-up 4 non-compliant 2 unrelated medical reasons 3 psychiatric hospitalization 1 incarcerated	2 withdrew consent 3 lost to follow-up 3 non-compliant 2 moved away 2 medical reasons 5 psychiatric hospitalization	

Comments

On average, 86% of available subjects (i.e., of subjects still in the study) underwent assessment at each assessment point. Percentages undergoing assessment at key evaluation points were as follows: 84% at week 2; 77% at week 4; 88% at week 8; 82% at week 12; 87% at week 16; 81% at week 20, and 100% at week 24.

Risk of bias	Mellan/låg?

AE = adverse effect; **ASI** = Addiction Severity Index; **AUD** = alcohol use disorder; **BRMS** = Bech-Rafaelsen Mania Scale; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; **HRSD-25** = Hamilton Rating Scale for Depression; **mITT** = modified intention to treat; **NR** = not reported; **RCT** = randomized controlled trial; **SCID-IV** = Structured Clinical Interview for DSM-IV; **SD** = standard deviation; **TAU** = treatment as usual; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report.

Sherwood Brown et al. 2021

Study	**Sherwood Brown, 2021 [51]**
Study design	RCT, double blind
Intervention	**Pharmacotherapy: ondansetron** Co-interventions: most were also treated with mood stabilizers
Trial registration	NCT02082678
Country	USA
Setting	Outpatient
Aims	The aims were to determine if ondansetron decreased alcohol use and improved mood symptoms in people with bipolar disorders and AUD.
Participants	**AUD & bipolar disorder** Outpatients with bipolar spectrum disorders and early onset alcohol use disorder.
Baseline characteristics	

	Total	**Ondansetron**	**Placebo**
N=	70	35	35
Women: n (%)	28 (40.0)	11 (31.4)	17 (48.6)
Age: M (SD, range)	44.91 (9.41)	46.54 (8.60)	43.29 (10.01)
Education	12.74 (2.20)	12.70 (1.82)	12.79 (2.55)
AUD status			
Mild: n (%)	3 (4.3)	1 (2.9)	2 (5.7)
Moderate: n (%)	8 (11.4)	7 (20.0)	1 (2.9)
Severe: n (%)	58 (82.9)	26 (74.3)	32 (91.4)
Severity unknown: n (%)	1 (1.4)	0 (0)	1 (2.9)
Drinking Days /days covered: M (SD)*	0.58 (0.34)	0.48 (0.33)	0.67 (0.33)
Standard Drinks /days covered: M (SD)	4.49 (4.07)	4.06 (4.07)	4.92 (4.09)
Heavy Drinking Days /days covered: M (SD)	0.40 (0.35)	0.34 (0.33)	0.45 (0.37)

Study	Sherwood Brown, 2021 [51]			
	Mental health status			
	Bipolar I: n (%)	30 (42.9)	17 (48.6)	13 (37.1)
	Bipolar II: n (%)	20 (28.6)	9 (25.7)	11 (31.4)
	Bipolar NOS: n (%)	14 (20.0)	5 (14.3)	9 (25.7)
	MDD mixed: n (%)	2 (2.9)	1 (2.9)	1 (2.9)
	Schizoaffective: n (%)	4 (5.7)	3 (8.6)	1 (2.9)
	YMRS: M (SD)	8.49 (6.21)	9.51 (6.88)	7.46 (5.37)
	HRSD: M (SD)	14.00 (6.35)	13.77 (5.39)	14.23 (7.25)
	IDS-SR: M (SD)	29.34 (16.50)	29.18 (16.73)	29.53 (16.52)
	Concomitant Medications			
	Anxiolytic: % (n)	16 (22.9)	7 (20.0)	9 (25.7)
	Antidepressant: % (n)	38 (54.3)	18 (51.4)	20 (57.1)
	Antipsychotic: % (n)	34 (48.6)	21 (60.0)	13 (37.1)
	Hypnotic: % (n)	2 (2.9)	0 (0.0)	2 (5.7)
	Mood stabilizer: % (n)	49 (70.0)	21 (60.0)	28 (80.0)
	Stimulant: % (n)	1 (1.4)	0 (0.0)	1 (2.9)
	* Baseline statistical difference: Number of drinking days (p=0.018) Days covered for baseline measures is likely 1 week.			
	Inclusion criteria Men and women, age 18–70 years old with bipolar I, II or NOS disorder, or schizoaffective disorder (bipolar type), or cyclothymic disorder, or major depressive disorder (MDD) with mixed features, a current diagnosis of AUD with onset ≤ age 25 and alcohol use (by self-report) of at least 15 drinks in the 7 days prior to intake.			
	Exclusion criteria Very severe mood symptoms (baseline YMRS or HRSD scores ≥35), clinically significant alcohol withdrawal symptoms, therapy in past 14 days with naltrexone, acamprosate, disulfiram, or topiramate, vulnerable populations (e.g. pregnant, breastfeeding, cognitively impaired (e.g. dementia), incarcerate, high risk for suicide, intensive outpatient treatment for substance abuse (Alcoholics Anonymous meetings, or less intensive counseling at baseline will be allowed), severe or life-threatening medical condition (e.g., hepatic cirrhosis) or laboratory or physical examination findings consistent with serious medical illness (e.g., dangerously abnormal electrolytes), aspartate transaminase or alanine transaminase > 3x the upper limit of normal, history of			

Study	Sherwood Brown, 2021 [51]
	severe side effects or allergic reaction with prior ondansetron therapy (e.g. for emesis) or use of medications with significant drug-drug interactions with ondansetron (phenytoin, carbamazepine, and rifampicin apomor phine, tramodol).
	Recruitment & screening 135 patients were assessed for eligibility, 54 did not meet inclusion criteria and 11 did not return for randomisation
	Remuneration NR
Comparison	**Ondansetron vs. placebo**
	Duration of treatment 12 weeks
	Follow ups Measurements during treatment: weekly Endpoint / time of last treatment: 12 weeks
	Ondansetron, flexible dose Dosing started at 0.5 mg twice daily. At week 4, participants with < 30% reduction in both drinks per week and score on the HRSD, who tolerated the medication well had a dose increase to 1.0 mg twice daily, with an additional increase to 2.0 mg twice daily in those with < 50% reduction in drinks per week and the HRSD at week 8. If they still had not achieved a 50% reduction in drinks per week and HRSD at week 10, they had a dose increase to 4.0 mg twice daily. The mean ondansetron dose at exit was 3.24 ±2.64 mg/day and the mean week 12 dose was 3.82 ±2.84 mg/day.
	Co-interventions <u>Concomitant pharmacological treatment</u> A majority of participant had concomitant pharmacological treatment, including mood stabilizers, antidepressants, antipsychotic, anxiolytics, hypnotics, and stimulants.
	Placebo Matching placebo delivered as for active substrate.
	<u>Concomitant pharmacological treatment</u> A majority of participant had concomitant pharmacological treatment, including mood stabilizers, antidepressants, antipsychotic, anxiolytics, and hypnotics.

Study	Sherwood Brown, 2021 [51]
Outcomes	**Substance use** Primary outcome Drinks per week (TLFB), weekly Secondary outcome Drinking Days/days covered (TLFB), weekly Standard Drinks per drinking day (TLFB), weekly Heavy Drinking Days/days covered (TLFB), weekly CDT levels (blood test), weekly GGT levels (blood test), weekly
	Mental health Primary outcome Depressive symptoms (HRSD), weekly Sedondary outcomes: Depressive symptoms (IDS-SR), self-reported, weekly Manic symptoms (YMRS), weekly
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Not assessed
	Adverse effects Side effects (PRD-III Somatic Symptom Scale)
Results	**Substance use** **Group effect**

Study	Sherwood Brown, 2021 [51]

	F-value	p-value	β	Cohen's d
Drinking Days/days covered	0.823	0.368	0.03	−0.29
Standard Drinks /days covered	0.146	0.704	0.06	−0.10
Heavy Drinking Days/days covered	0.317	0.575	0.02	−0.15

Participants with at least two valid measurement points were included in the analyses. Treatment effects were estimated with linear mixed effects models (estimates of fixed effects) using age and sex as covariates. REML method was used to estimate model parameters. Reference treatment group is Ondansetron. Negative Cohen's d values represent lower average scores for the treatment group. Days covered is likely the number of days they have data for.

Mental health

	Group effect			
Primary outcomes	**F-value**	**p-value**	**β**	**Cohen's d**
HRSD	4.166	0.045	1.22	−0.53
Secondary outcomes	**F-value**	**p-value**	**β**	**Cohen's d**
YMRS	0.232	0.632	−1.87	0.12
IDS-SR	2.718	0.104	4.69	−0.43

Participants with at least two valid measurement points were included in the analyses. Treatment effects were estimated with linear mixed effects models (estimates of fixed effects) using age and sex as covariates. REML method was used to estimate model parameters. Reference treatment group is Ondansetron. Negative Cohen's d values represent lower average scores for the treatment group. Days covered is likely the number of days they have data for.

Adverse effects

	Group effect			
	F-value	**p-value**	**β**	**Cohen's d**
PRD-III	F(1, 62.28)=4.380	0.040	NR	−0.55

Study	Sherwood Brown, 2021 [51]
	Comments Ondansetron was well tolerated as indicated by the statistically significant treatment group effect on the PRD outcome with a greater decrease in overall somatic complaints with ondansetron than with placebo. A total of 41 AE across 20 participants were noted during the study. Thirteen of the 20 participants with adverse events were in ondansetron group, however the difference in the occurrence of events between the placebo and treatment group was statistically non-significant [$\chi 2$ (1) = 2.52, p = 0.112]. The most common events for the placebo group were gastrointestinal (27%), suicide attempt/ideation (13%), hyperglycemia (13%), and auditory hallucinations (13%). For the ondansetron group, the most frequent events were gastrointestinal (23%), neurological (19%), and cardiovascular (11%).
	Loss to follow up Endpoint: Ondansetron: 11 participants (31.4%) withdrew or discontinued, placebo: 13 participants (37.1%) withdrew or discontinued
Comments	Results regarding the secondary aim (SNP analysis) were not extracted.
Risk of bias	Low

AE = adverse effects; **AUD** = alcohol use disorder; **CDT** = carbohydrate deficient transferrin; **GGT** = γ-glutamyltransferase; **HRSD** = Hamilton Rating Scale for Depression; **IDS-SR** = Inventory of Depressive Symptomatology–Self-report; **NOS** = Not Otherwise Specified; **NR** = not reported; **RCT** = randomized controlled trial; **REML** = restricted maximum likelihood; **SNP** = single nucleotide polymorphism; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **YMRS** = Young mania rating scale.

Schmitz 2001

Study	Schmitz, 2001 [52]
Study design	RCT, double-blind, placebo controlled
Intervention	**Pharmacotherapy: Fluoxetine** Co-intervention: CBT psychotherapy
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	Primary objective: was to test the hypothesis that fluoxetine would produce favorable effects on outcome measures of retention, depression, and cocaine use compared with placebo for the treatment of comorbid cocaine dependence and depression. Secondary

Study	Schmitz, 2001 [52]
	objectives (data not extracted): To explore the relationship between depression and cocaine use during treatment, and whether baseline levels of severity predict outcome in either or both domains.
Participants	**Cocaine dependence & MDD** Individuals with both DSM-IV diagnoses of cocaine dependence and major depressive disorder
	Baseline characteristics See table below NS baseline differences.
	Inclusion criteria English-speaking adults of the age between 18 and 50; diagnosed dually with major depressive disorder (an intake BDI score >10) and cocaine dependence based on DSM-IV; free of serious legal and medical problems; competent to give informed consent.
	Exclusion criteria Currently dependent on alcohol or any other psychoactive substance (except nicotine or cannabis); met DSM-IV criteria for current primary Axis I disorders other than depression; cases where mood symptoms were judged to be etiologically related to substance use on the basis of the patient's history
	Recruitment & screening NR how participants were contacted and whether detoxification took place

	Total	Fluoxetine	Placebo
N=		**34**	**34**
Women: n (%)		14 (41%)	15 (44%)
Age: M (SD)	37.3 (5.9)	37.2 (5.1)	37.4 (6.6)
Education level: M (SD)		13.0 (2.5)	13.4 (2.2)
Employed: n (%)	56%	21 (61.8%)	17 (50%)
Substance use status			
Cocaine use, number of days in the past 30 days: M (SD)		14.7 (9.7)	15.5 (8.8)
Cocaine use, years: M (SD)		9.2 (6.7)	12.2 (7.2)
Intake urine screen cocaine-positive: n (%)		22 (64.7%)	21 (61.8%)
Mental health status			
BDI: M (SD)		29.1 (9.1)	31.1 (10.7)
HRSD: M (SD)		27.8 (7.8)	30.1 (8.3)
Co-morbidities:			
Antisocial personality: %	36.4%		
Bordeline personality: %	25.8%		
Dependent personality: %	9.1%		

Study	Schmitz, 2001 [52]
	Numbers screened = 94; numbers randomized = 68; randomization to treatment group was stratified by intake urine screen (cocaine-positive, cocaine-negative) and intake BDI score (mild, 10–15; moderate, 16–23; severe, >24).
	Remuneration NR
Comparison	**Fluoxetine vs placebo**
	Duration of treatment 12 weeks
	Follow ups Measurements taken during weekly study visits Endpoint
Experimental arm	**Fluoxetine** Administered at a fixed dose (40 mg/day) throughout the 12 week-study at the dispensing window at spaced visits 2x /week and given in strip packing for intervening days. All capsules contained 50 mg of riboflavin as a marker to monitor compliance.
	Co-interventions CBT (psychotherapy) 24 sessions of individual CBT (twice per week), targeting both cocaine use and depression; including the key ingredients self-monitoring of thoughts and behaviors, functional analysis, recognition of faulty attributions, goal-setting, and self-reinforcement.
Comparison	**Placebo** Not described
	Co-interventions CBT (psychotherapy) As the intervention group
Outcomes	**Substance use** Primary outcomes: Cocaine use (urine tests), administered twice weekly (at each clinic visit)
	Mental health Primary outcomes:

Study: Schmitz, 2001 [52]

Intensity of depression symptomatology (21-item BDI), assessed weekly

Intensity of depression symptomatology (HRSD), using the patient-self-report form at intake, weeks 6 and 12

Quality of life

Not assessed

Function

Not assessed

Mortality

Not assessed

Compliance

Primary outcomes:

Retention (time to dropout); completing treatment was defined as attending at least 50% (12/24) of the sessions.

Adherence to medication was monitored by riboflavin; detection in urine samples was based on judgements of fluorescence (percentage 10) using a UV lighting device.

Adverse effects

Assessed weekly by a checklist consisting of 22 possible side effects with total scores ranging from 0 to 22.

Results

Substance use

	Fluoxetine (n = 34)		Placebo (n = 34)		Test of difference in treatment effect over the whole study period
Primary outcomes	**Baseline**	**Endpoint**	**Baseline**	**Endpoint**	**p-value**
Cocaine use (percent cocaine-positive urines)*, mean	65.3%	49.9	61.5%	81.9%	NS

* Baseline and endpoint data extracted by SBU from figure 1, no measures of variance indicated.

Comments

The REML mixed model ANOVA was used to assess treatment effects in percentage cocaine-positive urines during treatment. The best fitting model was selected based on Akaike's Information Criterion.

During the first 6 weeks of treatment, subjects in the placebo group used less cocaine than those in the fluoxetine group, a significant group by time interaction, F (11, 349) =1.97, p=0.03, however, this difference did not persist during the final weeks of treatment.

Mental health

	Fluoxetine		Placebo		Test of difference in treatment effect

Study	Schmitz, 2001 [52]

	(n = 34)		(n = 34)		by time and group over the whole study period
Primary outcomes	**Baseline**	**Endpoint**	**Baseline**	**Endpoint**	**p-value**
BDI scores*, mean (SD)	29.1 (9.1)	12.9 (NR)	31.1 (10.7)	12.9 (NR)	NS
HRDS scores, mean (SD)	27.8 (7.8)	NR	30.1 (8.3)	NR	NS

* Endpoint data extracted by SBU from figure 1, no measure of variance indicated.

Comments

The REML mixed model ANOVA was used to assess treatment effects in percentage cocaine-positive urines during treatment. The best fitting model was selected based on Akaike's Information Criterion.

Compliance

	Fluoxetine n = 34	***Placebo n = 34***	***Test of difference***
Retention, time to dropout	NR	NR	Log Rank Statistic 0.6, df=1, p=0.43
Retention, proportion remaining at endpoint*: %	29.6%	29.6%	NR
Completing treatment (attending at least 50% of the sessions: n (%)	18 (52.9%)	14 (41%))	X^2=0.94, df=1, ns
Number of subjects attending all therapy sessions: n	10	10	NR
Adherence to medication, percentage of urine samples positive for riboflavin: M	78%	79%	ns

* Endpoint data extracted by SBU from figure 1, no measure of variance indicated.

Adverse effects

	Fluoxetine n = 34	**Placebo n = 34**
Number of weekly side effects reported: M (SD)	6.2 (3.7)	6.1 (4.4)

Comments

The authors stated that no participant in either group discontinued treatment prematurely because of adverse events.

Loss to follow up

Proportion remaining at endpoint*: about 30% in both groups, i.e. about 70% drop-out in both groups.

* Data extracted by SBU from figure 1.

Risk of bias	Moderate

ANOVA = repeated measures analysis of variance; **BDI** = Beck Depression Inventory; **CBT** = cognitive behavioural therapy; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; **HRSD** = Hamilton Rating Scale for Depression; **M** = mean; **MDD** = major depressive disorder; **NR** = not reported; **RCT** = randomized controlled trial; **REML** = Restricted maximum likelihood estimation; **SD** = standard deviation.

Schubiner et al. 2002

Study	Schubiner, 2002 [53]
Study design	RCT, double-blind
Intervention	**Pharmacotherapy: methylphenidate** Co-intervention: psychotherapy (group + individual)
Trial registration	NR
Country	USA
Setting	Outpatient
Aims	To determine whether MTP would be safe, control ADHD symptoms, and affect cocaine use.
Participants	**Cocaine dependence & ADHD**
	Baseline characteristics

	MPH	Placebo
n	**24**	**24**
Women: n (%)	3 (12%)	2 (8%)
Age: M (SD)	38.3 (6.3)	35.8 (6.8)
ASI, employment: M (SD)	0.5007 (0.2176)	0.4000 (0.2276)
Substance use status		
No. days using cocaine in last 30 days: M (SD)	13.29 (9.86)	13.75 (8.50)
Mental health status		
Number of hyperactive symptoms: M (SD)	5.42 (2.80)	6.25 (2.79)
Number of inattentive symptoms: M (SD)	4.92 (2.99)	4.79 (2.84)
BDI scores: M (SD)	24.7 (9.50)	20.2 (7.76)
ASI, psychiatric status: M (SD)	0.3910 (0.1987)*	0.2738 (0.1747)
Comorbidities		
Any Axis I: %	62.5%	50.0%
Affective disorders: %	58.3%	50.0%
Anxiety disorders: %	12.5%	12.5%
Other Axis I disorders: %	8.3%	0

*The MTP group had higher mean ASI psychiatric composite scores than the placebo group, t(43) = 2.10, p = .042; otherwise no statistically significant baseline differences

	Inclusion criteria

Study	Schubiner, 2002 [53]
	Between 18 and 55 years old; meet DSM–IV criteria for current cocaine dependence; provide a positive urine toxicology result for cocaine metabolite; meet criteria for the diagnosis of ADHD as a child and as an adult (described later); be willing to enter an intensive outpatient treatment program; to be diagnosed with ADHD, the participant must have (a) met full DSM–IV criteria for ADHD (i.e., have at least six of the nine inattentive or hyperactive-impulsive symptoms to a clinically significant degree) as an adult, (b) met full DSM–IV criteria for ADHD as a child (in retrospect), and (c) had no other psychiatric disorder that would better explain the ADHD symptomatology (e.g., drug-induced symptoms, bipolar disorder)
	Exclusion criteria Scored less than an estimated IQ of 75 on the Shipley Institute of Living scale (concerns that they may not be capable of providing informed consent, complying with the study requirements, and providing reliable and valid data); schizophrenia, bipolar disorder, dementia, and delirium (candidates with other Axis I and Axis II psychopathology were allowed to participate if they were capable of giving informed consent, were not in need of emergency psychiatric treatment, and were able to comply with study requirements); any clinically significant medical condition or clinically significant abnormality in routine laboratory testing; were pregnant; were unable to comprehend and respond to the measures used in the study.
	Recruitment & screening Recruitment via advertisements in local newspapers and radio broadcasts; responders were screened over the telephone for basic enrolment criteria. Numbers screened by telephone = 932; numbers eligible based of telephone screening = 338; numbers attending screening visit = 106; numbers eligible based on screening visit = 79; numbers randomized = 59 (11 of which to a third study arm – pemoline – that was later dropped) Randomization stratified by gender, antisocial personality disorder, and borderline personality disorder; no information on detoxification period before enrolment
	Remuneration NR
Comparison	**MPH vs. placebo**
	Duration of treatment 12 weeks (1 week of baseline testing + 12 weeks of treatment)
	Follow ups

Study	Schubiner, 2002 [53]
	Assessments performed 3x / week in conjunction with clinic visits. Endpoint: week 13
Experimental arm	**Methylphenidate (MPH)** Titrated from an initial dosage for the first 2 or 3 days (10 mg 3x /day) to a second-level dosage (20 mg 3x /day) for the next 4 to 5 days and finally to the target dosage of 30 mg 3x /day by Day 8; participants were seen weekly by a physician or nurse practitioner to assess response to medications and the development of any adverse effects; the treating physician was able to request a lower dose of medication if warranted by the emergence of perceived side effects; participants attended the clinic 3x /day, at each visit, medication was provided for the time period between the current visit and the next scheduled visit
	Co-interventions Group CBT Group CBT with 2 to 6 participants, 2 x / week, aimed at cocaine dependence, led by an experienced, certified substance use counsellor; a manual was developed to specify the format and content of the 24 group therapy sessions, guided by the principles and strategies outlined in the Project MATCH CBT manual and a cognitive–behavioral cocaine treatment manual. Individual CBT Weekly individual CBT sessions were held by a senior psychologist and four predoctoral master's level psychologists to help participants cope with ADHD symptoms in general and as they relate to substance abuse. An individual CBT manual for ADHD was developed for the study
Control arm	**Placebo** Not specifically described, but likely following the same protocol as the treatment group: "an independent pharmacist compounded study medications."
	Co-interventions Group CBT As the treatment group Individual CBT As the treatment group
Outcomes	**Substance use** Cocaine, opiate, barbiturate, phencyclidine, and amphetamine use (observed urine sample), collected 3 times/week Cocaine use (ASI), self-reported in interview monthly, including at endpoint

Study	Schubiner, 2002 [53]
	Drug use, e.g., nicotine, alcohol, cocaine, opiates, marijuana, benzodiazepines, barbiturates, amphetamine, hallucinogens (study specific form), self-reported at each visit Out of pocket-expense for each drug (study specific form), self-reported at each visit
	Mental health Depression (BDI), administered at baseline and weekly Number and severity of ADHD symptoms (ADHD Symptom Checklist), self-reported at baseline and weekly Physician-rated efficacy rating (Global Improvement Scale), physician-reported at weeks 5, 9 and 13 Patient-rated efficacy rating (Global Improvement Scale), patient-reported at weeks 5, 9 and 13
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Retention in the study reported as percentage completers, mean number of visits attended, and percentage of dropout before 4 weeks. Medication compliance was assessed at every visit by participants completing a computerized questionnaire on the number of pills taken each day since the previous visit
	Adverse effects Weekly side effects checklist
Results	**Substance use**

	MTP (n = 24)	MTP (n = 24)	Placebo (n = 24)	Placebo (n = 24)	Test of treatment effect
	Baseline	**Endpoint**	**Baseline**	**Endpoint**	**p-value**
Number of days using cocaine in past 30 days, mean (SD)*	13.29 (9.86)	15.42 (3.29)	13.75 (8.50)	14.58 (2.91)	NS
Urine samples tested negative for cocaine over the study (%), mean (SD)**	NR	50% (50)	NR	42% (32)	NS

Study	Schubiner, 2002 [53]

Amount (dollars) spent on cocaine in past 30 days, mean (SD)***	-	62.54 (48.53)		97.19 (124.88)	NS
Longest continuous abstinence (days) over the study, mean (SD)*	-	5.17 (6.22)	-	5.17 (5.53)	NS

* Analysed using mixed-effects models that incorporate all follow-up information

** Assessed by t-tests

*** Assessed by Mann-Whitney tests

Mental health

	MTP (n = 24)	MTP (n = 24)	Placebo (n = 24)	Placebo (n = 24)	Test of treatment effect
	Baseline	**Endpoint**	**Baseline**	**Endpoint**	**p-value**
Number of inattentive symptoms, mean (SD)*	4.92 (2.99)	2.13 (2.85)	4.79 (2.84)	2.83 (2.96)	NS
Number of hyperactive symptoms, mean (SD)*	5.42 (2.80)	3.42 (2.67)	6.25 (2.79)	4.78 (3.18)	NS
Physician-rated efficacy (percentage of participants improved since admission): %**	-	50%	-	56%	NS
Participant-rated efficacy (mean improvement since admission): mean (SD)***	-	1.75 (0.89)	-	2.64 (0.92	NS

* Analysed using mixed-effects models that incorporate all follow-up information

** Because of the highly skewed responses on the 7-point physician efficacy index, group differences were tested using the chi-square statistic on the participant's last visit, MTP: n = 8; placebo: n = 11

*** The self-rated efficacy index had more dispersion and was tested using t-tests, MTP: n = 8; placebo: n = 11

Compliance

	MPT n = 24	Placebo n = 24	Overall
Completers: % (n)	45%	58%	NR
No. of visits attended: M	24.1	28.4	NR
Dropout before 4 weeks: %	29%	8%	NR
Pills taken as indicated: %	NR	NR	88.5%

Adverse effects

	MPT n = 24	Placebo n = 24
Elevated blood pressure: n	1	-

Study	Schubiner, 2002 [53]
	Episode of disorientation, insomnia, and anxiety, lasting several hours: n 1 -
	Comments The authors state: "Side effects were common before receiving medication (e.g., 83% of the placebo group and 67% of the MTP group complained of being anxious) and remained so for the duration of the study."
	Loss to follow up Endpoint (%): MPT group = 55%; placebo group = 42% Comment Some study completers do not seem to have contributed with full endpoint data.
Comments	The study was initially structured to have three arms, including one with pemoline. However, the pemoline arm was dropped after the first year because of recruitment difficulties.
Risk of bias	Moderate

ADHD = attention-deficit/hyperactivity disorder; ASI - Addiction Severity Index; **BDI** - Beck Depression Inventory; **CBT** = cognitive behavioural therapy; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; **MTP** = methylphenidate; **NR** = not reported; **NS** = not significant; **RCT** = randomized controlled trial.

Simpson et al. 2015

Study	Simpson, 2015 [54]
Study design	RCT, double blind, pilot
Intervention	**Pharmacotherapy: Prazosin** Co-intervention: medical management
Trial registration	NCT01518972
Country	USA
Setting	Outpatient
Aims	To evaluate whether the α-1 adrenergic antagonist, prazosin, is useful in reducing drinking behavior and PTSD symptomatology among individuals with comorbid AD and PTSD.
Participants	**AD & PTSD**

Study	Simpson, 2015 [54]

Baseline characteristics

	Praozin	Placebo
N=	15	15
Women: n (%)	6 (40.0)	5 (33.3)
Age: M (SD)	43.5 (12.4)	43.5 (12.4)
College/Post Graduate Education: n (%)	11 (78.6)	12 (80.0)
Stable housing: n (%)	10 (66.7)	12 (85.7)
Homeless: n (%)	2 (13.3)	1 (7.1)
Employed: n (%)	2 (14.3)	0 (0.0)
Disability/Pension: n (%)	7 (50.0)	7 (50.0)
Unemployed: n (%)	3 (21.4)	7 (50.0)
Substance use status		
Drinks per day, past 90 days: M (SD)	11.0 (10.8)	8.5 (5.1)
Total drinks, past 7 days: M (SD)	80.1 (75.1)	49.6 (44.6)
Drinking days, past 7 days: M (SD)	5.1 (1.7)	4.2 (2.8)
Mental health status		
PSS-I (PTSD) score: M (SD)	31.5 (8.9)	31.6 (7.7)

Inclusion criteria

Current DSM-IV diagnoses of AD and PTSD (APA, 2000) and recent alcohol consumption at or above 14 (women) or 21 (men) drinks per week AND at least 2 days of heavy drinking (>4 drinks per occasion for women and >5 drinks for men) over a 30-day period in the last 90 days.

Exclusion criteria

1) uncontrolled psychosis or mania; 2) current opioid dependence or abuse or positive urine screen (UDAS) for opioids, methamphetamines, benzodiazepines or sedative hypnotics; 3) systolic blood pressure <110mmHg or pre-existing orthostatic hypotension; 4) health conditions including unstable angina, Meniere's disease, narcolepsy, benign positional vertigo, chronic renal or hepatic failure, pancreatitis or insulin-dependent diabetes mellitus, 5) use of any anti-alcohol medication (e.g., naltrexone, acamprosate, or disulfiram), 6) unstable psychiatric medication regimen in the past month, 9) engagement in trauma-focused PTSD treatment or behaviorally focused addiction treatment, and 10) for males only, concomitant use of trazodone, tadalafil, or vardenafil due to increased risk of priapism. Female participants of child-bearing age were excluded unless they reported using a birth control method judged by the study clinician to be effective.

Recruitment & screening

Study	Simpson, 2015 [54]
	Participants were recruited through advertisements in local newspapers and posted flyers. After signing the informed consent and demonstrating a breath alcohol level of 0, participants underwent screening. Those found eligible at screening were invited to participate in a baseline assessment to complete additional study measures and receive study medication. 354 persons were contacted, 321 were screened by phone, 115 were found eligible. Of the 54 persons who consented, 2 declined and 22 were found ineligible at screen. 30 were randomized.
	Remuneration NR
Comparison	**Prazosin vs. placebo**
	Duration of treatment 6 weeks*, including 2 week dose titration *Planned 12 weeks, but study was ended early due to large drop out (39% withdrew prior to week 12)
	Follow ups Visits 2x/ week for weeks 1 and 2, and weekly for weeks 3 to 6 (total 10 visits). Adjusted endpoint/time of last treatment: 6 weeks
Experimental arm	**Prazosin** Medications were titrated to a target dose of 4mg q AM, 4mg q PM and 8mg qhs (or highest tolerated dose) by the end of week 2, which was continued for an additional 4 weeks. Dosing was targeted for three times per day.
	Co-interventions Psychosocial, Medical Management Participants received 5 Medical Management counselling visits with a study clinician over the course of the 6-week study. Additional compliance component Participants were given a watch with pre-set alarms to remind them to take their medication and call a toll-free number for daily reports on symptoms and compliance (IVR)
Control arm	**Placebo** Matching placebo delivered as for active treatment.
	Co-interventions Psychosocial, adjunct Medical Management

Study	Simpson, 2015 [54]
	As for active treatment. Additional compliance component As for active treatment.
Outcomes	**Substance use** Primary outcomes: Drinking days per week (TLFB), self-reported, daily (IVR) Heavy drinking days per week (TLFB), self-reported, daily (IVR) Standard drinks per week (TLFB), self-reported, daily (IVR) Comments TLFB refers to what the authors call Form-42, and which is closely related to TLFB: "*The Form-42 was adapted from the Form-90 and uses the timeline follow-back and steady drinking pattern method…"*
	Mental health Secondary outcomes: Total PTSD symptoms (12 symptoms adapted from the PTSD Checklist-Civilian version), self-reported, daily (IVR) Re-experiencing (adapted from the PTSD Checklist-Civilian version), self-reported, daily (IVR) Avoidance/numbing (adapted from the PTSD Checklist-Civilian version), self-reported, daily (IVR) Hypervigilance (adapted from the PTSD Checklist-Civilian version), self-reported, daily (IVR) Dream item (adapted from the PTSD Checklist-Civilian version), self-reported, daily (IVR)
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance Self-reported daily (IVR)
	Adverse effects

Study: Simpson, 2015 [54]

NR

Results

Substance use

Primary outcomes	Prazosin (ITT, n = 30) Baseline	Prazosin (ITT, n = 30) Week 6	Placebo (ITT, n = 30) Baseline	Placebo (ITT, n = 30) Week 6	Group difference Baseline to weeks 6
Percent Drinking Days per Week: M (95% CI)	73.4 (56.7–90.1)	18.1 (−1.1–37.4)	59.7 (43.0–76.4)	49.3 (31.7–66.9)	χ2(6)=19.3, p=0.004*
Percent Heavy Drinking Days per Week: M (95% CI)	67.6 (52.7–82.5)	3.7 (−14.4–21.8)	50.6 (35.7–65.6)	27.4 (11.3–43.5)	χ2(6)=21.3, p=0.002*
Drinks per Week: M (95% CI)	80.3 (60.7–100.0)	7.9 (−15.7–31.4)	50.0 (30.3–69.7)	27.0 (5.9–48.1)	χ2(6)=19.0, p=0.004*

Comments

Analyses used multilevel mixed-effects linear regression models with random slope that included treatment group, time, and treatment group X time interaction.

Data not reported: analyses involving only those who received medication through the week 4 visit. Outcomes week 7-12 for 10 individuals (5 in each group) enrolled in the 12-week trial with adequate data. Analysis of Potential Treatment Mediators and Craving, Alcohol Reinforcement, and Reasons Associated with Not Drinking.

Mental health

Secondary outcomes	Prazosin (ITT, n = 30) Week 1*	Prazosin (ITT, n = 30) Week 6	Placebo (ITT, n = 30) Week 1*	Placebo (ITT, n = 30) Week 6	Group difference Baseline to weeks 6
Total PTSD Score: M (95% CI)	3.7 (2.6–4.8)	3.1 (1.9–4.2)	2.7 (1.6–3.8)	2.5 (1.4–3.6)	NS
Re-experiencing: M (95% CI)	3.8 (2.7–5.0)	3.2 (1.9–4.4)	2.6 (1.4–3.8)	2.6 (1.4–3.8)	NS
Avoidance/Numbing: M (95% CI)	3.6 (2.4–4.8)	2.9 (1.6–4.2)	2.7 (1.5–3.9)	2.4 (1.2–3.6)	NS
Hypervigilance: M (95% CI)	3.6 (2.5–4.8)	3.2 (2.0–4.4)	2.8 (1.7–3.9)	2.4 (1.3–3.6)	NS
Disturbing Dreams: M (95% CI)	3.2 (1.9–4.6)	2.5 (1.0–3.9)	2.4 (1.1–3.7)	2.8 (1.5–4.1)	NS

* Those with adequate IVR data at Week 1 (at least 4 of 7 days completed; n = 26)

Comments

Data not reported: analyses involving only those who received medication through the week 4 visit.

Study: Simpson, 2015 [54]

Compliance

	Prazosin n = 15	Placebo n = 15	t-test
Received medication through week 6: n (%)	9 (60)	11 (73.3)	NS
Daily IVR compliance: %	70.6	83.5	NS
Number of study visits: M (SD)	4.8 (2.2)	6.4 (2.2)	NS
Medication positive urines			NS
Days reported taking medication (IVR): %	88.1	83.0	NS

Comments

Twenty of the 30 (66.7%) randomized individuals received study medication through week 6, with somewhat higher rates of completion in the placebo condition [prazosin: 9 (60.0%); placebo: 11 (73.3%), NS].

Adverse effects

	Prazosin n = 15	Placebo n = 15
Any adverse event: % (SD)	25% (SD 33.1)	13% (SD 10.6)
Downward dose adjustments: n	6	1
Dizziness on standing, Days endorsed*: M (SD)	5.4 (7.0)	1.9 (3.6)
Lack of energy, Days endorsed*: M (SD)	13.9 (14.7)	7.8 (8.9)
Drowsiness, Days endorsed: M (SD)**	19.0 (18.8)	5.7 (7.9)

* $p < 0.10$, ** $p < 0.05$

Comments

There were two non-study related serious adverse events: one psychiatry admission for suicidality and one admission for surgery for a pre-existing condition. The most frequently reported side effects were headaches, nausea, lightheadedness, and drowsiness. The prazosin group endorsed significantly higher mean number of days of drowsiness relative to placebo as well as higher mean days of dizziness on standing and low energy. More data on specific adverse events in paper.

Loss to follow up

Endpoint (week 6): Prazosin 6/15; Placebo: 3/15

Risk of bias: Moderate

AD = alcohol dependence; **ANCOVA** = analysis of covariance; **CI** = confidence interval; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; **DSM-IV-TR** = Diagnostic and Statistical Manual of Mental Disorders – fourth edition – Text Revision; **IVR** = Interactive Voice Response, used for symptom monitoring; **LOCF** = last observation carried forward; **M** = mean; **mITT** = modified intention to treat; **NR** = not reported; **NS** = not significant; **PACS** = Penn Alcohol Craving Scale; **PSS-I** = **PTSD** Symptom Scale-Interview Version, 17 items; **PTSD** = post traumatic stress disorder; **RCT** = randomized controlled trial; **SCID-IV-TR** = Structured Clinical Interview for DSM-IV-TR; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report, referred to as Form-42.

Stedman et al. 2010

Study	**Stedman, 2010 [55]**
Study design	RCT, double blind, multi-center
Intervention	**Pharmacotherapy: quetiapine** Co-interventions: lithium or divalproex was administered for mood stabilization
Trial registration	NCT00114686, D144AL00002
Country	USA
Setting	Outpatient, 43 centers
Aims	To evaluate the efficacy of quetiapine versus placebo as adjunct therapy to lithium or divalproex in reducing alcohol consumption in patients with bipolar I disorder and coexisting alcohol dependence.
Participants	**AUD & Bipolar I** Male or female outpatients, aged 21 to 60, with a clinical diagnosis of bipolar I disorder (manic, hypomanic, depressed, or mixed) as defined by DSM-IV and with alcohol dependence confirmed by the SCID-IV
	Baseline characteristics **Quetiapine** / **Placebo** / **Total** **N =** 176 / 186 / 362 **Women: % (n)** 36.9% (65) / 36.6% (68) **Age: M (SD)** 39.0 (9.1) / 38.3 (9.8) * mITT analysis included all randomized patients who took at least 1 dose of randomized treatment and had both baseline and at least 7 consecutive days of postbaseline TLFB data. Comments: Participants' baseline characteristics were described as follows in the text: 177 of 362 were maintained on divalproex 185 of 362 were maintained on lithium

Study	Stedman, 2010 [55]
	The most recent Bipolar I episode was: - depressed moderate or mixed moderate, “nearly 70%” - mania⁄hypomania, 15% - depressed mild ⁄ severe, 8.9% - mixed mild ⁄ severe, 8.3% Drinks per day: ”approximately 7” in both the placebo and quetiapine groups.
	Inclusion criteria Male or female outpatients, aged 21 to 60, with a clinical diagnosis of bipolar I disorder (manic, hypomanic, depressed, or mixed) as defined by DSM-IV criteria, and with alcohol dependence confirmed using SCID-IV And ≥10 heavy drinking days in the 28 days prior to screening visit ≤0.04% blood alcohol content at screening visit and did not appear to be clinically impaired by recent alcohol intake so they could provide informed consent for the study
	Exclusion criteria Patients were excluded if they had a DSM-IV diagnosis of axis I disorder other than bipolar I disorder and alcohol, nicotine, or cannabis dependence coexisting with substance abuse that had been the primary focus of attention and treatment within 6 months of the screening visit. Additional exclusion criteria included participation in another clinical study within 12 weeks prior to the screening visit, a diagnosis of unstable illness including unstable diabetes mellitus, high suicidal or homicidal risk, current episode of depression or mania lasting >12 months, and hospitalization or maintenance in a controlled facility during the screening period. Patients requiring detoxification treatment for alcohol withdrawal or dependence, with a history of seizure disorders other than febrile convulsions, or with a diagnosis of hepatic impairment were also excluded. Female patients with childbearing potential and not using a reliable method of birth control or those who were pregnant or lactating were not allowed to participate in this study.
	Recruitment & screening 858 people were screened.

Study	Stedman, 2010 [55]
	The screening phase included a washout period that lasted for up to 28 days, during which patients discontinued other psychotropic medications unless permitted per protocol. Patients with a positive UTS for cocaine and/or opiates at screening, underwent repeated UTS within 3 days and were excluded if they retested positive. 362 people were randomized after washout period. 361 received study medications (175 to Quetiapine group / 186 in placebo group)
	Remuneration None reported
Comparison	**Quetiapine vs. placebo**
	Duration of treatment 12 weeks
	Follow ups Weekly visits and Endpoint / time of last treatment
Experimental arm	**Quetiapine, adjunct** Quetiapine was titrated from 50 mg/d (administered once in the evening) on Day 1 to 400 mg/d (divided doses, twice a day) from Day 5 through Day 7. From Day 8 onward, quetiapine dosing was flexible (300 to 800 mg/d) based on efficacy and tolerability, at the investigator's discretion. Patients were instructed to take the tablets twice daily, in the morning and in the evening (with or without food), including on study visit days.
	Co-interventions <u>Pharmacotherapy, Maintenance treatment</u> During the initial screening phase, all eligible participants were to be administered lithium or divalproex to achieve trough serum concentrations of 0.7 to 1.0 mEq/l or 50 to 100 µg/ml, respectively. <u>Concomitant medication use</u> Hypnotics/sedatives, 19.8%; opioids, 13.6%; other antidepressants, 8.6%; lorazepam, <3%; antidiabetic medication, <3%; haloperidol: 0.6% (n=1). Sleep medication: 7.4% /week maximum
Control arm	**Placebo** Same as for quetiapine, placebo administered as matching tablets

Study	Stedman, 2010 [55]
	Co-interventions Pharmacotherapy, Maintenance treatment Lithium or divalproex, as for quetiapine. Concomitant medication use Hypnotics / sedatives, 14.8%; opioids, 18.2%; other antidepressants 13.6%; lorazepam <3%; antidiabetic medication <3%; haloperidol: 0.5% (n=1). Sleep medication: 4.5% /week maximum
Outcomes	**Substance use** Drinking outcomes (TLFB, self-reported) were collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12. Primary outcomes: Change in the proportion of heavy drinking days, baseline to 12 weeks, Proportion of heavy drinking days, calculated over four 28-day intervals: Days 1 to 28, Days 29 to 56, Days 57 to 84, and the last 28 days recorded (Visit 10 or end of study). Change from baseline was calculated as the proportion of heavy drinking days derived over the specific 28-day interval minus the proportion of heavy drinking days derived from baseline (28 days prior to screening visit). Secondary outcomes: Proportion of non-drinking days, baseline to 12 weeks Mean number of standardized drinks per day, baseline to 12 weeks Time to first consecutive 2 weeks of abstinence, baseline to 12 weeks GGT levels (blood test), blood samples collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12 Obsessive Compulsive Drinking (OCDS, total score), self reported, collected at baseline and week 12. Craving (BSCS, total score), self reported, collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12 Number of drug use days (BSCS, subscale), self reported, collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12 Amount of money spent on concomitant drug use (BSCS, subscale), self reported, collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12 Cigarettes smoked per day, baseline to 12 w, (TLFB), self-reported, collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12
	Mental health

Study	Stedman, 2010 [55]
	Secondary outcomes: Mania symptoms (YMRS, total score), collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12 Depressive symptoms (MADRS, total score), collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12 Severity of illness and improvement (CGI-S, total score), collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12 Anxiety (HAM-A, total score), collected at baseline and week 12.
	Quality of life Secondary outcomes: Quality of life (Q-LES-Q, total score), self-reported, collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12
	Function Secondary outcomes: Level of disability (SDS, total score), self-reported, collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12 Number of lost and unproductive days (SDS, subscale), self-reported, collected at baseline, weekly for weeks 1 to 4, and every other week for weeks 5 to 12
	Mortality Not assessed
	Compliance Tablet count, not described
	Adverse effects Symptoms related to extrapyramidal symptoms (SAS and BARS), recorded weekly for weeks 1 to 4, and every other week for weeks 5 to 12
Results	**Substance use**

Primary outcomes		Quetiapine			Placebo			
		Baseline	Difference[c]		Baseline	Difference[c]		
Measure	N[d] =	M (SD)	MD (SE)	N[d] =	M (SD)	MD (SE)	P-value	

Study	Stedman, 2010 [55]							
	Proportion of heavy drinking days[a]	159	0.66 (0.24)	-0.36 (0.02)	169	0.67 (0.23)	-0.36 (0.02)	0.93
	Secondary outcomes	**N[d] =**	**M (SD)**	**MD (SE)**	**N[d] =**	**M (SD)**	**MD (SE)**	**P-value**
	Proportion of non-drinking days[a]	159	0.26 (0.21)	0.25 (0.03)	169	0.25 (0.21)	0.26 (0.03)	0.73
	Number of standardized drinks per drinking day[a,b]	159	6.99 (3.76)	-3.85 (0.25)	169	7.17 (4.92)	-3.84 (0.24)	0.95
	GGT	138	3.6 (0.9)	-0.05 (0.06)	142	3.6 (0.9)	-0.16 (0.06)	0.19
	OCDS, total score	157	18.6 (7.3)	-6.66 (0.53)	165	19.0 (7.1)	-7.29 (0.51)	0.39
	BSCS, total score	155	8.8 (6.6)	-1.79 (0.42)	169	8.6 (6.6)	-1.84 (0.41)	0.93
	BSCS, number of drug use days	71	4.9 (2.6)	-0.09 (0.29)	77	4.5 (2.6)	-0.18 (0.28)	0.80
	BSCS, $ spent on drugs	141	92.6 (169.3)	-30.97 (4.27)	161	74.9 (82.6)	-31.46 (3.99)	0.93
	a- Baseline values for the proportion of heavy drinking days, proportion of non-drinking days, and number of standardized drinks per day are from the observed cases data set (not ITT). b- Likely that the number of participants is incorrect in the publication. c- Data was analyzed using ANCOVA; missing data for week 12 efficacy measures were imputed using LOCF. d- The number of patients in each group for the efficacy analyses. Comments: Authors refer to analysis as ITT, however they include only participants who took at least 1 dose of randomized treatment and had both baseline and at least 7 consecutive days of post-baseline; each outcome type analyzes a different number of participants. Authors state in the text that the time from randomization to the first 14 consecutive days of abstinence from alcohol did not differ significantly between treatment groups (p = 0.90). Data not extracted for outcome cigarettes smoked per day.							
Comments								
	Mental health **Quetiapine** **Placebo** **Change** **Change** **Secondary outcomes** **Baseline** **at week 12** **Baseline** **at week 12**							

Study | **Stedman, 2010 [55]**

Measure	N[c] =	M (SD)	MD (SE)	N[c] =	M (SD)	MD (SE)	p-value
YMRS, total score[a]	158	11.6 (6.6)	-4.89 (0.44)	169	10.6 (7.0)	-4.00 (0.43)	0.11
MADRS, total score[a]	158	19.0 (8.7)	-6.30 (0.70)	169	17.2 (8.6)	-6.22 (0.68)	0.93
CGI-S, total score[b]	157	4.0 (0.7)	-1.04 (0.11)	169	3.9 (0.7)	-0.83 (0.11)	0.06
HAM-A, total score[a]	109	13.9 (6.2)	-4.39 (0.63)	105	13.1 (6.2)	-4.17 (0.64)	0.77

a- Data was analyzed using ANCOVA; missing data for week 12 were imputed using LOCF.
b- Data was analyzed using GEE modelling; missing data for week 12 were imputed using LOCF.
c- The number of patients in each group for the efficacy analysis.
Comments:
Authors refer to analysis as ITT, however they include only participants who took at least 1 dose of randomized treatment and had both baseline and at least 7 consecutive days of post-baseline; each outcome type analyzes a different number of participants.

Quality of life

Secondary outcomes		Quetiapine			Placebo		
		Baseline	Difference		Baseline	Difference	
Measure	N[a] =	M (SD)	MD (SE)	N[a] =	M (SD)	MD (SE)	P-value
Q-LES-Q, total score	108	44.8 (9.3)	2.07 (1.04)	105	44.9	2.76 (1.05)	0.63

a- The number of patients in each group for the efficacy analysis, observed cases data set (not ITT, no LOCF)

Function

Secondary outcomes		Quetiapine			Placebo		
		Baseline	Difference		Baseline	Difference	
Measure	N[a] =	M (SD)	MD (SE)	N[a] =	M (SD)	MD (SE)	P-value
SDS, total score	105	13.6 (8.2)	-2.57 (0.76)	104	12.1 (7.7)	-2.93 (0.76)	0.74
SDS, number of lost / week	95	1.5 (2.3)	-0.36 (0.18)	94	1.3 (1.9)	-0.64 (0.18)	0.25
SDS, number of unproductive days	97	2.1 (2.4)	-0.27 (0.23)	94	1.7 (2.0)	-0.43 (0.23)	0.62

Study	Stedman, 2010 [55]
	a- The number of patients in each group for the efficacy analysis, observed cases data set (not ITT, no LOCF)
	Compliance ”Returned-tablet counts were similar between treatment groups, with 83.4% of the quetiapine group and 79.0% of the placebo group classified as compliant (defined as dose consumption ≥80 and ≤120%).”
	Adverse effects **Quetiapine N = 175** / **Placebo N = 186** **Measure** — **% (N)** / **% (N)** **Any AE** 81.7% (143) / 69.9% (130) **Sedation** 34.9% (61) / 9.1% (17) **Somnolence** 21.7% (38) / 3.8% (7) **Dry mouth** 18.9% (33) / 4.3% (8) **Weight increased** 12.0% (21) / 1.6% (3) **Dizziness** 8.0% (14) / 4.3% (8) **Headache** 8.0% (14) / 9.7% (18) **Tremor** 7.4% (13) / 8.1% (15) **Constipation** 6.9% (12) / 1.1% (2) **Dyspepsia** 6.3% (11) / 0.5% (1) **Increased appetite** 6.3% (11) / 4.8% (9) **Diarrhea** 5.7% (10) / 5.4% (10) **Fatigue** 5.1% (9) / 6.5% (12) **Nausea** 4.6% (8) / 6.5% (12) **Upper respiratory tract infection** 4.6% (8) / 5.4% (10) **Vomiting** 3.4% (6) / 5.4% (10) Comments Two deaths were reported during the study (1 in each treatment group) and both were judged to be unrelated to the study medication by the investigators. Treatment discontinuations owing to AEs were higher in the quetiapine group (23.9%) than that in the placebo group (11.3%).

Study	Stedman, 2010 [55]
	SAS total scores were unchanged from baseline to end of treatment in a majority of patients in the quetiapine (68.1%) and placebo (69.2%) groups and improved in 17.7 and 14.4% of patients in the respective groups. BARS scores at last assessment were unchanged from baseline to end of treatment in 84.1 and 82.9% of patients in the quetiapine and the placebo groups, respectively, and showed improvement in 8.8 and 8.6% of the patients in the respective groups.
	Loss to follow up **Total** / **Quetiapine** / **Placebo** / **p-value** **Randomized, n**: 362 **Randomized and received study medication, n**: 361 / 175 / 186 **Completed trial, % (n)**: 43% (154) / 42% (74) / 43% (80) **Discontinued before week 12, % (n)**: 57% (208) / 58% (10) / 57% (14) **Reasons for discontinuation**: 25 severe non-compliance / 7 severe non-compliance / 18 severe non-compliance 63 AE / 42 AE / 21 AE 3 no therapeutic response / 0 no therapeutic response / 3 no therapeutic response 68 lost to follow-up / 29 lost to follow-up / 39 lost to follow-up 47 discontinued treatment / 23 discontinued treatment / 24 discontinued treatment 1 other / 0 other / 1 other
Risk of bias	Moderate

AE = adverse effect; **ANCOVA** = analysis of covariance; **AUD** = alcohol use disorder; **BARS** = Barnes Akathisia Rating Scale; **BSCS** = brief substance craving scale; **CGI-S** = Clinical Global Impression-Severity of Illness; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; **GEE** = generalized estimation equations; **GTG** = gamma glutamyl transferase; **HAM-A** = Hamilton Rating Scale for Anxiety; **ITT** = intention to treat; **LOCF** = last observation carried forward; **M** = mean; **MADRS** = ontgomery–A° sberg Depression Rating Scale; **MD** = mean difference; **NR** = not reported; **OCDS** = Obsessive Compulsive Drinking Scale; **QLES-Q** = Quality of Life Enjoyment and Satisfaction Questionnaire; **RCT** = randomized controlled trial; SAS = Simpson-Angus Scale; **SCID-IV** = Structured Clinical Interview for DSM-IV; **SD** = standard deviation; **SDS** = Sheehan Disability Scale; **SE** = standard error; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **UTS** = urine toxicology screen; **YMRS** = Young Mania Rating Scale.

Tolliver et al. 2012

Study	Tolliver, 2012 [56]
Study design	RCT, double blind
Intervention	**Pharmacotherapy: acamprostate** Co-interventions: brief non-manualized counselling & pharmaceutical mood stabilizing treatment
Trial registration	NR

Study	**Tolliver, 2012 [56]**
Country	USA
Setting	Outpatient research clinic
Aims	To assess the effects of acamprosate on alcohol use and mood symptoms in subjects with co-occurring bipolar disorder and active alcohol dependence
Participants	**AUD & Bipolar disorder type I or II** Participants had co-occurring bipolar disorder and active alcohol dependence **Baseline characteristics**

	Acamprostate	**Placebo**
n	14	16
Women: % (n)	28.6% (4)	43.7% (7)
Age: M (SD)	40.8 (6.7)	43.7 (11.3)
Education level >12 years, %	57.1%	62.5
Housing situation	NR	NR
Employed, %	28.6	31.3
Substance use status, M (SD)		
Drinks /day, past 30 days	7.9 (8.3)	8.3 (8.5)
Drinks /week, past 30 days	16.4 (20.8)	20.8 (19.6)
Drinks /drinking day, past 30 days	10.9 (10.3)	10.3 (14.6)
Heavy drinking days, past 30 days	5.1 (7.9)	7.9 (5.4)
Days since last drink	20.1 (23.5)	23.5 (16.5)
Concomitant medications (%)		
Mood stabilizer, monotherapy	71.4	43.8
Lithium	28.6	18.8
Anticonvulsants	64.3	75.0
Antipsychotics	35.7	62.5
Antidepressants	42.9	56.3
Benzodiazepines	14.3	12.5
Mental health status, % (n)		
Bipolar I	50 % (7)	37.5 % (6)
Bipolar II	50 % (7)	62.5 % (10)
Mood stabilizer monotherapy	71.4 % (10)	44% (7)
Number of hospitalizations	78.6 % (11)	44% (7)
Comorbidities		
Any anxiety disorder: % (n)	78.6% (11)	75.0% (12)

Comments

No significant differences, p-values and some additional baseline characteristics were not extracted.

Study	Tolliver, 2012 [56]
	Inclusion criteria Treatment-seeking men and women aged 18–65 years with a primary DSM-IV diagnosis of bipolar I or bipolar II disorder and alcohol dependence with any use of alcohol in the previous 90 days. Participants were required to be taking stable doses of mood-stabilizing medications (lithium, valproic acid, carbamazepine, lamotrigine, or first or second-generation antipsychotic medications) for one month prior to randomization. Other comorbid Axis I diagnoses, including co-occurring dependence on substances other than alcohol, were not exclusionary, as long as bipolar disorder and alcohol dependence diagnoses were primary. Participants were required to remain abstinent from alcohol for three consecutive days prior to the baseline visit as a condition for randomization. Subjects who continued to meet all study criteria after two weeks of baseline assessment were randomized into the study. **Exclusion criteria** Subjects who failed to establish 3 consecutive abstinent days prior to the baseline visit were discontinued from the study. Subjects with extreme depressive or manic symptoms at baseline; subjects with active suicidal or homicidal ideation, or who were considered by the study psychiatrist to be at acutely high risk of suicide／homicide, were excluded from the study and referred immediately for appropriate treatment. Other exclusions included significant cognitive impairment, history of closed-head injury, epilepsy, or significant medical conditions such as human immunodeficiency virus, renal failure, hepatic failure, unstable angina, or chronic obstructive pulmonary disease. Females of childbearing age who were pregnant, breastfeeding, or who refused adequate forms of contraception were also excluded. **Recruitment & screening** Referral from inpatient and outpatient clinics of a local veterans hospital, and from community mental health and substance abuse treatment centres. Pre-screened by telephone (N = 103) In-person screening conducted after informed consent (N = 45) Included: N = 33 Screened for alcohol dependence (SCID-IV) Assessed for bipolar disorder and Axis I psychiatric diagnoses (MINI and OCDS) Received a full medical evaluation, including screening for biomarkers of alcohol use

Study	Tolliver, 2012 [56]
	Remuneration
	NR
Comparisons	**Acamprosate vs. placebo, adjunct to mood stabilization**
	Duration of treatment
	8 weeks
	Participants were asked to attend a total of 11 study visits over 14 weeks, with a two-week screening and baseline assessment period, followed by weekly visits for eight weeks during the active (medication) phase of the trial and one final safety visit four weeks after discontinuing the study medication.
	Follow ups
	Endpoint, time of last treatment (8 weeks after baseline)
Experimental arm	**Acamprosate, adjunct pharmacotherapy**
	2x 333 mg tablets of Acamprosate taken 3x per day
	Co-interventions
	Pharmacotherapy
	Maintenance of stable pharmaceutical mood stabilizing treatment.
	Brief counselling, psychosocial
	Base treatment consisted of weekly brief (5–10 minutes) non-manualized counselling for 8 weeks, conducted by the study psychiatrist, aimed at encouraging alcohol abstinence and treatment adherence, consistent with medical management approaches used previously.
Control arm	**Placebo**
	Matching placebo delivered as for active substrate
	Co-interventions
	Pharmacotherapy
	Same as for Experimental arm
	Brief counselling, psychosocial
	Same as for Experimental arm
Outcomes	**Substance use**
	Time to first drinking day (breathalyser & TLFB), weekly

<table>
<tr><th>Study</th><th>Tolliver, 2012 [56]</th></tr>
<tr><td></td><td>Time to first heavy drinking day (breathalyser & TLFB), weekly
Days abstinent (breathalyser & TLFB), weekly
Heavy drinking days, (breathalyser & TLFB), weekly
Mental health
Depressive symptoms (MADRS), biweekly
Manic symptoms (YMRS), biweekly
Quality of life
Not assessed
Function
Not assessed
Mortality
Not assessed
Other (not extracted)
Changes to concomitant medications, weekly
Alcohol biomarkers GGT, CDT, AST, ALT (blood tests), measured at baseline and endpoint
Alcohol craving (OCDS), biweekly
Compliance
Pill count: Participants were dispensed a ten-day supply of study medication and asked to return the unused portion the following week for estimation of adherence.
Attendance to scheduled appointments recorded
Adverse effects
Assessed weekly with a standard questionnaire</td></tr>
<tr><td>Results</td><td>Substance use
<table><tr><th></th><th colspan="2">Acamprosate (mITT, n = 14)</th><th colspan="2">Placebo (mITT, n = 16)</th></tr><tr><th>Outcome</th><th>Baseline</th><th>Endpoint</th><th>Baseline</th><th>Endpoint</th></tr><tr><td>% days abstinent: M (SD)*</td><td>63.9 (30.1)</td><td>77 (28.2)</td><td>55.7 (30)</td><td>73 (29.5)</td></tr><tr><td>% heavy drinking days: M (SD)*</td><td>22.4 (27.3)</td><td>6.4 (8.4)</td><td>31.9 (28.6)</td><td>10.7 (14.6)</td></tr></table></td></tr>
</table>

Study	Tolliver, 2012 [56]

Alcohol craving (OCDS): M (SD)*	16.4 (9.8)	10.8 (9.5)	23.9 (10.7)	16.5 (12.6)
CGI-substance: M (SD)*	3.7 (0.9)	2.7 (1.4)	3.8 (0.9)	3.7 (1.1)
Time to first DD**	HR = 1.99 (95% CI: 0.38 to 10.36)			
Time to first HDD**	HR = 1.99 (95% CI: 0.58 to 6.88)			

* The authors indicated these outcomes were calculated ad-hoc but are included here because they are closer to the raw data.

** Calculated using Cox proportional hazards model & adjusted for baseline OCDS & alcohol use

Comments

mITT: Analyses only included participants with at least 1 post-baseline measurement; LOCF was used to account for missing data.

Total days abstinent was only reported per protocol; data not extracted.

Mean CGI scale scores for substance dependence are provided graphically for weeks 0 to 8 (Figure 3); no measurement of variation is provided; data not extracted.

The authors did not indicate which outcomes were primary or secondary.

Mental health

Outcome	Acamprosate (mITT, n = 14) Baseline	Acamprosate (mITT, n = 14) Endpoint	Placebo (mITT, n = 16) Baseline	Placebo (mITT, n = 16) Endpoint
MADRS: M (SD)*	11.9 (5.2)	8.7 (6.5)	11.7 (6.7)	11.3 (8.5)
YMRS: M (SD)*	7.2 (6.3)	5.3 (2.9)	5.9 (2.3)	5.4 (3.4)
CGI-mood: M (SD)*	3.4 (0.9)	2.9 (0.9)	3.3 (0.6)	3.1 (0.9)

* The authors indicated these outcomes were calculated ad-hoc but are included here because they are closer to the raw data.

Comments

mITT: Analyses only included participants with at least 1 post-baseline measurement; LOCF was used to account for missing data.

The authors did not indicate which outcomes were primary or secondary.

Compliance

	Intervention n = 14	Control n = 16

Study	Tolliver, 2012 [56]

Pill counts: % (n) 81.3% (11) C: 81.5% (13)

Attendance "Approximately 70% (23 of 33 randomized) of subjects completed all active phase visits in the study."

Adverse effects

AE, n (%)	Acamprosate n = 14	Placebo n = 16
Any	10 (71.4)	10 (62.5)
Hospitalization	2 (14.3)	2 (12.5)
Seizure	0 (0)	1 (6.3)
Anaphylactoid skin reaction	1 (7.1)	0 (0)

Comments

Authors state: "Acamprosate was well-tolerated, with no worsening of depressive or manic symptoms"

Multiple less severe AE listed in Table 3; data not extracted.

Loss to follow up

Loss to follow-up	Total	Acamrosate	Placebo
Randomized: n	33	16	17
Not included in mITT*: n	3	2	1
Loss to follow up (endpoint)	6	2	4
mITT*: completed at least 1 visit: n	30	14	16
Completed all visits	23	12	11

* mITT analysis included only participants who attended at least one visit. Participants who never returned after baseline visit were removed from analyses.

Comments	Trial was ended early because funding was withdrawn.
Risk of bias	Moderate

AE = adverse effects; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders, fourth edition; **M** = mean; **MADRS** = Montgomery– Åsberg Depression Rating Scale; **MINI** = Mini International Neuropsychiatric Interview; **mITT** = modified intention to treat (only participants with at least 1 post-baseline measurement); **NR** = not reported; **OCDS** = Obsessive Compulsive Drinking Scale; **RCT** = randomized controlled trial; **SCID-IV** = Structured Clinical Interview for DSM-IV; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report; **YMRS** = Young Mania Rating Scale; **LOCF** = last observation carried forward.

Wilens et al. 2008

Study	Wilens, 2008 [57]
Study design	RCT, double blind, multi-center
Intervention	**Pharmacotherapy: atomoxetine** Co-interventions: not permitted
Trial registration	NCT00190957
Country	USA, Canada
Setting	Outpatient
Aims	The study aim was to determine if atomoxetine was superior to placebo in improving ADHD and alcohol use in recently abstinent adults with ADHD and comorbid AUD.

Study	Wilens, 2008 [57]
Participants	**AUD & ADHD** Recently abstinent adults with AUD and ADHD at high relapse risk to heavy alcohol use. Participants were from 13 sites in US and one site in Canada.
	Baseline characteristics
Inclusion criteria	**Inclusion criteria** Adults ≥18 years of age meeting DSM-IV-TR criteria for ADHD (any subtype), determined by clinical interview and confirmed that symptom severity was ≥20 on AISRS. Subjects also met DSM-IV-TR criteria for alcohol use disorders (abuse or dependence). All subjects were alcohol-free for at least 4 days before randomization but not longer than 30 days. The minimum four abstinent days had to be consecutive and overlap with the week before randomization.

	Atomoxine	Placebo
N=	72	75
Male: n (%)	61 (84.7)	64 (85.3)
Age: M (SD)	34.3 (10.2)	34.8 (9.9)
Education level	NR	NR
Housing situation	NR	NR
Paid employment: n (%)	61 (84.7)	64 (86.5)
Substance use status		
Alcohol abuse: n (%)	33 (45.8)	32 (42.7)
Alcohol dependence: n (%)	39 (54.2)	43 (57.3)
Childhood history of ADHD		
Inattentive: n (%)	11 (15.3)	10 (13.3)
Hyperactive impulsive: n (%)	1 (1.4)	1 (1.3)
Combined type: n (%)	60 (83.3)	63 (84.0)
ADHD family history		
Mother: n (%)	8 (11.1)	8 (10.7)
Father: n (%)	6 (8.3)	9 (12.0)
Grandparents: n (%)	1 (1.4)	0
Siblings: n (%)	17 (23.6)	14 (18.7)

Study	Wilens, 2008 [57]
	Exclusion criteria Exclusion criteria included diagnosis of current bipolar disorder, major depressive disorder, or psychosis as determined by SCID-IV-TR or HAM-D17 or HAM-A scores >18 at the evaluation visit. Subjects with significant cognitive impairment, judged by the investigator, were excluded.
	Recruitment & screening Of 215 subjects screened, 147 met entry criteria and were randomized.
	Remuneration NR
Interventions	**Atomoxetine vs. placebo**
	Duration of treatment 12 weeks (double blind) All subjects also received open-label atomoxetine for approximately 12 additional weeks after trial ended.
	Follow ups Measurements during treatment: weekly Endpoint / time of last double-blind treatment: 12 weeks
Experimental arm	**Atomoxetine** Atomoxetine treatment was initiated at 25 mg/day once daily in the morning for the first week. Dosage was increased to 40 mg at the beginning of the second week and 80 mg at the end of the second week. At any visit after 4 weeks of treatment, the dose could be increased to 100 mg/day. Eighty or 100 mg doses could be administered either as single daily doses or equally divided doses according to tolerability.
	Co-interventions None Psychotherapy, pharmacological, or other interventions for substance abuse (other than 12-step participation) were ***NOT*** permitted.
Control arm	**Placebo** Matching placebo delivered as for active treatment

Study	Wilens, 2008 [57]
	Co-interventions None
Outcomes	**Substance use** Primary outcomes: Time to initial relapse to heavy drinking (TLFB), weekly Secondary outcomes: Cumulative heavy drinking days (TLFB), weekly Drinks per day (TLFB), weekly Proportion of drinking days (TLFB), weekly Number of drinks per drinking day (TLFB), weekly Proportion of days on which substances other than alcohol were used (TLFB), weekly
	Mental health Primary outcomes: ADHD symptoms (AISRS), interview Secondary outcomes: ADHD symptoms (ASRS), self-reported ADHD symptoms severity (CGI-ADHD-S), observer-rated ADHD symptoms improvement (CGI-ADHD-I), observer-rated
	Quality of life Not assessed
	Function Not assessed
	Mortality Not assessed
	Compliance NR

Study	Wilens, 2008 [57]
	Adverse effects NR
Results	**Substance use**

	Atomoxetine (ITT, n = 72)	Atomoxetine (ITT, n = 72)	Placebo (ITT, n = 75)	Placebo (ITT, n = 75)	Difference
Primary outcomes	**Endpoint**		**Endpoint**		**Log-rank test**
Initial relapse to heavy drinking*: n (%)**	64/68 (94.1%)		69/72 (95.8%)		p = 0.93
Secondary outcomes	**Baseline**	**Change from baseline**	**Baseline**	**Change from baseline**	**p-value***
Mean drinks per day: M (SD)**	2.0 (1.5)	1.0 (3.2)	2.0 (1.8)	1.5 (2.6)	0.35
Proportion of drinking days: M (SD)**	0.3 (0.2)	0.2 (0.3)	0.3 (0. 2)	0.3 (0.3)	0.26
Drinks per drinking day: M (SD)**	6.5 (2.9)	−1.1 (3.1)	6.7 (3.5)	−0.6 (2.4)	0.14
Proportion days using substances other than alcohol: M (SD)**	0.07 (0.2)	−0.01 (0.08)	0.04 (0.1)	0.01 (0.08)	0.27

* Between-groups comparison of change from baseline to end of double-blind treatment (12 weeks). P-values are based on an ANCOVA with only treatment and investigator included in the model. ** Baseline drinking was assessed for three weeks either preceding study entry or from the beginning of the current period of sobriety. Post-randomization drinking variables were measured each week and represent the amount of drinking behavior in the week preceding the last visit in study period 2. *** Based on data from 68 participants in the atomoxetine group and 72 participants in the placebo group.

Comments

Data not extracted: time to relapse, post hoc cumulative heavy drinking days, and OCDS outcomes.

All subjects with at least one post-baseline measurement were included in analyses, and change scores were computed using a LOCF approach where patients lost to follow-up were counted as relapsed.

Study | **Wilens, 2008 [57]**

Mental health

	Atomoxetine (ITT, n = 72)	Atomoxetine (ITT, n = 72)	Placebo (ITT, n = 75)	Placebo (ITT, n = 75)	Difference*
Primary outcomes	**Baseline**	**Change from baseline**	**Baseline**	**Change from baseline**	**p-value**
AISRS total score: M (SD)	40.6 (7.8)	−13.6 (11.4)	40.1 (7.9)	−8.3 (11.4)	0.007
AISRS Hyperactive/impulsive subscale: M (SD)	19.0 (5.0)	−6.5 (6.0)	18.7 (5.2)	−3.9 (5.6)	0.009
AISRS Inattentive subscale: M (SD)	21.7 (3.9)	−7.2 (6.2)	21.4 (4.1)	−4.4 (6.7)	0.013
Secondary outcomes	**Baseline**	**Change from baseline**	**Baseline**	**Change from baseline**	**p-value**
ASRS Total score: M (SD)	48.5 (10.1)	−12.9 (12.8)	51.3 (9.3)	−8.3 (12.9)	.029
ASRS Hyperactive/impulsive subscale: M (SD)	23.6 (6.1)	−6.4 (7.0)	24.6 (6.0)	−4.1 (6.6)	0.034
ASRS Inattentive subscale: M (SD)	24.9 (5.5)	−6.5 (6.7)	26.7 (5. 6)	−4.2 (7.1)	0.032
CGI-ADHD-S: M (SD)	4.8 (0.8)	−1.0 (1.2)	4.8 (0.6)	−0.7 (1.1)	0.048
CGI-ADHD-I: M (SD)**	-	2.9 (1.1)	-	3.4 (1.2)	0.006
HAM-D-17: M (SD)	8.0 (3.6)	−1.0 (4.3)	8.0 (3.7)	−1.1 (5.8)	0.89
HAM-A total score: M (SD)	9.7 (3.5)	−1.5 (4.3)	9.5 (3.8)	−1.2 (6.3)	0.84

* Between-groups comparison of change from baseline to end of double-blind treatment (12 weeks). P-values are based on an ANCOVA with only treatment and investigator included in the model. ** There is no baseline measure for this variable. Values shown are from last visit during double blind treatment.

Comments

All subjects with at least one post-baseline measurement were included, and change scores were computed using a LOCF approach where patients lost to follow-up were counted as relapsed.

Compliance

NR

Study: Wilens, 2008 [57]

Adverse effects

Symptom	Atomoxetine n = 72	Control n = 75	p-value
nausea: % (n)	43.3%	9.6%	< 0.001
dry mouth: % (n)	26.9%	11.0%	0.018
decreased appetite: % (n)	17.9%	2.7%	0.004
dizziness	14.9%	2.7%	0.014
fatigue	13.4%	2.7%	0.026
constipation	11.9%	1.4%	0.014
urinary hesitation	7.5%	0%	0.023
hot flush	6.0%	0%	0.050
paraesthesia	6.0%	0%	0.050

Comments

There were no serious adverse events reported. Discontinuation rates due to an adverse event were low in both groups and not significantly different. Adverse events significantly more prevalent in atomoxetine-treated subjects were nausea, dry mouth, decreased appetite, dizziness, fatigue, constipation, urinary hesitation, hot flush, and paraesthesia.

Loss to follow up

Endpoint: Atomoxetine: 35/72 (49%), Placebo: 25/75 (33%)

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Risk of bias: Moderate

ADHD = attention-deficit/hyperactivity disorder; **AISRS** = Adult ADHD Investigator Symptom Rating Scale; **ANCOVA** = analysis of covariance; **AUD** = alcohol use disorder; **DSM-IV-TR** = Diagnostic and Statistical Manual of Mental Disorders - fourth edition - Text Revision; **HAM-A** = Hamilton Rating Scale for Anxiety; **HAM-D17** = Hamilton Rating Scale for Depression, 17 item; **ITT** = modified intention to treat; **LOCF** = last observation carried forward; **M** = mean; **NR** = not reported; **RCT** = randomized controlled trial; **SCID-IV-TR** = Structured Clinical Interview for DSM-IV-TR; **SD** = standard deviation; **TLFB** = Time-Line Follow-Back, self-reported substance use, self-report.

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