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Influence of adjuvant clonidine on mania, sleep disturbances and cognitive performance – Results from a double-blind and placebo-controlled randomized study in individuals with bipolar I disorder during their manic phase

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ABSTRACT

Background: While the favorable effect of adjuvant clonidine in the treatment of acute mania has been observed already about 40 years ago, this line of treatment has not been further investigated. Here, we resumed this topic, and we tested the effect of adjuvant clonidine, an antihypertensive stimulating the alpha-$_2$ central adrenergic receptor, on symptoms of mania, cognitive performance, and subjective sleep. To this end, we performed a randomized, double-blind and placebo-controlled clinical trial among inpatients with bipolar disorder I during their acute phase of mania.

Methods: A total of 70 inpatients (mean age: 37.40 years; 15.7% females) with diagnosed bipolar disorder I and during their acute manic phase were randomly assigned either to the adjuvant clonidine (0.2 mg/d to a maximum of 0.6 mg/d) or to the placebo condition. Standard medication was lithium at therapeutic dosages. At baseline, participants completed a series of self-rating questionnaires covering sociodemographic information and subjective sleep. Subjective sleep was re-assessed 24 days later at the end of the study. Experts rated participants' acute state of mania with the Young Mania Rating Scale at baseline and at day 12 and day 24. Participants' cognitive performance was assessed at baseline and at day 24 at the end of the study.

Results: Over time, mania scores significantly decreased (large effect size), but more so in the clonidine condition, compared to the placebo condition (medium effect size). Likewise, over time, subjective sleep improved (large effect size), but more so in the clonidine, compared to the placebo condition (medium effect size). Over time, cognitive performance improved (medium effect size), irrespective from the study condition.

Conclusions: Compared to placebo, adjuvant clonidine to lithium improved symptoms of mania, as rated by experts', and subjective sleep quality. Adjuvant clonidine had no further favorable (or detrimental) impact on cognitive performance.

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1. Introduction

Individuals with bipolar disorder report recurrent and intense fluctuations of mood, energy and behavior (Grande et al., 2016; McIntyre et al., 2020; Vieta et al., 2018). Further, individuals with bipolar disorder report that their mood swings are persistent, intense, frequent and disrupting the continuity of private, educational, professional, social, cognitive, emotional, behavioral and economic stability (Angst et al., 2003; Grande et al., 2016; Macneil et al., 2011; McIntyre et al., 2020; Vieta et al., 2018). As such, bipolar disorders are a chronic mental disorder characterized by periods of intense and frequent moods swings which are defined as states of depressive disorders and hypomanic and manic states (Grande et al., 2016; McIntyre et al., 2020; Müller and Leweke, 2016; Vieta et al., 2018).

The onset of such fluctuations is often observed during the psychosexually, psychosocially and economically demanding developmental stage of early adulthood; as such, bipolar disorders affect the economically most active population (Grande et al., 2016), and the population with the highest pressure to prevail and assert for successful mating (Brüne, 2015; Buss, 2019; Miller, 2000). Further, clinical observations suggest that bipolar disorders are often not recognized and under-diagnosed (Grande et al., 2016; McIntyre et al., 2020; Vieta et al., 2018). Not surprising, the average time lapse between disease onset and diagnose and first treatment is five to ten years (Grande et al., 2016).

Both the ICD-10/11 (World Health, 2004, 2019) and the DSM-5 (American Psychiatric Association, 2013) characterize bipolar disorders as a chronic psychiatric disease with the presence of manic (bipolar disorder I) or hypomanic (bipolar disorder II) episodes and major depressive disorders (Müller and Leweke, 2016). Concomitantly and compared to the general population, individuals with bipolar disorder have an increased risk of premature death; such premature death is either a direct consequence of suicide, or an indirect consequence of further concomitant psychiatric disorders such as substance use disorder (e.g., tobacco, alcohol, cannabis), personality disorders, schizophrenia spectrum disorder, or an indirect consequence of further concomitant somatic diseases such as diabetes, overweight, metabolic syndrome, and cardiovascular diseases. Compared to the general population, the risk of death by suicide is up to 20 times higher in individuals with bipolar disorders (Grande et al., 2016; McIntyre et al., 2020; Vieta et al., 2018). Last, lifetime prevalence rates are 0.6% for bipolar disorder I, 0.4% for bipolar disorder II, 1.4% for subthreshold bipolar disorder II, and 2.4% for bipolar disorder spectrum (Merikangas et al., 2011).

Individuals with bipolar I disorder also show higher cognitive dysfunctions (Vieta et al., 2018), either at short-term during the manic phase, or at long-term during the life span (Sheffield et al., 2018; Solé et al., 2017). More specifically, both during an acute phase of mania and periods of euthymia individuals with bipolar I disorder showed significant impairment in every domain of executive functioning (Peters et al., 2014). Importantly, such executive functioning problems were not merily mood-dependent. Lower cognitive functioning was also related to higher riks of work disability (Boland et al., 2015). During the acute phase of mania, cognitive flexibility (Daglas et al., 2015) and verbal and working memory performance (Vrabie et al., 2015) were impaired, compared to healthy controls. Further, it appeared that a severe course of illness was associated with a more impaired cognitive performance (Vrabie et al., 2015). Always compared to controls, individuals with bipolar disorder showed lower executive function and verbal memory, irrespective from an acute manic/hypomanic or depressed stage (Martínez-Arán et al., 2004). Given this background, we investigated the change of cognitive performance during the beginning of the pharmacological treatment of a manic phase. More specifically, we investigated, if clonidine, an antihypertensive stimulating the alpha-$_2$ central adrenergic receptor, adjuvant to lithium, could have improved the cognitive impairment, compared to placebo.

More recent research has focused on the importance of sleep in individuals with bipolar I disorder; while markedly reduced sleep need and sleep duration belong to the core symptoms of bipolar I disorder (American Psychiatric Association, 2013; World Health, 2004, 2019), the associations between higher illness intensity and illness oscillations and irregular sleep patterns have gained more attention (Grande et al., 2016; McIntyre et al., 2020; Vieta et al., 2018). According to this, re-synchronizing wake-sleep patterns to a more balanced daylight-night-time rhythms appears to be a promising, though adjunctive treatment option for individuals with bipolar I disorder (Dallaspezia and Benedetti, 2015; Gottlieb et al., 2019). In a related vein, individuals in a manic state and at the beginning of the psychopharmacologic treatment should report severe sleep disruptions. Given this assumption, the second aim of the present study was to investigate, to what extent adjuvant clonidine to the standard treatment with lithium could improve the subjective sleep quality, when compared to placebo.

To treat the acute phase of mania, mood stabilizers such as lithium, sodium valproate, carbamazepine, and lamotrigine, and second-generation antipsychotics such as aripiprazole, olanzapine, quetiapine, risperidone or ziprasidone are administered (just to name but a few; see McIntyre et al., 2020; Vieta et al., 2018 for a comprehensive overview). While typical side-effects of first-generation antipsychotics such as chlorpromazine and haloperidol were Parkinson's disease-like movements, internal restlessness and tardive dyskinesia, typical side-effects of the so-called second-generation antipsychotics are on metabolism, leading to weight gain, insulin-resistance (Grajales et al., 2019; Sarsenbayeva et al., 2019; Skonieczna-Żydecka et al., 2019) and extrapyramidal adverse effects (Divac et al., 2014). Given that such side-effects may have unfavorable effects on patients' medication adherence (Okanović and Živanović, 2016), the search for further treatment options is justified.

In this regard, clonidine is an antihypertensive acting as an alpha$_2$-receptor agonist with modest influence of the 5-HT and DA-receptors. Clonidine induces the release of somatotroph hormone (STH), which activates the alpha$_2$-receptors. Clonidine is a long-established anti-hypertensive agent with presynaptic agonistic effect resulting in the inhibition of neural release of noradrenaline (Maguire and Singh, 1987). Further, clonidine has been administered as stand-alone or as adjuvant in the treatment of individuals with bipolar disorder during their acute manic phase since the mid 80ties of the last century (Giannini et al., 1986; Hardy et al., 1986; Maguire and Singh, 1987; Shen, 1986; Tudorache and Diacicov, 1991; Zubenko et al., 1984), with sample sizes ranging from three patients (Maguire and Singh, 1987; Zubenko et al., 1984) to 20 (Tudorache and Diacicov, 1991) to 24 patients (Hardy et al., 1986). Further, we note that the studies mentioned above were either case studies (Maguire and Singh, 1987; Zubenko et al., 1984), or not-blinded interventional studies with no control conditions (Giannini et al., 1986; Hardy et al., 1986; Tudorache and Diacicov, 1991; Zubenko et al., 1984).

In the present study, we expanded the methodological part upon previous study in the following six ways: 1. The samples size was quite large (N = 70); 2. The study was a double-blind, placebo-controlled clinical trial; 3. Clonidine was given adjunctively to lithium, a standard mood stabilizer; 4. We relied on both participants' and experts' ratings; this means: 5. We assessed not only the intensity of mania, as rated by experts, but we also assessed participants' cognitive performance; 6. We assessed subjective sleep quality.

One hypothesis and two research questions were formulated. The hypothesis was: Following previous results (Giannini et al., 1986; Hardy et al., 1986; Maguire and Singh, 1987; Shen, 1986; Tudorache and Diacicov, 1991; Zubenko et al., 1984), we expected improvements of mania intensity in the adjuvant clonidine condition over time and compared to the placebo condition. The exploratory research questions were: First, compared to placebo, did adjuvant clonidine improve subjective sleep quality over time? Second, compared to placebo, did adjuvant clonidine improve the cognitive performance over time? Thus, the primary endpoint of the study was the YMRS score at the end of the study after 24 days, while secondary endpoints of the study were

subjective sleep and cognitive performance at end of the study after 24 days.

We hold that the present results might be of both clinical and practical importance, as the study results could improve the pharmacologic treatment of individuals in an acute manic state. This claim holds particularly true as regards participants' cognitive performance and sleep quality. First, there is extant research to show that both cognitive performance (Boland et al., 2015; Daglas et al., 2015; Peters et al., 2014; Sheffield et al., 2018; Solé et al., 2017; Vieta et al., 2018; Vrabie et al., 2015) and sleep (Grande et al., 2016; McIntyre et al., 2020; Vieta et al., 2018) are deteriorated during the manic state; second, to our knowledge, the effect of adjuvant clonidine on cognitive performance and sleep among individuals with bipolar I disorder and during their manic phase were not assessed so far.

2. Methods

2.1. Procedure

Inpatients of the Sina Hospital of Hamadan (Hamadan, Iran) with diagnosed bipolar disorder and currently in an acute phase of mania were approached to participate in this double-blind study. Participants were fully informed about the study design and about the confidential and secure data handling. Further, they were informed that participation or non-participation had no advantages or disadvantages for the current treatment regimen and treatment quality. Participants signed the written informed consent. Thereafter, they were assigned either to the clonidine or to the placebo condition. Participants completed the Pittsburgh Sleep Quality Index at baseline and at day 24, at the end of the study. Experts blind to participants' study condition assignment rated participants' intensity of mania with the Young Mania Rating Scale (see below) at baseline, day 12 and day 24, the end of the study. Participants cognitive performance was rated with the Mini Mental State Examination (MMSE) at baseline and at day 24. The study was registered at the Iran Clinical Trial Register (IRCT20120215009014N295). The local ethics committee approved the study (IR.UMSHA.REC.1398.954), which was performed in accordance with the seventh and current edition (World Medical Association, 2013) of the Declaration of Helsinki.

2.2. Sample size calculation

The sample size calculation was performed with G*Power® (Faul et al., 2007). As mentioned above, studies on the effect of (adjuvant) clonidine on acute mania were performed 40–50 years ago. For want of reliable data, the sample size calculation assumed to achieve at least a medium effect size ($\eta p^2 > 0.059$); given this, the following sample size was calculated: $\eta p^2 > 0.059$; f = 0.253; alpha = .05; power: (1-beta error probability = .99), groups = 2; measurements = 3; epsilon correction = 0.9; total sample size: 64; to compensate for possible dropouts, the sample size was set at N = 84.

2.3. Participants

Inclusion criteria were: 1. Age between 18 and 65 years; 2. Diagnosis of bipolar I disorder, based on the DSM-5 (American Psychiatric Association, 2013), as ascertained by an experienced clinical psychologist or psychiatrist following a thorough clinical interview for DSM-5 disorders (First, 2015); 3. Young Mania Rating Scale: 20 or more points; 4. Hospitalized for bipolar disorders for at least once within the last two years. 5. Compliance with the study requirements; 6. Signed written informed consent. Exclusion criteria were: 1. Known allergies against lithium and/or alpha-2 adrenergic receptor stimulant drugs, based on participants' self-reports and on medical records; 2. Suicide attempt within the last eight weeks before study admission; 3. Risk of suicide attempts, 4. Severe further psychiatric disorders such as substance use disorder, personality disorder, post-traumatic stress disorder or adjustment disorder; 5. Current use of anticholinergic medications or tricyclic antidepressants, based on self-reports and medical records; 6. Females: breastfeeding, pregnant, or planning to get pregnant the next ten weeks; 7. The coordinator of the study excluded a participant due to unexpected events such as sudden suicidal behavior or medication side effects, or change of patients' adherence to the study conditions.

As shown in Fig. 1, of the 90 inpatients approached, 84 (93.3%) of them were randomized. However, of the 84 randomized patients, 14 of those did withdraw from the study before they got the first medications (clonidine; placebo), before they completed the sleep questionnaire, and before their cognitive performance was assessed (see below for details).

2.4. Randomization

As in other studies (Jahangard et al., 2014, 2018; Shayganfard et al., 2016; Zakiei et al., 2021), randomization was accomplished with randomization.com to create a list to assign 84 participants randomly to one of the two study conditions. Thereafter, a psychologist not otherwise involved in the study managed the assignments.

2.5. Drop-outs after randomization and before the psychiatric and psychological assessment

After the randomization, but before the through psychiatric (YMRS) and psychological (MSSE; sleep) assessment, 14 out of the 84 randomized patients withdraw from the study. Of those, seven out of 14 who withdraw from the study after randomization were assigned to the adjuvant clonidine condition, and seven out of 14 who dropped from the study were assigned to the placebo condition. Compared to those who completed the study (n = 70; mean age: 37.40; SD = 11.75), those who dropped after randomization (n = 14; mean age: 24.28; SD = 3.49) were statistically significantly younger ($t(82) = 4.12$, $p < .01$, $d = 1.21$), had a significantly higher YMRS score at baseline (28.21; SD = 5.89 vs 36.93, SD = 8.58; $t(82) = 4.66$, $p < .001$; $d = 1.36$), had a significantly lower educational level ($X^2(N = 84, df = 2) = 10.35$, $p < .01$), were more often singles ($X^2(N = 84, df = 1) = 7.48$, $p < .01$), and reported more often to misuse substances ($X^2(N = 84, df = 1) = 84.00$, $p < .001$), while no gender- or job-related differences were observed. To summarize, patients who dropped drop-out after randomization, but before the begin of the study were younger, had higher mania scores, reported a lower education and more substance abuse, and were rather singles.

2.6. Measurements

2.6.1. Demographic and treatment-related information

Participants reported their age (years), gender (male, female at birth), civil status (single, married), employment status (employed, unemployed), educational level (diploma or lower, academic degree); further; tobacco use (yes, no), use of antipsychotics (yes, no), mood stabilizers (yes, no), sodium valproate (yes, no), both mood stabilizers and sodium valproate (yes, no), always before being admitted to the psychiatric hospital and before starting lithium monotherapy.

2.6.2. Severity of mania; Young Mania Rating Scale; expert ratings

Experts assessed participants' mania severity with the Farsi version (Ebrahimi et al., 2017) of Young Mania Rating Scale (YMRS) (Young et al., 1978). The YMRS consists of 11 items; seven items are graded from zero to four, and four items are graded from zero to eight. The total score ranges from zero to 60, with a higher score reflecting a higher severity of mania.

2.6.3. Subjective sleep: Pittsburgh Sleep Quality Index (PSQI)

To rate subjective sleep quality, participants completed the Farsi version (Chehri et al., 2020; Khosravifar et al., 2015; Nazifi et al., 2014) of the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al., 1989). The PSQI is a self-report scale completed in 5 min. It consists of 19 items and

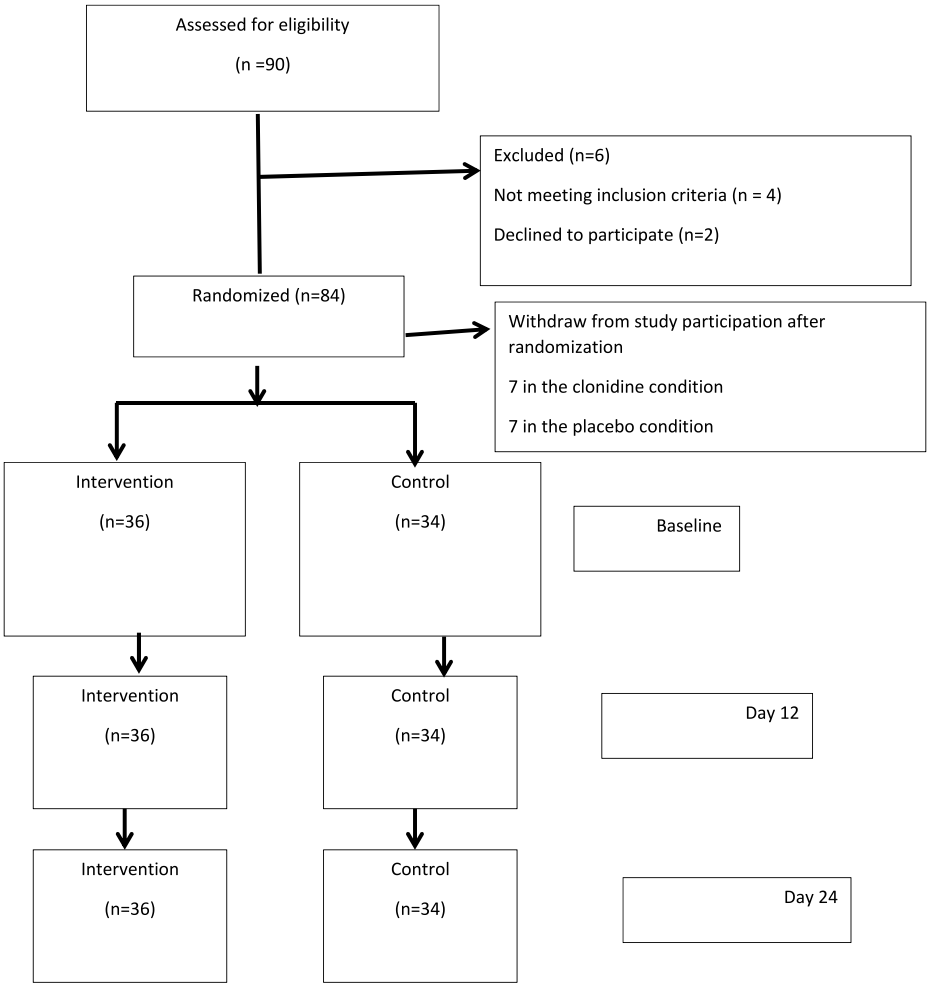

Fig. 1. Provides the flow chart of the number of participants approached, screened and included in the study.

contains seven subscales (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleeping medication, and daytime dysfunction), each weighted equally on a scale from 0 to 3, with higher scores indicating poorer sleep quality. The seven components are then summed to obtain an overall PSQI score, ranging from 0 (good sleep quality) to 21 (poor sleep quality). Total scores of $\geq$5 reflect poor sleep, associated with considerable sleep complaints (Cronbach's alpha = 0.85).

2.6.4. Cognitive performance

To assess participants' cognitive performance, the Persian version (Ansari et al., 2010; Gharaeipour and Andrew, 2013) of the Mini Mental State Examination (Folstein et al., 1975) was employed. The MMSE has satisfactory psychometric properties (Ansari et al., 2010; Gharaeipour and Andrew, 2013; Pangman et al., 2000). This expert rating assesses participants' orientation to time and place, attention and calculation, recall, language, repetition and complex commands such as drawing shapes, with higher scores reflecting a higher cognitive performance; 24 to 30 points reflect normal cognitive performances, while scores of 23 and lower reflect an impaired cognitive performance.

2.7. Standard medication

All patients received 900–1200 mg/d of lithium tablet at three divided doses, such to achieve the therapeutic blood level of lithium (0.5–1.5 mmol/lit).

2.8. Clonidine

Participants in the clonidine condition received (pills of 0.2 mg/d to a maximum of 0.6 mg/d) of adjuvant clonidine in the morning and in the evening at two divided doses. Tolerance to clonidine was assessed daily, and blood pressure was measured before and 1 h after clonidine administration.

2.9. Placebo

Participants in the placebo condition received placebo pills, which consisted of lactose powder, glycerin, methylparaben, and propylparaben. Pills of clonidine and placebo were identical in shape, color, weight, and smell. To keep the assessment identical to the clonidine assessment, tolerance to the placebo was assessed daily, and blood pressure was measured before and 1 h after placebo administration.

2.10. Blood pressure

A nurse not otherwise involved in the study measured twice the day participants' plood pressure. If blood pressure was below 100/60 mm Hg for two consecutive days, the participant was excluded from the study.

2.11. Statistical analyses

Statistical analyses were performed per protocol.

With a series of X^2-tests and t-tests sociodemographic and illness-related information were compared between participants in the clonidine and placebo condition.

One ANOVA for repeated measures was performed with the following factors: Time (baseline; day 12; day 24), Group (clonidine vs. placebo) and the Time x Group-interaction; dependent variable was: Young Mania Rating Scale scores.

Two ANOVAs for repeated measures were performed with the following factors: Time (baseline; day 24), Group (clonidine vs. placebo) and the Time x Group-interaction; the dependent variables were: Subjective sleep quality; cognitive performance.

A series of Pearson's correlations was performed between mania scores, cognitive performance and sleep quality at baseline, day 12 and day 24, separately for participants in the clonidine condition and placebo condition.

The nominal significance level was set at alpha <0.05. Effect sizes for F-statistics were reported as partial eta squared (ηp^2), with $\eta p^2 < 0.019$ = trivial effect size [T]; $0.020 < \eta p^2 < 0.059$ = small effect size [S], $0.06 < \eta p^2 < 0.139$ = medium effect size [M], and $\eta p^2 \geq 0.14$ = large effect size [L]. Following the examples from previous studies (Sadeghi Bahmani et al., 2019, 2020), we have also reported Cohen's ds effect sizes of mean differences within and between the clonidine and placebo conditions. All calculations were performed with SPSS® 28.0 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

3. Results

3.1. General information

Table 1 provides the descriptive and statistical overview of sociodemographic and treatment-related information between participants in the clonidine and placebo condition.

Overall, participants in the clonidine and placebo condition did not differ as regards age, the number of episodes (trivial to small effect sizes), sociodemographic information and medication treatment.

3.2. Young Mania Rating Scale scores between and within the clonidine and placebo group and over time

Table 2 provides the descriptive statistical overview of the Young Mania Rating Scale scores at baseline, day 12 and day 24 within and between the clonidine and placebo condition. Table 3 provides the inferential statistical overview (see also Fig. 2).

Young Mania Rating Scale scores statistically significantly decreased from baseline to day 24 (large effect size), but more so in the clonidine condition, compared to the placebo condition (interaction with medium effect size). There was no group difference (small effect size).

3.3. Sleep quality between and within the clonidine and placebo group and over time

Table 2 also provides the descriptive overview of sleep quality between and within the clonidine and placebo condition at baseline and day 24; Table 3 provides the inferential statistical overview (see also Fig. 3).

Sleep quality statistically significantly improved over time (large effect size), but more so in the clonidine condition, compared to the placebo condition (medium effect size). There was no group difference (small effect size).

3.4. Cognitive performance between and within the clonidine and placebo group and over time

Table 2 also provides the descriptive overview of cognitive performance between and within the clonidine and placebo condition at baseline and day 24; Table 3 provides the inferential statistical overview (see also Fig. 4).

Cognitive performance statistically significantly improved over time (medium effect size), tough, with no difference between the clonidine and placebo condition (trivial effect sizes).

Table 1
Descriptive and inferential statistical overview of sociodemographic and treatment-related information between participants in the verum and placebo condition.

Variable		Groups		Statistics
		Clonidine condition	Placebo condition	
N		36	34	
		M (SD)	M (SD)	
Age (years)		36.86 (11.31)	37.97 (12.35)	t(68) = 0.39 d = 0.13 (T)
Number of episodes		2.36 (0.77)	1.98 (0.76)	t(68) = 2.15*, d = .27 (S)
		N (%)	N (%)	
Gender	Male	31 (86.1)	28 (82.3)	X^2(N = 70, df = 1) = 0.19
	Female	5 (13.9)	6 (17.7)	
Civil status	Married	(58.3)21	(50.0)17	X^2(N = 70, df = 1) = 0.49
	Single	(41.7)15	(50.0)17	
Employment status	Unemployed	32 (89.9)	28 (82.3)	X^2(N = 70, df = 1) = 0.61
	Employed	4 (11.1)	6 (17.7)	
Education	Diploma or lower	23 (63.9)	25 (73.3)	X^2(N = 70, df = 1) = 0.75
	Academic	13 (36.1)	9 (26.5)	
Tobacco use	Yes	32 (89.9)	29 (85.3)	X^2(N = 70, df = 1) = 0.20
	No	4 (11.1)	5 (14.7)	
History of psychiatric disease	Yes	11 (30.6)	9 (26.5)	X^2(N = 70, df = 1) = 0.14
	No	25 (69.4)	25 (73.5)	
Antipsychotic	Yes	31 (83.8)	28 (82.3)	X^2(N = 70, df = 1) = 0.80
	No	6 (16.2)	6 (17.7)	
Mood stabilizer	Lithium	15 (41.7)	16 (47.1)	X^2(N = 70, df = 1) = 0.50
Valproate sodium		18 (50.0)	17 (50.0)	X^2(N = 70, df = 1) = 0.49
Both		3 (8.3)	1 (2.9)	X^2(N = 70, df = 1) = 0.70

Notes: * = p < .05; T = trivial effect size; S = small effect size.

3.5. Mean changes between the clonidine and placebo condition at the end of the study (day 24), and within the clonidine and placebo condition from baseline to the end of the study

Table 4 provides the overview of effect size calculations between the clonidine and placebo condition at the end of the study, and within the clonidine and placebo condition from baseline to the end of the study.

At the end of the study, mania scores (large effect size) and sleep disturbances (medium effect size) were lower in the clonidine condition, compared to the placebo condition. No difference was observed for the cognitive performance (trivial effect size).

Within the clonidine condition, mania and sleep disturbances scores

Table 2
Descriptive statistical indices of severity of mania (Yuong Mania Rating Scale), sleep quality (Pittsburgh Sleep Quality Index) and cognitive performance (Mini Mental Status Examination) at baseline, day 12 and day 24 (end of the study), separately for participants in the clonidine and placebo condition.

N	Time points					
	Baseline		Day 12		Day 24	
	Clonidine	Placebo	Clonidine	Placebo	Clonidine	Placebo
	36	34	36	34	36	34
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Mania severity (YMRS)	29.11 (5.83)	27.26 (5.88)	16.75 (4.83)	18.09 (4.35)	9.81 (3.49)	13.62 (5.67)
Sleep quality (PSQI)	8.11 (2.13)	7.88 (2.06)	–	–	4.53 (1.63)	5.94 (2.31)
Cognitive performance (MMSE)	21.78 (5.21)	22.00 (4.52)	–	–	23.44 (4.66)	23.64 (4.42)

Notes: YMRS = Young Mania Rating Scale; PSQI = Pittsburgh Sleep Quality Index; MMSE = Mini Mental Status Examination.

Table 3
Inferential statistical indices of severity of mania (Yong Mania Rating Scale), sleep quality (Pittsburgh Sleep Quality Index) and cognitive performance (Mini Mental Status Examination) over time and between and within the study conditions (clonidine vs. placebo).

	Factors			
	Time	Group	Time × Group interaction	Greenhouse-Geisser Epsilon
	F (2, 136) η_p^2	F (1, 68) η_p^2	F (2, 136) η_p^2	
Mania severity (YMRS)	255.74*** .790 [L]	1.63 .023 [S]	7.39*** .098 [M]	.842
	F (1, 68) η_p^2	F (1, 68) η_p^2	F (1, 68) η_p^2	
Sleep quality (PSQI)	83.11*** .550 [L]	2.39 .034 [S]	7.34*** .097 [M]	1
Cognitive performance (MMSE)	10.03** .129 [M]	0.05 .001 [T]	0.00. .000 [T]	1

Notes: YMRS = Young Mania Rating Scale; PSQI = Pittsburgh Sleep Quality Index; MMSE = Mini Mental Status Examination; * = $p < .05$; ** = $p < .01$; *** = $p < .001$. [T] = trivial effect size; [S] = small effect size; [M] = medium effect size; [L] = large effect size.

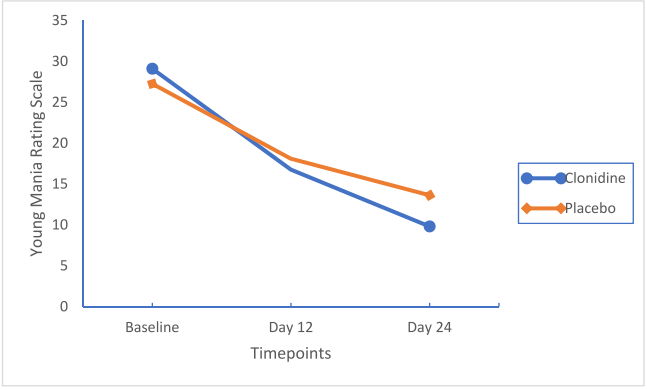

Fig. 2. Young Mania Rating Scale scores at baseline, day 12, and day 24, separately for the clonidine and placebo condition. Mania decreased over time (large effect size), but more so in the clonidine condition, compared to the placebo condition (medium effect size). Points are means.

improved from baseline to the study end (large effect sizes), while cognitive performance did not improve (small effect size).

Within the placebo condition, mania and sleep disturbances scores improved from baseline to the study end (large effect sizes), while cognitive performance did not improve (small effect size).

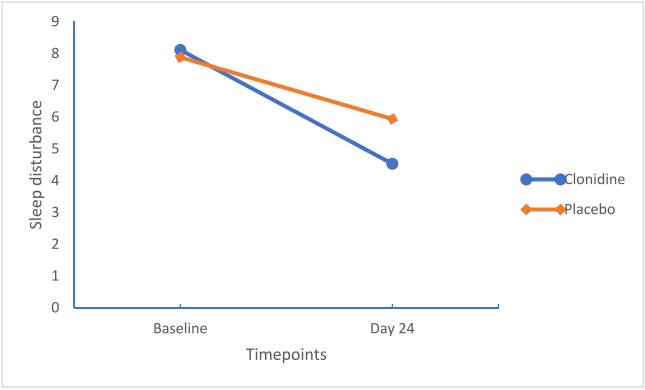

Fig. 3. Pittsburgh Sleep Quality Index scores at baseline and at the end of the study. Sleep disturbances scores decreased over time (large effect size), but more so in the clonidine, compared to the placebo condition (medium effect size). Lower scores reflect a better subjective sleep quality. Points are means.

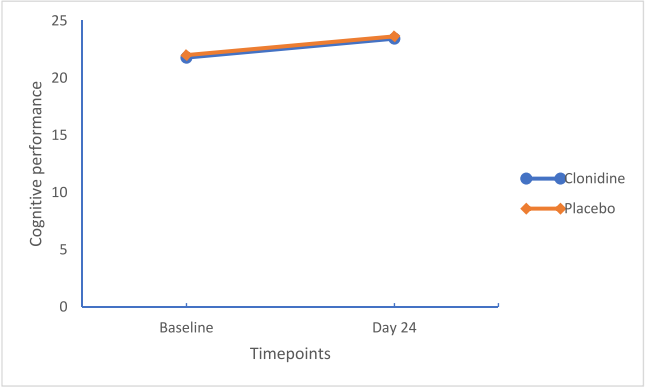

Fig. 4. Cognitive performance improved over time (medium effect size), irrespective from the study condition (trivial effect size). Points are means.

3.6. Correlations between mania, cognitive performance, and sleep quality at baseline, day 12 and day 24 (end of the study), separately for the clonidine and placebo condition

Table 5 provides the overview of the correlations.

3.6.1. Clonidine condition

At baseline, mania scores were unrelated to cognition and sleep at every time point.

Cognitive performance predicted a higher cognitive performance at day 24. Otherwise, no further statistically significant correlations were observed between mania and sleep quality at every time point.

Table 4
Overview of effect sizes; between group comparisons at the end of the study; within group comparisons from baseline to the end of the study.

	Effect size comparisons		
	Between the clonidine and placebo condition at the end of the study	Within the clonidine condition from baseline to the study end	Within the placebo condition from baseline to the study end
Mania severity (YMRS)	0.90 [L]	6.90 [L]	3.23 [L]
Sleep quality (PSQI)	0.67 [M]	2.04 [L]	0.93 [L]
Cognitive performance (MMSE)	0.06 [T]	0.47 [S]	0.48 [S]

Notes: [T] = trivial effect size; [S] = small effect size; [M] = medium effect size; [L] = large effect size.

Sleep quality was unrelated to mania and cognition at every time point.

At day 12 mania scores were unrelated to mania, sleep, and cognitive performance at every timepoint.

At day 24, higher mania scores were associated with a higher sleep disturbance; otherwise, no further statistically significant correlations were observed between mania, cognitive performance and sleep disturbances.

3.6.2. Placebo condition

At baseline, higher mania scores were associated with a lower cognitive performance at baseline. Otherwise, no further statistically significant correlations were observed between mania, cognitive performance and sleep disturbances.

A higher cognitive performance was associated with higher sleep disturbances at baseline and a higher cognitive performance at day 24.

As mentioned, sleep and cognition were related, but sleep was unrelated to mania and cognition at every time point.

At day 12, higher mania scores predicted higher mania scores and lower sleep disturbance at day 24.

At day 24, as mentioned, higher mania scores were predicted by higher mania scores at day 12.

A higher cognitive performance was associated with lower mania scores; no further statistically significant correlations were observed between mania, cognitive performance and sleep disturbances.

4. Discussion

The key findings of the present study were that among inpatients with diagnosed bipolar I disorder in an acute manic phase and undergoing standard medication treatment with lithium, adjuvant clonidine improved symptom severity and subjective sleep (medium to large effect sizes), while no further improvements were observed for cognitive performance, always compared to placebo. The present results expand upon the sparse and timely literature on the possible effect of adjuvant clonidine in the treatment of manic states in individuals with bipolar I disorder in three important ways: First, compared to previous studies (N's from 3 to 24), we assessed a larger sample size (N = 70); second, compared to previous studies (case studies; not-blind intervention studies with no control conditions), the present study was a double-blind, placebo-controlled clinical trial; third; compared to previous studies (assessment of mania scores), we assessed also participants' cognitive performance, as assessed by experts, along with subjective sleep quality. Overall, the pattern of results suggests that adjuvant clonidine to lithium should be considered to enhance the treatment speed among patients with bipolar I disorder and during their acute manic phase.

One hypothesis and two research questions were formulated and each of these is considered now in turn.

The hypothesis was that compared to placebo, adjuvant clonidine to lithium improved symptoms of mania intensity, as rated by experts, and data did confirm this (see Tables 2–4). At day 24, the last day of the study, improvements were about 4 points on the Young Mania Rating Scale (YMRS). As such, the present data confirm previous results (Giannini et al., 1986; Hardy et al., 1986; Maguire and Singh, 1987; Shen, 1986; Tudorache and Diacicov, 1991; Zubenko et al., 1984).

Table 5
Correlations between symptoms of mania, cognitive performance, and sleep at baseline, day 12 and day 24 (end of the study), separately for participants in the adjuvant clonidine condition or placebo condition.

Clonidine	Timepoints							
N = 36		Baseline			Day 12	Day 24		
		Mania	Cognition	Sleep	Mania	Mania	Cognition	Sleep
Baseline	Mania	–	.06	-.06	.19	-.06	.07	-.24
	Cognition	.06	–	.02	.10	-.13	.61***	.27
	Sleep	-.06	.02	–	-.00	.18	.01	.16
Day 12	Mania	.19	.10	-.00	–	.26	.09	.06
Day 24	Mania	-.06	-.13	.18		–	-.03	.46*
	Cognition	.07	.61***	.01	.09	-.03	–	.14
	Sleep	-.24	.27	.16	.06	.46**	.14	–
Placebo				Timepoints				
N = 34		Baseline			Day 12	Day 24		
		Mania	Cognition	Sleep	Mania	Mania	Cognition	Sleep
Baseline	Mania	–	-.33	.05	.31	.22	-.23	-.20
	Cognition	.33	–	.42*	.05	-.05	.53**	.03
	Sleep	.05	.42*	–	-.13	.02	.16	.29
Day 12	Mania	.31	.05	-.13	–	.68***	-.15	-.35*
Day 24	Mania	.22	-.05	.02	.68***	–	-.45**	-.02
	Cognition	-.23	.53***	.16	-.15	-.45***	–	-.23
	Sleep	-.20	.03	.29	-.35*	-.02	-.32	–

Notes: * = p < .05; ** = p < .01; *** = p < .001.

However, we expanded upon previous studies in two ways: the sample was quite larger and data were gathered from a double-blind, placebo-controlled clinical trial. As such we claim that the data quality is robust.

While the study design did not allow a thorough neurophysiological examination of the underlying mechanisms, to explain the favorable effect of clonidine, we refer to previous results. Schildkraut (in Hardy et al., 1986) claimed in his catecholamine hypothesis an increased noradrenergic concentration during a manic state. Next, clonidine is an antihypertensive stimulating the presynaptic alpha$_2$ central adrenergic receptor, and as such, clonidine reduces the release of noradrenaline on the synaptic cleft, and down-regulates cellular firing rates (Langer, 1974). Further, recurrent axonal and dendritic collaterals stimulate alpha$_2$ receptors, which branch back to inhibit the firing of their own cells (Roehrich and Gold, 1987).

The first exploratory research question was: Did adjuvant clonidine improve the cognitive performance, when compared to placebo, and the answer was no. As shown in Table 4, changes in the cognitive performance from baseline to day 24 within and between the two study conditions were trivial. Further, as shown in Table 5, associations between the cognitive performance and dimensions of mania and sleep were trivial in the clonidine condition. In the placebo condition, at day 24, a higher cognitive performance was associated with lower mania scores.

Overall, a gap between improvements of symptoms and of cognitive performance was observable. In our opinion, this pattern of results reflects well what is already known from longitudinal studies (Rosa et al., 2012; Tohen et al., 2000): Even in remission as regards symptoms, functional and cognitive impairment appeared to persist, such that functional and cognitive recovery was delayed, when compared to symptomatic recovery. Given this, we claim that already during the pharmacologic treatment of manic states cognitive performance lagged behind syndromal recovery.

The second exploratory research question was, if subjective sleep improved in the adjuvant clonidine condition, compared to the placebo condition, and the answer was yes. As shown in Tables 2–4, subjective sleep improved over time, but more so in the adjuvant clonidine condition. We note that improvements in both conditions were medium to large; as such, it appears difficult to draw conclusive answers as to if and to what extent the pharmacologic impact of clonidine was solely responsible for subjective sleep improvement. We note that clonidine was administered as a sleep-promoting medication in 9% out of 257 children with diagnosed attention-deficit/hyperactivity disorders (Efron et al., 2014). Given this, it remains undisclosed if and to what extent adjuvant clonidine might have been causally involved in improving sleep, or if and to what extent improvements of sleep should be rather understood as an epiphenomenon of improved symptoms of mania.

The quality of the data does not allow a deeper understanding of the underlying neurophysiological and psychological mechanisms. Further, the overview of correlations in Table 5 suggests that no straightforward and linear association between improved sleep, cognition and manic symptoms could be observed. However, in the clonidine condition, poor sleep quality and higher mania scores were associated at day 24, suggesting thus an overlap between experts' rated symptoms of mania and participants' subjective sleep quality.

Despite the novelty of the results, the following limitations should be considered. First, inclusion and exclusion criteria were such to assess individuals with bipolar I disorder without concomitant substance use, or without concomitant use of further stimulants and mood- and sleep-altering medications; however, experience of everyday clinical work with individuals with bipolar I disorder show that such "pure" individuals are the exception and not the standard. As such, transferability of the present results to everyday clinical work should be done with caution. Second, and relatedly, compared to those patients who were randomized, but did not begin the study, those who completed the study were older, had a higher education, were rather married and had a lower YMRS score at baseline. Thus, a positive selection bias could not fully be ruled out. Third, only about 16% of participants were females; this gender-ratio is at odds compared to the higher prevalence rates of bipolar I disorder among females compared to males, as reported in Carvalho et al. (2020). As such, the present sample again does not necessarily reflect the clinical reality. Fourth, the time frame of the study was set at 24 days; a longer-term assessment might have allowed further insights as regards progression of symptoms, cognition and sleep. Fifth, to assess the cognitive performance, we used the Mini Mental State Examination (MMSE) (Folstein et al., 1975), which is rather a coarse-grained screener; assessing dimensions of working memory, long-term memory of executive functions might have allowed a more detailed investigation of cognitive processes. Sixth, a major issue of individuals with bipolar I disorder is their psychosocial impairment; as such, it would have been interesting to investigate, if adjuvant clonidine impacted favorably on social behavior.

5. Conclusions

Over a time lapse of 24 days, symptoms of mania and subjective sleep improved, but more so in the adjuvant clonidine condition, compared to placebo. In contrast, cognitive improvements were modest, with no differences between adjunctive clonidine and placebo.

Declaration of competing interest

All authors declare no conflicts of interest.

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