Clinical Trial Protocol
Iranian Registry of Clinical Trials

07 Nov 2026

Title : The efficacy of amantadine as an adjunctive therapy in treating depression and cognitive impairment in patients with bipolar depression at Imam Hossein, Shariati, andImam Ali hospitals in Karaj a randomized double-blind placebo-controlled clinical trial

Protocol summary

Study aim
The aim of this study is to determine the efficacy of amantadine as an adjunctive therapy in improving depression and cognitive impairment in patients with bipolar depression.

Design
Double-blind, randomized, placebo-controlled, parallel-group clinical trial, phase 3, with 64 patients (32 per group), block randomization with block size of four, and allocation concealment by sealed envelopes.

Settings and conduct
The study will be conducted at psychiatry outpatient clinics of Imam Hossein, Shariati and Imam Ali hospitals in Karaj, Iran. Eligible patients will be randomized to amantadine or placebo. Participants, caregivers, investigators, outcome assessors and data analyst will be blinded. Identical capsules will be prepared by the hospital pharmacy.

Participants/Inclusion and exclusion criteria
Inclusion criteria: age 30 to 60 years; bipolar disorder type I or II in active depressive episode based on DSM-5-TR; literacy; Beck Depression Inventory-II score of 20 or higher; informed consent. Exclusion criteria: age outside 30 to 60 years; illiteracy; Beck score below 20; inappropriate serum lithium level; recent electroconvulsive therapy or substance use; amantadine hypersensitivity; active post-traumatic stress disorder, cluster B personality disorder or psychosis; active neurological, severe liver, renal or cardiovascular disease; pregnancy or breastfeeding; monoamine oxidase inhibitor or strong anticholinergic use; seizure history.

Intervention groups
Intervention group: lithium (serum level 0.8 to 1.2 milliequivalent per liter) plus amantadine 100 milligrams daily for 12 weeks. Control group: lithium plus placebo for 12 weeks.

Main outcome variables
Depression severity by Beck Depression Inventory-II; cognitive function by Neuropsychiatry Unit Cognitive Assessment Tool, Trail Making Test parts A and B, and Wisconsin Card Sorting Test; assessed at baseline, weeks 4, 8 and 12.

General information

Reason for update

Acronym

IRCT registration information
IRCT registration number: **IRCT20200317046801N3**
Registration date: **2026-11-06, 1405/08/15**
Registration timing: **prospective**

Last update: **2026-11-06, 1405/08/15**
Update count: **0**

Registration date
2026-11-06, 1405/08/15

Registrant information

Name
Rahim Badrfam

Name of organization / entity

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Iran (Islamic Republic of)

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Recruitment status
Not yet recruiting

Funding source

Expected recruitment start date
2026-12-22, 1405/10/01
Expected recruitment end date
2027-04-21, 1406/02/01
Actual recruitment start date
empty
Actual recruitment end date
empty
Trial completion date
empty

Scientific title
Title : The efficacy of amantadine as an adjunctive therapy in treating depression and cognitive impairment in patients with bipolar depression at Imam Hossein, Shariati, andImam Ali hospitals in Karaj a randomized double-blind placebo-controlled clinical trial

Public title
Effect of Amantadine as Adjunctive Therapy on Depression and Cognitive Impairment in Bipolar Depression
Purpose
Treatment
Inclusion/Exclusion criteria
Inclusion criteria:
Age between 30 and 60 years) Diagnosis of bipolar disorder type I or II in an active depressive episode based on DSM-5-TR criteria confirmed by two psychiatrists Ability to read and write BDI-II score ≥ 20 (active depression Written informed consent obtained from the patient and their guardian
Exclusion criteria:
Age < 30 or > 60 years Inability to read and write BDI-II score < 20 Inappropriate serum lithium level (>0.8 or <1.2 mEq/L) in patients receiving lithium ECT treatment within the past 2 months Alcohol or illicit substance use within the past 3 months (confirmed by urine test) Known hypersensitivity to amantadine Active major comorbid psychiatric disorder: Active PTSD, Cluster B personality disorder (especially borderline and antisocial), Active psychosis (schizophrenia, schizoaffective disorder) Active neurological diseases (epilepsy, Parkinson's disease, MS, dementia) Severe liver disease (Child-Pugh C), renal failure (GFR < 30 ml/min), unstable cardiovascular disease Pregnancy, breastfeeding, or lack of effective contraception Concomitant use of MAO inhibitors or strong anticholinergic drugs (e.g., trihexyphenidyl) History of seizure or epilepsy
Age
From **30 years** old to **60 years** old
Gender
Both

Phase
3
Groups that have been masked

- Participant
- Care provider
- Investigator
- Outcome assessor
- Data analyser

Sample size
Target sample size: **64**
Randomization (investigator's opinion)
Randomized
Randomization description
Randomization will be performed using a block randomization method with fixed block sizes of four (1:1 allocation ratio). The unit of randomization is the individual patient. The randomization sequence will be generated by a statistician independent of the research team using computer-generated random numbers (e.g., Random Allocation Software). Allocation concealment will be ensured using sequentially numbered, opaque, sealed envelopes (SNOSE) prepared by the same independent person. Each envelope will contain the allocation code (amantadine or placebo) and will be opened by the clinical investigator only after the participant has been enrolled, completed baseline assessments, and signed the informed consent form. No stratification will be applied.
Blinding (investigator's opinion)
Double blinded
Blinding description
This study is a double-blind trial. Participants, clinical caregivers (psychiatrists and nurses responsible for patient care), the principal investigator and research team, outcome assessors, and the data analyst will all be blinded to treatment allocation. Amantadine and placebo will be provided as identical capsules in terms of appearance, size, color, and packaging, prepared by the hospital pharmacy under a code. Neither the participants nor any member of the research team will know which treatment a participant is receiving. The randomization codes will be kept by an independent person outside the research team and will be revealed only after the statistical analysis is complete, or in case of a medical emergency requiring unblinding. The data analyst will receive coded group labels (A/B) and will perform the analysis without knowledge of the actual treatment.
Placebo
Used
Assignment
Parallel
Other design features
This is a randomized, double-blind, placebo-controlled, parallel-group clinical trial with a 1:1 allocation ratio. Block randomization (block size of 4) will be used. Participants will receive either amantadine 100 mg daily or placebo, in addition to standard lithium therapy, for 12 weeks. The primary outcome measures will be assessed at baseline and weeks 4, 8, and 12.

Secondary Ids

empty

Ethics committees

1

Ethics committee
Name of ethics committee

Ethics committee of Alborz University of Medical Sciences

Street address
Faculty of Medicine, above the University of Art, West Bu Ali Street, s,Nabuwwat,karaj,,

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Approval date
2026-10-24, 1405/08/02

Ethics committee reference number
IR.ABZUMS.REC.1405.266

Health conditions studied

1

Description of health condition studied
Bipolar depression

ICD-10 code
F31.3

ICD-10 code description
Bipolar disorder, current episode depressed, mild or moderate severity

Primary outcomes

1

Description
Severity of depression

Timepoint
At baseline (before intervention) and at weeks 4, 8 and 12 after starting the intervention

Method of measurement
Beck Depression Inventory, second edition

2

Description
Cognitive function

Timepoint
At baseline (before intervention) and at weeks 4, 8 and 12 after starting the intervention

Method of measurement
Neuropsychiatry Unit Cognitive Assessment Tool, Trail Making Test parts A and B, and Wisconsin Card Sorting Test

Secondary outcomes

1

Description
Depression response rate, defined as a 50 percent or greater reduction in Beck Depression Inventory second edition score from baseline to week 12

Timepoint
At baseline (before intervention) and at week 12 after starting the intervention

Method of measurement
Beck Depression Inventory, second edition

2

Description
Depression remission rate, defined as Beck Depression Inventory second edition score below 10 at week 12

Timepoint
At week 12 after starting the intervention

Method of measurement
Beck Depression Inventory, second edition

3

Description
Cognitive response rate, defined as a 50 percent or greater increase in Neuropsychiatry Unit Cognitive Assessment Tool score from baseline to week 12, or a 50 percent reduction in Trail Making Test part B duration, or improvement in Wisconsin Card Sorting Test performance

Timepoint
At baseline (before intervention) and at week 12 after starting the intervention

Method of measurement
Neuropsychiatry Unit Cognitive Assessment Tool, Trail Making Test parts A and B, and Wisconsin Card Sorting Test

4

Description
Frequency of adverse drug effects

Timepoint
At weeks 4, 8 and 12 after starting the intervention

Method of measurement
Clinical interview and physical examination by the treating psychiatrist

Intervention groups

1

Description
Intervention group: Intervention group: Lithium carbonate with a target serum level of 0.8 to 1.2 milliequivalent per liter (starting dose of 300 milligrams three times daily, titrated by the treating psychiatrist to a final dose of 900 to 1200 milligrams per day) plus amantadine capsule 100 milligrams daily for 12 weeks. Amantadine and placebo capsules are identical in appearance, size, color and packaging and are prepared by the hospital pharmacy. Patients take one capsule orally each day.

Category
Treatment - Drugs

2

Description
Control group: Control group: Lithium carbonate with a

target serum level of 0.8 to 1.2 milliequivalent per liter (starting dose of 300 milligrams three times daily, titrated by the treating psychiatrist to a final dose of 900 to 1200 milligrams per day) plus placebo capsule daily for 12 weeks. Placebo capsules are identical in appearance, size, color and packaging to amantadine capsules and are prepared by the hospital pharmacy. Patients take one capsule orally each day.

Category
Treatment - Drugs

Recruitment centers

1

Recruitment center
Name of recruitment center
Imam Hossein Hospital
Full name of responsible person
Rahim Badrfam
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Emam Hossein Hospital, Mansour Bakht St., 300 Meters Below Refah Store, Imam Khomeini Blvd. (Main Mohammadshahr Road), Karaj, Alborz, Iran
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2

Recruitment center
Name of recruitment center
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Full name of responsible person
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Recruitment center
Name of recruitment center
Imam Ali Hospital
Full name of responsible person
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Sponsors / Funding sources

1

Sponsor
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Grant name
Grant code / Reference number
Is the source of funding the same sponsor organization/entity?
Yes
Title of funding source
Karaj University of Medical Sciences
Proportion provided by this source
100
Public or private sector
Public
Domestic or foreign origin
Domestic
Category of foreign source of funding
empty
Country of origin
Type of organization providing the funding
Academic

Person responsible for general inquiries

Contact
Name of organization / entity
Karaj University of Medical Sciences
Full name of responsible person

Rahim Badrfam

Position
psychiatrist and researcher

Latest degree
Specialist

Other areas of specialty/work
Psychiatrics

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Person responsible for scientific inquiries

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Position
Psychiatrist and Researcher

Latest degree
Specialist

Other areas of specialty/work
Psychiatrics

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Person responsible for updating data

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Position
Psychiatrist and Researcher

Latest degree
Specialist

Other areas of specialty/work
Psychiatrics

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Sharing plan

Deidentified Individual Participant Data Set (IPD)
Yes - There is a plan to make this available

Study Protocol
Yes - There is a plan to make this available

Statistical Analysis Plan
Yes - There is a plan to make this available

Informed Consent Form
Yes - There is a plan to make this available

Clinical Study Report
Yes - There is a plan to make this available

Analytic Code
No - There is not a plan to make this available

Data Dictionary
Yes - There is a plan to make this available

Title and more details about the data/document
De-identified individual participant data (IPD) underlying the primary and secondary outcomes, study protocol, statistical analysis plan, informed consent form, analysis codes, and data dictionary.

When the data will become available and for how long
Access will begin 6 months after publication of the main results and will remain available for 5 years.

To whom data/document is available
Researchers affiliated with academic or scientific institutions.

Under which criteria data/document could be used
Data will be shared for non-commercial research purposes, including re-analysis and verification of published results. Requesters must sign a data access agreement and agree not to attempt re-identification of participants.

From where data/document is obtainable
Requests should be sent to the principal investigator, Dr. Rahim Badrfam, at the Clinical Research Development Unit of Imam Hossein Hospital, Alborz University of Medical Sciences, Karaj, Iran. Email:rbadrfam@gmail.com

What processes are involved for a request to access data/document
The request will be reviewed by the principal investigator and the Clinical Research Development Unit within 2 weeks. If approved, a data access agreement will be sent to the requester. Upon signing the agreement, the de-identified data will be transferred securely within 4 weeks.

Comments