Clinical Trial Protocol
Iranian Registry of Clinical Trials

08 Nov 2026

Comparative Effectiveness of Atomoxetine and Amantadine in the Level of consciousness of Patients with Traumatic Brain Injury: A Randomized Controlled Trial

Protocol summary

Study aim

To evaluate and compare the effectiveness of atomoxetine and amantadine, versus placebo, in improving functional recovery during a 12-week intervention period in patients with moderate to severe traumatic brain injury.

Design

A controlled, triple-blind, randomized, phase 3 clinical trial with parallel groups on 306 patients. The rand function of Excel software was used for randomization.

Settings and conduct

This trial will evaluate the effectiveness of atomoxetine, amantadine, and placebo in patients with TBI attending Imam Khomeini Hospital in Sari during a 12-week intervention period. The study will be conducted in a triple-blind manner: participants, clinical assessors, and data analysts will be unaware of treatment allocation. All capsules will be in identical packages. Drug packages will be coded by the pharmacy.

Participants/Inclusion and exclusion criteria

Inclusion criteria: Age 18 to 65 years Recorded history of moderate to severe TBI Time since injury: 1 to 12 months Persistent functional disability Ability to give informed consent Medically stable Exclusion criteria: History of previous neurological disease unrelated to TBI Recent or current substance abuse Use of medications with contraindications and use of medications that interact with atomoxetine or amantadine Severe neuropsychiatric disorders Known prior hypersensitivity to atomoxetine or amantadine Uncontrolled cardiovascular disease Severe hepatic or renal impairment Pregnancy or lactation

Intervention groups

Intervention group 1: 20 mg atomoxetine twice daily (one week), then 40 mg twice daily (weeks 2 to 12) Intervention group 2: 100 mg amantadine twice daily (two weeks), 150 mg (week 3), 200 mg if tolerated (weeks 4 to 12) Control group: Placebo in capsule form and similar schedule

Main outcome variables

Functional status, cognitive function assessment, behavioral assessments, safety assessments including vital signs

General information

Reason for update

Acronym

IRCT registration information

IRCT registration number: **IRCT20221101056357N2**
Registration date: **2026-05-12, 1405/02/22**
Registration timing: **prospective**

Last update: **2026-05-12, 1405/02/22**
Update count: **0**

Registration date

2026-05-12, 1405/02/22

Registrant information

Name

sajad najafi

Name of organization / entity

Country

Iran (Islamic Republic of)

Phone

+98 11 3336 1700

Email address

s.najafi@mazums.ac.ir

Recruitment status

Recruitment complete

Funding source

Expected recruitment start date

2026-05-17, 1405/02/27

Expected recruitment end date

2026-08-20, 1405/05/29

Actual recruitment start date
empty
Actual recruitment end date
empty
Trial completion date
empty

Scientific title
Comparative Effectiveness of Atomoxetine and Amantadine in the Level of consciousness of Patients with Traumatic Brain Injury: A Randomized Controlled Trial

Public title
Comparative Effectiveness of Atomoxetine and Amantadine in the Level of consciousness of Patients with Traumatic Brain Injury: A Randomized Controlled Trial
Purpose
Treatment
Inclusion/Exclusion criteria
Inclusion criteria:
Age 18 to 65 years Documented history of moderate to severe traumatic brain injury (TBI) (GCS ≤ 12 or evidence of intracranial injury on CT or MRI imaging) Recovery time from injury: 1 to 12 months Persistent functional disability (DRS ≥ 6 from baseline) Ability to give informed consent Medical stability in patients undergoing treatment and evaluation outside the hospital
Exclusion criteria:
History of previous neurological conditions unrelated to TBI (such as epilepsy, stroke, dementia) Recent or current (within the past three months) substance abuse according to DSM-5 criteria Use of contraindicated medications such as monoamine oxidase inhibitors (MAOIs), stimulants or norepinephrine reuptake inhibitors (e.g., methylphenidate, bupropion), and use of medications that interact with atomoxetine or amantadine Having severe neuropsychiatric disorders (such as severe psychosis, severe major depression, or suicidal thoughts requiring immediate treatment) Known prior allergy to atomoxetine or amantadine Having uncontrolled cardiovascular disease (such as significant arrhythmia, recent MI, or severe hypertension) Having severe liver or kidney disorders Pregnancy or breastfeeding
Age
From **18 years** old to **65 years** old
Gender
Both

Phase
3
Groups that have been masked

- Participant
- Care provider
- Investigator
- Outcome assessor
- Data analyser
- Data and Safety Monitoring Board

Sample size
Target sample size: **306**
Randomization (investigator's opinion)
Randomized
Randomization description
This randomized, controlled trial will use a parallel group design with three arms: atomoxetine, amantadine, and placebo. Eligible participants will be randomly assigned in a 1:1:1 ratio using a computerized randomization sequence. Block randomization with varying block sizes (such as blocks of 6 or 9) will be used to maintain allocation concealment and ensure a balanced distribution of participants across the three study arms during the sampling period. The randomization sequence will be performed by an independent biostatistician who is not involved in the sampling or patient assessment. Allocation will be performed by the hospital pharmacy or a central randomization center, which will allocate participants based on the randomization list after enrollment is confirmed.
Blinding (investigator's opinion)
Triple blinded
Blinding description
. The study will be triple-blind: participants, clinical assessors, and data analysts will all be unaware of treatment allocation. To ensure integrity of blinding, active treatments (amantadine and atomoxetine) and placebo will be encapsulated in identical gelatin capsules to mask differences in size, color, or flavor. All capsules will be packaged in identical packages. The dosing schedule will be standardized across groups to minimize the risk of blinding due to dietary differences. Drug packages will be coded by the pharmacy with unique identifiers related to the treatment group but without revealing the contents. Only the pharmacy will have the decryption key. The study team (including prescribing physicians, outcome assessors, and coordinators) will not have access to the randomization list or the decryption key until the trial is over and the database is locked. In the event of an emergency, the treating physician may request a participant's allocation to be determined through a secure process, but such cases will be recorded and reported to the trial supervisor and ethics board.
Placebo
Used
Assignment
Parallel
Other design features

Secondary Ids

empty

Ethics committees

1

Ethics committee
Name of ethics committee
Ethics Committee in Organizational Research, Imam (RA) Teaching and Medical Hospital, Sari
Street address

Amir Mazandarani Blvd

City
Sari

Province
Mazandaran

Postal code
33131 - 48166

Approval date
2025-08-16, 1404/05/25

Ethics committee reference number
IR.MAZUMS.IMAMHOSPITAL.REC.1404.048

Health conditions studied

1

Description of health condition studied
Assessing the level of consciousness

ICD-10 code
S06.0X0

ICD-10 code description
Concussion without loss of consciousness

Primary outcomes

1

Description
Functional status

Timepoint
At weeks 0, 4, 8, and 12

Method of measurement
Disability Rating Scale

Secondary outcomes

1

Description
Cognitive function assessment

Timepoint
At weeks 0, 4, 8, and 12

Method of measurement
Using the Stroop Color-Word Test and MoCA

2

Description
Behavioral assessments

Timepoint
Every two weeks

Method of measurement
Using ASRS and WCFS

3

Description
Safety assessments including vital signs

Timepoint
In week 2

Method of measurement
ECG

Intervention groups

1

Description
Intervention group: Atomoxetine, manufactured in Iran by Tehran Darou Pharmaceutical Company, will be given 20 mg twice daily (7 am and 12 pm) during the first week (1st week BD mg 20). After 7 days, 40 mg will be given twice daily for the next 11 weeks (weeks 2 to 12, BD mg 40).

Category
Treatment - Drugs

2

Description
Intervention group: Amantadine, manufactured in Iran, Tehran Darou Pharmaceutical Company Patients will receive 100 mg twice daily during weeks one and two. If tolerated, this will be increased to 150 mg BD during week three. This will be increased to 200 mg BD during weeks four to twelve, if tolerated and DRS responsive. If a participant cannot tolerate the full dose, they may remain at 100 or 150 mg daily, depending on their response and tolerance, as individual dose adjustment is part of the protocol.

Category
Treatment - Drugs

3

Description
Control group:Placebo mg 20, product of Iran, Tehran Pharmaceutical Company, will receive the drug twice a day (7 am and 12 pm) during the first week (first week BD mg 20). After 7 days, they will receive mg 40 twice a day for the next 11 weeks (weeks 2 to 12, BD mg 40).

Category
Placebo

Recruitment centers

1

Recruitment center

Name of recruitment center
Imam Khomeini Hospital

Full name of responsible person
Sajad Najafi

Street address
Neurosurgery Department, Imam Khomeini Hospital, Amir Mazandarani Blvd.

City
Sari

Province
Mazandaran

Postal code
48166-33131

Phone
+98 11 3336 1630

Fax

+98 11 3336 1630

Email

drsajjad_najafi@yahoo.com

Sponsors / Funding sources

1

Sponsor

Name of organization / entity

Mazandaran University of Medical Sciences

Full name of responsible person

Ahmadali Enayati

Street address

Moalem Square

City

Sari

Province

Mazandaran

Postal code

۴۸۱۵۷۳۳۹۷۱

Phone

+98 11 3325 7230

Email

ahmadali_enayati@yahoo.com

Grant name

Grant code / Reference number

Is the source of funding the same sponsor organization/entity?

Yes

Title of funding source

Mazandaran 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

Mazandaran University of Medical Sciences

Full name of responsible person

Sajad Najafi

Position

Assistant Professor

Latest degree

Specialist

Other areas of specialty/work

Neurosurgery

Street address

Neurosurgery Department, Imam Khomeini Hospital, Amir Mazandarani Blvd.

City

Sari

Province

Mazandaran

Postal code

48166-33131

Phone

+98 11 3336 1630

Fax

+98 11 3336 1630

Email

drsajjad_najafi@yahoo.com

Person responsible for scientific inquiries

Contact

Name of organization / entity

Mazandaran University of Medical Sciences

Full name of responsible person

Sajad Najafi

Position

Assistant Professor

Latest degree

Specialist

Other areas of specialty/work

Neurosurgery

Street address

Neurosurgery Department, Imam Khomeini Hospital, Amir Mazandarani Blvd.

City

Sari

Province

Mazandaran

Postal code

48166-33131

Phone

+98 11 3336 1630

Fax

+98 11 3336 1630

Email

drsajjad_najafi@yahoo.com

Person responsible for updating data

Contact

Name of organization / entity

Mazandaran University of Medical Sciences

Full name of responsible person

سجاد نجفی

Position

Assistant Professor

Latest degree

Specialist

Other areas of specialty/work

Neurosurgery

Street address

Neurosurgery Department, Imam Khomeini Hospital, Amir Mazandarani Blvd.

City

Sari

Province

Mazandaran

Postal code

48166-33131

Phone

+98 11 3336 1630

Fax

+98 11 3336 1630

Email

drsajjad_najafi@yahoo.com

Sharing plan

Deidentified Individual Participant Data Set (IPD)

Undecided - It is not yet known if there will be a plan to make this available

Study Protocol

Undecided - It is not yet known if there will be a plan to make this available

Statistical Analysis Plan

Undecided - It is not yet known if there will be a plan to make this available

Informed Consent Form

Undecided - It is not yet known if there will be a plan to make this available

Clinical Study Report

Undecided - It is not yet known if there will be a plan to make this available

Analytic Code

Undecided - It is not yet known if there will be a plan to make this available

Data Dictionary

Undecided - It is not yet known if there will be a plan to make this available