Clinical Trial Protocol
Iranian Registry of Clinical Trials

07 Nov 2026

Evaluation and comparison of efficacy of atropine eye drops and ipratropium bromide oral spray and amitriptyline tablet in the management of clozapine-induced sialorrhea in patients with refractory schizophrenia using the TNHS(Toronto Nocturnal in the management of clozapine-induced sialorrhea in patients with refractory schizophrenia using the TNHS(Toronto Nocturnal Hypersalivation) scale Hypersalivation) scale

Protocol summary

Study aim

Evaluation and comparison of efficacy of atropine eye drops and ipratropium bromide oral spray and amitriptyline tablet in the management of clozapine-induced sialorrhea

Design

Clinical trial without control group and in parallel and one-way blind and randomized by the following method and in phase 2 for six months cross-sectionally on schizophrenic patients with DSM-V criterion diagnosis. For random allocation, the quadruple random permutation block method is used. A represents the person receiving the atropine drop and B represents the person receiving the spray Is ipratropium. The total number of 4 permutation block states is equal to 6 (BABA, ABAB, BAAB, ABBA, BBAA, AABB (; we assign 0 to 9 to each of the states (using a random number table).

Settings and conduct

In this cross-sectional study, patients with schizophrenia were randomly assigned to Imam Reza Clinic, Ibn Sina Hospital, and Hafez Hospital. For one month, each patient should be evaluated according to the TNHS scale for the management of clozapine-induced sialorrhea. It should be noted that the study is a single-blind study. In this way, the medicines are given to the doctor in numbered envelopes, then he gives the medicine to the patient without knowing the contents of the envelopes.

Participants/Inclusion and exclusion criteria

Patients between the ages of 18 and 65 with a diagnosis of schizophrenia without comorbid conditions such as Parkinson's or cerebral palsy that cause sialorrhea, as well as no pregnancy and lactating.

Intervention groups

In this study, patients with schizophrenia were randomly assigned to take one of the drugs amitriptyline, atropine drops, and ipratropium bromide nasal spray for one month according to the TNHS scale are supposed to be evaluated.

Main outcome variables

Reduction of clozapine-induced sialorrhea through intervention of atropine drops, ipratropium spray and amitriptyline tablets

General information

Reason for update

Acronym

CIH

IRCT registration information

IRCT registration number: **IRCT20211110053031N1**
Registration date: **2022-06-14, 1401/03/24**
Registration timing: **prospective**

Last update: **2022-06-14, 1401/03/24**
Update count: **0**

Registration date

2022-06-14, 1401/03/24

Registrant information

Name

Fatema Mohammadgholizad

Name of organization / entity

Country

Iran (Islamic Republic of)

Phone
+98 44 3344 3294
Email address
pha.fa.chess@gmail.com

Recruitment status
Recruitment complete
Funding source

Expected recruitment start date
2022-07-24, 1401/05/02
Expected recruitment end date
2023-01-21, 1401/11/01
Actual recruitment start date
empty
Actual recruitment end date
empty
Trial completion date
empty

Scientific title
Evaluation and comparison of efficacy of atropine eye drops and ipratropium bromide oral spray and amitriptyline tablet in the management of clozapine-induced sialorrhea in patients with refractory schizophrenia using the TNHS(Toronto Nocturnal in the management of clozapine-induced sialorrhea in patients with refractory schizophrenia using the TNHS(Toronto Nocturnal Hypersalivation) scale Hypersalivation) scale

Public title
Evaluation and comparison of efficacy of atropine eye drops and ipratropium bromide oral spray and amitriptyline tablet in the management of clozapine-induced sialorrhea
Purpose
Treatment
Inclusion/Exclusion criteria
Inclusion criteria:
Patients aged 18 to 65 years with a diagnosis of schizophrenia according to the DSM-V criteria Patients should be receiving clozapine for at least 30 days Patients should have a minimum score of 2 on the TNHS scale for sialorrhea
Exclusion criteria:
Development of allergies or history of allergies to amitriptyline, atropine and ipratropium bromide Has an underlying disease such as Parkinson's or cerebral palsy that causes sialorrhea The patient has problems and comorbidities such as untreated constipation or urinary retention or bladder obstruction Concomitant use of drugs such as tricyclic antidepressants and atropine and ipratropium bromide and other anticholinergic drugs Breastfeeding and pregnancy History of diseases such as myasthenia gravis, seizures, cardiac arrhythmias, glaucoma, pyloric obstruction, prostate hypertrophy, renal failure, severe autonomic dysfunction, mental retardation, and paralytic paralysis
Age
From **18 years** old to **65 years** old
Gender
Both

Phase
2
Groups that have been masked

- Care provider

Sample size
Target sample size: **1**
Randomization (investigator's opinion)
Randomized
Randomization description
For random allocation, the quadruple random permutation block method is used. A represents the person receiving the atropine drop and B represents the person receiving the spray Is ipratropium. The total number of 4 permutation block states is 6 (BABA, ABAB, BAAB, ABBA, BBAA, AABB; you assign 0 to 9 to each of the states (using a random number table). And then we produce 12 blocks of 4 (12 * 4 = 48) until 48 people are randomly assigned to two groups.
Blinding (investigator's opinion)
Single blinded
Blinding description
The study is a blind. In this way, only the treating physician does not know what kind of medicine he prescribes, and thus the medicines are placed in numbered envelopes and given to patients.
Placebo
Not used
Assignment
Parallel
Other design features

Secondary Ids

empty

Ethics committees

1

Ethics committee
Name of ethics committee
Ethics committee of Shiraz University of Medical Sciences
Street address
Vice-Chancellor for Research, Shiraz University of Medical Sciences, Zand Blvd., Shiraz, Iran
City
Shiraz
Province
Fars
Postal code
711345-1978
Approval date
2021-11-16, 1400/08/25
Ethics committee reference number
IR.SUMS.REC.1400.619

Health conditions studied

1

Description of health condition studied
Clozapine-resistant schizophrenic patients with clozapine-induced sialorrhea
ICD-10 code
F20
ICD-10 code description
Schizophrenia

Primary outcomes

1

Description
Effectiveness score of amitriptyline in reducing clozapine-induced sialorrhea according to TNHS (Toronto Nocturnal Hypersalivation scale)
Timepoint
At the beginning of the study, then daily for 7 days, then on days 14, 21 and 28
Method of measurement
Toronto Nocturnal Hypersalivation scale

2

Description
The effectiveness of atropine eye drops in reducing clozapine-induced sialorrhea according to the TNHS Toronto Nocturnal Hypersalivation Scale
Timepoint
At the beginning of the study, then daily for 7 days, then on days 14, 21 and 28
Method of measurement
Toronto Nocturnal Hypersalivation scale

3

Description
Effective score of ipratropium bromide nasal spray in reducing clozapine-induced sialorrhea according to TNHS (Toronto Nocturnal Hypersalivation scale)
Timepoint
At the beginning of the study, then daily for 7 days, then on days 14, 21 and 28
Method of measurement
TNHS (Toronto Nocturnal Hypersalivation scale)

Secondary outcomes

empty

Intervention groups

1

Description
Intervention group: In this group, patients are supposed to receive amitriptyline tablets from Iran Daroo Company at a dose of 25 mg first, and if the clozapine-induced sialorrhea complication does not improve with this dose of amitriptyline, then the dose of amitriptyline can be increased to 100 mg, Administered overnight before bedtime.
Category
Treatment - Drugs

2

Description
Control group: In this group, patients are supposed to use 1% atropine eye drops sublingually from Sinadaru company as one drop three times a day, and if the patient has sialorrhea over night, he can take an extra drop Dissolved in a glass of water and gargle and spill it out. The maximum dose is two drops three times per day.
Category
Treatment - Drugs

3

Description
Intervention group: In this group, patients are supposed to use 0.03% ipratropium bromide nasal spray as one puff twice a day sublingually. If sialorrhea is not controlled, the maximum dose that can be used is two puffs twice a day.
Category
Treatment - Drugs

Recruitment centers

1

Recruitment center
Name of recruitment center
Ebnesina hospital
Full name of responsible person
Fatemeh Mohammadgholizad
Street address
Shiraz, Hafez St., next to 13 Aban Park, Ibn Sina Medical Educational Center, Shiraz
City
Shiraz
Province
Fars
Postal code
۱۴۳۳۶ - ۷۱۳۴۸
Phone
+98 71 3228 9601
Email
pha.fa.chess@gmail.com

2

Recruitment center
Name of recruitment center
Imam Reza clinic
Full name of responsible person
Fatemeh Mohammadgholizad
Street address
Shiraz, Namazi Square, next to Namazi Hospital, Imam Reza (AS) Specialized and Sub-Specialized Clinic
City

Shiraz

Province
Fars

Postal code
71348-14734

Phone
+98 71 3212 7000

Email
pha.fa.chess@gmail.com

3

Recruitment center

Name of recruitment center
Hafez hospital

Full name of responsible person
Fatemeh Mohammadgholizad

Street address
Shiraz, Chamran St., Abivardi beginning, Hafez Educational and Medical Center

City
Shiraz

Province
Fars

Postal code
۷۱۹۴۶۳۴۷۸۶

Phone
+98 71 3647 9531

Email
pha.fa.chess@gmail.com

Sponsors / Funding sources

1

Sponsor

Name of organization / entity
Shiraz University of Medical Sciences

Full name of responsible person
Mahtab Memarpour

Street address
Shiraz University of Medical Sciences, Next to red Crescent, Zand street, Shiraz

City
Shiraz

Province
Fars

Postal code
71348-14336

Phone
+98 71 3235 7282

Email
memarpour@sums.ac.ir

Grant name

Grant code / Reference number

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

Title of funding source
Shiraz 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
Shiraz University of Medical Sciences

Full name of responsible person
Iman Karimzadeh

Position
Associated professor

Latest degree
Ph.D.

Other areas of specialty/work
Medical Pharmacy

Street address
Roknabad, Shiraz 5Km, Karafarin St., Faculty of Pharmacy

City
Shiraz

Province
Fars

Postal code
7146864685

Phone
+98 71 3242 4127

Email
karimzadehiman@yahoo.com

Person responsible for scientific inquiries

Contact

Name of organization / entity
Shiraz University of Medical Sciences

Full name of responsible person
Iman Karimzadeh

Position
Associate Professor

Latest degree
Ph.D.

Other areas of specialty/work
Medical Pharmacy

Street address
Roknabad, Shiraz 5Km, Karafarin St., Faculty of Pharmacy

City
Shiraz

Province
Fars

Postal code
7146864685

Phone
+98 71 3242 4127

Email
karimzadehiman@yahoo.com

Person responsible for updating data

Contact

Name of organization / entity
Shiraz University of Medical Sciences

Full name of responsible person
Fatema Mohammadgholizad

Position
Clinical pharmacotherapy candidate

Latest degree
Specialist

Other areas of specialty/work
Medical Pharmacy

Street address
Chamran Blvd.,Abiverdi street.,Gholestan dormitory

City
Shiraz

Province
Fars

Postal code
7193613311

Phone
+98 71 3647 4332

Fax

Email
pha.fa.chess@gmail.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
No - There is not 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