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REVIEW

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Cycloserine-induced psychosis in patients with drug-resistant tuberculosis: a systematic review of case reports

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Abstract

Objectives To describe the clinical characteristics and outcomes of cycloserine (CS)-induced psychosis in adults diagnosed with drug-resistant tuberculosis (DR-TB).

Materials and methods A systematic review of case reports was carried out according to PRISMA guidelines. Subsequently, information was extracted concerning sociodemographic variables, clinical characteristics of psychosis, treatment, and clinical outcomes, as well as the quality of the articles using a standardized tool (Joanna Briggs Institute—JBI—Case Reports Tool).

Results Of 3416 articles, 20 reports from seven countries were included, encompassing 22 patients (68.18% male participants, mean age: 31.45 ± 10.88 years). Delusions (68.2%, primarily persecutory) were the most frequent psychotic symptom. The median duration of the psychotic episode was 13 days (interquartile range: 35). Other frequently appearing symptoms in CS-induced psychosis were aggressiveness (68.2%), insomnia (59.1%), hallucinations (54.5%), incoherent/disorganized speech (45.5%), and irritability (45.5%). After antipsychotic treatment (81.81% of the reported cases were treated with at least one antipsychotic), 95.5% presented improvement, while 4.54% died by suicide. Finally, after the quality assessment of studies using the JBI tool, 85% of the articles showed a low risk of bias.

Conclusions CS-induced psychosis is a rare presentation, generally of short duration, that includes delusions (mostly persecutory) as its main psychotic symptom and shows mostly a symptom improvement after medical treatment.

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Keywords Cycloserine, Systematic review, Psychoses, Substance-induced, Tuberculosis, Multidrug-resistant, Extensively drug-resistant tuberculosis

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Introduction

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis*, currently having one of the highest mortality rates [1–3] and causing the death of approximately 1.3 million people worldwide [4–6]. In the last decades, a growing issue concerning this infectious disease is the increasing number of cases resistant to first-line antibiotics (i.e., rifampicin and isoniazid), which also represents higher costs for health services and a higher burden of disease [7, 8]. As a solution to the treatment of TB-resistant patients, evidence-based guidelines and world medical societies contemplated different treatment options, including extended-spectrum antibiotics with robust effectiveness, such as cycloserine (D-4-amino-3-isoxazolidine) [9–11]. The latter competitively inhibits two essential enzymes for the synthesis of the cell wall of *Mycobacterium tuberculosis*, exerting its antibiotic effect [12, 13]. However, the therapy with cycloserine (CS) also correlates with the appearance of psychotic symptoms, since CS can penetrate the brain–blood barrier, inhibits GABA-transferase, and interacts with *N*-methyl-D-aspartate (NMDA) receptors in the central nervous system [14–16]. Although CS may induce psychosis during treatment, its appearance is considered a non-frequent condition among drug-resistant (DR) TB patients [17–19]. For instance, a longitudinal study reported that in a group of 144 patients with multidrug-resistant (MDR-TB) treated with CS, four patients (8%) developed psychosis [12].

Moreover, a pharmacological safety and surveillance study estimated that the global combined prevalence of adverse drug reactions due to CS was 9%, and 5.7% for psychiatric disorders [17]. In addition, of the 445 safety reports of cases reported since 1970 attributed to CS, 75% were attributed to neuropsychiatric conditions, and of these, 14% related to psychosis [17], considered in this study also a not very frequent condition. Since the appearance of induced psychosis during a CS treatment is very low, most published studies concerning cycloserine-induced psychosis are restricted to case reports. Although case reports are unsuitable for inferring causality and cannot be extrapolated, they often provide essential aspects missing in population studies, especially in rare conditions [20], such as cycloserine-induced psychosis. In this sense, conducting a systematic review of case reports would help summarize clinical and therapeutical aspects of CS-induced psychosis in MDR-TB over time [20–23]. Therefore, the main objective of this study is to perform a systematic review to describe the main clinical characteristics, comorbidities, therapy, and clinical outcomes of the cases reported in the literature on cycloserine-induced psychosis in DR-TB adult patients.

Materials and methods

Study selection criteria

First, we included studies that met the following inclusion criteria: (1) case reports of patients over 18 years; (2) patients with the diagnosis of DR-TB (MDR-TB or extreme drug-resistant TB-XDR-TB-); (3) patients with DR-TB, which have developed psychosis due to the administration of CS; (4) case report articles, case series and letters to the editor describing TB patients with CS-induced psychosis including at least the following criteria: socioeconomic data, clinical presentation and description of the psychosis, course of the illness, psychosis treatment, and clinical outcomes of the psychosis treatment.

In addition, we excluded studies if the reported participants were under 18 years, did not have TB, or were not in treatment with CS. Furthermore, we excluded studies with patients with a previous history of schizophrenia spectrum disorders or bipolar disorder, with illegal substance misuse during CS treatment, and with a current disease that could explain the induced psychosis (e.g., cerebral tumor or stroke) during the CS treatment. Studies that were not case report articles, case series articles, or manuscripts describing TB patients with CS-induced psychosis were excluded. Finally, articles that were not available as full-text were also excluded.

Search strategies

First, a systematic literature search was conducted between 07/23/2022 and 08/24/2022 in different scientific literature databases, including MEDLINE (PubMed, National Center for Biotechnology Information, National Library of Medicine, United States of America), EBSCO (EBSCO Industries Incorporate, United States of America), Web of Science (Clarivate Analytics, United States of America), CENTRAL (Cochrane Central Register of Controlled Trials, Cochrane Library, United States of America), SciELO (Scientific Electronic Library Online, Brazil), and Google Scholar (Google Incorporate, United States of America). In each case, the literature search was carried out by combining different Boolean operators (e.g., "*psychosis*", "*tuberculosis*"), having the word "*cycloserine*" in the operator. More details concerning the systematic literature search, combination of Booleans, and the Boolean formulae are described in Additional file 1.

Finally, between 10/03/2022 and 10/05/2022, the search for articles was conducted again in the databases mentioned above using the same search strategy. We found 21 additional articles (3437 articles, Additional file 1); however, the additional articles were not relevant publications to this systematic review or they not fulfill the inclusion criteria, not affecting the results that we found, concluding the search on 10/05/2022.

Selection process

Posteriorly, the literature search results were extracted as .csv, .ris, or .txt files, depending mainly on the search platform and database used. In the case of the search platform Google Scholar, we used the free access software *Publish or Perish* [24, 25] to extract the results of the systematic literature search in the formats mentioned above. After extraction, all obtained data files were imported into the free access software Zotero v.6.09 (Corporation for Digital Scholarship, United States of America) to remove duplicated articles or records.

Afterward, we exported the remaining data without duplicates in the web application Rayyan.ai [26], where the authors ACS, SVQ, and LUE independently selected all case reports, case series, and correspondence using the title or abstract related to cycloserine-induced psychosis. Disagreements in the articles' selection were resolved by consensus among all the authors. Later, each author performed a screening of the articles to exclude all those articles that did not meet the inclusion criteria. Likewise, the disagreements concerning inclusion and exclusion criteria were resolved under the consensus modality. Neither the year of publication of the articles nor their language was an exclusion criterion. In case of possible language issues, we used a free access translator (Google Translate, Google Inc., United States of America) to obtain the main information of the manuscript.

Quality of studies

The evaluation of the risk of bias and the quality assessment was carried out using The Joanna Briggs Institute (JBI) Critical Appraisal tool for use in Systematic Reviews [27], which was designed to evaluate the methodological quality and the risk of bias in case report studies [28–31].

The remaining articles were randomly assigned to three authors (ACS, SVQ, and LUE). During the quality assessment, each author could not reveal to the other colleagues the title or content of randomly assigned articles to make the quality assessment procedure as blind as possible. Authors were also asked not to ask for help or support from other authors while reading and assessing the quality of the assigned case reports.

If the articles did not meet the criteria for a low risk of bias described in the JBI tool, the article was sent to a second reviewer for evaluation before exclusion. In this case, the second reviewer received the article without any previous assessment or judgment of the first one to avoid bias at the moment of the second quality assessment. Finally, a third reviewer determined the article's inclusion or exclusion in case of discrepancies between the first and the second evaluators. For this purpose, we established a structure for the quality assessment in the following order (first–second–third reviewer): ACS–SVQ–LUE, LUE–ACS–SVQ, SVQ–LUE–ACS.

Naranjo adverse reaction probability scale

A frequent limitation of case reports is to establish causality in adverse drug reactions, and this is due to different factors, such as the subjectivity of the case report and specific characteristics of the patient. One way to deal with these limitations and standardize the information presented is through the Naranjo algorithm (Naranjo Adverse Reaction Probability Scale) [32]. This tool is widely used in case reports and consists of 10 criteria with which a score is assigned that determines one of the four categories: doubtful (0 points), possible (1 to 4 points), probable (5 to 8 points), and definite (≥ 9 points) [33].

If the included case report article did not report the scores following the Naranjo algorithm, we used the information described in the case reports to estimate the category corresponding to the Naranjo algorithm, as also recommended in other studies [34].

Data extraction

Concerning the data extraction, three authors (ACS, SVQ, LUE) independently carried out this process using a template programmed for the study in Microsoft Excel. Again, all included articles were randomly assigned among these three authors, collecting and registering information concerning (1) the year of publication, (2) patients' sociodemographic characteristics (e.g., sex, age, and country), (3) clinical characteristics of the CS-induced psychosis, (4) treatment used against the psychotic episode (e.g., antipsychotic treatment, CS treatment discontinuation, CS dose reduction or maintenance), and (4) clinical outcomes of the CS-induced psychosis.

Statistical analysis

Since this systematic review sought mainly to describe the characteristics of CS-induced psychosis in the literature, we applied descriptive statistics to present the most frequent symptoms of CS-induced psychosis and the sociodemographic characteristics and treatment used. For this purpose, we presented the quantitative data using the appropriate measures of central tendency (mean with standard deviation and median with interquartile range). Qualitative data, mostly dichotomous, were expressed using percentages and frequencies. If needed, data were presented in tables and graphs for better readability. Concerning data analysis, SPSS software (International Business Machines Corporation, New York, United States of America), version 26.0, was used for the descriptive data.

Results

General characteristics of the included reports and patients

Figure 1 shows the flow diagram according to the PRISMA protocol for the studies included in this systematic review of case reports. Initially, 3416 articles were identified; 1837 duplicates were eliminated, and 1579 publications remained. Subsequently, 1531 articles were removed after reviewing the titles and abstracts because of irrelevance to the study objective. Of the remaining 48 articles, 24 could not be retrieved and were excluded, and 3 articles were excluded, since the reported patients were underage. Finally, 21 articles were assessed with the JBI tool after the screening. One article [35] was excluded from the quality assessment process due to the low quality of information presented and the high risk of bias.

A total of 20 articles [36–55] met the inclusion criteria and survived the quality process, encompassing 22 patients from eight different countries (Table 1) and most patients from India (10 patients, 45.45% of the cases included). One of the articles was published in Spanish [53] and another in Japanese [37], while the rest were published in English.

Of the 22 patients included in the case reports, 15 (68.18%) were male, and 7 (31.82%) were female patients. In addition, the mean age (standard deviation) among the participants was 31.45 (10.88) years.

Regarding past medical history, 15 (68.18%) had no medical conditions. However, 2 (9.09%) patients had diabetes mellitus as comorbidity, 1 (4.54%) had hypothyroidism, 1 (4.54%) had an episode of meningeal tuberculosis in the past, and 1 (4.54%) had suicide attempts during TB therapy. In this patient's case, the study authors reported no relevant psychiatric history. Of the included studies, one patient had a family history of psychiatric disorders (major depression and bipolar disorder), and one patient had a family history of alcoholism; however, there were no reports of medical comorbidities for both patients. Finally, 19 (86.36%) reported having no illegal drug, alcohol, or nicotine dependency. However, 3 (13.64%) participants reported having used alcohol regularly in the past, and one (4.54%) patient reported the last use of cannabis and cocaine 9 weeks before admission. No reported patient consumed concomitantly illegal drugs or alcohol during the treatment with CS.

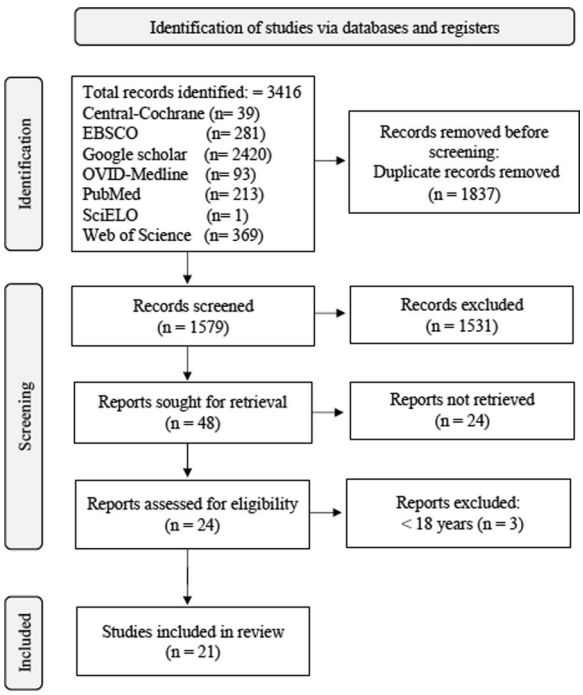

Fig. 1 PRISMA 2020 flow diagram of systematic search for case reports concerning CS-induced psychosis and tuberculosis. Flow diagram sample extracted from: Page et al. [63]

Clinical characteristics of DR-TB patients and CS-induced psychosis

Concerning the type of DR-TB patients, 21 of 22 patients (95.45%) had multidrug-resistant TB (MDR-TB), and one patient (4.54%) had renal tuberculosis (Table 1). Moreover, there were no patients with extreme drug-resistant TB (XDR-TB). Concerning the CS therapy, the mean dose (standard deviation) of CS given as treatment was 631.58 (174.17) mg/die, and the mean duration of CS treatment (standard deviation) until the onset of psychotic symptoms was 169.09 (239.52) days. Within the antitubercular treatment, the reported patients included in this systematic review received mostly drugs, such as pyrazinamide (14 patients, 63.6%), levofloxacin (12 patients, 54.5%), ethionamide (12 patients, 54.5%), kanamycin (11 patients, 50%) and pyridoxine (10 patients, 45.5%) (Table 1).

Table 1 also mentions the details of the clinical presentations of the patients in the included case reports with MDR-TB and cycloserine-induced psychosis. Regarding the duration of psychosis, the median duration of psychosis during treatment with cycloserine was 13 days (39–4 days; interquartile range: 35). The most common symptoms reported in patients with MDR-TB and cycloserine-induced psychosis were delusions (15 patients; 68.2%), followed by aggressiveness (15 patients; 68.2%), insomnia/decreased sleep (13 patients; 59.1%), hallucinations (12 patients; 54.5%), irritability (10 patients; 45.5%) and incoherent or disorganized speech (10 patients; 45.5%). Concerning the aggression observed in the case reports, 14 of 22 reported patients presented aggressive behavior, mostly against other persons, while one of the

Table 1 Included case report studies and their characteristics

Author and year of publication	AoP, sex and country	Main diagnosis	PMH	CS daily dose (in mg)	ATT	Psychotic symptoms	Other psychiatric symptoms	Duration of CS-induced psychosis (in days)	Treatment	Auxiliary examination and imaging procedures	Naranjo ADR score	Outcome
Shekhar et al., 2022	23, F, India	MDR tubercular chest wall abscess	None	750	CS, ethionamide, levofloxacin, ethambutol	Delusions (of persecusion, of reference)	Diminished appetite, emotional lability, disturbed sleep, suspiciousness, fearful affect and absent insight	2	ATT withhold (including CS), treatment with risperidone (2 mg/d) and lorazepam (2 mg/d). After 2d of treatment showed improvement	Hb: 11.2 g/dL, Leukocytes: 11000mm3, BUN: 21 mg/dL, Na+: 142 mEq/L, K+: 2.9 mEq/L, TSH: 2.32 µIU/mL, AST: 92 U/L, ALT: 82 U/L; cCT, cMRI, Thorax Rx, HIV-test: no anormalities detected	Probable	Symptom improvement (BPRS score improvement from 52 to 19 points in 1 month)
Wazir et al., 2020	22, F, Malaysia	MDR-TB	None	Not reported	CS (after 9d stopped), isoniazide, ethionamide, rifampicine (after 40d stopped), pyrazinamide, moxifloxacin, kanamycin, PAS (suspended 2 times)	Hypersexuality ("*she took off her clothes in presence of male and making kissing gestures*"), psychomotor agitation, disorganized behavior	Emotional lability, aggressive behavior (e.g., shouting, yelling), irritability, elated mood	aprox. 90	ATT withhold (including CS). Initially treatment w/ haloperidol (1.5–3 mg/d), then olanzapine (20 mg/d) and valproic acid (800 mg/d)	cCT, LP: no anormalities detected	Possible[d]	Discharge against medical advice, psychotropic medication withhold after 3d discharge, symptom improvement (no BPRS or YMRS reported)
Intini et al., 2019	48, F, India	Ganglionar MDR-TB	None	500	CS, kanamycin, ethionamide, clofazimine, linezolid, PAS and moxifloxacin	Hallucinations ns, "unsocial" behavior	Drowsiness, "depression", social withdrawal, "impairment at work", suicide attempts (3× from a 6th floor balcony)	570	CS withhold, steroids administrated (swelling in the right axilla, mg unknown) patient refused to take antipsychotics and took homeopathic treatments	Thorax Rx: no anormalities detected	Probable[d]	Symptom improvement (no BPRS or YMRS reported)

Table 1 (continued)

Author and year of publication	AoP, sex and country	Main diagnosis	PMH	CS daily dose (in mg)	ATT	Psychotic symptoms	Other psychiatric symptoms	Duration of CS-induced psychosis (in days)	Treatment	Auxiliary examination and imaging procedures	Naranjo ADR score	Outcome
Mahajan et al., 2017	36, M, India	MDR-TB	Hypothyroidism	750	CS, kanamycin, ethionamide, levofloxacin, ethambutol, pyrazinamide, pyridoxine	Disorganized speech ("irrelevant talking"), incoherent answers	Insomnia, drop attacks, "inability to do routine work", vertigo	60	CS withhold and some ATT switched, treatment with olanzapine (2.5 mg/d) and lorazepam (2 mg/d)	Hb: 10.6 g/dL, Leukocytes 14,000 mm^3, ESR: 30 mm/h, BUN: 34, Creatinine: 1.1 mg/dL, AST: 22 IU/mL, ALT:25, TSH: 25.6 µIU/mL, T3:1.02 ng/mL, T4: 5.6 ng/mL, HIV-Test negative	Probable	Symptom improvement (no BPRS or YMRS reported; HAMD/HAMA at the beginning: 18/13)
Çakmak et al., 2016	38, M, Turkey	Skeletal MDR-TB (spondylodiscitis)	None	1000	CS, ethambutol, pyrazinamide, PAS, thioacetazone	Persecutory delusions ("family were trying to harm him or poison him"), visual hallucinations, hypersexuality	Accelerated speech, insomnia, suspiciousness, irritability, stereotypical behavior ("licking and sucking his lips")	14	ATT withhold (including CS), treatment w/olanzapine (20 mg/d)	EEG: slow and dysrhythmic activity in temporal lobe; biochemical analysis, cMRI, thorax Rx, LP: no anormalities detected	Probable[d]	Symptom improvement (YMRS from 44 to 2)
Jain et al., 2016	24, F, New Zealand	MDR-TB	None	750	CS, moxifloxacin, amikacin, prothionamide, PAS, pyridoxine	Persecutory delusions	Labile mood, hypervigilance, daytime somnolence, change in personality, suicidal ideation	14	CS discontinued cycloserine and initiated clofazamine 50 mg. No antipsychotic treatment was given	cMRI: bilateral hyperintensity in cerebellar hemispheres (dentate nuclei and adjacent white matter); CBC, biochemical analysis, thorax Rx, LP: no anormalities detected	Probable[d]	Partial symptom improvement (persistent low grade labile mood and psychotic symptoms). Resolution of cMRI anormalities

Table 1 (continued)

Author and year of publication	AoP, sex and country	Main diagnosis	PMH	CS daily dose (in mg)	ATT	Psychotic symptoms	Other psychiatric symptoms	Duration of CS-induced psychosis (in days)	Treatment	Auxiliary examination and imaging procedures	Naranjo ADR score	Outcome
Kennedy et al., 2016	22, M, Nigeria	MDR-TB, tubercular abscess neck and groin	None	750	CS, rifampicin, isoniazid, ethionamide, ofloxacin and streptomycin	Persecutory and grandiose delusions, visual hallucinations, disorganized speech ("irrational talks"), psychomotor agitation	Accelerated speech, irritable-aggressive behavior, insomnia, refusal to eat, restlessness, euphoria, absent insight	3	CS was discontinuated; Nitrazepam (2.5 mg/d), Vitamin B complex	CBC, electrolyte, urea and Cr and urinalysis, thyroid function test, HIV-test: no anormalities detected	Probable	Within 48 h BPRS reduction from 62 to 33; within 72 h marked symptom improvement
Okpataku et al., 2015	26, M, Nigeria	MDR-TB	None	500	CS, pyrazinamide, proteonamide, kanamycin, levofloxacin and vitamin B6	Persecutory delusions, acoustic and visual hallucinations	Insomnia, verbal aggressiveness, restlessness, social withdrawal, blunted affect	12	CS was maintained; treatment with haloperidol (10 mg/d) and benzhexol (5 mg/d)	Leukocytes: 41,000 mm^3, HCT: 41%; biochemical analysis, HIV-test: no anormalities detected	Probable	Symptom improvement after treatment. New psychotic episode 5 weeks after hospital discharge and antitubercular treatment (7 weeks)
Sawant et al., 2015	33, F, India	MDR-TB	None	750	CS, kanamycin, levofloxacin, ethionamide and pyridoxine	Delusional jealousy	Irritability, aggressive behavior (not specified), appetite loss	60	Changes in CS treatment were not specified, but recommended; treatment with haloperidol (1.5–10 mg/d), benzhexol (4 mg/d) and olanzapine (5–30 mg/d)	Leukocytes: 12,000 mm^3, CPK: 1650 UI, BUN: 10 mg/dL, serum Cr: 1.2 mg/dL, myoglobine in urine; hepatic enzymes, cMRI, thorax Rx, LP: no anormalities detected. Results were obtained during the NMS developed by the patient	Probable	Symptom improvement, however, patient developed NMS

Table 1 (continued)

Author and year of publication	AoP, sex and country	Main diagnosis	PMH	CS daily dose (in mg)	ATT	Psychotic symptoms	Other psychiatric symptoms	Duration of CS-induced psychosis (in days)	Treatment	Auxiliary examination and imaging procedures	Naranjo ADR score	Outcome
Holla et al., 2015	42, M, India	MDR-TB	Family history of bipolar disorder and MDD	750	CS, levofloxacin, kanamcyin, ethionamide, pyrazinamide, ethambutol, pyridoxine	Persecutory delusions, hallucinations ns, disorganized speech with monologues, disorganized behavior, apathic	Logorrhea, crying, insomnia, irritability, constant suicidal ideations, suicide attempts (2–3), emotional lability, mood swings, verbal aggressive behavior, restlessness, social withdrawal, fearful	194	CS was stopped immediately; treatment first with quetiapine (25 mg/d), then olanzapine (20 mg/d)	Not reported	Probable	Symptom improvement (no BPRS or YMRS reported)
Tandon et al., 2015	45, M, India	MDR-TB	None	500	CS, kanamycin, levofloxacin, ethionamide, pyrazinamide, pyridoxine	Disorganized speech	Aggressive behavior (verbal), anxiety, restlessness, insomnia, loss of interest (work, family and clothes), appetite loss	7	CS suspended. Treatment with haloperidol (10 mg/d), promethazine (50 mg/d), olanzapine (20 mg/d), nitrazepam (20 mg/d) and thiamine (300 mg/d)	Hb: 8.2 g/dL, Leukocytes 18,000 mm^3, Glucose: 80 mg/dL, ESR: 42 mm/h, BUN: 23 mg/dL, serum Cr: 0.5 mg/dL, serum bilirubin: 5.4 mg/dL, AST: 192 mg/dL, ALT: 202 mg/dL, HIV-Test negative; thorax X-ray: bilateral fibrotic lesions in upper zones, ultrasonography abdomen and computed tomography scan: no anormalities detected	Probable	Symptom improvement (BPRS 3rd day: 33, no post-value), patient showed hepatic dysfunction during treatment

Table 1 (continued)

Author and year of publication	AoP, sex and country	Main diagnosis	PMH	CS daily dose (in mg)	ATT	Psychotic symptoms	Other psychiatric symptoms	Duration of CS-induced psychosis (in days)	Treatment	Auxiliary examination and imaging procedures	Naranjo ADR score	Outcome
Behera et al., 2014	25, M, India	MDR-TB	2 suicide attempts (hanging, jumping from a 1st floor)	Not reported	CS, ethionamide, ethambutol, levofloxacin, pyrazinamide	Visual and acoustic hallucinations ("reported of a sense of machines moving and talking inside his brain"), disorganized speech ("incoherent speech, abnormal talk")	Insomnia, anxiety symptoms (not described), abnormal whistling sounds in the ears	32	CS withhold; treatment with risperidone and clonazepam (doses not specified)	Not reported	Possible[d]	Violent suicide with multiple self-injuries with a knife to the chest and abdomen
Arias, G et al., 2014	22, M, Peru	MDR-TB	Alcohol, cocaine and cannabis consumption[a]	750	CS, amikacin, PAS, pyrazinamide, ethambutol, ciprofloxacin	Persecutory delusions, delusions of reference, acoustic hallucinations	Irritability, aggressive behavior (verbal)	5	CS withhold; treatment with haloperidol (3 mg/d)	Not reported	Probable	Symptom improvement (BPRS or YMRS not specified)
Sharma et al., 2014	20, F, India	Meningeal MDR-TB	None	750	CS, levofloxacin, isoniazide, rifampicine	Persecutory delusions, delusions of reference, hallucinations ns, disorganized speech ("talking irrelevantly") and behavior (monologues)	Irritability, aggressive behavior (verbal), accelerated speech	3	CS suspended; treatment with quetiapine (25 mg/d)	(Before psychosis) ESR elevated, LP: increased proteins (140 mg%), increased cell number (80 cells, 90% lymphocytes); cMRI: no anormalities detected	Probable	Symptom improvement (BPRS or YMRS not specified)

Table 1 (continued)

Author and year of publication	AoP, sex and country	Main diagnosis	PMH	CS daily dose (in mg)	ATT	Psychotic symptoms	Other psychiatric symptoms	Duration of CS-induced psychosis (in days)	Treatment	Auxiliary examination and imaging procedures	Naranjo ADR score	Outcome
Otu et al., 2014	28, M, Nigeria	MDR-TB	None	750	CS, pyrazinamide, kanamycin, levofloxacin, prothionamide, pyridoxine	Persecutory delusions with negativism, disorganized behavior (monologues), visual and acoustic hallucinations	Aggressive behavior (physical), appetite loss, insomnia	9	CS reduction (500 mg/d); treatment initially with diazepam, chlorpromazine, haloperidol and benzhexol; then chlorpromazine withholds and olanzapine was added (doses not specified)	(Before psychosis) Hb: 11.6 g/dL, thorax Rx: fibrotic strands in the left upper lung zone with diffuse pulmonary infiltrates in the left middle and lower lung zones; other routinary evaluations were unremarkable	Probable[d]	Symptom improvement (BPRS or YMRS not specified)
Bakhla et al., 2013	21, M, India	Ganglionar MDR-TB	Meningeal TB	500	CS, ethionamide, ofloxacin, streptomycin	Delusions of grandeur, psychomotor agitation ("increased psychomotor activity")	Logorrhea, elated affect, decreased need for sleep, irritable-aggressive behavior (not specified), increased energy, overfamiliarity, and inflated self-esteem	10	CS withhold; treatment with valproic acid (750 mg/d) and olanzapine (5 mg/d)	Not reported	Probable	Symptom improvement (at beginning: YMRS of 38, BPRS of 51; after 3d: YMRS of 15, BPRS of 33; after 10d: no sign of manic symptoms)

Table 1 (continued)

Author and year of publication	AoP, sex and country	Main diagnosis	PMH	CS daily dose (in mg)	ATT	Psychotic symptoms	Other psychiatric symptoms	Duration of CS-induced psychosis (in days)	Treatment	Auxiliary examination and imaging procedures	Naranjo ADR score	Outcome
Sarkar et al., 2011	18, M, India	MDR-TB	None	Not reported	CS, kanamycin, pyrazinamide, ofloxacin, ethionamide and ethambutol	Persecutory delusions, delusions of reference, visual and acoustic hallucinations, disorganized behavior (monologues)	Insomnia, appetite loss, social withdrawal, anxious and fearful appearance, neglect of personal hygiene, reduced psychomotor activity with increased reaction time	14	CS was maintained; treatment with olanzapine (10 mg/d)	Not reported	Possible[d]	Symptom improvement (no BPRS or YMRS reported)
Fujita et al., 2008	45, M, Japan	MDR-TB	Alcohol[b] and tobacco consumption (12.5 py)	500	CS, ethionamide, kanamycin, pyrazinamide, PAS, gatifloxacin	Self-disorders ("my other self is trying to help me"), disorganized speech ("I'm obsessed with something bad"), derealization ("Is it real or not?")	"Abnormal" behavior (not specified), "gradually" worsened	30	CS withhold, no psychopharmacologic treatment given	Hb 11.4 g/dL, leukocytes 6080/µL, platelets 334,000/µL, AST: 15 IU/L, ALT 18 IU/L, LDH 110 IU/L, serum bilirubin 0.4 mg/dL, BUN 14 mg/dL, Cr: 0.75 mg/dL, ESR 46 mm/h, thorax Rx: bilateral upper lobe radiopacities, thorax CT: cavities in both upper lobes; cMRI, LP, HIV-test: no abnormalities detected	Possible[d]	Symptom improvement (BPRS or YMRS not specified)

Table 1 (continued)

Author and year of publication	AoP, sex and country	Main diagnosis	PMH	CS daily dose (in mg)	ATT	Psychotic symptoms	Other psychiatric symptoms	Duration of CS-induced psychosis (in days)	Treatment	Auxiliary examination and imaging procedures	Naranjo ADR score	Outcome
Bankier et al., 1965	31, M, Canada	Right renal TB	Alcohol use[c], family history of alcoholism	250	CS, streptomycin, PAS, isoniazide	Persecutory delusions, delusions of grandeur, disorganized speech	Aggressive behavior (physical), restlessness, flat affect, judgement impairment, depersonalization ("a feeling of strangeness about his body, as if his brain was changed")	4	CS suspended; treatment with chlorpromazine (400 mg/d)	BUN: 13 mg/dL, Glucose: 116 mg/dL; CBC, urine test, EEG and ECG: no abnormalities detected	Probable[d]	Symptom improvement (BPRS and YMRS not reported)
Dunga et al., 2015	48, F, Nigeria	MDR-TB	DM	500	CS, kanamycin, prothionamide, levofloxacin, pyrazinamide and pyridoxine	Persecutory delusions, hallucinations ns, disorganized behavior ("irrational")	Social withdrawn, suspiciousness, aggressive behavior (not specified), and insomnia	3	CS temporal withholding for 72 h; treatment with chlorpromazine (100 mg/d), haloperidol (10 mg/d) and benzhexol (10 mg/d)	CBC, HIV-test, biochemical analysis, glucose, liver enzymes and renal parameters: no anormalities detected	Probable	Symptom improvement (BPRS and YMRS not reported)
	23, M, Nigeria		None	500	CS, capreomycin, prothionamide, levofloxacin, pyrazinamide and pyridoxine	Disorganized speech ("irrelevant talk", "unusual claims"), psychomotor agitation	Insomnia	14	CS temporal withholding (72 h); treatment with chlorpromazine (200 mg/d), risperidone (10 mg/d) and haloperidol (10 mg/d)		Probable	

Table 1 (continued)

Author and year of publication	AoP, sex and country	Main diagnosis	PMH	CS daily dose (in mg)	ATT	Psychotic symptoms	Other psychiatric symptoms	Duration of CS-induced psychosis (in days)	Treatment	Auxiliary examination and imaging procedures	Naranjo ADR score	Outcome
	52, M, Nigeria		DM	500	CS, capreomycin, prothionamide, levofloxacin, pyrazinamide and pyridoxine	Persecutory delusions, visual and acoustic hallucinations, disorganized speech ("talked irrationaly")	Social withdrawn, logorrhea, aggressive behavior (destructive, violent)	4	CS dose temporarily reduced (250 mg) and increased back; treatment with chlorpromazine (200 mg/d), risperidone (10 mg/d), haloperidol (10 mg/d)		Probable	

AoP age of participant, *ALT* alanine aminotransferase, *ATT* antitubercular treatment, *AST* aspartate aminotransferase, *BPRS* brief psychiatric rating scale, *BUN* blood urea nitrogen, *CBC* complete blood count, *cCT* cerebral computed tomography, *CT* computed tomography, *cMRI* cranial magnetic resonance imaging, *CPK* creatinine phosphokinase, *Cr* creatinine, *CS* cycloserine, *DM* diabetes mellitus, *EEG* electroencephalogram, *ECG* electrocardiogram, *ESR* erythrocyte sedimentation rate, *F* female, *HAMD/HAMA* Hamilton depression scale/Hamilton anxiety scale, *HCT* hematocrit, *Hb* hemoglobin, *HIV* human immunodeficiency virus, *K* potassium, *LP* lumbar puncture, *LDH* lactate dehydrogenase, *MRI* magnetic resonance imaging, *M* male, *MDR-TB* multidrug-resistant tuberculosis, *MDD* major depressive disorder, *NMS* neuroleptic malignant syndrome, *Na* sodium, *PAS* para-amino salicylic acid, *PMH* past medical history, *T3* triiodothyronine, *T4* thyroxine, *TSH* thyroid-stimulating hormone, *TB* tuberculosis, *Rx* radiography, *YRMS* Young Mania Rating Scale

[a] Last alcohol consumption 9 weeks before admission

[b] Patient did not present signs of alcohol dependency or consumption before and during the CS therapy

[c] Due to his renal infection, the patient had been drinking very little and was not intoxicated. Patient denied current alcohol dependency

[d] In case the Naranjo algorithm had not been described in the case reports, we calculated the score according to the information presented in the article

Table 2 Main characteristics of psychiatric symptoms in patients with cycloserine-associated psychosis

Symptoms	*n*	Percentage (%)
Delusions	15	
Participants with one delusion	9	
Persecutory	7	77.8
Delusions of grandeur	1	11.11
Jealousy	1	11.11
Participants with two delusions	6	
Persecutory and delusion of grandeur	4	66.67
Persecutory and delusions of reference	2	33.33
Aggressiveness	14	
Aggressiveness against others	13	59.1
Self-aggressiveness	1	4.54
Formal thought disorders (FTD)	13	
Participants with one FTD	10	
Incoherent/disorganized speech	7	36.8
Monologues	2	10.5
Accelerated speech	1	5.3
Participants with two FTDs	3	
Incoherent/disorganized speech and monologues	2	66.67
Incoherent/disorganized speech and accelerated speech	1	33.33
Hallucinations	12	
Visual and acoustic hallucinations	5	22.7
Only visual hallucinations	2	9.1
Only acoustic hallucinations	1	4.54
Not specified/not described	4	18.2

22 included patients presented self-aggression (Table 2). In this last case, the patient died as a result of suicide due to exsanguination as a cause of self-injury cuts in the peripheral vessels.

In the case of the registry of the type of hallucinations, there are records of 12 (54.5%) patients reported in the included clinical cases. Of these, two (9.1%) of the patients presented visual hallucinations, one (4.54%) presented auditory hallucinations, five (22.7%) a combination of both, and in four cases (18.2%), the hallucination type was not specified (Table 2).

Concerning the type of delusions, 7 of 9 patients (77.8%) reported persecutory delusions, one of 9 patients (11.11%) reported delusions of grandeur and 1 of 9 patients (11.11%) reported jealous delusions. Finally, 6 patients reported two delusional symptoms (Table 2). Of them, four of 6 patients (66.67%) reference and persecutory delusions, and two of 6 patients (33.33%) had persecutory and delusions of grandeur (Table 2).

Clinical treatment of MDR-TB patients with CS-induced psychosis

Treatment of cycloserine-induced psychosis varied between reported patients. Of the 22 patients reported, only 4 (18.2%) did not receive antipsychotic treatment. Of the remaining 18 (81.8%) patients reported, the majority (10 patients; 45.5%) received monotherapy with one antipsychotic (2 participants received risperidone, four olanzapine, two haloperidol, 1 received quetiapine, and 1 received chlorpromazine). Of the patients who received a combination of 2 antipsychotics (4 patients, 18.2%), two received a combination with olanzapine and haloperidol, 1 received chlorpromazine and haloperidol, and one patient received olanzapine and quetiapine. Finally, four patients (18.2%) received a combination of three antipsychotics: 2 of them received chlorpromazine + risperidone + haloperidol, 1 of them received haloperidol + promethazine + olanzapine, and 1 of them received haloperidol + chlorpromazine + olanzapine.

Of the adjuvant treatments to antipsychotic therapy, six (27.2%) patients received benzodiazepines (lorazepam, nitrazepam, and clonazepam), 3 (13.6%) patients received anticholinergic agents (benzhexol), and 1 (4.54%) received valproic acid.

Parallel to psychopharmacological therapy, 11 (50%) of the reported patients stopped receiving CS, while 2 (9.19%) continued CS treatment, and 2 (9.19%) reported patients the dose of CS was reduced (Table 1).

In addition, two reported patients (9.19%) had their cycloserine dose wholly suspended for a defined period (Table 1). Finally, in 3 (13.6%) reported cases, the antitubercular therapy (including CS) was withheld (Table 1).

Finally, 20 of the 22 reported patients (90.9%) presented a clinical improvement of psychotic symptoms with the reported therapeutic strategies. On the other hand, only one patient reported partial symptom improvement with low-grade labile mood and psychosis (Table 1). Finally, in the case of one patient, suicide was committed by exsanguination by cutting himself in different regions of the body and did not present an improvement in psychotic symptoms despite treatment (Table 1).

Quality assessment of case reports: CS-induced psychosis in DR-TB patients

In general, the quality of the case reports was good, showing that the vast majority of the articles had a low risk of bias (Additional file 2). In this sense, it was determined that 17 (85%) of the reports presented a very low risk, while 3 (15%) presented a low risk. A total of 3 (15%) studies did not report the number of doses of cycloserine used in patients with MDR-TB. On the other hand, in the case of the record of symptoms, of the reported cases that described the presence of hallucinations, 4 (20%) studies did not specify what type of hallucinations they were (e.g., visual or auditory). Finally, only one study described the use of cycloserine for treating MDR-TB after using other antibiotics. At the same time, the rest of the reported cases indicate a concomitant use of cycloserine with other antibiotics. The quality assessment of the individual studies is in detail in Additional file 2.

In the case of the probability of the reaction to an adverse event, in this case, psychosis induced by cycloserine, a total of 6 articles used the Naranjo algorithm in patients who use cycloserine. In case this algorithm had not been described in the case reports, the score was established according to the information presented in the article. Of the reported articles, 18 showed a "probable" Naranjo index for cycloserine-induced psychosis (5–8 points), while the rest scored as "possible" (1–4 points).

Discussion

The following systematic review of case reports identified 20 articles (years of publication between 1965 and 2022) concerning CS-induced psychosis in DR-TB patients (mean age: 31.45 years), whose majority did not present comorbidities. Furthermore, the median duration of the CS-induced psychosis was 13 days, and the most prevalent psychotic symptom among the patients was delusions (mostly persecutory). Concerning the antipsychotic treatment against CS-induced psychosis, it was found that most received at least one antipsychotic, and parallelly CS treatment was stopped. Of the reports included in this review, 20 of 22 patients showed a clinical improvement. However, only one reported patient (treatment: risperidone and clonazepam) committed suicide by inflicting himself on multiple cuts and, therefore, dying of exsanguination. Finally, most of the included case reports showed a very low risk of bias at the time of evaluation; also, the Naranjo index showed psychosis as a "probable" adverse reaction of CS in most of the reports.

Regarding the sociodemographic data, there are similarities between our findings and previous studies with CS-induced psychosis. For example, a retrospective study reported that younger ages represented a risk factor for CS-induced psychosis [56]. In another observational study, a mean age of 35.7 years was reported in a sample of 144 patients, as well as a predominance of males in the sample, similar to the sample characteristics of our study [12].

To the best of our knowledge, this is the first systematic review of case reports which describes the psychopathology of CS-induced psychosis in reported DR-TB patients. Our results showed that delusions of persecution are the most frequent psychotic symptoms among the reported cases. Other studies with experimental designs, for instance that used CS as adjuvant treatment for 8 weeks in schizophrenic patients, also demonstrated a frequency increase in delusions, grandiosity, and hostility [57]. Finally, similar results are reported in an experimental study that found an exacerbation of psychotic symptoms through CS in a small group of patients with schizophrenia (hallucinations, an acute persecutory delusion, psychomotor agitation, thought disorganization, and catatonic symptoms) or caused a confusional psychosis (mainly including an obnubilation of consciousness and formal thought disorders with speech acceleration, that occur especially in intoxications) with circadian disorders [58].

Currently, some studies support the role of CS as a partial agonist of NMDA receptors binding to glycine sites [57, 59]. However, at high doses, CS can act as NMDA receptor ($NMDA_R$) antagonists [60, 61], generating or worsening psychotic symptoms, as reported, for instance, in patients with schizophrenia [57, 62]. In addition, the dose-dependent NMDA antagonism could also explain the induced psychosis of the reported patients with DR-TB, receiving CS doses between 250 and 1000 mg. However, an observational study found that CS concentrations and the area under the curve were not associated with the appearance of psychotic symptoms in patients with MDR-TB [12], remaining unclear the pharmacological mechanisms of CS psychosis induction in patients with DR-TB.

Regarding the treatment of CS-induced psychosis, most reported patients presented an improvement with

the administration of antipsychotic agents and the discontinuation of CS. This characteristic varies according to the literature reports, since a retrospective study shows the improvement of psychosis in most patients by reducing or temporarily suspending the CS dose [56]. However, the results of both studies agree that a reduction in CS exposure and the administration of antipsychotics reduces the frequency of the appearance of psychotic symptoms produced by CS.

Finally, the Naranjo adverse reaction scale showed that the induction of psychosis due to CS is probable (5 to 8 points). Some case reports presented values on the Naranjo scale (6 articles); however, the remaining reports did not mention a score in the Naranjo algorithm, which the authors of this study finally calculated. Naranjo's tool may have some disadvantages, among which is the variability of the numerical score due to the evaluator's opinion. In addition, the lack of information described in the article to qualify certain criteria could make it difficult to assess the probability of an adverse reaction in the case, for example, of external evaluators who were not involved in the treatment of the patient. This difficulty in reproducibility has been analyzed in other studies by comparing the score assigned by the same authors of the case report and that obtained by evaluators only with the information provided by the article [34]. In this case, it is observed that despite variation in the numerical score, this did not influence a significant change in the assigned category [34].

The main strength of the present study includes a description, through a systematic search, of psychotic symptoms in patients who use CS due to DR-TB, since psychosis due to CS is less frequent (between 8 and 14%) [12, 17].

However, it is important to mention that this study has limitations that must be considered. First, the small sample size of this systematic review. Second, some reports presented incomplete data (e.g., the characterization of hallucinations or the dose of CS). In addition, five articles did not present auxiliary tests (routine laboratories, diagnostic imaging, electrophysiology, etc.). Regarding the study's methodology, this systematic review of case reports is based on non-systematized clinical information, which influenced the presentation of the details and the quality of the articles included, being a limitation of the study. Likewise, this study is not appropriate to determine the causality of the psychotic event due to the non-randomized and anecdotal methodology of the clinical cases. Finally, the accessibility of some articles was very restricted, despite contacting the corresponding authors on multiple occasions, in such a way that in these cases, only the abstract of the case report or the title of the report was available.

Conclusions

In light of our results, we conclude that the most frequent psychotic symptom of CS-induced psychosis was persecutory delusions. In addition, CS-induced psychosis is of short duration that shows mostly a symptom improvement after medical treatment, involving the CS withhold/suspension and antipsychotic treatment. Future studies should clarify possible associations between psychotic symptoms and CS serum concentrations and observe the risk factors associated with the development of psychosis due to CS in patients with DR-TB.

In clinical practice, it is important for practitioners to be aware of the potential adverse effect of cycloserine (psychosis) and conduct thorough patient evaluations during admission and follow-up rounds. If there are symptoms that suggest acute psychotic disorders, it is advisable to consult with a hospital psychiatrist, such as a liaison psychiatry service. In cases where a patient may be developing psychosis, coordination with a hospital psychiatrist is crucial to explore possible organic causes of psychosis and conduct a comprehensive third-party medical history to assess if there were similar psychotic symptoms in the past. The diagnosis of a cycloserine adverse effect should be considered if the induced psychosis is causally related and other causes are ruled out. Unfortunatelly, there are no biomarkers to indicate drug-induced psychosis, so close clinical examination and follow-up of the patient is essential in such cases.

Abbreviations

ALT	Alanine aminotransferase
AoP	Age of participant
AST	Aspartate aminotransferase
ATT	Antitubercular treatment
BPRS	Brief psychiatric rating scale
BUN	Blood urea nitrogen
CBC	Complete blood count
cCT	Cerebral computed tomography
cMRI	Cranial magnetic resonance imaging
CPK	Creatinine phosphokinase
Cr	Creatinine
CS	Cycloserine
CT	Computed tomography
DM	Diabetes mellitus
DR	Drug-resistant
DR-TB	Drug-resistant tuberculosis
ECG	Electrocardiogram
EEG	Electroencephalogram
ESR	Erythrocyte sedimentation rate
F	Female
GABA	Gamma-aminobutyric acid
HAMD/HAMA	Hamilton depression scale/Hamilton anxiety scale
Hb	Hemoglobin
HCT	Hematocrit
HIV	Human immunodeficiency virus
JBI	Joanna Briggs Institute
K	Potassium
LDH	Lactate dehydrogenase
LP	Lumbar puncture

M	Male
MDD	Major depressive disorder
MDR-TB	Multidrug-resistant tuberculosis
MRI	Magnetic resonance imaging
Na	Sodium
NMDA	*N*-Methyl-D-aspartate
$NMDA_R$	NMDA receptor
NMS	Neuroleptic malignant syndrome
PAS	Para-amino salicylic acid
PHM	Past medical history
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
Rx	Radiography
T3	Triiodothyronine
T4	Thyroxine
TB	Tuberculosis
TSH	Thyroid-stimulating hormone
XDR-TB	Extreme drug-resistant tuberculosis
YRMS	Young Mania Rating Scale

Supplementary Information

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Additional file 1. The systematic literature search, combination of Booleans, and the Boolean formulae are described.

Additional file 2. The quality assessment of the individual studies is in detail.

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Author contributions
ACS, LUE, and SVQ: shared first author. ACS, LUE, and SVQ: helped to develop the idea of the study and wrote the introduction and methods; helped with the results and the discussion; performed the literature search for the introduction and discussion and carried out the systematic search using *Rayyan*.ai and *Publish or Perish*; involved in selecting case reports, quality control, data extraction, and data analysis. MAF: co-author. Corrected the manuscript, helped with the data analysis, and helped with the paper's discussion, proofreading, and paper mentoring. BPP: this is the corresponding author and the senior author. BPP is responsible for everything concerning the submission process for all paper authors. BPP developed the idea of the study. In addition, BPP wrote the results, discussion, and conclusions. Corrected the manuscript and did the data analysis and the literature search. All authors read and approved the final manuscript.

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Availability of data and materials
The data are available from the corresponding author on strictly grounded reasonable requests.

Declarations

Ethics approval and consent to participate
This study was approved by the human ethics committee of the Peruvian University Cayetano Heredia. The code of this project in the ethics committee is SIDISI 208894. The study is conceived as secondary data analysis and systematic research. Therefore, no human or animal beings were harmed or assessed in this study. No informed consent was required.

Consent for publication
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Competing interests
The authors declare no conflict of interests.

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