Psychosis Related to Baclofen Withdrawal or Overdose: A Systematic Review

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CME

Abstract

Objective: To systematically review case reports of psychosis related to withdrawal or overdose of baclofen, which is a gamma-aminobutyric acid (GABA)$_B$ agonist.

Methods: PubMed, MEDLINE, CINAHL, and PsychINFO were searched to identify articles related to psychosis secondary to withdrawal or overdose of baclofen using the terms 'baclofen' and ' psychosis'. Comparisons were made between cases in terms of concomitant antipsychotic use, diagnosis of delirium, and evidence of association. Quality of case reports was assessed using the CARE Case Report Guidelines checklist.

Results: In total, 34 patients from 28 case reports were reviewed. Twenty-three patients experienced psychosis upon baclofen withdrawal; among them, 18 had resolution of psychosis upon reinitiation of baclofen, whereas antipsychotic monotherapy was less successful (only four of eight patients responded). An additional baclofen withdrawal period led to recurrence of psychotic symptoms in four of seven patients. Eleven patients had psychosis on induction or after overdose of baclofen; among them, four patients had resolution of psychosis upon cessation of baclofen. The mean quality of the case reports was 6.4 of 13.

Conclusion: Considering its GABAergic agonism, along with evidence of psychosis on induction or withdrawal, baclofen may have some antipsychotic and pro-psychotic properties.

Key words: *Baclofen; GABA-B receptor agonists; Psychotic disorders; Schizophrenia*

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Introduction

Baclofen is a gamma-aminobutyric acid (GABA)$_B$ agonist commonly used to treat muscle spasms and dystonia (eg, in multiple sclerosis).[1] In the 1970s, clinical trials of baclofen treatment for schizophrenia demonstrated mixed results.[2-4] Currently, the most widely used treatments for schizophrenia involve antipsychotic agents, which are primarily dopamine blockers. Approximately 15% to 30% of patients who do not respond to these antipsychotic medications are considered to have treatment-resistant schizophrenia.[5,6] Clozapine, the only effective medication for treatment-resistant schizophrenia, targets multiple receptor pathways (eg, dopaminergic, cholinergic, glutamatergic, and GABAergic).[5] Its efficacy may be mediated by the GABA$_B$ pathway,[7] and abrupt clozapine cessation can lead to withdrawal psychosis.[8,9] Considering the pharmacological modes of action of baclofen and clozapine,[7] as well as their association with withdrawal psychosis,[9,10] GABA$_B$ receptor signalling may be involved in the pathophysiology of psychosis. Research of GABA involvement in the pathophysiology of psychosis is needed to determine how baclofen may cause psychosis on induction.

Sensory gating in schizophrenia can be studied using the P50 wave on electroencephalography, which occurs early during stimulus processing.[11] Cholinergic neurons are modulated by GABA interneurons in the context of a second stimulus, which reduces second stimulus amplitude in healthy individuals. However, in schizophrenia, the stimulus is not effectively diminished with a P50 ratio >50%, whereas healthy individuals exhibit a P50 ratio of <40%.[12] The absence of sensory gating and presence of stimulus misperception[13,14] may be influenced by GABA$_B$ receptor modulation of cholinergic neurons in schizophrenia. The

use of clozapine reduces this lack of P50 gating in patients with schizophrenia,[12] in a manner modulated by the GABA system. Molecular modelling studies have demonstrated that clozapine directly binds to the $GABA_B$ receptor,[7] indicating a possible mechanism of action.[7] Autoradiography findings of lower pre-pulse inhibition have been demonstrated in baclofen- and clozapine-treated schizophrenia mouse models, suggesting similar effects at a neurobiological level.[15]

Baclofen has been used in epilepsy, but it is now mainly used to treat muscle spasticity[1] and alcohol withdrawal.[16] Its use requires caution because it has been associated with toxicity leading to life-threatening symptoms (eg, arrhythmias, respiratory failure, and coma).[17] Its dosing for neuropsychiatric disorders is challenging because it cannot easily pass the blood-brain barrier via passive diffusion and its plasma-to–cerebrospinal fluid concentrations are poorly correlated.[18] Although baclofen targets $GABA_B$ agonism to dampen neuronal signalling in skeletal muscle, GABA interneurons affect multiple neuromodulators including dopamine, which may affect the pathophysiology of psychosis.[19]

Here, we explored the association between baclofen and psychosis by conducting a narrative review of case reports of psychosis related to baclofen withdrawal or overdose.

Methods

This systematic review was registered in PROSPERO (reference: CRD42022371450). In September 2021, databases of PubMed, MEDLINE, CINAHL, and PsychINFO were searched using terms 'baclofen' and 'psychosis' to identify case series and case reports related to psychosis secondary to baclofen withdrawal/induction/overdose (Figure). The reference lists of selected articles were also screened to identify additional case reports regarding baclofen-related psychosis. All articles were manually retrieved by one reviewer; each article's relevance to baclofen-related psychosis was confirmed by another reviewer.[10,20-61]

All selected articles were manually categorised. Baclofen withdrawal cases were those with a history of baclofen use, no overdose event, and a period of baclofen cessation or dose reduction prior to psychosis symptom onset. Baclofen overdose to withdrawal cases were those with an overdose event (>200 mg orally or >1300 μg intrathecally) and a period of cessation prior to symptom onset. Baclofen overdose or induction cases were those with either an overdose or usual dosage that resulted in psychosis symptom onset. A maximum oral dose of ≥200 mg has been associated with an increased incidence of adverse events,[17] and an intrathecal dose of 1300 μg/day is the recommended maximum daily dose.[20]

Relevant clinical information was retrieved by one reviewer and then confirmed by another reviewer. This information included psychosis history, antipsychotics use, psychosis treatment, and delirium status. Delirium was considered present if a diagnosis of delirium was recorded; otherwise, symptoms suggesting or refuting a diagnosis

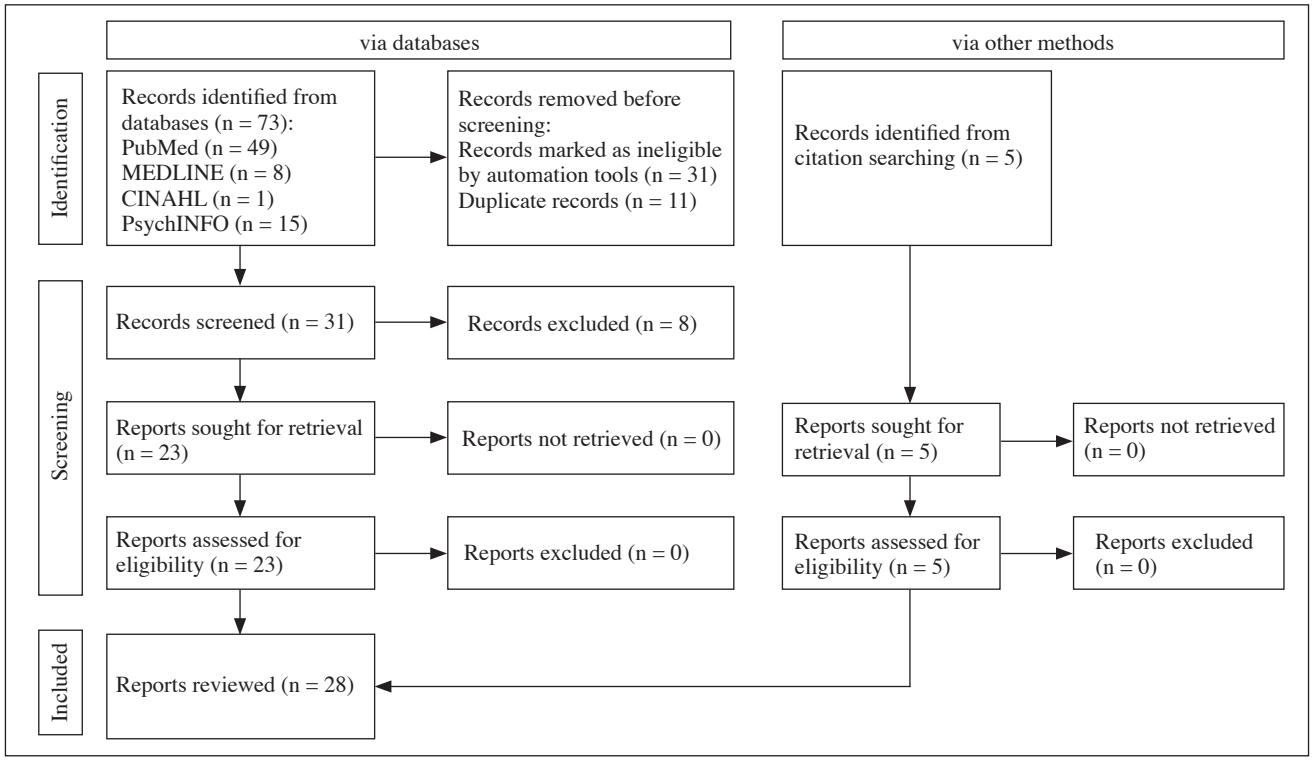

Figure. Flow diagram of the process of identification of case reports of baclofen-related psychosis

of delirium were noted. Other recorded data included any further trials of baclofen and responses to those trials, any changes in symptoms, specific antipsychotics used, and relevant history. The Naranjo Probability Scale was noted to be used in some case reports to determine the association of baclofen with psychosis in overdose and induction cases.[62] Quality of case reports was assessed using the 13-item CARE Case Report Guidelines.[63]

Results

In total, 34 patients from 28 case reports were analysed: 18 patients had baclofen withdrawal psychosis,[10,42-52] five patients had baclofen overdose followed by withdrawal psychosis,[21-23,53,54] and 11 patients had baclofen overdose or induction psychosis (two with higher than usual dose and nine with normal dose).[24-26,34,55-61]

Baclofen withdrawal psychosis

Eighteen patients exhibited some form of psychotic symptoms after baclofen withdrawal (Table 1[10,42-52]). The mean duration of prior baclofen use was 2.4 (range, 0.5-5) years, and the mean duration of withdrawal was 43 (range, 12-144) hours. Most common psychosis-related symptoms were hallucinations including visual (75%), auditory (50%), both (37.5%), or unspecified (12.5%). Delusions were present in five (28%) patients, three of whom experienced both delusions and hallucinations. None of the reports used a formal schizophrenia rating scale for symptom assessment. The maximum daily baclofen dose was 160 mg (oral) or 800 μg (intrathecal), and the mean oral dose was 83 mg/day. One patient had prior antipsychotic use for schizophrenia, 11 patients did not have, and the remaining six patients had no such data.

Fourteen of the 18 patients restarted or increased the original baclofen dose and exhibited a positive response. Seven patients had another period of baclofen withdrawal: four had symptom recurrence (and responded to subsequent reinitiation of baclofen) and three did not. Four of the 18 patients received antipsychotic treatment for their psychotic symptoms: one patient responded to antipsychotics with concomitant benzodiazepines, two patients responded to adjunctive antipsychotics along with reinitiation of baclofen, and one patient exhibited an equivocal response to antipsychotic monotherapy.

Only one patient had fluctuating orientation and confusion consistent with delirium. Five patients had possible delirium, with terms such as ‘confused’ being recorded. Others did not have comments on specific delirium symptoms.

The mean quality of these case reports was poor: 6.16 of 13 (range, 3-9), as determined by the CARE Case Report Guidelines checklist. No standardised diagnostic scales for psychosis or delirium were used. Although patient identification, clinical findings, and therapeutic intervention were generally reported, detailed patient histories were absent.

Baclofen overdose followed by withdrawal psychosis

Five patients overdosed on baclofen and then developed withdrawal psychosis (Table 2[21-23,53,54]). The duration of withdrawal after baclofen overdose ranged from 24 hours to 4 days. Psychotic symptoms were reported in a descriptive manner, without assessments by standardised symptom rating scales. Most symptoms were hallucinations: both visual and auditory (in three patients), visual only (in one patient), and auditory only (in one patient). Four patients also experienced accompanying delusions. The rates of auditory hallucinations and delusions were higher in these patients than in patients with baclofen withdrawal psychosis. Of the five patients, four responded to reinitiation of baclofen (one of them required concomitant antipsychotics) and one recovered with antipsychotics and benzodiazepines alone. Delirium was identified in three of the five patients via clinical assessment, whereas delirium was ruled out in the remaining two patients. Only one case report[23] included Naranjo Probability Scale results, which indicated that the adverse reaction had a probable association with the use of baclofen. The mean quality of these case reports was poor: 6.6 of 13 (range, 4-8).

Baclofen overdose or induction psychosis

Two patients with baclofen overdose psychosis had particularly high doses of baclofen (300 mg orally and 1400 μg intrathecally) [Table 3[24-26,34,55-61]]. Reported symptoms included both hallucinations and delusions. The first patient did not experience delirium and had no history of psychosis or prior antipsychotic use.[24] Her psychotic symptoms resolved when the baclofen dose was reduced to 50 μg. Although the Naranjo Probability Scale was not used to evaluate the association of psychosis with baclofen, baclofen dose increases led to the recurrence of similar symptoms, which resolved with dose reduction. The second patient had a history of binge-eating disorder and received supratherapeutic levels of baclofen. He experienced visual hallucinations, delusions, and psychomotor agitation.[25] Reinitiation of baclofen at a lower dose led to psychosis resolution. Notably, signs of confusion were reported, but no other delirium criteria were specified. The Naranjo Probability Scale results indicated a possible causal relationship between baclofen overdose and psychosis. The quality of the two case reports was low: 6 and 8 of 13, respectively.

Nine patients exhibited psychosis while receiving therapeutic doses of baclofen. The mean oral dose was 47 mg/day, and the treatment duration ranged from 1 day to 4 months. Eight patients experienced auditory (n = 6), visual (n = 4), and both (n = 3) hallucinations. Seven patients experienced delusions. Three patients were diagnosed with delirium and the remaining six patients were ruled out or did not suggest having delirium. One patient had prior antipsychotic use for severe idiopathic dystonia, six patients had no history of psychotic disorder, and three patients had no specifically reported history of psychosis.

Table 1. Case reports of baclofen withdrawal psychosis

Study	Patient sex/age, y	Reason for baclofen use	History of psychosis specified	Baclofen dose; past duration; withdrawal time	Antipsychotic use	
					Past	During
Lees et al,[42] 1977	M/61	Spastic paraparesis, ceased because it was found to be ineffective, dyskinesias	No (unspecified)	90 mg/day; 1 year; 12 hours	No	No
Stien et al,[43] 1977	F/45	Spastic tetraparesis, accidentally ceased	No (unspecified)	60 mg/day; 2 years; 24 hours	No	No
Arnold et al,[44] 1980	M/71	Cervical myelopathy, self-ceased	No	15 mg/day increased to 30 mg/day then 60 mg/day; 6 months (10 days increased); within 24 hours	No	Yes
Terrence & Fromm,[45] 1981	M/21	Spasticity, ceased because of mildly elevated liver enzymes	No (unspecified)	160 mg/day; 6 months; 3 days	No	No
	M/59	Trigeminal neuralgia, held for surgery	No (unspecified)	80 mg/day; 1 year; 3 days	No	No
	F/18	Spasticity, dose reduced	No (unspecified)	80 mg/day; 4 years; reduced dose 2 days	No	No
Kirubakaran et al,[46] 1984	M/33	Paraplegia, held for neurosurgery	No	80 mg/day; 2 years; 6 days	No	No
Yassa & Iskandar,[47] 1988	M/38	Tardive dystonia, did not renew prescription	Yes (paranoid schizophrenia)	30 mg/day increased to 90 mg/day; 1 year; 4 days	Yes	Yes
Rivas et al,[48] 1993	F/32	Muscle spasticity, held because of ileus	No	160 mg/day; 5 years; 38 hours	Unspecified	No
D'Aleo et al,[10] 2007	M/73	Spastic tetraparesis, held prior to intrathecal pump surgery	No	75 mg/day (oral) changed to 50 μg (intrathecal); unspecified past; 31 hours	Unspecified	Yes
	M/31	Spastic paraparesis, held prior to intrathecal pump surgery	No	75 mg/day (oral) changed to 50 μg (intrathecal); unspecified past; 18 hours	Unspecified	No
	M/52	Spastic tetraparesis, held prior to intrathecal pump replacement	No	800 μg/day (intrathecal) temporarily changed to 100 mg/day (oral); 5 years; 25 hours	Unspecified	No
	M/41	Spastic paraparesis, held for intrathecal bolus test	No	75 mg/day; unspecified past; 29 hours	Unspecified	No
	F/48	Spastic paraparesis, held for intrathecal bolus test	No	50 mg/day; unspecified past; 26 hours	Unspecified	No
Cherella et al,[49] 2013	F/17	Cerebral palsy muscle spasticity, ceased accidentally	No	80 mg/day; unspecified past; 4 days	No	Yes
Alvis & Sobey,[50] 2017	F/62	Chronic pain, did not refill prescription	No (unspecified)	60 mg/day; unspecified past; 3 days	Yes	No
Leandre & Ginory,[51] 2019	M/47	Bladder spasms, self-ceased	No	30 mg/day; 'years' (no specific number given); 5 days	Unspecified	No
Sanders & Ali,[52] 2021	F/58	Back pain, ran out of medication	No	30 mg/day (possibly up to 90 mg/day); unspecified past; 4 days	No	Yes

Psychotic symptoms	Delirium	Treatment of withdrawal psychosis		Other
		Method	Response	
Auditory and visual hallucinations, paranoia	Unspecified	Restarted baclofen	Yes (within 48 hours)	Re-emergence of symptoms on cessation of baclofen and resolution with reinitiation of baclofen; successful tapering of baclofen without re-emergence of symptoms
Visual hallucinations, confusion	Unspecified 'confused'	Restarted baclofen	Yes (within 4 hours)	No re-emergence on repeated abrupt cessation
Grandiose delusional thoughts	Unspecified 'alert'	Antipsychotic (adjunctive)	Yes (within 24 hours)	Haloperidol used; manic psychosis
Auditory and visual hallucinations, confusion, agitation	Unspecified 'confused'	Restarted baclofen	Yes (within 48 hours)	Seizures and convulsions prior to symptom onset; symptoms intermittent for 10 days
Auditory and visual hallucinations, confusion, combativeness	Unspecified 'confused'	Unspecified	Unspecified	Seizures occurred on same day as symptoms; 2 months later, restarted baclofen for trigeminal neuralgia
Auditory and visual hallucinations	Unspecified	Re-increased baclofen	Yes	Re-emergence of symptoms when reducing from 60 mg to 40 mg with resolution when re-increasing baclofen
Flight of ideas, visual and auditory hallucinations, grandiose delusions, abnormal movements	Unspecified	Restarted baclofen	Yes (within 72 hours)	Concomitant use of benzodiazepines, opioids, and paracetamol
Delusions of persecution, agitation	Unspecified 'disoriented'	Restarted baclofen	Yes (within 72 hours)	Intramuscular haloperidol; no episodes during 1 month of follow-up
Visual and tactile hallucinations, delusions	Unspecified	Restarted baclofen	Yes (within 48 hours)	Ceased oral medications because of postoperative ileus
Visual hallucinations	Unspecified	First, antipsychotic and benzodiazepine (without baclofen); second, restarted baclofen	First, no; second, yes (within 12 hours)	Risperidone and diazepam used; ceased baclofen 1 month later without hallucinations
Visual hallucinations	Unspecified	Restarted baclofen	Yes (within 3 hours)	Re-emergence because of intrathecal catheter dislocation, treated with oral baclofen leading to resolution in 12 hours
Visual hallucinations	Unspecified	Restarted baclofen	Yes (within 3 hours)	Re-emergence of hallucinations in another withdrawal of baclofen, with resolution 3 hours after intrathecal baclofen
Hallucinations	Unspecified	Restarted baclofen	Yes (within 2.5 hours)	No re-emergence in two other episodes of baclofen withdrawal
Hallucinations	Unspecified	Restarted baclofen	Yes (within 3.5 hours)	No re-emergence in one other episode of baclofen withdrawal
Auditory hallucinations and delusions	Unspecified 'alert and fully oriented'	First, restarted baclofen; second, antipsychotics (adjunctive)	First, yes (partial improvement); second, yes (almost complete resolution)	Risperidone used; alert and fully oriented
Visual hallucinations	Unspecified 'altered mentation'	Restarted baclofen	Yes (within hours)	Other medication: clonazepam, venlafaxine, and opioids; altered mentation and inattention
Visual and auditory hallucinations, guarded interactions, paranoia	Unspecified	Benzodiazepine	Yes	History of anxiety
Auditory hallucinations, inappropriate affect, thought blocking, poverty of thought	Present	Antipsychotics (without baclofen)	Unclear response, resolved in 4 days	History of depression; olanzapine, ziprasidone, and risperidone used; overuse of baclofen prior to withdrawal

Table 2. Case reports of baclofen overdose followed by withdrawal psychosis

Study	Patient sex/age, y	Reason for baclofen use	History of psychosis	Baclofen dose and duration; withdrawal time	Antipsychotic use	
					Past	During
Peng et al,[21] 1998	M/42	Spasticity, suicide attempt	No (unspecified)	800 mg usual: 20 mg/day for 5 months; 28 hours	No	No
Auger & Potash,[53] 2005	M/39	Spasticity, suicide attempt	No (unspecified)	Unspecified, usual: 120 mg/day for unspecified duration; 48 hours	No	Yes
Malhotra & Rosenzweig,[54] 2009	F/45	Spastic quadriparesis, accidental pump dosage	No	20x unspecified usual dose for unspecified duration; 24 hours	No	Yes
Karol et al,[22] 2011	M/59	Misuse	No (unspecified)	Up to 240 mg/day for unspecified duration; unspecified	No	Yes
Nahar et al,[23] 2017	F/30	Intentional overdose	No	300 mg, no past use; 4 days	No	Yes

Resolution of psychotic symptoms was achieved by cessation of baclofen, treatment with antipsychotics, or both. Two patients had monotherapy with antipsychotics; one of them responded positively (ie, resolution of symptoms). Five patients were treated by cessation of baclofen; four of them had symptom resolution, although three required concomitant antipsychotic treatment. Two of the three patients who were treated with baclofen cessation and concomitant antipsychotic treatment exhibited recurrence of psychosis upon reinitiation of baclofen and then resolution after cessation of baclofen. One case report did not indicate whether psychosis resolved after baclofen cessation.[26] The remaining two patients had symptom resolution after haemodialysis (n = 1) or reduction of baclofen dose with antipsychotic use (n = 1). The mean quality of these case reports was low: 6.4 of 13 (range, 3-8).

Discussion

Most case reports of baclofen-related psychosis involve withdrawal rather than overdose or therapeutic use. Although findings suggesting a causal relationship between baclofen withdrawal and psychosis have been reported, attempts to confirm this relationship (through repeat withdrawal periods, antipsychotics use, and reinitiation of baclofen to ameliorate adverse symptoms) have been inconclusive. The occurrence of withdrawal psychosis implicates baclofen, and therefore $GABA_BR$, in the pathophysiology of psychosis. Although cases of baclofen overdose are rare, these cases suggest a psychosis pattern that is consistent with classical positive schizophrenia symptoms (ie, greater tendency for auditory hallucinations and delusions, rather than visual hallucinations associated with baclofen withdrawal in the absence of overdose). Psychosis after therapeutic use of baclofen suggests a complex pathophysiology; they may involve direct $GABA_BR$ agonism or the effects of baclofen on dopamine network modulation. The likelihood of psychosis appears to be greater after baclofen withdrawal than after baclofen overdose or therapeutic use. However, the strength of these observations is weak considering the low quantity and variable quality of cases in terms of patient history, description of symptoms and signs, quality of diagnostic assessment, and duration of follow-up (Table 4[10,21-26,34,42-61]).

There were 18 cases of baclofen withdrawal psychosis and five cases of overdose followed by withdrawal psychosis; the mean withdrawal durations were 43 hours and 46.5 hours after baclofen cessation, respectively. Overall, the duration of prior baclofen use was poorly reported and ranged from months to years. Other than clozapine, few medications have been associated with withdrawal psychosis.[27] Clozapine withdrawal psychosis usually develops within 24 to 48 hours.[28] However, pharmacological studies of the effect of the duration of baclofen use on $GABA_B$ signalling are ongoing.[29-31] A proportion of patients receiving baclofen have tolerance.[32] These findings highlight the variability in

Psychotic symptoms or rating scales	Delirium	Treatment of withdrawal psychosis		Other
		Method	Response	
Auditory and visual hallucinations, delusions	Present	Restarted baclofen	Yes	Period of alertness after overdose before symptom onset
Auditory and visual hallucinations, delusions, Mini-Mental State Examination (MMSE)	Present (using MMSE scores, without specifying symptoms)	Antipsychotic	No, discontinued	Fluphenazine used; unclear which medications were used in overdose
		Restarted baclofen	Yes	
Visual, auditory, tactile hallucinations, derealisation, depersonalisation, paranoid delusions, Schneiderian first-rank symptoms	Absent 'fully oriented and attentive'	Restarted baclofen	Yes, mild improvement	Risperidone used; ceased baclofen for 24 hours after overdose
		Antipsychotic	Yes, improvement within 24 hours	
Visual hallucinations	Present before baclofen cessation	Antipsychotic	No, discontinued	Haloperidol used; hallucinations began after abrupt baclofen cessation
		Restarted baclofen	Yes, improvement within 24 hours	
Auditory hallucinations, grandiose delusions, delusions of persecution, catatonia, Bush-Francis Catatonia Rating Scale score	Absent 'clear consciousness'	Antipsychotic and benzodiazepine	Yes	Olanzapine used; lorazepam 3 mg/day dramatically improved catatonia; Naranjo Probability Scale: 'probable association'

$GABA_BR$ subtypes, which may affect baclofen efficacy.[33] Additionally, the wide range in duration of prior use, from months to years, suggests variability in $GABA_BR$ subtypes, with the potential for greater susceptibility to baclofen withdrawal psychosis.

The mechanism of baclofen-related psychosis is largely unknown. Baclofen may indirectly modulate dopamine.[34] Baclofen acts on $GABA_B$ receptors within the ventral tegmental area, leading to negative inhibition of dopaminergic projections in the mesolimbic pathway.[35] Chronic suppression of these neurons may result in dopamine receptor hypersensitivity and neuronal excitability, predisposing to psychosis upon baclofen withdrawal.[36] However, because $GABA_B$ signalling is modulated in a complex manner, inhibition or excitation may occur on the basis of specific activation profiles.[37-40]

One major limitation of this review was the quality of the case reports, as determined by the CARE Case Report Guidelines. None of the included reports used a standardised symptom rating scale to assess psychotic symptoms,[41] nor did most reports evaluate the probably of a drug reaction using the Naranjo Probability Scale.[62] Additionally, some case details (eg, medical history and follow-up periods) were missing, inconsistent, or poorly reported. There was limited consideration of delirium as a differential diagnosis, rather than as psychosis solely related to baclofen use. Notably, only 34 cases have been reported in the English-language medical literature. Thus, baclofen withdrawal psychosis cases may be underreported because there have been no formal cohort or controlled studies of baclofen withdrawal psychosis.

Conclusion

The pharmacological agonism of baclofen at the GABA receptor suggests that the GABAergic system is involved in the pathophysiology of psychosis. However, the quality of published case reports of baclofen-related psychosis is low.

Contributors

All authors designed the study, acquired the data, analysed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As the editor of the journal, SKWC was not involved in the peer review process. Other authors have disclosed no conflicts of interest.

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Data availability

All data generated or analysed during the present study are available from the corresponding author on reasonable request.

Table 3. Case reports of baclofen overdose or induction psychosis

Study	Patient sex/age, y	Reason for baclofen use	History of psychosis	Baclofen dose and duration	Antipsychotic use	
					Past	During
Sagawa et al,[24] 2011	F/50	Limb dystonia	No	1400 μg/day intrathecal (temporary increase) for 1 year (increased for 'a few days')	No	Yes
Ricoux et al,[25] 2019	M/60	Binge-eating disorder, accidental overdose	No	Increased to >300 mg/day (blood level 562 μg/L) for 1 year (unspecified duration at increased dose)	No	No
Skausig & Korsgaard,[26] 1977	F/72	Dyskinesias	No (unspecified)	5 mg/day for unspecified duration	No	No
Roy & Wakefield,[55] 1986	M/37	C6 tetraplegia	No	60 mg/day increased to 80 mg/day for 5 years (unspecified increased duration)	No	Yes
Lee et al,[56] 1992	M/64	Myalgia	No (unspecified)	75 mg/day for 1 day	No	No
Sommer & Petrides,[57] 1992	M/32	Idiopathic dystonia	No	80 mg/day for 4 months	Yes	No
Chawla & Sagar,[58] 2006	M/32	Generalised tetanus	No	20 mg/day for 1 month	No	Yes
Lim & Krystal,[59] 2007	F/61	Central pontine myelinolysis	No	30 mg/day for 2 weeks	No	Yes
Osmolak et al,[60] 2012	F/26	Spastic paraplegia	No	Unspecified for 6 days	No	Yes
Bole et al,[61] 2015	M/25	Alcohol and nicotine dependence	No (unspecified)	40 mg/day for 15 days	Unspecified	Yes
Maneyapanda et al,[34] 2016	M/24	Spasticity	No	75.1 μg/day increased to 98.04 μg/day for 1.5 years (1 week increased)	No	Yes

Psychotic symptoms or rating scales	Delirium	Treatment of overdose or induction psychosis		Naranjo Probability Scale	Other
		Method	Response		
Negativism, delusions, persecutory delusions, delusions of interpretation, auditory hallucinations	Absent	Antipsychotic	No	Not utilised	Re-emergence of symptoms with re-increasing baclofen and resolution with re-reduction; olanzapine and risperidone used
		Reduced baclofen	Yes		
Delusional ideas, aggressiveness, visual hallucinations, psychomotor agitation (during high blood level)	Unspecified 'confusion' after abrupt cessation	Restarted baclofen	Yes (within 2 days)	Possible causality reported	Occasional cannabis use
Hallucinations, confusion, agitation, paranoia	Unspecified 'confused'	Ceased baclofen	Unspecified	Not utilised	Unspecified prior dosage or resolution of psychosis
Auditory and visual hallucination	Unspecified 'confusion'	Antipsychotic	Yes (partially)	Not utilised	Chlorpromazine, zuclopenthixol, thioridazine, and trifluoperazine used; increase in symptoms with baclofen dosage; septic with renal abscess
		Ceased baclofen	Yes		
Delusions of persecution and visual hallucinations	Unspecified 'confused, disoriented, agitated'	Haemodialysis	Yes	Not utilised	Full recovery with haemodialysis; diabetic nephropathy
Cotard's delusion	Absent	Ceased baclofen	Yes	Not utilised	Haloperidol used in past; no history of depression; symptoms in 1 week
Third person auditory hallucinations, persecutory and referential delusions	Absent	Ceased baclofen	Yes	Probable association reported	Reinitiation of baclofen had re-emergence of symptoms that remitted on cessation; olanzapine used (ceased at same time as baclofen)
		Antipsychotic	Unspecified		
Persecutory delusions, auditory and visual hallucinations, loosening of associations	Absent	Antipsychotic	No	Not utilised	Risperidone used; unclear if symptom resolution achieved
Olfactory, auditory, and visual hallucinations, homicidal ideation, delusions, insomnia	Unspecified	Antipsychotic	Yes (within 4 days)	Not utilised	Risperidone, ziprasidone, olanzapine, and aripiprazole used
Auditory hallucinations, delusions	Unspecified	Ceased baclofen	Yes (within 5 days and 3 days)	Not utilised	Reinitiation of baclofen with re-emergence of symptoms that remitted on cessation; olanzapine and lorazepam were used
		Antipsychotic	Unspecified		
Auditory hallucinations, ideas of reference, grandiose delusions, odd behaviour	Unspecified	Antipsychotic	Yes (within 25 days)	Not utilised	Olanzapine used, history of depression
		Reduced baclofen	No		

Table 4. Assessment of quality of case reports using the CARE Case Report Guidelines checklist

Study	Components (x/13)	Title	Key words	Abstract	Introduction	Patient identification	Clinical findings	Timeline	Diagnostic assessment	Therapeutic intervention	Follow-up	Discussion	Patient perspective	Informed consent
Baclofen withdrawal psychosis														
Lees et al,[42] 1977	4				✓	✓	✓			✓				
Stien et al,[43] 1977	3					✓	✓			✓				
Arnold et al,[44] 1980	7				✓	✓	✓		✓	✓	✓	✓		
Terrence & Fromm,[45] 1981	7				✓	✓	✓		✓	✓	✓	✓		
Kirubakaran et al,[46] 1984	6				✓	✓	✓		✓	✓		✓		
Yassa & Iskandar,[47] 1988	5				✓	✓	✓			✓		✓		
Rivas et al,[48] 1993	7			✓	✓	✓	✓		✓	✓		✓		
D'Aleo et al,[10] 2007	6			✓	✓	✓	✓			✓		✓		
Cherella et al,[49] 2013	7			✓	✓	✓	✓		✓	✓		✓		
Alvis & Sobey,[50] 2017	7			✓	✓	✓	✓			✓		✓		✓
Leandre & Ginory,[51] 2019	6				✓	✓	✓			✓	✓	✓		
Sanders & Ali,[52] 2021	9	✓		✓	✓	✓	✓		✓	✓		✓		✓
Baclofen overdose followed by withdrawal psychosis														
Peng et al,[21] 1998	8			✓	✓	✓	✓		✓	✓	✓	✓		
Auger & Potash,[53] 2005	4					✓	✓		✓	✓				
Malhotra & Rosenzweig,[54] 2009	7				✓	✓	✓		✓	✓	✓	✓		
Karol et al,[22] 2011	7			✓	✓	✓	✓		✓	✓		✓		
Nahar et al,[23] 2017	7				✓	✓	✓		✓	✓	✓	✓		
Baclofen overdose or induction psychosis														
Sagawa et al,[24] 2011	6				✓	✓	✓			✓			✓	✓
Ricoux et al,[25] 2019	8				✓	✓	✓		✓	✓	✓	✓		✓
Skausig & Korsgaard,[26] 1977	3					✓	✓			✓				
Roy & Wakefield,[55] 1986	8	✓			✓	✓	✓		✓	✓	✓	✓		
Lee et al,[56] 1992	7			✓	✓	✓	✓		✓	✓		✓		
Sommer & Petrides,[57] 1992	6				✓	✓	✓			✓	✓	✓		
Chawla et al,[58] 2006	8			✓	✓	✓	✓			✓	✓	✓		✓
Lim & Krystal,[59] 2007	8			✓	✓	✓	✓		✓	✓		✓		✓
Osmolak et al,[60] 2012	6				✓	✓	✓		✓	✓		✓		
Bole et al,[61] 2015	5	✓				✓	✓			✓	✓			
Maneyapanda et al,[34] 2016	7			✓	✓	✓	✓		✓	✓		✓		

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