



Original Article

Psychotropics-Associated Hiccups: A Qualitative Systematic Review of Case-Based Literature

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ABSTRACT

Background Hiccups are involuntary, repetitive contractions of the diaphragm and intercostal musculature that may occasionally occur as adverse drug reactions. Although psychotropics are increasingly recognized as potential precipitants, evidence remains fragmented and largely limited to isolated case reports and small case series.

Objective To systematically review published case-based literature describing hiccups associated with commonly used psychotropic medications and to synthesize the implicated drug classes, temporal patterns, putative mechanisms, and management approaches.

Methods A PRISMA-oriented qualitative systematic review was conducted using PubMed and Google Scholar. Literature published between 1976 and 2024 was screened using combinations of terms related to hiccups and psychotropic medications. Primary human case reports, case series, and original case-based publications describing psychotropic-associated hiccups were included. Narrative reviews, editorials, animal studies, duplicate reports, and purely mechanistic discussions without clinical cases were excluded.

Results Thirty-three unique publications involving at least 35 identifiable clinical episodes were included. Antipsychotics represented the predominant implicated class, particularly aripiprazole, which was involved in 18 publications. Benzodiazepines, antidepressants, stimulants, mood stabilizers, hypnotics, and cognitive enhancers were also represented. Hiccups most commonly emerged during treatment initiation, dose escalation, medication switching, or combination therapy. Persistent and protracted hiccups were more frequently associated with antipsychotic exposure. Proposed mechanisms included dopaminergic dysregulation, serotonergic imbalance, GABAergic modulation, and altered brainstem reflex activity. Limited management data suggested benefit from drug discontinuation, dose reduction, gabapentin, chlorpromazine, metoclopramide, flumazenil, and add-on risperidone in selected cases.

Conclusion Psychotropics-associated hiccups appear to represent a rare but clinically relevant adverse effect signal, particularly with aripiprazole-containing regimens. Although evidence is limited to case-based literature, clinicians should consider medication exposure when evaluating new-onset or persistent hiccups in psychiatric populations.

Keywords: Hiccups; psychotropics; aripiprazole; antipsychotics; adverse drug reactions; qualitative systematic review

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INTRODUCTION

Hiccups are abrupt, involuntary contractions of the diaphragm and inspiratory musculature followed by sudden glottic closure, producing the characteristic sound⁽¹⁾. Although transient hiccups are common and usually benign, persistent or intractable hiccups may cause substantial distress, sleep disturbance, impaired oral intake, fatigue, and reduced quality of

life⁽²⁾. Persistent hiccups may additionally indicate underlying neurological, gastrointestinal, metabolic, infectious, or pharmacological etiologies.⁽³⁾

Drug-induced hiccups are uncommon but increasingly recognized in clinical practice. Multiple pharmacological agents, including corticosteroids, anesthetics, chemotherapeutics, and psychotropic medications, have been implicated. Among psychotropics, antipsychotics—particularly aripiprazole—appear repeatedly in published literature, although antidepressants, benzodiazepines, stimulants, mood stabilizers, and sedative-hypnotics have also been reported.⁽⁴⁻⁵⁾

The neurobiology of hiccups remains incompletely understood. Current evidence suggests involvement of a complex reflex arc incorporating central dopaminergic, serotonergic, and GABAergic pathways, vagal and phrenic nerve inputs, medullary centers, and respiratory musculature. Psychotropic medications may influence this circuitry through receptor-level effects, neurotransmitter modulation, or pharmacodynamic interactions.⁽⁶⁾

Despite growing recognition of psychotropics-associated hiccups, available evidence remains dispersed across isolated case reports and small case series. No large controlled studies or meta-analytic datasets currently exist. Therefore, synthesis of existing case-based evidence may help identify recurring clinical patterns, implicated drug classes, temporal associations, and therapeutic responses.

The present review aims to systematically synthesize published case-based literature on psychotropics-associated hiccups and provide clinically relevant insights regarding epidemiology, mechanistic hypotheses, and management considerations.

METHODOLOGY

Study Design

This review was conducted as a PRISMA-oriented qualitative systematic review with narrative synthesis focusing on published human case-based literature describing hiccups associated with psychotropic medications.

Literature Search Strategy

Literature searches were performed using PubMed and Google Scholar. Searches were conducted without date restrictions initially and ultimately covered case reports of hiccups induced by commonly used psychotropics between 1976 and 2024.

Following keywords and Boolean operators were used:

("hiccup*" OR hiccups OR hiccough OR singultus)
AND

(psychotropic* OR antipsychotic* OR antidepressant* OR benzodiazepine* OR stimulant* OR mood stabilizer* OR aripiprazole OR sertraline OR fluvoxamine OR clozapine OR perphenazine OR methylphenidate OR carbamazepine OR donepezil OR midazolam)

Manual bibliography screening was additionally performed to identify potentially relevant reports.

Eligibility Criteria

Inclusion Criteria

- Primary human case reports
- Case series
- Original case-based publications
- Reports explicitly describing hiccups temporally associated with psychotropic exposure

Exclusion Criteria

- Narrative reviews
- Editorials and commentaries
- Animal studies
- Duplicate case reports
- Purely mechanistic articles without clinical cases

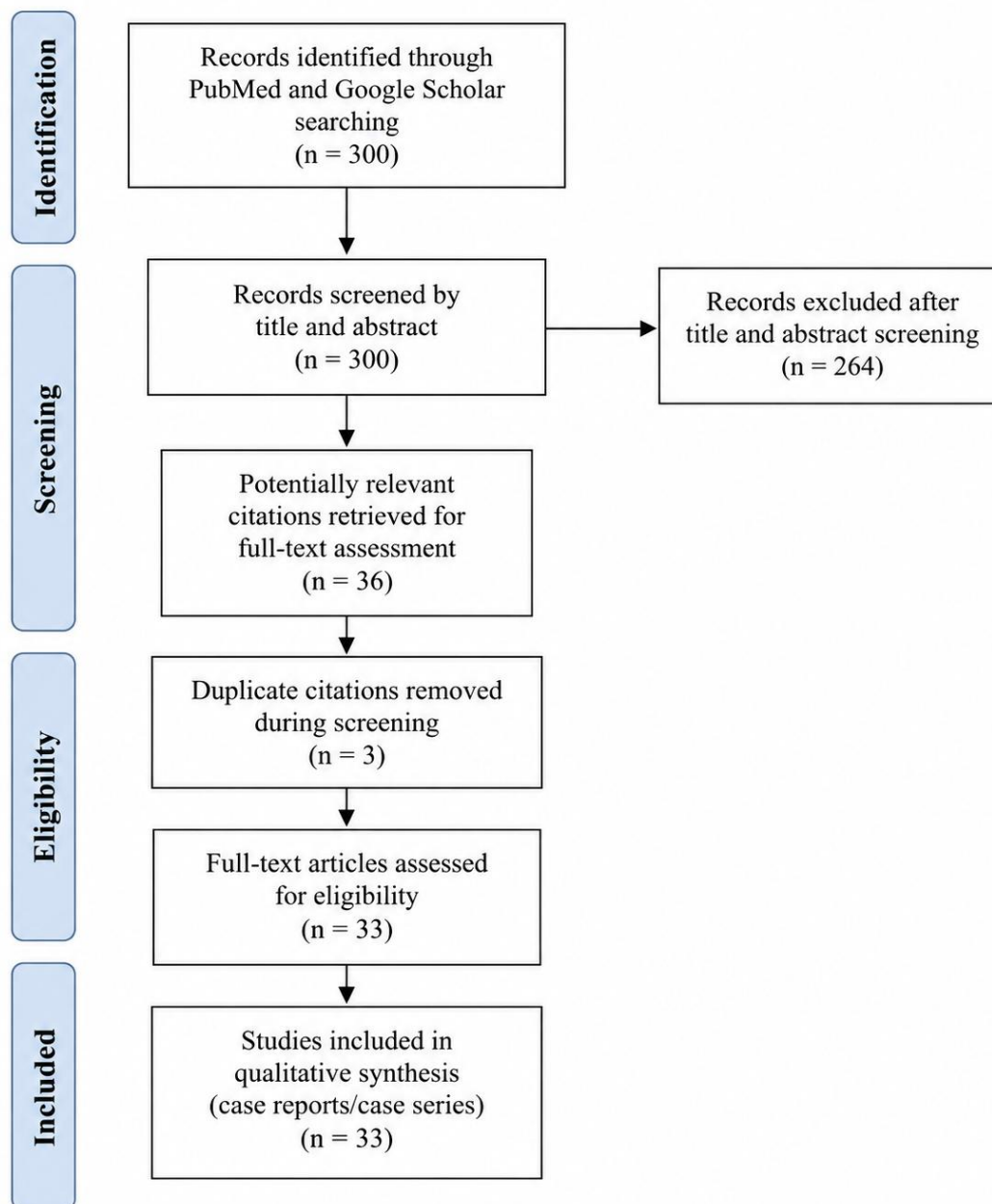
Articles titled as “case report and review of literature” were included only when primary clinical data were presented.

Study Selection

Titles and abstracts were screened for relevance. Full-text evaluation was subsequently performed where available. Duplicate citations and overlapping reports were excluded. Approximately 300 records were initially screened, with 33 unique publications ultimately meeting eligibility criteria.

Quality Considerations

Given the predominance of isolated case reports and small case series, formal quantitative risk-of-bias analysis was not feasible. Instead, emphasis was placed on temporal plausibility, dechallenge/rechallenge relationships, consistency of reported patterns, and clinical coherence.



Reviewer Screening Procedure

Two authors participated independently in the screening and selection process. Initially, titles and abstracts retrieved by literature search were independently screened for relevance by one reviewer. Full texts or detailed abstracts of potentially eligible studies were subsequently assessed independently for inclusion. Any disagreements regarding study eligibility, inclusion, exclusion, or categorization were resolved through discussion and consensus with the second reviewer.

Data Extraction

The following variables were extracted where available:

- Patient demographics
- Psychiatric diagnosis
- Implicated psychotropic agent
- Dosage and route
- Temporal relationship to treatment
- Clinical course
- Management strategies
- Outcomes
- Rechallenge/dechallenge observations

Due to inconsistent reporting across publications, some variables were unavailable in individual reports. GENERATIVE AI was used to create the figures and helping prepare final draft of study.

Data Synthesis

A qualitative synthesis of the included studies which are case reports and case series were performed.

RESULTS

Study Characteristics

Thirty-three unique publications involving at least 35 identifiable clinical episodes were included. Publications spanned from 1976 to 2024. Most reports consisted of isolated case reports, while a minority represented small case series.

Antipsychotics represented the dominant implicated class. Aripiprazole alone accounted for 18 publications. Additional implicated agents included methylphenidate, sertraline, fluvoxamine, clozapine, risperidone, amisulpride, carbamazepine, donepezil, benzodiazepines, and hypnotics.

Several reports involved adolescents or pediatric populations.

Drug-Class Distribution

Antipsychotics accounted for the majority of reported cases, followed by benzodiazepines and antidepressants. Less commonly implicated categories included stimulants, mood stabilizers, hypnotics, and cognitive enhancers.

Principal Implicated Drug Classes

Table 1

Drug Class	Publications
Antipsychotics	20
Benzodiazepines	5
Antidepressants	3
Stimulants	3
Mood stabilizer/antiepileptic	1
Cognitive enhancer	1

Individual Agent Involvement

Aripiprazole emerged as the most frequently implicated individual medication. Other repeatedly identified agents included methylphenidate and sertraline.

Frequently Reported Agents

Table 2

Agent	Publications
Aripiprazole	15
Methylphenidate	3
Sertraline	2
Perphenazine	1
Clozapine	1
Risperidone	2
Amisulpride	1
Fluvoxamine	1
Midazolam	1
Carbamazepine	1
Donepezil	1
Chlordizaepoxide	1
midazolam	1
Benzodiazepines(unspecified)	2

Temporal Patterns

Hiccups commonly developed during:

- Treatment initiation
- Dose escalation
- Medication switching
- Combination therapy

Persistent or protracted hiccups were particularly associated with aripiprazole-containing regimens. Several cases described symptom emergence shortly after medication exposure, supporting a plausible temporal relationship.

Clinical Management and Outcomes

Management strategies varied substantially across reports. Interventions included:

- Drug discontinuation
- Dose reduction
- Medication switching
- Gabapentin
- Chlorpromazine
- Metoclopramide
- Flumazenil
- Add-on risperidone

Clinical improvement frequently followed withdrawal or reduction of the implicated medication.

Table 3. Characteristics of Included Case Reports/Case Series on Psychotropics-Associated Hiccups

n o	Author, Year	Stud y type	Implicated psychotropic agent	Drug class	Clinical context / diagnosis reported	Key clinical pattern	Management outcome reported /
1	Miyaoka & Kamijima, 1999 ⁽⁷⁾	Case report	Perphenazine	Antipsychotic	Psychiatric illness	Hiccups temporally associated with perphenazine exposure	Not fully detailed in current draft
2	Ray et al., 2009 ⁽⁸⁾	Case report	Aripiprazole	Antipsychotic	Psychiatric illness	Aripiprazole-induced hiccups	Improvement after intervention/discontinuation reported in literature
3	Zhang et al., 2024 ⁽⁹⁾	Case report + review	Aripiprazole	Antipsychotic	Psychiatric illness	Persistent hiccups due to aripiprazole	Managed with medication modification/supportive treatment
4	Carbone et al., 2021 ⁽¹⁰⁾	Case report	Aripiprazole	Antipsychotic	Psychiatric illness	Protracted hiccups after aripiprazole	Regressed after gabapentin
5	Kutuk et al., 2021 ⁽¹¹⁾	Case report	Aripiprazole	Antipsychotic	Schizophrenia	Hiccups in adult patient following aripiprazole	Not fully detailed in current draft
6	Kutuk et al., 2016 ⁽¹²⁾	Case report	Aripiprazole	Antipsychotic	Adolescent with OCD	Persistent hiccups after aripiprazole	Responded to dose reduction; rechallenge noted
7	Serafini et al., 2019 ⁽¹³⁾	Case report + review	Aripiprazole	Antipsychotic	Psychiatric illness	Persistent hiccups associated with aripiprazole	Not fully detailed in current draft
8	Sakalli Kani et al., 2015 ⁽¹⁴⁾	Case report	Aripiprazole	Antipsychotic	Psychiatric illness	Acute hiccups after aripiprazole	Not fully detailed in current draft

9	Silverman et al., 2014 ¹⁵⁾	Case report	Aripiprazole	Antipsychotic	Psychiatric illness	Aripiprazole-associated hiccups	Not fully detailed in current draft
10	Rao et al., 2021 ⁽¹⁶⁾	Case report	Midazolam	Benzodiazepine	Procedural/anesthetic setting	Midazolam-induced hiccups	Reversed by flumazenil
11	Li et al., 2022 ⁽¹⁷⁾	Case report	Aripiprazole + sertraline	Antipsychotic + SSRI	Adolescent with olfactory reference disorder	Hiccups after combined therapy	Improved after medication modification
12	Hori & Nakamura, 2014 ⁽¹⁸⁾	Case report	Switch from olanzapine to aripiprazole	Antipsychotic switch	Paranoid schizophrenia	Hiccups after switching to aripiprazole	Not fully detailed in current draft
13	Bilgiç, 2019 ⁽¹⁹⁾	Case report	Sertraline	Antidepressant / SSRI	Boy with OCD and ADHD	Possible sertraline-induced hiccups	Not fully detailed in current draft
14	Alamiri & Naguy, 2021 ⁽²⁰⁾	Case report	Methylphenidate	Stimulant	Child with ADHD	Persistent hiccups after methylphenidate	Relieved by add-on risperidone
15	Chang et al., 2022 ⁽²¹⁾	Case report	Long-acting injectable aripiprazole	Antipsychotic	Psychiatric illness	Persistent hiccups related to LAI aripiprazole	Not fully detailed in current draft
16	Micallef et al., 2005 ⁽²²⁾	Case series	Benzodiazepines	Benzodiazepines	Three clinical cases	Hiccups temporally associated with benzodiazepines	Not fully detailed in current draft
17	Kutuk et al., 2017 ⁽²³⁾	Case report	Aripiprazole + methylphenidate	Antipsychotic + stimulant	Adolescent with ADHD and conduct disorder	Hiccups after combination treatment	Not fully detailed in current draft
18	Solla et al., 2006 ⁽²⁴⁾	Case report	Clozapine	Antipsychotic	Alzheimer's disease	Clozapine-induced persistent hiccups	Not fully detailed in current draft
19	Cheng & Tsai, 2015 ⁽²⁵⁾	Case report	Switch from paliperidone to amisulpride	Antipsychotic switch	Psychiatric illness	Persistent hiccups after switch to amisulpride	Not fully detailed in current draft
20	Yeh, 2011 ⁽²⁶⁾	Case report	Switch from risperidone to aripiprazole	Antipsychotic switch	Schizophrenia with cerebral palsy	Persistent hiccups after switch to aripiprazole	Not fully detailed in current draft
21	Cheng et al., 2011 ⁽²⁷⁾	Case report	Risperidone	Antipsychotic	Youth with Down syndrome	Risperidone-induced hiccups	Not fully detailed in current draft
22	Bilgiç et al., 2016 ⁽²⁸⁾	Case report	Aripiprazole	Antipsychotic	Adolescent with bipolar disorder	Hiccups associated with aripiprazole	Not fully detailed in current draft
23	Winstead, 1976 ⁽²⁹⁾	Case report	Chlordiazepoxide	Benzodiazepine	Clinical case	Hiccups after oral chlordiazepoxide	Not fully detailed in current draft

24	Mathews et al., 2018 ⁽³⁰⁾	Case report	Aripiprazole	Antipsychotic	Psychiatric illness	Hiccups during aripiprazole dose titration	Not fully detailed in current draft
25	Benyakorn, 2017 ⁽³¹⁾	Case report	Aripiprazole	Antipsychotic	Psychiatric illness	Persistent hiccups after aripiprazole	Not fully detailed in current draft
26	Casanovas et al., 2020 ⁽³²⁾	Case report	Antidepressant, unspecified in current draft	Antidepressant	Psychiatric illness	Hiccups as uncommon antidepressant adverse effect	Not fully detailed in current draft
27	Ozen et al., 2018 ⁽³³⁾	Case report	Aripiprazole	Antipsychotic	Psychiatric illness	Hiccups possibly induced by aripiprazole	Mechanistic discussion included
28	Akaltun et al., 2018 ⁽³⁴⁾	Case report	Methylphenidate	Stimulant	ADHD	Hiccups during methylphenidate treatment	Not fully detailed in current draft
29	Bozhüyükk et al., 2009 ⁽³⁵⁾	Case report	Fluvoxamine	Antidepressant / SSRI	Psychiatric illness	Persistent hiccups with fluvoxamine	Not fully detailed in current draft
30	Inecik & Herguner, 2022 ⁽³⁶⁾	Case report	Carbamazepine	Mood stabilizer / antiepileptic	Pediatric clinical case	Carbamazepine-induced hiccups	Not fully detailed in current draft
31	McGrane et al., 2015 ⁽³⁷⁾	Case report	Donepezil	Cognitive enhancer	Cognitive disorder/dementia context	Donepezil-related intractable hiccups	Not fully detailed in current draft
32	Besenek, 2020 ⁽³⁸⁾	Case report	Switch from quetiapine to aripiprazole	Antipsychotic switch	Adolescent psychiatric patient	Hiccups after switching to aripiprazole	Not fully detailed in current draft
33	Vorona et al., 2014 ⁽³⁹⁾	Case report	Hypnotic agent	Sedative-hypnotic	Sleep/hypnotic medication exposure	Hypnotic-associated hiccups	Not fully detailed in current draft

Table footnote: Several reports lacked complete patient-level details regarding dose, route, exact latency, and follow-up; therefore, unavailable variables were recorded as “not fully detailed in current draft.”

DISCUSSION

This review synthesizes available case-based literature concerning psychotropics-associated hiccups across multiple psychotropic classes. Although evidence remains limited to case reports and small case series, several clinically meaningful patterns emerge.

The most striking observation is the predominance of aripiprazole-associated cases. Aripiprazole’s unique pharmacodynamic profile as a partial dopamine D2 receptor agonist with serotonergic activity may contribute to dysregulation within the hiccup reflex arc. Proposed mechanisms include alterations in dopaminergic modulation, serotonergic imbalance, and GABAergic signaling.

The hiccup reflex arc likely involves complex interactions between central neurotransmitter systems and peripheral neural pathways. Psychotropics may influence medullary respiratory centers, vagal and phrenic pathways, or brainstem interneuronal circuits. Individual susceptibility factors—including neurological vulnerability, concomitant medications, developmental stage, and psychiatric illness itself—may further modify risk.

Temporal patterns observed across reports strengthen the plausibility of psychotropics-associated hiccups as a genuine adverse drug reaction. Hiccups frequently emerged during treatment initiation, dose escalation, switching between antipsychotics, or exposure to combination regimens. Several reports also documented symptom resolution following drug discontinuation or dose reduction.

The predominance of antipsychotic-related cases may reflect both pharmacodynamic vulnerability and reporting bias. Antipsychotics are widely prescribed and often produce prominent neurophysiological effects capable of influencing respiratory and brainstem reflex pathways. Nevertheless, the repeated appearance of aripiprazole across multiple independent reports suggests a potentially meaningful signal warranting greater clinical attention.

Management approaches remain heterogeneous due to the absence of controlled studies. Drug discontinuation or dose reduction appeared most consistently beneficial. Gabapentin, chlorpromazine, metoclopramide, and flumazenil demonstrated benefit in selected cases. Clinicians should carefully evaluate temporal associations between medication exposure and symptom onset before initiating extensive diagnostic investigations.

Strengths and Limitations

This review provides a focused synthesis of psychotropics-associated hiccups across diverse psychotropic classes and highlights recurring clinical patterns within existing literature.

However, important limitations must be acknowledged:

- Evidence is limited predominantly to isolated case reports and small case series
- Publication bias is likely substantial
- Incidence and prevalence cannot be estimated
- Reporting quality varied considerably across studies
- Formal causality assessment was inconsistent
- Many reports lacked detailed dosing, management, or follow-up information

Consequently, conclusions should be interpreted cautiously.

CONCLUSION

Psychotropics-associated hiccups appear to represent an uncommon but clinically relevant adverse effect phenomenon. Antipsychotics—particularly aripiprazole—dominate the available case-based literature, although antidepressants, benzodiazepines, stimulants, mood stabilizers, and hypnotics have also been implicated.

Current evidence supports a probable role of dopaminergic, serotonergic, and GABAergic dysregulation within the hiccup reflex arc. Temporal associations with treatment initiation, dose escalation, switching, and combination therapy further support medication-related causality.

Clinicians should consider psychotropic exposure when evaluating persistent or unexplained hiccups in psychiatric populations. Greater pharmacovigilance and future prospective studies are needed to better define mechanisms, risk factors, and optimal management strategies.

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