The Use Of Antipsychotics In The Treatment Of Catatonia: A Systematic Review

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ABSTRACT

Background: Catatonia in psychotic patients presents unique challenges. While antipsychotics are the cornerstone of schizophrenia treatment, their use in catatonic patients is sometimes discouraged for fear of worsening the signs. Reports of successful use of second-generation antipsychotics have been published. We conducted a systematic review according to PRISMA guidelines to describe the outcomes of antipsychotic-treated catatonic events.

Methods: We searched Medline and Web of Science databases from 2000 to 2023 using search terms including “catatonia” and “antipsychotic agents” for all original peer-reviewed articles, including clinical trials, observational studies, and case-reports. We included antipsychotic-treated catatonic events and extracted data on patient characteristics, pharmacological context, agent involved, and treatment outcomes for each antipsychotic trial.

Results: After screening 6,219 records, 79 full-text articles were included. Among them, we identified 175 antipsychotic trials (in 110 patients). Only 41.1% benefited from a previous benzodiazepine trial. Antipsychotic use was considered beneficial in 60.0% of trials, neutral in 29.1%, and harmful in 10.9%. Trials tended to be reported as beneficial for amisulpride, clozapine and risperidone, equivocal for aripiprazole and olanzapine, and mostly detrimental for haloperidol and quetiapine. Psychotic disorders were the most common underlying etiology (65.8%).

Conclusions: Antipsychotics could be an option in the treatment of catatonia in psychotic patients. However, with few exceptions, we found non-beneficial outcomes with all second-generation antipsychotics in varying proportions in this largest review to date. While olanzapine is widely used in the few relevant studies and recommended in recent literature reviews, it is associated with mitigated reported outcomes.

Keywords: catatonia; schizophrenia; therapeutics; antipsychotics; systematic review

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1. INTRODUCTION

Catatonia, first described by Kahlbaum in 1874 [1], is a neuropsychiatric syndrome characterized by motor, affective, behavioral, and sometimes autonomic dysregulations. Signs can be assessed using the Bush-Francis Catatonia Rating Scale (BFCRS), which has high sensitivity and specificity [2,3]. Although under-recognized [4,5], catatonia has a mean prevalence of 9.2% among subjects diagnosed with psychiatric or general medical conditions (GMC) [6]. Catatonia frequently complicates mood (20,1%) and psychotic disorders (9.8%) but is also common in medical situations (20.6%) [6–9]. Iatrogenic catatonia, initially described as antipsychotic-induced [10,11], also occurs after abrupt clozapine discontinuation [12,13].

"Malignant" catatonia (MC), which is characterized by altered consciousness, autonomic dysfunction, and hyperthermia [14,15], can be life-threatening [8,16] while prognosis of uncomplicated catatonia remains good. Benzodiazepines (BZD) are the gold-standard treatment [17–19] with a response rate of around 80% [20]. Electroconvulsive therapy (ECT) is used as second-line treatment or as first-line treatment for patients with MC or unable to undergo a BZD trial [21–23].

The impact of catatonia on schizophrenia prognosis and therapeutic response is unclear [24,25]. Catatonic signs could be a marker of a less responsive subtype [24,26–28]. The use of antipsychotics in catatonic patients is discouraged even in the presence of underlying psychotic disorders because of an increased risk of ineffectiveness and clinical deterioration [8,14,15,29,30]. Fink and Taylor [8] recommended postponing antipsychotic introduction until syndrome resolution while others [7,31,32] proposed to introduce antipsychotics only in patients already treated with BZD.

Conversely, there has recently been an increase in successful cases involving second-generation antipsychotics (SGA) in catatonia. In the first years of their market introduction, some authors believed that SGA were safer and did not induce neuroleptic malignant syndrome (NMS) [8]. While catatonia or NMS has since been reported with all SGA [33–36], some authors suggest that the

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incidence and mortality of NMS might be lower with SGA [37–42]. Similarly, SGA may cause less catatonic syndromes than FGA [43]. A previous review of 10 successful cases suggested their potential usefulness in non-MC patients [44]. The Maudsley prescribing guidelines suggest "careful consideration" of olanzapine or clozapine in schizophrenic patients with catatonia when NMS has been ruled out [45]. Another recent review suggests using SGA "if psychosis is a prominent feature" [46]. Finally, abrupt clozapine withdrawal has been associated with the onset of catatonia, effectively treated by its reintroduction [12,13]. However, the use of antipsychotics remains one of the most controversial areas in catatonia management [47].

To determine whether antipsychotics could be an alternative treatment for catatonia, we conducted a systematic review of the literature investigating the outcomes of catatonic events treated with antipsychotics.

2. METHODS

2.1 SEARCH STRATEGY

A systematic literature search was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [48]. We searched 2 electronic databases (Medline and Web of Science) using MeSH terms and keyword-based queries. In each database, we searched for "cataton*" in combination with antipsychotic-related keywords using Boolean operators. Searches including all antipsychotics by name according to the Anatomical Therapeutic Chemical classification were also conducted. Searches were restricted to adult humans and included articles published between January 1st, 1951 (distribution of chlorpromazine) and December 31, 2023. During title screening, the period of interest was narrowed from 2000 to 2023 to capture more actual prescribing habits.

Duplicate references were removed. Titles and abstracts were independently screened for inclusion by two authors (MR, JV). When there was disagreement in the assessment, the article was retained

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for full-text screening. Any disagreement on the inclusion of a full-text article was resolved by consensual discussion with all authors, including 2 senior psychiatrists with expertise in catatonia (EV, JDC) and one clinical psychopharmacologist (FM).

Attempts were made to contact authors if the article was unavailable. The reference lists of all eligible publications and review articles were hand-searched to identify other relevant articles.

2.2 Eligibility criteria

We included all original peer-reviewed articles (case-control studies, cohort studies, case reports and case series) reporting on the successful or unsuccessful use of antipsychotics after the onset of catatonia, either as a monotherapy or as an adjunct to conventional treatments.

As standardized tools (such as the BFCRS) were not systematically used to report diagnosis, we decided to assess the presence of catatonia by comparing the signs reported in the article with consensual psychiatric classifications (DSM-IV-TR, DSM-V), taking into account the date of publication. If the signs were unreported or did not meet the classification requirements, the publication was excluded as the presence of catatonia could not be confirmed.

As our aim was to investigate outcomes of catatonic events treated with antipsychotics, we chose the trial of an antipsychotic molecule as the unit of analysis. For each selected article, we isolated all the described “antipsychotic trials” which were defined as antipsychotic initiation or posology change after the onset of catatonia. Thus, multiple antipsychotic trials with different antipsychotics for a single patient were considered as separate antipsychotic trials and recorded as such. Mentions of previous antipsychotic-treated catatonic episodes, if any, were also included in addition to the index episode.

Relevant data for each antipsychotic trial was extracted from eligible articles reporting patient-level data and coded into an Excel database using a standardized method. Publications that did not report detailed patient-level data were not included in the analysis, as descriptive variables related to the

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antipsychotic trials could not be extracted. Any uncertainty concerning the eligibility of an antipsychotic trial or the data extraction was supervised by a senior author (EV) or discussed with the entire research team.

Thus, exclusion criteria were the following: [1] absence of diagnosed catatonia (i.e. absence of diagnostic criteria as defined in DSM, clearly specified in the article) before antipsychotic initiation, [2] unclear treatment strategy or treatment without antipsychotics, [3] lack of clinical evaluation after antipsychotic initiation, [4] patients under 18 years-old, [5] theoretical reviews, and [6] publications in languages other than English and French.

2.3 Data extraction and analysis

Descriptive variables extracted for each antipsychotic trial were demographic characteristics (age, sex), underlying diagnosis (schizophrenia, schizoaffective disorder, other psychotic disorder, bipolar disorder, unipolar depression, GMC, others), personal history of catatonia, characteristics of catatonia (form, periodic, malignant, clozapine withdrawal, BFCRS score), previous treatments (BZD, ECT, antipsychotics), current adjunctive treatments (ECT, BZD, anticonvulsant mood-stabilizers, N-methyl-D-aspartate (NMDA) antagonists, others), characteristics related to antipsychotic exposure (agent, posology, single or combination therapy, delay before introduction, final BFCRS score), and outcome. Unavailable and unclear data were recorded as “unspecified”. Clozapine withdrawal events were defined as occurring in 14 days or less after clozapine discontinuation, as events occurring after a longer interval would likely be due to another mechanism (e.g., a relapse) [12,49].

Outcome was qualitatively defined as “detrimental” (worsening of catatonic signs, onset of MC or NMS, death), “neutral” (no effect on catatonic signs), or “beneficial” (improvement of catatonic signs or complete recovery). When reported in the publication, the results of standardised assessment tools were used to determine the outcome. If multiple agents were introduced at the same time, all were considered as effective or ineffective.

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No criteria for NMS have been fully agreed upon [50,51]. Since DSM-V does not define a number of criteria to reach to diagnose NMS and DSM-IV-TR does not specify decision thresholds for quotation, we choose to use modified DSM-IV-TR criteria with thresholds mentioned in DSM-V: hyperthermia ≥ 38°C, tachycardia ≥ 25% increase, elevated blood pressure ≥ 25% increase, labile blood pressure ≥ 25% modification of systolic BP or ≥ 20% modification of diastolic BP, elevated CPK ≥ four times the upper limit [52,53]. MC was defined as fever and/or elevated or labile blood pressure not due to another cause [14].

Descriptive statistical analysis was performed using Microsoft Excel.

3. RESULTS

3.1 SEARCH RESULTS

6,219 records were initially identified. After the removal of 1,693 duplicates, 4,560 records (including 34 additional records identified through citation searching) underwent title and abstract screening. Of the 125 articles retained for full-text assessment, 79 were included. The PRISMA flowchart is shown in **Figure 1**. The full list of included articles is provided in **Appendix 1.**

Few clinical studies reported patient-level data in line with our inclusion criteria. An open-label study [54] in a sample of 15 patients presenting retarded catatonia with underlying diagnoses of acute psychosis (n=8), undifferentiated schizophrenia (n=6), and depression (n=1) investigated the time to symptom resolution with an augmentation strategy of lorazepam (2-4 mg/d) with low-dose amisulpride (100 mg/d). All catatonic signs resolved by day 2 without adverse effects.

In contrast, another author reported 17 cases of patients with catatonia who progressed to NMS after administration of FGA [29]. Five had autonomic dysfunction and mild pyrexia before antipsychotic administration. Fifteen patients (88%) showed gradual resolution of signs but 2 died.

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In addition, 148 antipsychotic trials were extracted from 77 case reports. As such, 175 distinct antipsychotic trials occurring in 110 patients were analyzed.

3.2 Population' characteristics

Eighty-three antipsychotic trials (47.4%) were on male patients. Age ranged from 18 to 95 years, with a mean age of 33.50 years.

Psychotic disorders were the most common etiology (62.9%) with 84 antipsychotic trials involving patients suffering from schizophrenia (48.0%), 5 schizoaffective patients (2.9%), and 26 other psychotic patients (14.9%). Mood-related disorders were implicated in 28 trials (16.0%): 16 with bipolar disorder (9.1%) and 12 with major depressive disorder (6.9%). Catatonia was due to GMC in 12 trials (6.9%). Among the "other" underlying etiologies, 4 trials were reported in the context of obsessive-compulsive disorders, 2 were substance-induced, 3 occurred in patients with autism spectrum disorder, and 6 were idiopathic. The underlying diagnosis was not specified in 5 trials.

Seventy-one (40.6%) involved a first episode of catatonia. Fifteen (8.6%) involved periodic catatonia, while 24 (13.7%) occurred after clozapine withdrawal. Features of MC were present for 14 trials (8.0%) but data was frequently missing. Notably, catatonia was of stuporous form in 129 (73.7%) trials, excited in 17 (9.7%) and mixed in 29 (16.6%). Pre-trial BFCRS scores were reported for only 59 trials (33.7%) and ranged from 13 to 52 (mean of 26). The BFCRS after antipsychotic introduction was only reported in 23 (13%) trials. The delay between catatonia onset and antipsychotic initiation was almost systematically missing or unclear but ranged from a few days to 3–4 months.

Benzodiazepines were tried before antipsychotics in 72 trials (41.1%) and ECT in 28 (18.1%). A summary of the characteristics of the population and the context of antipsychotic exposure is presented in **Table 1**.

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3.3 ANTIPSYCHOTIC EXPOSURE AND OUTCOME

SGA were used in 140 antipsychotic trials (80.0%), while 38 trials (21.7%) involved FGA. Olanzapine was involved in 39 trials (22.3%), clozapine in 32 (18.3%), risperidone in 22 (12.6%), haloperidol in 19 (10.9%), amisulpride in 18 (10.3%), aripiprazole in 17 (9.7%), quetiapine in 8 (4.6%), clothiapine in 6 (3.4%), chlopromazine in 4 (2.3%), and fluphenazine and ziprasidone in 3 (< 2%). Sulpiride, paliperidone, benperidol and zuclopenthixol were involved in 2 trials each. Loxapine, flupenthixol, perphenazine and asenapine only appeared in one trial each.

In some antipsychotic trials (44.0%), several concomitant therapies were used. BZD were co-prescribed in 64 trials (36.6%), whereas ECT was only used in 6 trials (3.4%). Anti-epileptic agents were reported in 11 trials (6.3%), NMDA agonists in 5 (2.9%) and antidepressants in 6 (3.4%). Detailed data was missing for a significant proportion of trials.

Treatment with antipsychotics was considered beneficial in 105 trials (60.0%), neutral in 51 trials (29.1%), and detrimental in 19 trials (10.9%). For detrimental outcomes, FGA were the most represented with 14 trials (73.7%), including the use of clothiapine (6 trials), haloperidol (4 trials), fluphenazine (2 trials), chlorpromazine (2 trials), and perphenazine (1 trial). Only 5 trials involved SGA: 4 with olanzapine and 1 with clozapine. NMS occurred in 4 patients (2 with olanzapine, 1 with clozapine, 1 with haloperidol). Three patients died (2 with clothiapine and 1 with olanzapine).

Fourteen trials featured MC, with underlying diagnosis of psychotic disorders (5 trials), mood-related disorders (6 trials), and GMC (3 trial). None reported worsening after antipsychotic initiation. The outcome was stable in 3 trials and beneficial in 11 trials. Only 9 cases benefited from a previous BZD trial and only 1 from ECT.

Eight trials (4.6%) involved antipsychotic bi-therapy, mainly through augmentation therapy. One patient remained stable after bi-therapy with aripiprazole and haloperidol [55]. In another case, the combination of quetiapine and risperidone did not produce positive results but the evolution was

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favorable with amisulpride and risperidone [56]. Similarly, the combination of zuclopenthixol and olanzapine followed by a switch to clozapine was ineffective, but the addition of asenapine yielded results [57]. A beneficial outcome was reported after co-prescription of haloperidol and olanzapine [58]. Worsening of signs and death were reported after association of clothiapine and perphenazine [29].

In terms of clozapine-withdrawal induced catatonia, 17 trials (70.8%) showed beneficial evolution, mostly with clozapine reintroduction but also with risperidone [59], amisulpride [60], and olanzapine [61].

3.4 "Beneficial" versus "Neutral/Detrimental" trials

To get a more precise description of the parameters associated with a beneficial response to antipsychotics, we compared the characteristics of "beneficial" trials to "neutral" and "detrimental" trials.

Only beneficial interventions were reported for amisulpride and asenapine. In contrast, all interventions with clothiapine, fluphenazine, sulpiride, zuclopenthixol, flupenthixol, loxapine, and perphenazine were neutral or detrimental. The ratio of "beneficial" to "neutral/detrimental" reported outcome was favorable for clozapine (7.0), risperidone (2.7), and ziprasidone (2.0). It appeared almost balanced for aripiprazole (1.4) and olanzapine (1.2) but unfavorable for haloperidol (0.6), quetiapine (0.6) and chlorpromazine (0.33). The distribution of trials for each agent is reported in **Figure 2**.

Males were slightly more represented in the "neutral/detrimental" group (54.3% versus 42.9%). Psychotic disorders were over-represented in the "beneficial" group with 71 trials (67.6%) compared to 39 trials (55.7%) in the "neutral/detrimental" group. This was particularly striking for haloperidol where all patients with "beneficial" trials suffered from psychotic disorders compared with only 40% of the "neutral/detrimental" trials. GMC were also more common in the "beneficial" group (8.6% vs.

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4.3%). Conversely, mood disorders appeared to be more common among “neutral/detrimental” trials (20.5% vs. 12.4%). Similarly, 50% of the 19 detrimental trials were associated with mood disorders. The mean BFCRS was similar between the groups but excited form was more common in “neutral/detrimental” trials (12.9% vs. 7.6%).

Regarding prior interventions, “beneficial” trials benefited more from BZD (45.7% vs. 34.3%) and ECT (18.1% vs. 12.9%) before antipsychotic exposure. Co-prescription of benzodiazepines (45.7% vs. 22.9%) and ECT (5.7% vs. 0%) was also higher in the “beneficial” group. Outcomes for bitherapy did not differ from monotherapy. Main differences are summarized in **Table 1**. Mean doses (reported in “defined daily doses”) [62] for FGA and SGA are presented in **Table 2**.

4. Discussion

This review presents the outcomes and the associated pharmacological context of 175 antipsychotic trials in patients presenting catatonia. Trials originate mainly from case reports and case series. Antipsychotic use was considered beneficial in 105 trials (60.0%), neutral in 51 trials (29.1%), and detrimental in 19 trials (10.9%). While amisulpride, clozapine, and risperidone tended to be reported with a beneficial outcome, olanzapine and aripiprazole showed mixed results. Outcomes for FGA and quetiapine were detrimental.

4.1 Antipsychotics in catatonia: an option?

The place of antipsychotics in the management of catatonia is still under debate. Withdrawal until the resolution of the episode is generally recommended with the argument that they may precipitate, maintain or worsen catatonia [11,63–65]. However, some authors argue that the risk of exacerbation may be concentrated in antipsychotics with a higher D2 dopamine receptor blockade [39,66,67], which is consistent with our findings.

The majority of the published reports over the last 20 years have described beneficial or at least well-tolerated SGA trials during catatonic events. Only a few cases reported worsening of signs and these

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were mainly associated with the use of FGA (representing 22% of trials), which was beneficial in only 9 trials but caused 74% of the detrimental outcomes, whereas SGA (80% of trials) were harmful in only 5 trials (4%) but were responsible for 92% of the improvements. FGA should be avoided as they carry a greater risk of worsening catatonia.

4.2 Differential response between SGA

In descending order, the most commonly used SGA were olanzapine, clozapine, risperidone, amisulpride, and aripiprazole. Despite being recommended by some authors [68,69], quetiapine was seldom used with poorer outcomes. In our review, olanzapine was ineffective in 46% of its trials and aripiprazole in 41%. In addition, of the 5 trials reporting detrimental outcomes with SGA, 4 were with olanzapine (including 2 NMS and 1 death). The mixed results for olanzapine and aripiprazole are particularly interesting as they are among the most recommended antipsychotics in recent reviews [22,46,70], which is likely based on studies that found olanzapine to be potentially effective in catatonia with underlying psychotic disorders. Indeed, a 6-week efficacy analysis [71] conducted on data from 35 patients diagnosed with schizophrenia found olanzapine to significantly reduce catatonic signs in the 25 remaining patients at week 6. Another study [72] investigated the treatment response of catatonic features after a one-month trial of antipsychotics (haloperidol, risperidone or olanzapine) in 24 antipsychotic-naive patients diagnosed with catatonia and non-affective psychosis. Catatonia scores improved significantly after one month with only 4 patients remaining catatonic. Nevertheless, our results appear to be consistent with those of a retrospective chart review [73] of 25 catatonic patients with various underlying psychiatric disorders. Aripiprazole was tried in 3 patients but worsened some catatonic signs (2 neutral, 1 likely detrimental). Nine patients received olanzapine with mixed results: 4 definitely beneficial, 2 neutral, and 3 likely detrimental.

Amisulpride, clozapine, and risperidone were associated with more positive outcomes in our review. However, almost all amisulpride trials were included from one open-label study that proposed its use at low dosages in addition to lorazepam [54]. For clozapine, in addition to the phenomenon of

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"clozapine-withdrawal catatonia" with a positive outcome with clozapine reintroduction [12,13], we identified 14 beneficial reports with clozapine, thus supporting its proposed use in recent recommendations [22,46,70], particularly for clozapine-withdrawal catatonia. Notably, clozapine induced NMS in one trial. In the retrospective chart review previously mentioned [73], 7 patients received clozapine with 6 definitely beneficial outcomes and one likely beneficial, all after long exposure (mean of 7 weeks). Concerning risperidone, a double-blind, randomized, controlled study compared its efficacy (2 mg/d increased to 4-6 mg/d) with bilateral ECT for 3 weeks in 14 non-affective, lorazepam-resistant, catatonic patients with schizophrenia [74]. BFCRS scores decreased in both groups but significantly more in the ECT group (90% vs 50%). No worsening of catatonia or onset of NMS was observed.

The numerous reports of ineffectiveness and the occurrence of NMS with olanzapine raise concerns about its use and its "recommended" status in algorithms. Although aripiprazole may be an option and seems well-tolerated, it appears to be only moderately effective in our review. It seems preferable to use low-potency drugs such as clozapine. Amisulpride, which preferentially blocks presynaptic D2 and D3 receptors causing dopamine release at low dose [75], could be another option.

4.3 CATATONIA WITH UNDERLYING PSYCHOTIC DISORDERS: A THERAPEUTIC NICHE

We found an over-representation of psychotic disorders in our results compared with prevalence studies [6]. Psychotic disorders were also over-represented in the "beneficial" group with 68% of trials compared to 56% in the "neutral/detrimental" group. Conversely, mood disorders were more common in the latter.

The treatment of catatonic schizophrenia is particularly difficult and remains challenging in clinical practice, as first-line treatments for catatonia may be less effective in this subgroup. There is increasing evidence to suggest that catatonic patients presenting with psychotic disorders respond

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less well to BZD [24,76–78]. ECT was also reported to be less effective in catatonic schizophrenia than in affective disorders in a case series [79]. Differences in response rates to different treatments depending on etiology support an influence of the underlying etiology on the response to a given treatment. Both FGA and SGA demonstrated clear and rapid efficacy in the treatment of schizophrenia [80–83]. One hypothesis might be that prescribing antipsychotics to people with catatonic schizophrenia might improve the catatonic syndrome by acting on the underlying disorder.

While understanding the mechanisms of SGA in catatonia remains complex given their multiple actions, some authors suggest that 5HT2A antagonism, 5-HT1A agonism, and GABA agonism may increase dopamine release in the prefrontal cortex, which could reduce catatonic signs [84,85]. Therefore, the use of SGA with a low D2 blockade, GABA-A-regulating potencies such as clozapine [86], or with D2 partial agonism such as aripiprazole [87] has already been proposed as a second- or third-line treatment for patients with underlying psychotic disorders [22,44,46].

Benzodiazepines had not been tried before antipsychotics in almost half of the trials. The particularly low trial rate of BZD in psychotic patients may be related to lower efficacy in this context. A randomized, double-blind, placebo-controlled, 12-weeks crossover study in 18 patients with chronic schizophrenia and catatonia reported a non-significant difference in response between placebo and lorazepam [88]. Response rates of only 20%-30% [63] or 59.1% [89] were reported compared with an overall response rate of over 80% with other underlying etiologies [20]. Finally, some recommendations advocate for a trial of SGA in stuporous catatonia in the context of psychotic disorders even before a BZD trial [45].

In our review, BZD were co-prescribed in only one third of the trials and were more commonly co-prescribed in the “beneficial” trials (42%) than in the “neutral/detrimental” (22%). In line with the suggestion of Caroff *et al.* [7] and the recommendation of recent consensus guidelines [47], we would recommend trying BZD monotherapy before antipsychotic initiation and to continue it as an

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adjunctive treatment after SGA initiation in the hope that this will reduce the risk of clinical deterioration and improve efficacy.

4.4 Strenghts and Limits

There are several limitations to our review. Almost all of the included data come from case reports, which are primarily written to report unusual events and are subject to various biases such as publication bias, recall bias and over-interpretation. As such, our results represent only the frequency of events reported in the literature, not the frequency of occurrence in real-world practice. Furthermore, data were collected without access to the overall relative usage of each class of antipsychotic or individual agent in the clinical setting where each case occurred. It is likely that FGA prescription decreases and SGA prescription increases over the study period. As poor response and clinical deterioration in antipsychotic-treated catatonic patients were established decades ago, adverse outcomes with newer drugs may be under-reported. Given these limitations, it is impossible to perform meaningful statistical analyses and generalize our results widely. Another limitation is the heterogeneity of the reported data between case reports. Clinical description varied from basic exposure of signs and mentions of antipsychotics used to extensive data on co-prescriptions and previous trials. The comparison between qualitatively-assigned “beneficial” and “neutral/detrimental” groups is limited by the lack of consistency and the high percentage of unspecified data. Additionally, the manuscripts did not use causality criteria; unreported confounding factors may be involved in the improvement of catatonic signs.

Despite the above-mentioned limitations, the present work has several strengths. To our knowledge, this is the largest review of antipsychotic-treated catatonic syndromes reported over a 20-year period using a systematic approach with only peer-reviewed cases. To increase our confidence in the diagnosis of catatonia, we restricted trial inclusion to detailed clinical description meeting DSM-5 criteria for catatonia. To be comprehensive, we included all reported antipsychotic trials in publications in addition to the index trial to capture broader information and possible ineffective

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previous trials. The detailed variables extracted from the reports enable thorough analysis of associated factors. Our findings add to recently published reviews of alternative treatments for catatonia and may help guide clinicians when dealing with patients suffering from disorders that warrant reliance on antipsychotic medication.

4.5 Conclusion

Although mostly based on case reports, this is the largest review published to date, providing new insights into how SGA might be useful in the treatment of catatonia in patients with psychotic disorders. Our findings support a higher risk of clinical deterioration with FGA, while SGA might be a possible therapeutic option in combination with BZD. Nevertheless, worsening of signs or ineffectiveness has been reported in varying proportions for almost every SGA, which should prompt caution in their use. Despite being the most widely used antipsychotic, the efficacy and safety profile of olanzapine appears mixed, which may temper the recommendations in favor of its use. Clinical trials designed to investigate the risk/benefit balance of SGA treatment in catatonic patients should be proposed.

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Conflicts of interest

Conflict of interest: the authors declare none.

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SUPPLEMENTARY MATERIAL

For supplementary material accompanying this paper, visit Cambridge.org/EPA.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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628 **Table 1 – Patient characteristics and context of antipsychotic trial**

	All trials (%)	Beneficial (%)	Neutral/Detrimental (%)
Number of trials	175 (100)	105 (60.0)	70 (40.0)
Age			
Average age	33.50	31.68	35.31
Median age	32	32	31
Age range	18–95	18–85	18–95
Unspecified	18	17	1
Sex			
Male	83 (47.4)	45 (42.9)	38 (54.3)
Female	77 (44.0)	45 (42.9)	32 (45.7)
Unspecified	15 (8.6)	15 (14.2)	-
Underlying disorder			
Schizophrenia	84 (48.0)	55 (52.4)	29 (41.4)
Other psychotic disorder	26 (14.9)	16 (15.2)	10 (14.3)
Schizoaffective disorder	5 (2.9)	4 (3.8)	1 (1.4)
Bipolar disorder	16 (9.1)	7 (6.7)	9 (12.9)
Unipolar depression	12 (6.9)	6 (5.7)	6 (8.6)
General medical condition	12 (6.9)	9 (8.6)	3 (4.3)
Other	15 (8.6)	8 (7.6)	7 (10.0)
Unspecified	5 (2.9)	-	5 (7.1)
First episode			
Yes	71 (40.6)	42 (40.0)	29 (41.4)
No	48 (27.4)	29 (27.6)	19 (27.1)
Unspecified	56 (32.0)	34 (32.4)	22 (31.4)
Periodic catatonia			
Yes	15 (8.6)	8 (7.6)	7 (10.0)
No	107 (61.1)	66 (62.9)	41 (58.6)

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Unspecified	53 (30.3)	31 (29.5)	22 (31.4)
Malignant catatonia			
Yes	14 (8.0)	11 (10.5)	3 (4.3)
No	61 (34.9)	42 (40.0)	19 (27.1)
Unspecified	100 (57.1)	52 (49.5)	48 (68.6)
Clozapine withdrawal			
Yes	24 (13.7)	19 (18.1)	5 (7.1)
No	119 (68.0)	68 (64.8)	51 (72.9)
Unspecified	32 (28.3)	18 (17.1)	14 (20.0)
Clinical form			
Stuporous	129 (73.7)	82 (78.1)	47 (67.1)
Mixed	29 (16.6)	15 (14.3)	14 (20.0)
Excited	17 (9.7)	8 (7.6)	9 (12.9)
Initial BFCRS			
Average	26.3	26	25.6
Range	13–52	13–52	13–41
Unspecified	116 (66.3)	67 (63.8)	49 (70.0)
Previous trials			
Benzodiazepines			
Yes	72 (41.1)	48 (45.7)	24 (34.3)
No	76 (43.4)	52 (49.5)	24 (34.3)
Unspecified	27 (15.4)	5 (4.8)	22 (31.4)
Electroconvulsive therapy			
Yes	28 (16.0)	19 (18.1)	9 (12.9)
No	120 (68.6)	81 (77.1)	39 (55.7)
Unspecified	27 (15.4)	5 (4.8)	22 (31.4)
Antipsychotic			
Yes	47 (26.9)	24 (22.9)	23 (32.9)

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No	107 (61.1)	76 (72.4)	31 (44.3)
Unspecified	21 (12.0)	5 (4.8)	16 (22.9)
Co-prescribed treatment			
Yes	77 (44.0)	58 (55.2)	19 (27.1)
No	58 (33.1)	37 (35.2)	21 (30.0)
Unspecified	40 (22.9)	10 (9.5)	30 (42.9)
Benzodiazepines			
Yes	64 (36.6)	48 (45.7)	16 (22.9)
No	69 (39.4)	44 (41.9)	25 (35.7)
Unspecified	42 (24.0)	13 (12.4)	29 (38.7)
Electroconvulsive therapy			
Yes	6 (3.4)	6 (5.7)	0 (0.0)
No	129 (73.7)	89 (84.8)	40 (57.1)
Unspecified	40 (22.9)	10 (9.5)	30 (42.9)
Anti-epileptic agent			
Yes	11 (6.3)	6 (5.7)	5 (7.1)
No	119 (68.0)	88 (83.9)	31 (44.3)
Unspecified	45 (25.7)	11 (10.5)	34 (48.6)
Anti-NMDA agent			
Yes	5 (2.9)	4 (3.8)	1 (1.4)
No	125 (71.4)	90 (85.7)	35 (50.0)
Unspecified	45 (25.7)	11 (10.5)	34 (48.6)
Antidepressant			
Yes	6 (3.4)	4 (3.8)	2 (2.9)
No	124 (70.9)	90 (85.7)	34 (48.6)
Unspecified	45 (25.7)	11 (10.5)	34 (48.6)
Use of P.R.N.			
Benzodiazepines	6 (3.4)	5 (4.8)	1 (1.4)

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Antipsychotics	3 (1.7)	1 (1.0)	2 (2.9)

Abbreviations: BFCRS = Bush-Francis Rating Scale, ECT = electroconvulsive therapy, NMDA = N-Methyl-D-Aspartic acid, P.R.N.= Pro Re Nata

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631 **Table 2 – Antipsychotic mean dose for FGA and SGA**

	Group	Number of reported trials with dose	Mean DDD Eq Chlorpromazine* ± SD (mg)
FGA	B	4	609.4 ± 386.5
	N/D	22	438.0 ± 227.5
	All	26	462.5 ± 267.6
SGA	B	90	266.9 ± 210.0
	N/D	32	341.8 ± 199.4
	All	122	301.8 ± 213.9

Abbreviations: B = Beneficial, N/D=Neutral/Detrimental, FGA = First-Generation Antipsychotic, SGA = Second-Generation Antipsychotic, DDD Eq = Defined Daily Doses Equivalents, SD = Standard Deviation

* Doses reported for each antipsychotic trial were converted in chlorpromazine equivalents based on defined daily doses (DDDs) calculated with a validated method [62]

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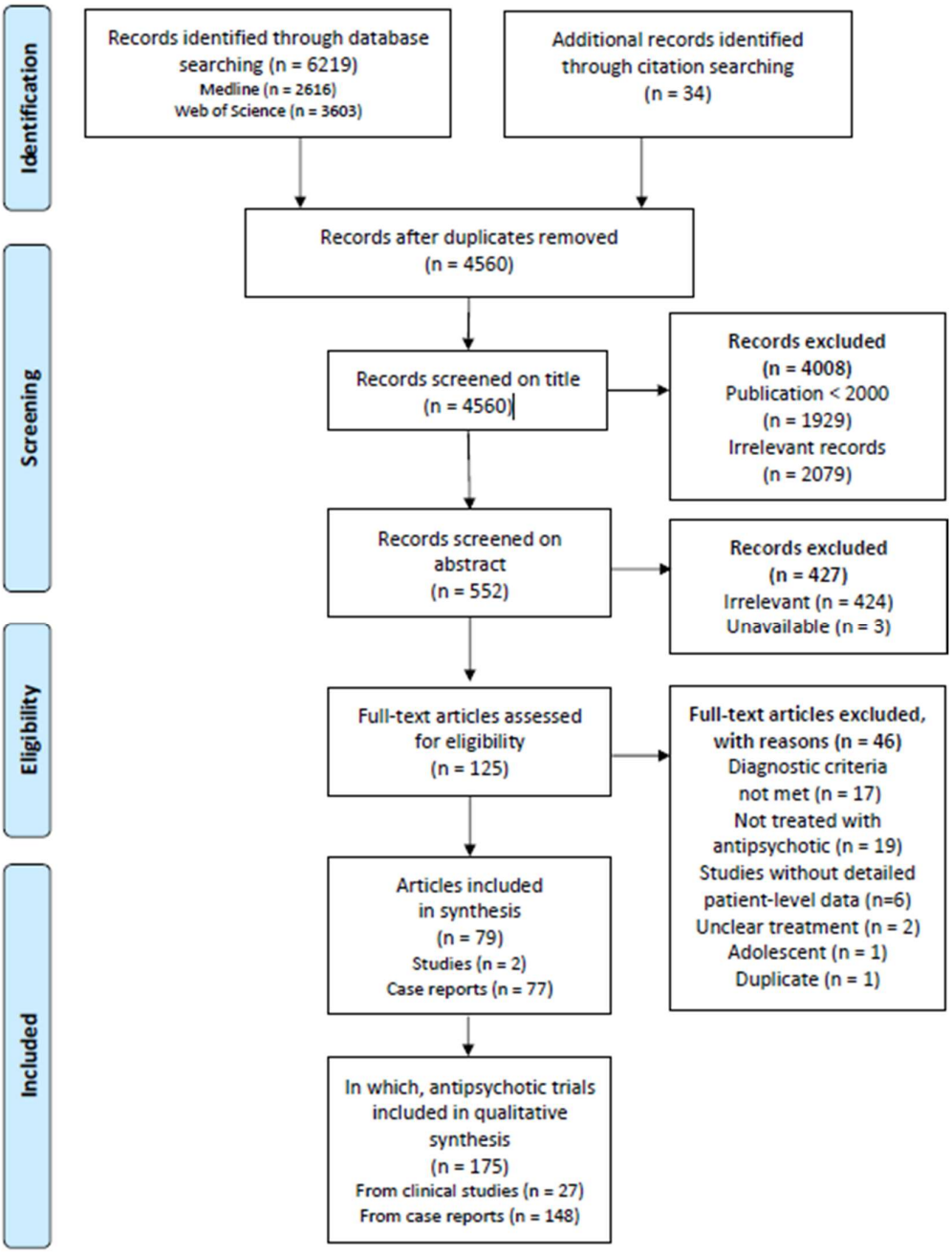
634 Figure 1



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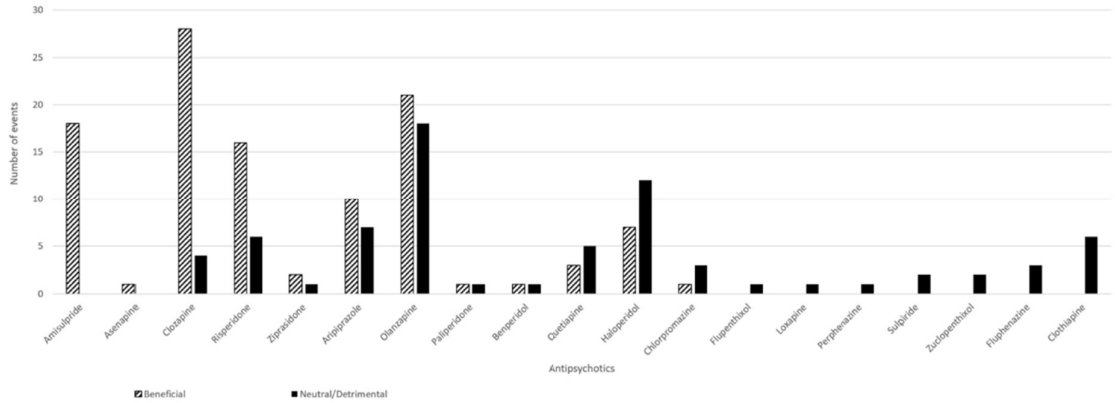
637 Figure 2 – Number of beneficial and neutral/detrimental trials reported for each antipsychotic
638 agent



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