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# Is there Any Relevance for the Use of Cyamemazine in the Treatment of Schizophrenia?

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## Abstract

**Introduction:** Cyamemazine is widely used in the treatment of schizophrenia despite a potential risk of QT interval prolongation on electrocardiogram and weak evidence for its antipsychotic efficacy. The aim of our study was to compare the level of anxiety and the co-prescription of benzodiazepines and hypnotics in schizophrenic patients who received cyamemazine (alone or in association with other antipsychotics) with those who did not receive cyamemazine.

**Materials and methods:** A total of 1,859 patients were enrolled according to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria for schizophrenia. We collected their medication prescriptions and assessment scale scores and compared patients receiving antipsychotic mono or polytherapy with or without cyamemazine at inclusion, 6-, and 12-months. As a comparison, we will use the same outcome measures in patients receiving loxapine or levomepromazine rather than cyamemazine.

**Results:** Brief psychiatric rating score (BPRS) scale anxiety subscores of patients under monotherapy of cyamemezine at inclusion was lower than for other antipsychotic medications but the patients received higher doses of anxiolytics. No differences in psychotropic drug use or anxiety subscores were observed between patients on antipsychotic polytherapy whether cyamemazine was used or not at inclusion, 6-, and 12-months. Patients under antipsychotic polytherapy including cyamemazine had better Global Assessment of Functioning (GAF) scores than patients under polytherapy excluding cyamemazine. Comparison of cyamemazine, loxapine, and levomepromazine groups showed no statistically significant differences in co-prescription of psychotropic drug use or anxiety subscores at inclusion, 6-, and 12-months of follow-up, respectively.

**Conclusion:** Our study does not find any evidence to recommend the use of cyamemazine in the anxiolytic or antipsychotic treatment in patients suffering from schizophrenia.


**Keywords:** Antipsychotic treatment, Anxiety, Cyamemazine, Schizophrenia.

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## Introduction

Antipsychotics are the reference treatments for schizophrenic disorder[1] and international guidelines recommend the prescription of a second-generation antipsychotic as monotherapy at a minimum effective dose in patients suffering from schizophrenia, to avoid side effects, mainly neurological and cardiometabolic.[2–4]

Among antipsychotic medications, cyamemazine seems to have a particular profile with different use depending on the country. It is widely used in France as Tercian®, whereas it is not even commercialized in the United States of America. In France, it represented 17% of antipsychotic prescriptions in 2000,[5] and in 2006, it was the most prescribed antipsychotic.[6] Most of the time, this medication is used as adjuvant therapy, especially in schizophrenia and major depressive episodes.[7,8]

Cyamemazine has a particular pharmacological profile. It is both dopamine and serotonin antagonist with a high affinity for 5-$HT_{2A}$, 5-$HT_{2C}$, and 5-$HT_3$ serotoninergic receptors and a lower affinity for 5-$HT_{1A}$ receptors;[9] as well as a high affinity for $D_3$ and $D_1$ dopaminergic receptors and a lower affinity for $D_2$ and $D_4$ receptors. It has also a high affinity for α-1 adrenergic, histaminergic $H_1$ receptors (associated with sedative effects), and muscarinic receptors. Finally, its affinity for 5-$HT_{2A}$ receptors is 4 times higher than for $D_2$ receptors.[10] The low level of $D_2$ occupancy (in association with a high level of 5-$HT_{2A}$ occupancy) may explain its low potential to induce extrapyramidal side effects as compared to other first-generation antipsychotics, as well as its weak antipsychotic activity at doses below 300 mg/day.[11] In mice, cyamemazine has anxiolytic-like properties at doses 3 times lower than those necessary to induce sedation and antipsychotic-like activities; inhibition of 5-$HT_{2C}$ and to a lesser extent 5-$HT_3$ serotonin receptors can mediate its anxiolytic effects.[8,9,12] Its low affinity for 5-$HT_{1A}$ receptors may also contribute to its anxiolytic properties.

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Levomepromazine is another phenothiazine, structurally similar to chlorpromazine. The receptor binding profile of levomepromazine in the human brain was compared with that of clozapine and chlorpromazine but showed a significantly greater binding affinity for both α-1 and $5HT_2$ binding sites than the two others, and significantly greater binding to α-2 sites than chlorpromazine.[13]

Loxapine has a chemical structure quite similar to clozapine and is a dibenzoxazepine tricyclic antipsychotic agent. Receptor binding, especially at $D_2$, 5-$HT_{2A}$ receptors, and its high 5-$HT_2/D_2$ ratio, is more characteristic of atypical antipsychotics. Loxapine has a similar binding affinity as clozapine and olanzapine with a more potent 5-$HT_{2A}$ antagonism.[14]

Cyamemazine has several side effects including QT interval prolongation that can induce torsades de pointes and ventricular fibrillation;[15] sedation (dose-dependent) and weight gain are also frequently observed. Often associated with antipsychotic polytherapy, cyamemazine is mainly metabolized through the $CYP_{1A2}$, $CYP_{2C8}$, $CYP_{2C9}$, and cytochrome P450 isoenzymes, respectively, which may be associated to interactions with other compounds and potentially to additive effects on QT prolongation.[16–18] Despite this potential severe side effect and the weak evidence in the literature for its antipsychotic efficacy, cyamemazine is still widely used in France in the treatment of schizophrenic patients.[16]

Recommended indications of cyamemazine in France are acute or chronic psychotic symptoms including schizophrenia, anxiety in case of the inefficacy of usual drugs, such as benzodiazepine or antihistaminic treatment, and as an adjuvant medication with an antidepressant in the treatment of severe major depressive episodes.[16] The French health authority considered that the medical service provided by oral cyamemazine in the management of acute and chronic psychotic conditions and during the first weeks of treatment of severe depressive disorders in combination with antidepressant treatment, remained important;[19] in contrast, the medical service provided by oral cyamemazine was moderate for short-term treatment of anxiety.[19]

The aim of our study was to compare the level of anxiety and the co-prescription of benzodiazepines and hypnotics in schizophrenic patients who received cyamemazine (alone or in polytherapy with other antipsychotics) with those who did not receive cyamemazine. As a comparison we will use the same outcome measures in patients receiving loxapine or levomepromazine rather than cyamemazine as sedative antipsychotics.

## Materials and Methods

An observational study was carried out in a large cohort of schizophrenic patients in France. This naturalistic and cross-sectional study aimed at measuring the effectiveness of risperidone long-acting injectable (RLAI), in comparison to other antipsychotic drugs, in patients with schizophrenia. Between December 2005 and July 2007, psychiatrists from 177 public or private hospitals in France, enrolled 1,859 patients. All patients fulfilling DSM-IV criteria for schizophrenia, aged between 15 years and 65 years, either outpatients or hospitalized for less than 3 months, benefiting from Social Security, and who agreed to participate were included. Patients who were not able to understand French, had a severe chronic somatic disease, had been hospitalized for more than 3 months were not included. Psychiatrists collected data at baseline, 6-, and 12-months. Data collected included the following: Socio–demographic data (age, gender, educational level, employment status, living situation, and legal guardianship if any), psychiatric and substance use disorder comorbidities [identified using the Mini-International Neuropsychiatric Interview (MINI);[20] comorbidities, suicide attempt in the past month if any, number and duration of hospitalizations in the past 6 months], symptom severity [using the 7-point Clinical Global Impression-Severity (CGI-S)[21] and the 18-item BPRS-18[22] and the level of psychological, social, and occupational functioning (quantified using the GAF scale[23])]. In addition, all psychotropic medications prescribed and used in the 6 months preceding inclusion were reported (especially antipsychotic, anxiolytic, hypnotic, and antidepressant drugs). For antipsychotic drugs, the type of medication, dose (in mg/day), route of administration (oral/injectable) and mode of action (short-acting/long-acting) have been reported.

We divided the patients into five different groups depending on their antipsychotic prescription as follows: (1) No antipsychotic therapy, (2) Cyamemazine only, (3) One antipsychotic excluding cyamemazine, (4) Antipsychotic polytherapy including cyamemazine, and (5) Antipsychotic polytherapy excluding cyamemazine.

Concerning the follow-up at 36 months, we only focused on patients receiving sedative antipsychotics: cyamemazine, loxapine, or levomepromazine. Patients were divided into three different groups depending on the sedative antipsychotic used in order to compare the therapeutic interest of these three antipsychotics, often used as anxiolytics.

We used the Statistical Analysis System Software, v.9.4 (The SAS Institute Inc., 2008) for statistical analyses. Prescription's percentages in different groups were compared using Chi-squared, Pearson, and Fisher's exact tests. All tests were two-sided and used a type I error $\alpha = 0.05$.

The study was conducted in accordance with the ethical principles regarding human experimentation as set out in the Declaration of Helsinki and was approved by a French Ethics Committee. Every patient, or patient's guardian, gave informed consent.

## Results

In total, 1,859 patients were included in the cohort. The mean age was 38 years (SD: 11). There were 68.6% of male and 37% of patients who had been hospitalized for less than 93 days at inclusion. At baseline, 1,747 (94.0%) patients were treated by an antipsychotic drug, including 649 patients (34.9%) with polypharmacy and 1,089 patients (59.1%) on monotherapy. 112 (6.0%) received no antipsychotic drugs at inclusion. Due to the protocol, oral or long-acting risperidone in 717 (41.0%) patients, was the most frequently prescribed antipsychotic drug. Cyamemazine was prescribed in 403 (23.0%) patients, olanzapine in 294 (16.9%) patients, and haloperidol in 245 (14.0%) patients, respectively. Table 1 describes the characteristics of patients at baseline.

In patients treated with cyamemazine at inclusion ($n = 403$), 94.5% were receiving at least another antipsychotic ($n = 381$). The most frequent combination of antipsychotic drugs consisted of the following: Cyamemazine and risperidone (37.5%, $n = 143$); cyamemazine and olanzapine (9.4%, $n = 36$); and cyamemazine and oral or long-acting form of haloperidol (7.9%, $n = 30$). The antipsychotics most commonly associated with cyamemazine were: oral or long-acting risperidone ($n = 132$), olanzapine ($n = 29$), oral

**Table 1:** Characteristics of patients at baseline

| | *N = 1,859* |
|---|---|
| Socio–demographic data (*N*, %) | |
| Age (years), mean (SD) | 38.1 (11.1) |
| Male gender | 1,276 (68.6%) |
| Living alone (yes) | 1,449 (78.2%) |
| Primary/secondary education (vs higher) | 1,287 (70.3%) |
| Unemployment (vs employed) | 1,521 (84.1%) |
| Schizophrenia history (*N*, %) | |
| Early-onset schizophrenia* | 42 (2.3%) |
| Legal guardianship (Yes) | 635 (35.0%) |
| Highest lifetime CGI-S mean score mean (SD) | 5.7 (0.9) |
| Duration of illness >5 years (Yes) | 1,304 (71.2%) |
| Current schizophrenia status (*N*, %) | |
| Current hospitalization (Yes) | 700 (37.9%) |
| Suicide attempt in the preceding month (Yes) | 44 (2.4%) |
| Schizophrenia relapse (Yes) | 192 (10.3%) |
| CGI-S mean score (SD) | 4.4 (1.2) |
| BPRS-18 mean score (SD) | 44.1 (14.7) |
| GAF mean score (SD) | 49.67 (17.0) |
| Antipsychotic prescription (*N*, %) | *n* = 1,747 |
| First-generation antipsychotic | |
| Cyamemazine | 403 (23.1%) |
| Fluphenazine | 37 (2.1%) |
| Haloperidol | 245 (14.0%) |
| Zoclupenthixol | 121 (6.9%) |
| Second-generation antipsychotic | |
| Amisulpride | 134 (7.7%) |
| Aripiprazole | 110 (6.3%) |
| Clozapine | 99 (5.7%) |
| Loxapine | 106 (6.1%) |
| Olanzapine | 294 (6.9%) |
| Risperidone | 717 (41.0%) |

*N*, number; %, percentage; *Defined as a schizophrenia onset before 15 years of age

haloperidol ($n = 26$), long-acting haloperidol ($n = 25$), amisulpride ($n = 19$), and aripiprazole ($n = 16$).

The characteristics of the patients included in the four subgroups were described in Table 2 at inclusion, 6-, and 12-months, respectively.

At inclusion, patients on cyamemazine monotherapy were more likely to be males (81.8%) with a younger age as compared to those receiving antipsychotic polytherapy ($p < 0.001$). Patients receiving cyamemazine as monotherapy at inclusion were less anxious ($p < 0.05$) as compared to other groups according to the BPRS subscores. Surprisingly, they were receiving more often anxiolytics at inclusion and 6 months ($p < 0.01$) and at 12-months ($p < 0.05$), respectively.

At inclusion, 6-, and 12-months, respectively, patients on antipsychotic monotherapy without cyamemazine received significantly less benzodiazepines and hypnotic prescriptions than other groups of patients ($p < 0.001$), but not significantly less antidepressant treatment. Moreover, at 12-months, patients on antipsychotic monotherapy (without cyamemazine) received significantly less benzodiazepines, hypnotics, and antidepressants ($p < 0.05$) than patients on polytherapy or monotherapy with cyamemazine.

There were no significant differences in terms of gender and mean age between patients on antipsychotic polytherapy with or without cyamemazine. Interestingly, at inclusion, patients on antipsychotic polytherapy including cyamemazine had better median GAF scores than patients receiving antipsychotic polytherapy excluding cyamemazine ($p < 0.05$). Concerning the CGI scale and the BPRS anxiety subscores, the median scores did not significantly differ between both groups at inclusion, 6-, and 12-months. No differences in terms of psychotropic drug use were observed between patients on antipsychotic polytherapy whether cyamemazine was used or not at inclusion, 6- and 12-months, respectively.

Then, we have compared the co-prescription of psychotropic drugs between the following three groups: Patients receiving (1) Cyamemazine, (2) Loxapine, and (3) Levopromazine respectively, in mono- or polytherapy. Table 3 summarizes the prescription of psychotropic drugs in these three groups.

Here, the mean dose of cyamemazine was 120 mg/day and the median dose was 100 mg/day. Concerning loxapine, the mean dose was 143 mg/day and the median dose was 100 mg/day. For levopromazine, the mean dose was 130 mg/day and the median dose was 100 mg/day. There was no significant difference between these doses, either raw or in chlorpromazine equivalent (eq. CPZ).

At inclusion in patients treated with cyamemazine ($n = 403$) 94.5% were receiving at least another antipsychotic. On comparison, in 96 patients receiving loxapine and 90 patients receiving levomepromazine, 87.5 and 96.6% were receiving another antipsychotic, respectively.

Comparison of cyamemazine, loxapine, and levomepromazine groups showed no statistically significant differences in co-prescription of antidepressants, benzodiazepines or hypnotics at, inclusion, 6-, and 12-months, respectively.

## Discussion

Cyamemazine remains the most prescribed antipsychotic in French hospitals, alone or more frequently in combination with other antipsychotics (in 70% of cases on average). It is considered to be of interest in the treatment of anxiety in combination with other antipsychotics, instead of benzodiazepines, making it possible to avoid the risk of misuse. In 2000, cyamemazine accounted for 16.6% of antipsychotic prescriptions in a population of 892 schizophrenia patients.[5] In 2006, it was the most prescribed antipsychotic in France with 45.1 and 39.2% of in-hospital and discharge prescriptions, respectively.[6] In a recent French study including 405 stable schizophrenic patients, 40 were still receiving cyamemazine (10% of cases, in most cases in association with another antipsychotic) as compared to risperidone (25%), aripiprazole (18%), olanzapine (16%), and clozapine (10%); in contrast, loxapine was used in only 4% of cases (28).[24] Cyamemazine, despite its potential side effects and its weak antipsychotic activity, is still widely used in France without scientific evidence. In this study our goal was to analyze the rationale for co-prescription of cyamemazine in a cohort of schizophrenic patients.

In our cohort, the anxiety BPRS subscore in patients with monotherapy of cyamemezine at inclusion was lower as compared to other patients but surprisingly anxiolytics were more often used (but not significantly). This difference was no longer observed at 6- and 12-months of follow-up, respectively. At inclusion, only patients under polytherapy including cyamemazine had better GAF scores than patients under polytherapy excluding cyamemazine. They may have less severe schizophrenia.

Patients on antipsychotic monotherapy other than cyamemazine received significantly less frequently anxiolytic, hypnotic treatment at baseline, 6- and 12-months, respectively. In this latter

**Table 2:** Comparison of clinical characteristics of the patients included in four different groups according to their antipsychotic prescription

| | *No antipsychotic* | *Antipsychotic polypharmacy with cyamemazine* | *Antipsychotic monotherapy with cyamemazine* | *Antipsychotic monotherapy other than cyamemazine* | *Antipsychotic polypharmacy without cyamemazine* |
|---|---|---|---|---|---|
| *Baseline* | *N* = 112 (6.0%) | *N* = 381 (20.5%) | *N* = 22 (1.2%) | *N* = 1,076 (57.9%) | *N* = 268 (14.4%) |
| Median age (years) | 37 | 38.5 | 32.5** | 37 | 38 |
| Male gender | 72 (64.3%) | 286 (75.1%) | 18 (81.8%)* | 688 (64.0%) | 212 (79.1%) |
| Anxiolytic treatment | 52 (46.4%) | 182 (47.8%) | 12 (54.5%) | 420 (39.0%)** | 121 (45.1%) |
| Hypnotic treatment | 33 (29.5%) | 161 (42.3%) | 8 (36.4%) | 302 (28.1%)** | 100 (37.3%) |
| Antidepressant treatment | 19 (17.0%) | 87 (22.8%) | 6 (27.3%) | 249 (23.1%) | 50 (18.7%) |
| CGI-S median score | 6 | 6 | 6 | 6 | 6 |
| BPRS median score | 4 | 4 | 3.5 | 4 | 4 |
| GAF median score | 50 | 45* | 45 | 51 | 41 |
| *6-months follow-up* | *N* = 39 (2.2%) | *N* = 308 (17.5%) | *N* = *11* (0.6%) | *N* = 1,041 (59.2%) | *N* = 359 (20.4%) |
| Median age | 40.5 | 38 | 34 | 37 | 37 |
| Anxiolytic treatment | 15 (38.5%) | 92 (29.9%) | 3 (27.3%) | 223 (21.4%)** | 112 (31.2%) |
| Hypnotic treatment | 13 (33.3%) | 81 (26.3%) | 2 (18.2%) | 155 (14.9%)** | 81 (22.6%) |
| Antidepressant treatment | 15 (38.5%) | 55 (17.6%) | 3 (27.3%) | 159 (15.3%) | 50 (13.9%) |
| CGI-S median score | 6 | 6 | 5.5 | 5 | 6 |
| BPRS median score | 3 | 4 | 3 | 3 | 4 |
| GAF median score | – | – | – | – | – |
| *12-months follow-up* | *N* = 35 (2.1%) | *N* = 298 (18.0%) | *N* = 7 (0.4%) | *N* = 984 (59.6%) | *N* = 328 (19.9%) |
| Median age | 37 | 38 | 30 | 37 | 38 |
| Anxiolytic treatment | 16 (45.7%) | 93 (31.2%) | 3 (42.9%)* | 230 (23.4%)* | 109 (33.2%) |
| Hypnotic treatment | 10 (28.6%) | 82 (27.5%) | 1 (14.3%) | 174 (17.7%)* | 83 (25.3%) |
| Antidepressant treatment | 12 (34.3%) | 68 (22.8%) | 2 (28.6%) | 156 (15.9%)* | 66 (20.1%) |
| CGI-S median score | 5.5 | 6 | 9 | 5 | 6 |
| BPRS median score | 3 | 3 | 3.5 | 3 | 3 |
| GAF median score | 60 | 55 | 45 | 60 | 50 |

*$p < 0.05$; **$p < 0.01$

**Table 3:** Psychotropic drug use in three groups of patients (cyamemazine, loxapine, and levomepromazine, respectively combined with another antipsychotic drug)

| | *Cyamemazine* | *Loxapine* | *Levomepromazine* |
|---|---|---|---|
| *At baseline* | *N* = 403 | *N* = 96 | *N* = 90 |
| Antipsychotic treatment | 381 (94.5%) | 84 (87.5%) | 87 (96.6%) |
| Antidepressant treatment | 93 (23.1%) | 17 (17.7%) | 16 (17.8%) |
| Hypnotic treatment | 169 (41.9%) | 41 (42.7%) | 30 (33.3%) |
| Anxiolytic treatment | 194 (48 .1%) | 43 (44.8%) | 41 (45.6%) |
| *At 6-month* | *N* = 319 | *N* = 74 | *N* = 84 |
| Antidepressant treatment | 58 (18.2%) | 12 (16.2%) | 8 (9.5%) |
| Hypnotic treatment | 83 (26.0%) | 20 (27.0%) | 22 (26.2%) |
| Anxiolytic treatment | 95 (29.8%) | 30 (40.5%) | 27 (32.1%) |
| *At 12-month* | *N* = 305 | *N* = 63 | *N* = 71 |
| Antidepressant treatment | 70 (23.0%) | 15 (23.8%) | 9 (12.7%) |
| Hypnotic treatment | 83 (27.2%) | 22 (34.9%) | 23 (32.4%) |
| Anxiolytic treatment | 96 (31.5%) | 24 (38.1%) | 24 (22.8%) |

group patients received also less often antidepressant treatment at 12-month. A greater severity of schizophrenia symptoms or a greater prevalence of akathisia in patients on combination antipsychotic therapy vs monotherapy may contribute to a more frequent co-prescription of benzodiazepines, hypnotics and even antidepressant drugs.[4] Antipsychotic monotherapy other than cyamemazine may also be associated with a lower risk of post-psychotic depression.[25,26]

In fact, phenothiazines are known to increase plasma concentrations of other antipsychotics, at least those partially metabolized by cytochrome P450 2D6, such as haloperidol. Interestingly, a study of risperidone plasma concentration in patients treated with cyamemazine showed that if cyamemazine raises the plasma concentration of risperidone (by 6-fold), it decreases the plasma concentration of 9-hydroxy-risperidone (by half), the active metabolite of risperidone and the sum of plasma risperidone and 9-hydroxy-risperidone remained unchanged with cyamemazine co-prescription. Only the risperidone/9-hydroxy-risperidone ratio was inverted.[27–29] However, in this study no difference was observed in CGI-S, BPRS, or GAF scores in patients receiving or not cyamemazine in combination with other antipsychotic drugs.

The potent muscarinic effects associated with cyamemazine may help reducing extrapyramidal effects often observed with first generation antipsychotics and may have contributed to its frequent use in combination with first-generation antipsychotics. However, the gradual decrease of first-generation antipsychotics should be associated to a parallel decrease in cyamemazine co-prescription.

In schizophrenia, the prevalence of any anxiety disorder redundancy is estimated to be up to 38%, with social anxiety disorder being the most prevalent. Achim et al.[30] have published a meta-analysis showing that, in schizophrenia and related psychotic disorders, pooled prevalence rates and confidence intervals (CIs) were 14.9% (8.1–21.8%) for social phobia, 12.4% (4.0–20.8%) for post-traumatic stress disorders, 12.1% (7.0–17.1%) for obsessive–compulsive disorders, 10.9% (2.9–18.8%) for generalized anxiety disorders, and 9.8% (4.3–15.4%) for panic disorders, respectively. In patients suffering from schizophrenia, anxiety can be associated with severe positive psychotic symptoms, but also with depression, suicidality, medical service utilization, and cognitive impairment and with greater levels of insight.[31] The potential anxiolytic effect of cyamemazine may have partly explained its high frequency of use. Yet, despite the prevalence of cyamemazine use in schizophrenia, there was no difference in terms of severity of anxiety, psychotic symptoms, total dose of antipsychotics or co-prescription of anxiolytics or antidepressants when loxapine or levomepromazine was used instead of cyamemazine in combination with other antipsychotics or alone. The "eq. CPZ" is defined as the dose of antipsychotic which is equivalent to 100 mg of oral dose of chlorpromazine.[32] In our study the mean dosages of cyamemazine, loxapine, and levomepromazine in eq. CPZ did not differ. In fact, we could not find any evidence for a higher anxiolytic effect when cyamemazine was compared to loxapine or levomepromazine; even if cyamemazine is usually associated to a lower incidence of neurological side effects as compared to loxapine and to less sedation and hypotension as compared to levomepromazine. In contrast the number of patients receiving anxiolytic treatment was even higher in patients with cyamemazine in monotherapy at 12-months.

In this study, we could not find any strong evidence in favor of persistent co-prescription of cyamemazine use in the treatment of schizophrenia. However, the dosage of cyamemazine used was low. International guidelines differ, but, in summary, a daily dose of 200–300 mg of eq. CPZ is considered the minimum antipsychotic effective dose and a dose above 1,000 mg of eq. CPZ per day is considered very high.[33,34] In this study, the median dosage of cyamemazine was 100 mg/day which is associated with anxiolytic and antimuscarinic effects but not with antipsychotic effects.

Our study has some limitations as follows: (1) Even if our sample of patients was representative of the general population of French patients with schizophrenia in terms of clinical symptoms and severity, the high prevalence of risperidone prescription is a possible bias. (2) Patient compliance is difficult to assess and yet important in the interpretation of data. Unfortunately, compliance could not be assessed. (3) We did not assess the characteristics of prescribers who may have played a role in treatment choice. (4) Finally, the date of establishment of our cohort of patients could be a limitation, even if the most recent studies have considered cyamemazine as a treatment of choice in schizophrenia.

However, to our knowledge, this is the first study focusing on the place of cyamemazine in the treatment of schizophrenia. Our multicenter data obtained from a large national representative cohort of French schizophrenic patients have made it possible to analyze the factors associated with cyamemazine use in schizophrenic patients. The more recent articles have focused on pharmacokinetics as well as side effects but not on the specific interest of cyamemazine in schizophrenia treatment.

## Conclusion

Taking into account the risk of side effects, and in agreement with data from the literature, our study does not find any evidence to recommend the use of cyamemazine alone or in combination with other antipsychotics in patients suffering from schizophrenia.

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