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Preclinical and Clinical Pharmacology of Cyamemazine: Anxiolytic Effects and Prevention of Alcohol and Benzodiazepine Withdrawal Syndrome

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ABSTRACT

Several studies have suggested that the antipsychotic compound, cyamemazine, possesses anxiolytic properties in humans. The original pharmacological profile of cyamemazine (D_2, 5-HT_{2A}, 5-HT_{2C}, and 5-HT_3 receptor antagonist), which was established by binding, microdialysis and behavioral studies, is consistent with these observations. In the light/dark exploration test, cyamemazine demonstrated anxiolytic-like activity by acute, but not chronic administration. By chronic administration, however, cyamemazine increased the time spent in the open arms of the elevated plus maze (EPM) test demonstrating anxiolytic-like activity. The discrepancy between the results obtained in these tests by acute and chronic administration, could be due to a combination of dopamine D_2 receptor antagonism with antagonism of the 5-HT_{2C} and 5-HT_3 receptors. The action of cyamemazine on both the dopaminergic system and 5-HT_3 receptors could also explain the activity of cyamemazine in the management of alcohol withdrawal demonstrated in preclinical studies. This potential indication for cyamemazine and its activity in benzodiazepine withdrawal syndrome have recently been investigated in clinical trials and the results of these studies are presented in this review.

INTRODUCTION

Antipsychotics, a heterogeneous group of compounds in terms of chemical structure and pharmacological profile, are the primary treatment in the management of schizo-

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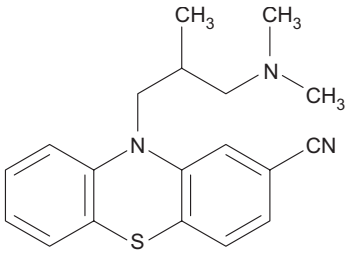

Fig. 1. Cyamemazine, or cyano-3 (dimethylamino-3 methyl-2 propyl)-10 phenothiazine.

phrenia. Antipsychotics are also widely used in the treatment of affective disorders, anxiety, restlessness and agitation. Anxiety is a symptom common to many syndromes and in schizophrenia antipsychotic therapy reduces anxiety concomitant with the alleviation of the psychosis. The direct influence of antipsychotics on anxiety or disinhibited behavior is substantiated by their use in the treatment of non-psychotic illnesses (9,35). Standard antipsychotics have been used by clinicians for many years to treat high degrees of agitation and anxiety in non-psychotic patients with severe personality disorders (38,59). In patients with non-psychotic recurrent and/or chronic major depression and high levels of anxiety, low doses of atypical antipsychotics may improve function through an anti-anxiety effect that is independent of their antipsychotic efficacy (15,38). Efficacy in affective disorders has been reported for atypical and typical antipsychotics and it has been speculated that potent serotonin receptor antagonism, rather than dopamine blockade, leads to an improvement in the symptoms of anxiety. This finding is supported by extensive literature demonstrating the role of serotonin in anxiety (17,37,45).

Conventional antipsychotics block dopamine D_2 receptors, muscarinic cholinergic receptors, α-adrenergic and histamine receptors. The newer antipsychotics, such as clozapine and risperidone, also possess an affinity for dopamine and 5-HT receptors (in particular for the 5-$HT_{2A/2C}$ and 5-HT_3 subtypes) but little or no affinity for histamine H_1 and α-adrenergic receptors (4,53). Cyamemazine (CMZ; Fig. 1), a phenothiazine, was originally used as a sedative antipsychotic (24), but is now often used as an anxiolytic, as well as in schizophrenic or depressed patients with suicidal tendencies (20,51). In light of these clinical effects, the pharmacological profile of CMZ has been recently established on the basis of behavioral, binding and microdialysis studies. This profile suggested new potential indications for CMZ. The aim of this review is to present the pharmacological rationale for these potential indications and the preliminary results of clinical trials.

PRECLINICAL PHARMACOLOGY

Binding and Microdialysis Studies

The affinity of CMZ for serotonin, dopamine, histamine, muscarine and GABA receptor subtypes was established recently by Hameg et al. using human recombinant receptors (30). CMZ exhibited a high affinity for dopamine receptors, which is consistent with its antipsychotic activity. It has a higher affinity for 5-HT_{2A} (K_i = 1.5 nM) than for 5-HT_{2C} (K_i = 12 nM) and 5-HT_3 receptors (K_i = 75 nM). Its affinity for $GABA_A$ receptors

is very low (K_i > 30 μM). This finding excludes direct action of CMZ on $GABA_A$ receptors as the explanation for its anxiolytic activity. The sedative activity of CMZ can be explained, in part, by the high affinity of CMZ for H_1 histamine receptors (K_i = 9.3 nM). The antagonist activity of CMZ at muscarinic receptors is consistent with its affinity for M_1 (K_i = 13 nM), M_2 (K_i = 42 nM), M_3 (K_i = 321 nM), M_4 (K_i = 12 nM), and M_5 (K_i = 35 nM) receptors.

The affinity of CMZ for serotonergic receptors is consistent with studies, which demonstrated its serotonin receptor antagonist properties. CMZ behaves as an antagonist at the 5-HT_3, 5-HT_{2C}, and 5-HT_{2A} receptors in 5-HT_3-dependent contraction of isolated guinea pig ileum and bradycardic responses in rats, in 5-HT_{2C}-dependent phospholipase C stimulation in the rat brain membrane (1), and in 5-HT_{2A}-dependent contraction of isolated rat aorta rings and isolated guinea pig trachea (2). These studies established that CMZ antagonizes 5-HT_3 and 5-HT_{2C} receptors and that this effect is partially involved in its therapeutic activity in anxiety disorders.

The results of binding are also consistent with a microdialysis study, which showed a reduction of extracellular dopamine and metabolite concentrations in rat striatum with acute administration of low doses of CMZ (50). This effect can be explained by the pharmacological profile of CMZ (potent D_2 and 5-HT_{2A} receptor antagonist with a lower antagonistic activity at 5-HT_{2C} receptors) and the model of Lucas et al. (43). In this model, for modulation of the nigrostriatal dopaminergic pathway, 5-HT_{2A} and 5-HT_{2C} receptors exert an opposite (respectively facilitating and inhibiting) influence on dopamine release. Thus, the higher antagonist potency for 5-HT_{2A} than for 5-HT_{2C} receptors can explain the decrease in small basal dopamine release. To our knowledge, CMZ is the only antipsychotic with this effect, since typical antipsychotics acutely block D_2 and D_3 autoreceptors, thus increasing the neuron firing rate as well as dopamine synthesis, while atypical antipsychotics acutely induce a small and sometimes undetectable increase in striatal dopamine release.

Behavioral Pharmacology

Antipsychotic activity

During the 1970s, preliminary pharmacological studies investigated the dopamine receptor antagonist activity of CMZ (26). In rats, CMZ was shown to be an antagonist of stereotypical behavior induced by amphetamine (ED_{50} = 0.12 mg/kg, s.c. or 6 mg/kg, p.o.) and apomorphine (ED_{50} = 6.25 mg/kg, s.c.; and 112 mg/kg, p.o.). In dogs, CMZ prevented apomorphine-induced vomiting. By either p.o. or s.c. routes the antipsychotic potency of CMZ is higher than that of levomepromazine or chlorpromazine, except in the amphetamine-induced stereotypical behavior. The low extrapyramidal potential of atypical antipsychotics has been explained by antagonist action at 5-HT_{2A} receptors (45). Consequently, this potential effect of CMZ was studied in a model of apomorphine-induced hypothermia in mice (10). Although dopamine receptor antagonist properties have been recognized, CMZ failed to antagonize apomorphine-induced hypothermia. However, if 2,5-dimethoxy-4-iodo-amphetamine hydrochloride (DOI, agonist of 5-HT_{2C} and 5-HT_{2A} receptors) is administered with CMZ at a sufficient dose to weaken the 5-HT_2 receptor antagonist properties of CMZ, CMZ is able to reduce dopamine agonist-induced hypothermia. From our knowledge of atypical antipsychotics, the 5-HT_2 receptor anta-

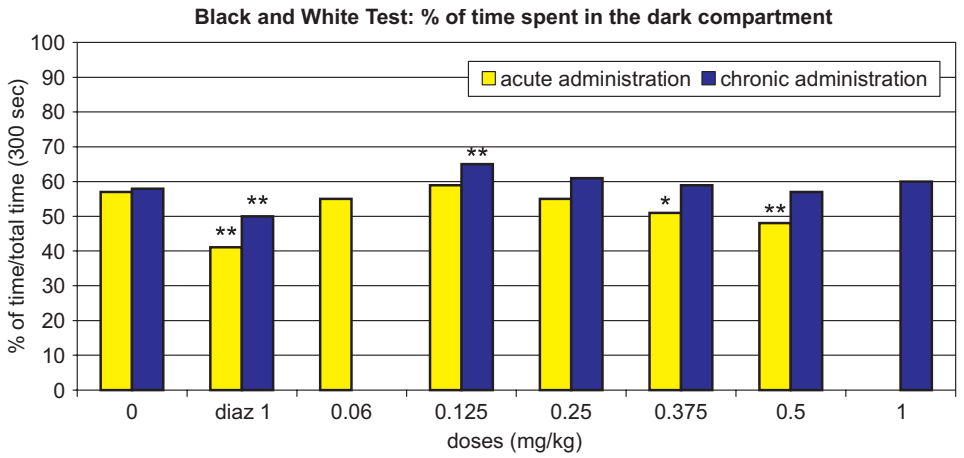

Fig. 2. Effects of acute and chronic intraperitoneal administration of cyamemazine on behavior parameters of mice (time spent in the dark area) in the light/dark test. Statistical analyses were performed by analysis of variance (ANOVA), followed by Dunnett's test for comparison with appropriate control groups. Diazepam (1 mg/kg; diaz) is the reference drug used in this test. *$p = 0.05$; **$p = 0.01$.

gonist properties of CMZ seem to play an important role in the control of central dopamine function.

CMZ showed anxiolytic activity in mice in two tests, which are known to select anxiolytic-like drugs, the elevated plus maze (EPM) test and the light/dark paradigm, both validated for benzodiazepines (11). The EPM test is based on the natural aversion of rodents to heights and open spaces, and can be considered a standard paradigm for testing anxiogenic- and anxiolytic-like responses in mice. The main anxiogenic factor suggested to underlie explorative behavior in the light-dark box is the aversive nature of an open, brightly illuminated area. Explorative anxiety paradigms like these have been proposed to measure state of anxiety (7). 5-HT receptor antagonists and drugs known to deplete brain 5-HT content can produce an anxiolytic effect in animal models sensitive to benzodiazepines, but usually to a lesser degree and less consistently than benzodiazepines themselves. Some antipsychotics have been found to be active in animal models of anxiety (13,15,47, 57,58,61). Many of the atypical antipsychotic drugs with 5-HT_2 and D_2 receptor antagonist properties, such as clozapine and risperidone, have demonstrated anxiolytic potential in animal models of fear and anxiety (14,25,47,57) as well as some clinical evidence in schizophrenics (9). In the light/dark box, CMZ was active after acute intraperitoneal administration at 0.375 and 0.5 mg/kg (two doses lacking sedative effects as measured in the actimeter) but not after chronic administration (Fig. 2). As the results for chronic administration were disappointing, the experiment was repeated to discard any ambiguity concerning the activity of CMZ in this test. This additional study, however, confirmed the lack of an anxiolytic effect seen in the earlier investigation and demonstrated no significant augmentation of time spent in the dark. The reason for this discrepancy remains unclear. The light/dark paradigm seems to be more sensitive to mechanisms implicating the 5-HT_3 receptor (34), whereas the mechanism of CMZ appears to be associated more with the 5-HT_2 receptor. On the other hand, the drug was active in the

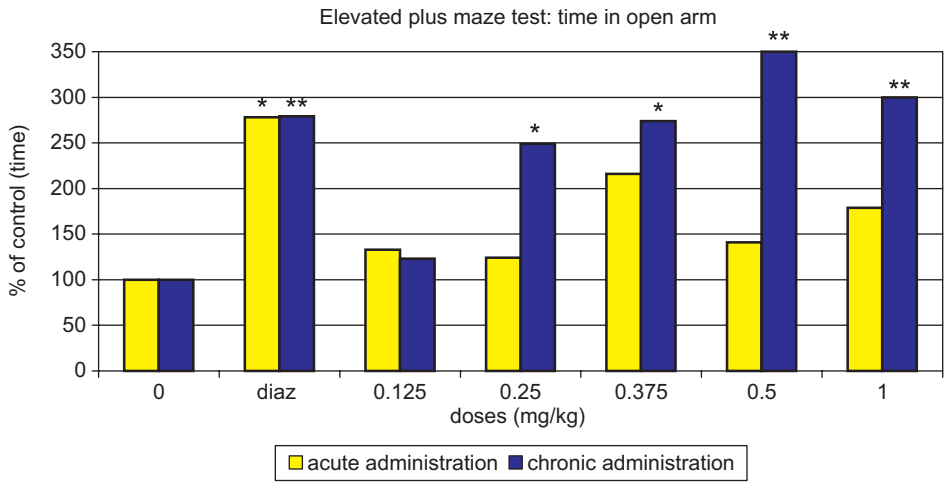

Fig. 3. Effects of acute and chronic intraperitoneal administration of cyamemazine on behavior parameters of mice (time spent in the open arm) in the elevated plus maze test. Statistical analyses were performed by analysis of variance (ANOVA), followed by Dunnett's test for comparison with appropriate control groups. Diazepam (1 mg/kg; diaz) is the reference drug used in this test. *$p = 0.05$; **$p = 0.01$.

EPM test at 0.25, 0.375, 0.5, and 1 mg/kg after chronic intraperitoneal administration but not after acute administration (Fig. 3). These results, which have been obtained for several doses, are consistent even if it is difficult to understand the reasons for activity after acute administration in the light/dark test and after chronic administration in the EPM test.

Many studies have been undertaken to investigate 5-HT systems and anxiety models (6,27–29,31,33). The literature indicates that conditioned procedures as well as more ethological-based tests are equal in revealing anxiolytic-like effects of drugs targeting 5-HT_{1A}, 5-HT_{2A}, and 5-HT_{2C} receptors (27). On the other hand, the anxiolytic-like effect of 5-HT_3 receptor antagonists has mainly been revealed by models based on spontaneous behavior (14,29). Several 5-HT_3 receptor antagonists have been or are being studied clinically as potential therapeutics in the treatment of anxiety disorders. However, the results of these studies are inconclusive (48,54). Various 5-HT receptor ligands have been reported as anxiolytic, anxiogenic and having no effect at all in different animal models. As most of these tests were validated on their sensitivity to benzodiazepines and with the introduction of only one non-benzodiazepine agent (buspirone) into clinical practice, the validity of these models in testing for non-benzodiazepine potential anxiolytics has been questioned. The possibility that these tests may be less sensitive to non-benzodiazepine agents may explain these inconsistencies. There is also the suggestion that each model reflects a different type of anxiety or fear and that the mechanism of 5-HT is different for each model (29,31–33).

The anxiolytic effect of CMZ in the EPM test can be explained by 5-HT_2 receptor antagonism of the drug, which is stronger than 5-HT_3 receptor antagonism. However, the differences observed between the two modes of administration (acute vs. chronic) could be due to a combination dopamine D_2 receptor antagonism with 5-HT_2 and 5-HT_3 receptor antagonism. Dopamine D_2 receptor antagonists have been found to possess anti-anxiety

activity using both traditional and novel methods such as risk assessment (55). Further studies on the potential involvement of dopamine are warranted. The activity may also involve modulation of 5-HT at the receptors studied in the tests, as variations in effects might also reflect differences in the degree to which the models themselves represent fear or anxiety. Identification of the mechanism which contributes to the action of CMZ as an anxiolytic drug in animals, as well as in humans, may provide a key to understanding the exact role of D_1, D_2, 5-HT_3 and 5-HT_{2C} receptors in the regulation of anxiety.

In conclusion, it appears that the mechanism of anxiolytic-action of CMZ after chronic administration observed in the EPM test is related to its activity at the level of the 5-HT_{2C} receptor. The use of more selective 5-HT_{2C} ligands may help to establish the involvement of this receptor in mediation of the anxiolytic-like effect.

CMZ and ethanol intake

Various neurotransmitters, including serotonin (44) and dopamine (5), modulate alcohol intake. Alcohol consumption and withdrawal can be modulated by drugs that regulate dopamine release when it is enhanced during chronic alcohol consumption (42). 5-HT_3 antagonists decrease ethanol intake (21). Naassila et al. demonstrated that CMZ (1 mg/kg, i.p. chronically) decreased ethanol consumption in rats by 45% and antagonized alcohol withdrawal syndrome in mice. CMZ (1 mg/kg, i.p. on the day of alcohol removal; or at 0.5 mg/kg, i.p. chronically, during alcohol consumption) significantly ($p < 0.0001$) decreased convulsion scores in the alcohol-withdrawal diet. These results were explained by the action of CMZ on both the dopaminergic system and 5-HT_3 receptors (46).

CLINICAL PHARMACOLOGY

Pharmacokinetics

Fewer data are available on the pharmacokinetics than on the pharmacodynamics of CMZ. Several pharmacokinetic studies were performed in the 1970s and submitted for approval by government agencies, but the results of these studies have not been published. The relative bioavailability of a single oral 100 mg dose of CMZ compared with a single intramuscular 100 mg dose was estimated to be 50%. In 12 healthy volunteers receiving a single 25 mg dose (tablet) of CMZ, the median T_{max}, C_{max} and elimination half-life were 2.25 h, 3.10 ng/mL and 10.99 h, respectively. CMZ and its two main metabolites (monodesmethyl CMZ and sulfoxide CMZ) are eliminated by urinary excretion over 72 h. After administration of CMZ (100 mg twice a day for 14 days) in five patients, no accumulation of CMZ or its metabolites was found.

Clinical adverse effects

The tolerance of CMZ was investigated by examination of 1158 medical records (8,12, 16,18,19,22,36,39,40,52). Tolerance was good or very good in 71.1% of patients, medium in 22.4% and poor in 4.5%. CMZ (25 mg tablet) is the galenic formulation with the best tolerance, since CMZ doses are usually low with this formulation. On the other hand, CMZ (50 mg, i.m.) used in acute disease state has been less well tolerated. The main adverse effects are presented in Table 1.

Clinical trials

CMZ: a sedative antipsychotic

Clinical trials with cyamemazine as a sedative antipsychotic were conducted in the 1970s. These studies were open with no comparative group, randomization or statistical analysis.

In a prospective study, 50 psychotic patients (43 schizophrenic patients and seven mentally retarded psychotic patients) were treated with CMZ (400–700 mg daily) and no other antipsychotic drugs. The therapeutic action of CMZ was evaluated by global impression. At the baseline, a full clinical evaluation was performed by the physician before treatment with CMZ. This evaluation was performed again on days 1, 3, 5, and every 5 days until day 50 and then every 10 days until the end of the observation period. The patients were followed until day 180 or less if clinical recovery was observed. The psychotic condition of 34 patients was found to have improved during the period of observation in comparison with the initial clinical evaluation (49).

The sedative activity of CMZ (100–600 mg daily) was investigated in 40 patients with various psychiatric diseases requiring sedation, and evaluated by the Brief Psychiatric Rating Scale (BPRS) of Overall and Gorham. For each patient, three psychiatric examinations were performed: the first before treatment with CMZ, the second and the third at 15

TABLE 1. Summary of the adverse effects of cyamemazine based on 1158 medical records (8,12,16,18,19,22,36,39,40,52)

	Adverse effect	Incidence (%)
Neurological	Sedation, somnolence	20.7
	Asthenia	10.8
	Extrapyramidal hypertonia	1.5
	Dyskinesia	4.4
Psychic	Paradoxical effect	2.4
	Opposition of patient	1.2
	Confusion syndrome	0.4
	Mood inversion	0.3
Cardiovascular	Hypotension	7.4
	Tachycardia-palpitations	3.2
	Vertigo	7.9
Atropinic	Dryness of mouth	5.9
	Constipation	4.0
	Accommodation disorder	2.1
	Retention of urine	0.2
Endocrine	Decrease of libido	0.9
	Galactorrhea	0.3
	Dysmenorrhea-amenorrhea	0.2
Metabolic	Increase in body weight	6.8
	Increase in appetite	2.0
	Decrease in body weight	0.3
Miscellaneous	Photosensitization	3.1
	Digestive disorders	1.6
	Hypersudation	0.6

days and 1 month, respectively, after the first day of treatment with CMZ. The results at the end of this period were found to be poor (BPRS value < 3) for 25% of patients, medium (BPRS value = 3) for 25%, good (BPRS value = 4) for 25% and very good (BPRS value = 5) for 25% (25). The authors also observed that CMZ proved particularly efficacious in patients with anxiety.

CMZ: a sedative antipsychotic with anxiolytic activity

In the 1980s, CMZ was evaluated as symptomatic treatment of anxious, impulsive and aggressive disorders but, once again, the methodology was limited. Ropert et al. (56) performed a prospective open study with 40 ambulatory patients presenting with anxious-depressive syndrome. These patients were treated with CMZ (mean daily dose intake: 97.5 mg, range: 45–300 mg daily) during a mean period of 37.7 days (range: 13–42 days) and the efficacy was evaluated with the Hamilton scale. The authors concluded that CMZ improved the anxious syndrome since 24 patients had a global score of <16 in the Hamilton scale after 21 days of treatment. The reduction in the depressive element was more limited and slower to appear.

CMZ and alcohol withdrawal syndrome

In the 1980s, open studies suggested the potential of CMZ in the treatment of patients with alcohol withdrawal syndrome (3). Recently, Favre et al. performed a multi-center, randomized, double-bind study with two parallel groups to compare the efficacy and safety of CMZ and diazepam in alcohol withdrawal therapy and to determine the optimum doses of CMZ in this indication (23). The main inclusion criterion was a CIWA-Ar [Clinical Institute Withdrawal Assessment for Alcohol (60)] score between 10 and 30. CMZ or diazepam (50 and 10 mg, respectively) were administered hourly on day 1 (up to a maximum of eight times). CIWA-Ar was determined before each drug treatment (when general status of each patient permitted it). An additional dose could be administered 12 h after the last dose if necessary and if the time of this treatment preceded the morning evaluation on the second day of therapy. Starting on day 2, all treatments were administered according to a decreasing schedule. The primary efficacy criterion was the rate of success at the eighth hour after the first drug intake on day 1 as indicated by a CIWA-Ar score of 5. The rate of efficacy was 74.4% with CMZ, a value very similar to that of diazepam (72.7%). The authors concluded that CMZ (at doses ranging from 100–300 mg) had an efficacy similar to that of diazepam at 10 and 50 mg.

CMZ and benzodiazepine withdrawal syndrome

Since CMZ seems to be effective in preventing alcohol withdrawal syndrome, and both alcohol and benzodiazepine bind to $GABA_A$ receptors, Lemoine et al. investigated the hypothesis that CMZ could be used in the management of benzodiazepine withdrawal syndrome (41). The efficacy of CMZ was assessed in a double-bind, bromazepam-controlled parallel group, randomized clinical trial. To be eligible for inclusion into the study, patients were required to be treated for anxiety with benzodiazepines (including either bromazepam, lorazepam, alprazolam or oxazepam) for at least 3 months. A Hamilton Anxiety Rating Scale of <18 was required since patients were not supposed to be anxious at the start of the withdrawal study. Patients were randomized to a 6-week treatment period composed of 4 weeks treatment with bromazepam (3–6 mg, q.d.) or CMZ (25–50 mg, q.d.),

during which benzodiazepines were withdrawn, followed by 2 weeks on placebo. Efficacy assessments were made at baseline and on days 7, 14, 21, 28, 35, and 42. The primary efficacy variable was maximal anxiety rebound as measured by the Hamilton scale during the 6 weeks of treatment. There was no difference in the extent or incidence of rebound anxiety between the two groups of patients. After 6 months follow-up, 90% of patients in the CMZ group and 75% in the bromazepam group were considered to have withdrawn successfully. Lemoine et al. concluded that CMZ was an alternative to bromazepam in the management of acute benzodiazepine withdrawal syndrome in patients for whom substitution with bromazepam is not appropriate.

CONCLUSIONS

For many years, CMZ has been considered as a sedative antipsychotic agent with anxiolytic activity. However, CMZ has an original pharmacological profile (potent D_2 and 5-HT_{2A} receptor antagonist with lower 5-HT_{2C} receptor antagonist activity) and appears to be different from other typical or atypical antipsychotics as suggested by animal studies. This activity on both dopamine and serotonin receptors could explain the efficacy of this drug in preventing alcohol and benzodiazepine withdrawal syndrome. These pharmacological activities of CMZ observed in animal models were recently confirmed in clinical trials and suggest new potential indications for CMZ.

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