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# Phenothiazine-Related Critical Conditions: a Mini-Review

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## Summary

**Objective.** The aim of this review is to summarize the pathological mechanisms associated with the toxicity of phenothiazines in overdose.

**Materials and methods.** A database search was conducted on PubMed, Google Scholar and eLibrary were used to identify original research articles, clinical reports, review articles, editorials, commentaries, and brief communications. Additional sources not identified through the search of these databases were analyzed after reviewing the reference lists of the selected articles. Articles were selected based on the relevance of the title and abstract to the purpose of this review.

**Results.** This review analyzes the mechanisms of action of phenothiazines in the context of their long-term clinical use and in overdose, as well as the mechanisms of action of proposed potential areas of application of phenothiazines. Clinical manifestations of phenothiazine poisoning are predominantly characterized by antagonism of dopamine $D_1$–$D_4$ receptors, histamine $H_1$ receptors, $\alpha_1$–$\alpha_2$ $\alpha$-adrenergic receptors and muscarinic acetylcholine receptors $M_1$–$M_2$. In addition, phenothiazines are able to increase the permeability of the blood-brain barrier through apoptosis, increase global methylation, effectively enhance chemotherapy of some tumors and provide neuroprotection by reducing GFAP production (PKC-δ/NOX/MnSOD pathway).

**Conclusions.** Given the potential for new applications of phenothiazines, further study of the effects of phenothiazines on the central nervous system in overdose, with a focus on repeat overdose episodes, is important at the morphological level to identify the underlying morphological substrate. Further study of the mechanisms associated with phenothiazine use is needed to develop more effective therapeutic strategies to improve patient outcome, not only in psychiatry but also in other disciplines.

***Keywords: phenothiazines; chlorpromazine; overdose; epigenetics; neuroprotection***

**Conflict of interest.** The authors declare no conflict of interest.

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## Introduction

Phenothiazines are used in psychiatry since their discovery in 1951 [1]. Chlorpromazine, a representative of phenothiazines, being the first antipsychotic drug, is widely used in the treatment of various mental illnesses, such as schizophrenia, manic episodes in bipolar affective disorder and various forms of psychosis. It has also found application in other areas of medicine, for example, for the treatment of migraines, nausea, hiccups, etc. The significance of the discovery of chlorpromazine for psychiatry is difficult to overestimate, so much so that, to this day, it remains the reference drug with which all antipsychotic drugs are compared [2].

Haloperidol, synthesized in 1958, became the new first-line neuroleptic due to its less pronounced sedative and more pronounced antipsychotic effect [3]. After the discovery of atypical antipsychotics, the prevalence of first-generation neuroleptics decreased significantly [4].

Despite this, phenothiazines have not been completely replaced by newer antipsychotic medications. They have been used for 74 years, and recent medical research has sparked renewed interest in the potential use of phenothiazines such as chlorpromazine in oncology and emergency care [3].

In all of the areas of medicine listed, patients are at increased risk of potential overdose, both intentional suicide and accidental, such as unintentional overdose due to cognitive impairment.

In 2021, 32,900 cases of drug- related poisoning were registered in the Russian Federation, of which 15,615 deaths were due to suicide [5, 6]. Although the global suicide rates are declining, intentional overdose remains a pressing problem, particularly among the younger segment of the population [7,8]. Worldwide, poisoning remains the most common form of suicide attempts, among which we observe the use of drugs, with psychopharmacological drugs making up the majority (up to 64.28%) [9, 10]. Most

of the drugs used in suicide attempts are those that have been prescribed to the patient, especially in the case of psychopharmacological drugs [11]. In addition, epigenetic factors, such as those responsible for the expression of the serotonin transporter, tryptophan hydroxylase 2 and brain-derived neurotrophic factor, may be one of the causes of suicidal behavior, which must be taken into account when prescribing phenothiazines, in particular, since they can affect gene expression [12]. Furthermore, patients eligible for the proposed expanded use options of phenothiazines, who have suffered ischemic stroke, or who are undergoing chemotherapy are more likely to experience an unintentional overdose of prescribed drugs [13].

Given the potential increase in phenothiazine prescriptions, as well as their existing use in psychiatry, the aim of this review is to analyze the mechanisms of phenothiazine toxicity in acute poisoning.

## Materials and Methods

The PubMed, Google Scholar, and eLibrary databases were searched for original research articles, clinical reports, review articles, editorials, commentaries, and brief communications. The search was conducted using the keywords:

- (chlorpromazine) AND (overdose mechanism) OR (overdose)
- (chlorpromazine) AND (blood brain barrier)
- (chlorpromazine) AND (toxicity)
- (antipsychotic) OR (chlorpromazine) AND (epigenetics)
- (phenothiazines) AND (neuroprotection)
- (antipsychotic) AND (apoptosis)

Articles were selected based on the relevance of the title and abstract to the review topic. Additional materials not identified during the main database search were included after manually reviewing the reference lists of the selected articles. The most relevant information was selected. Sources were excluded if they were inappropriate for the review objective and were of low informative value.

## Results

**Mechanism of action of phenothiazines.** The pharmacological properties of phenothiazines, in particular chlorpromazine, have been studied in sufficient detail. Metabolism occurs primarily in the liver (CYP3A4 substrate: CYP450 A12 and 2D6 enzymes) and kidneys. Excretion occurs with urine and bile. More than 40 metabolites have been identified, metabolized through several metabolic pathways, including hydroxylation, demethylation and sulfation, of which the most clinically significant are: Desmethylchlorpromazine, didemethylchlorpromazine, 7-hydroxychlorpromazine, 7-hydroxynorchlorpromazine, 7-hydroxynor-2-chlorpromazine [14]. Being first-generation antipsychotic drugs, phenothiazines exert their neuroleptic effect through antagonism of dopamine receptors, acting on $D_1$–$D_4$ receptors, with the most pronounced antagonism being to $D_2$ receptors. Phenothiazines are also antagonists of histamine ($H_1$), $\alpha$ -adrenergic ($\alpha_1$, $\alpha_2$) and muscarinic acetylcholine ($M_1$, $M_2$) receptors, as well as serotonin (5-$HT_2$, 5- $HT_6$, and 5-$HT_7$) receptor antagonists *in vitro*, although the serotonergic effect is not observed *in vivo*, since phenothiazine metabolites do not have serotonergic activity [15, 16]. The brain structures most affected by phenothiazine metabolites are the reticular formation, limbic system, hypothalamus and basal ganglia [17].

Phenothiazine metabolites readily cross the blood-brain barrier (BBB), whereas the parent drug does not, which may be the reason for the aforementioned difference in serotonin antagonism in *in vitro* and *in vivo*. Studies have also shown that high therapeutic doses of phenothiazines increase BBB permeability by increasing the activity of caspases-3, -8, -9, as well as fragmentation and condensation of chromatin in endothelial nuclei, which are signs of apoptosis [18].

In recent studies, antipsychotic drugs have demonstrated epigenetic activity through hypermethylation. In an experimental study by Swathy et al., antipsychotic drugs showed an increase in the expression of genes encoding DNA methyltransferases (by decreasing the expression of microRNAs targeting DNA methyltransferases), methyl-CpG-binding proteins, and TET-methylcytosine dioxygenases [19].

**Toxicology.** Phenothiazines, being typical first-generation antipsychotics, have a relatively higher association with adverse effect, when compared to second generation neuroleptics. Common side effects include orthostatic hypotension, extrapyramidal disturbances (but less common than with other first-generation antipsychotics), excessive sedation, and ophthalmological complications. Adverse effects with long-term use most often include hepatotoxicity, acute cholestatic liver injury, increased risk of seizures, and corneal damage [20, 21].

The toxic effects of phenothiazines are considered primarily as an extension of their pharmacological activity. The primary mechanism of action of phenothiazines is through antagonism of $D_2$ receptors in the reticular formation, limbic system, and hypothalamus, which is likely the cause of side effects such as extrapyramidal symptoms and hyperprolactinemia [17]. Phenothiazines have also been shown to inhibit vasomotor reflexes, suppress the secretion of prolactin-releasing inhibitory hormone (PRIH), and reduce the secretion of corticotropin-regulating hormone (CRH), and significant prolongation of the QTc interval [22].

Phenothiazines are characterized by an overlap between therapeutic and toxic doses. The toxic concentration of chlorpromazine in the blood ranges

from 0.5 to 2 μg/ml. The LD50 for rats is 210 mg $kg^{-1}$ for oral administration. The potentially lethal dose of chlorpromazine (3000 mg) is ten times the average daily dose (300 mg); however, the maximum daily dose can reach 2000 mg [23, 24].

Clinical manifestations of acute phenothiazine intoxication, especially in cases of overdose, include severe extrapyramidal reactions, hypotension, and sedation. In the late stages of intoxication, CNS stimulation and seizures are often observed, followed by respiratory and/or CNS depression, as well as cardiovascular conduction disturbances, arrhythmias, anticholinergic effects, impaired body temperature regulation, vomiting, difficulty breathing, pulmonary edema, and coma. Treatment of phenothiazine intoxication consists of symptomatic therapy [23]. Currently, there is no specific antidote for phenothiazine overdose. Regarding extrapyramidal side effects anti-Parkinson's drugs are effective in mitigating adverse effects. Also, S. Naeem et al. [25], in their study using chlorpromazine to model Parkinson's disease-associated cell death in rats, showed that diclofenac exerted a neuroprotective effect, with significant improvement in motor control in treated rats compared to controls.

Discoveries in recent years have renewed interest in the study of the biological aspects of psychiatric disorders. In recent years, the volume of information on morphological, epigenetic, and immunohistochemical studies of psychiatric diseases, particularly suicides, has increased. These studies have revealed morphological changes in microglia, astrocytes, and oligodendrocytes of the central nervous system, as well as in the blood-brain barrier [26].

An important role in understanding the mechanisms of exposure to phenothiazines belongs to the study of autopsy material, which showed a correlation between the occurrence of suicidal behavior and the content of cytokines: IL-4, IL-10, IL-13, TNF-$\alpha$ [12, 27, 28]. S. G. Torres-Platas et al., in their study showed that fibrous astrocytes in the white matter of the anterior cingulate cortex in individuals who died from completed suicide with a history of depressive disorders were twice as large and had 50–60% more branches, compared with controls. Also, studies have shown that in the dorsal part of the anterior cingulate cortex, in completed suicide, there is a significant increase in the ratio of amoeboid to branched microglia, as well as, blood vessels surrounded by macrophages are detected more than twice as often compared to controls. This is accompanied by an increase in the expression of IBA1 and MCP-1 genes and an increase in mRNA and CD45 [29–31]. In the amygdala, a decrease in the density of oligodendrocytes is observed [32]. M. J. Chandley et al. showed that, in oligodendrocytes of the occipital cortex of the cerebral hemispheres and the brainstem, in the context of completed suicide, signs of oxidative stress (decreased expression of SOD1, SOD2, GPX1, and a significant increase in the expression of AGPS) can be observed [33].

It should be noted that signs of oxidative damage to the central nervous system are also observed in cases of phenothiazine poisoning. With prolonged therapeutic use of chlorpromazine, the activity of copper- and manganese-containing superoxide dismutase (SOD), which have a pronounced antioxidant function, decreases, but the concentration of malondialdehyde (MDA) increases, indicating lipid peroxidation [34].

Phenothiazine poisoning is also characterized by organ dysfunction, such as: prolongation of the QT period; ventricular arrhythmias, in particular ventricular tachycardia, which can lead to fibrillation; hypothalamic thermoregulation disorder, mainly in the form of hyperthermia, however, hypothermia is possible; neuroleptic malignant syndrome. In autopsies, agranulocytosis, drug-induced lupus syndrome, rhabdomyolysis, necrotic damage to hepatocytes, myocardial lipomatosis are observed [20, 24, 35].

**Use of phenothiazines in other diseases.** A statistically significant correlation has been observed indicating that patients with schizophrenia have a lower incidence of certain types of cancer compared to the general population [36]. This difference was long thought to be genetic in nature, but more recent studies have shown a high probability that the cause is related to the use of first-generation antipsychotic drugs in the treatment of schizophrenia.

Studies have identified apoptosis and cytotoxicity as the primary mechanisms by which first-generation antipsychotics, particularly phenothiazines, can influence tumor growth. First-generation antipsychotics have also been shown to modulate the effectiveness of cancer treatments through various mechanisms, including increasing BBB permeability, modulating cellular signaling pathways such as PI3K/Akt/GSK-3β, STAT 3, improving the accumulation of chemotherapeutic drugs in the body, and increasing cell susceptibility to chemotherapy through inhibition of P-gp pumps [37–39].

Another potential application of phenothiazines that has attracted attention in recent years is that phenothiazines, particularly chlorpromazine, have demonstrated neuroprotective effects in ischemic stroke. In their study, H.-J. Li et al., showed that administration of chlorpromazine to rats before induction of middle cerebral artery occlusion reduced infarction size by 20.1% [40]. The proposed mechanism of action was activation of BKCa channels, compared to a reduction of neuroprotective activity with administration of chlorpromazine with a blockade of BKCa channels. Recent studies have shown the efficacy of combined treatment of ischemic stroke using chlorpromazine and promethazine, which have been shown to reduce oxidative stress associated

with the production of reactive oxygen species NADPH via the PKC-δ/NOX/MnSOD pathway [41–43].

Antimicrobial, antiviral, antiprotozoal, antifungal and antiprion activities of phenothiazines have also been reported [38].

## Conclusion

Thus, in recent years, there has been increased interest in studying the effects of phenothiazine drugs. Epigenetic factors responsible for the expression of the serotonin transporter, tryptophan hydroxylase 2, and brain-derived neurotrophic factor may be a cause of suicidal behavior. These findings are important for further research.

Given that, patients receiving phenothiazines are at higher risk of poisoning, studies of the direct effects of repeated acute phenothiazine poisoning caused by overdose, both intentional and unintentional, are of particular interest. Although the clinical manifestations of phenothiazine poisoning are well documented, modern morphological and immunohistochemical studies of acute phenothiazine intoxication are scarce.

Given the potential for new applications for phenothiazines, further study of the direct effects of phenothiazines on the central nervous system in overdosing, with a focus on repeated overdose-linked events, is important for identifying the morphological substrate of phenothiazine poisoning. Furthermore, phenothiazines increase global methylation, while suicidal behavior is potentially associated with increased methylation in specific DNA regions, which may serve as a differentiating factor in the study of suicide causes. Research focused on the development of new approaches for treating phenothiazine poisoning, as well as their possible neuroprotective properties in ischemic stroke, offer potential for the field of intensive care. The aforementioned ability of phenothiazines to enhance the effectiveness of cancer treatment offers significant potential for clinical application, not only for symptomatic treatment, but also for mitigating the side effects of chemotherapy for patients with malignant tumors.

Renewed interest in expanding the use of this pharmacological group should lead to further study of the mechanisms associated with the use of phenothiazines, with the aim of developing more effective therapeutic strategies and improving patient outcomes not only in psychiatry but also in other diseases.

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