Edinoff AN, Armistead G, Rosa CA, et al. Phenothiazines and their Evolving Roles in Clinical Practice: A Narrative Review. *Health Psychology Research*. 2022;10(4). doi:10.52965/001c.38930

General

Phenothiazines and their Evolving Roles in Clinical Practice: A Narrative Review

Amber N. Edinoff[1] [a], Grace Armistead[1], Christina A Rosa[2], Alexandra Anderson[3], Ronan Patil[4], Elyse M Cornett[5], Kevin S. Murnane[6], Adam M. Kaye[7], Alan D. Kaye[5]

[1] Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Shreveport, [2] Department of Psychology, University of California, Santa Barbara, [3] School of Medicine, Louisiana State University Health Shreveport, [4] School of Medicine, The George Washington University, [5] Department of Anesthesiology, Louisiana State University Health Shreveport, [6] Department of Psychiatry and Behavioral Medicine, Louisiana State University Health Shreveport; Louisiana State University Health Shreveport, Department of Pharmacology, Toxicology & Neuroscience; Louisiana Addiction Research Center, [7] Department of Pharmacy Practice, Thomas J. Long School of Pharmacy, University of the Pacific, Stockton

Keywords: Phenothiazines, chlorpromazine, perphenazine, migraines, hiccups, nausea and vomiting, adverse effects

https://doi.org/10.52965/001c.38930

Health Psychology Research

Vol. 10, Issue 4, 2022

Phenothiazines, a diverse class of drugs, can be used to treat multiple mental health and physical conditions. Phenothiazines have been used for decades to treat mental illnesses, including schizophrenia, mania in bipolar disorder, and psychosis. Additionally, these drugs offer relief for physical illnesses, including migraines, hiccups, nausea, and vomiting in both adults and children. Further research is needed to prove the efficacy of phenothiazines in treating physical symptoms. Phenothiazines are dopaminergic antagonists that inhibit D2 receptors with varying potency. High potency phenothiazines such as perphenazine are used to treat various psychiatric conditions such as the positive symptoms of schizophrenia, the symptoms of psychosis, and mania that can occur with bipolar disorder. Low/mid potency phenothiazines such as chlorpromazine antipsychotic drugs that have been used to treat schizophrenia and schizophrenia-like disorders since the 1950s and are utilized in numerous disease states. The present investigation aims to elucidate the effects of phenothiazines in clinical practice.

INTRODUCTION

Phenothiazines, a diverse class of medications, can be utilized in the treatment of both psychiatric and non-psychiatric conditions, including schizophrenia, bipolar disorder, nausea, and even parasitic infections. Given their wide array of pharmacological effects, these drugs collectively have been the subject of investigation by numerous researchers for decades and are one of the first-generation antipsychotic medications.

Phenothiazines are dopaminergic antagonists that inhibit D2 receptors with varying potency.[1,2] Phenothiazines can be subclassified into high and low potency depending on their receptor binding profile.[2] This stratification helps further identify adverse symptoms associated with this class of medication. These classifications also enable providers to effectively weigh the benefits of such drugs with the cost of their extensive side effects. For example, long-term adherence to antipsychotics in severe cases of psychiatric illness has been suggested to negatively affect a patient's overall mortality.[3] In this regard, a study found that patients with schizophrenia who were on antipsychotics had increased overall mortality relative to patients who were not on any antipsychotics.[3] Another study found that high-dose antipsychotics over a long period could cause tardive dyskinesia, a condition defined as abnormal movements of the face, tongue, limbs, or trunks, which can be debilitating for individuals who already have severe psychiatric conditions.[4]

Given the variable side effects of phenothiazines, our literature describes numerous antipsychotic class side effects; however, few studies to date have focused on phe-

a **Corresponding author:**
Dr. Amber Edinoff, MD
Louisiana State University Health Science Center Shreveport
Department of Psychiatry and Behavioral medicine
1501 Kings Hwy
Shreveport, LA 71103
Phone: (318) 675-8969
amber.edinoff@lsuhs.edu

nothiazines alone. Therefore, the present investigation focused on the role of phenothiazines and untoward effects in clinical practice.

PHENOTHIAZINES

Fluphenazine is an antipsychotic agent that can be administered in the form of a depot injection and can be administered each month.[5] Depots are administered by physicians to maintain medication compliance in patients who may not prefer or have the means to take daily oral medications.[5] Fluphenazine can also be given as a short-acting injection, which can be used for agitation, as fluphenazine hydrochloride. There are two forms of the depot available, the decanoate and the enanthate.[5] The enanthate form may last up to three weeks, and the decanoate may last up to six weeks.[5] However, fluphenazine in the form of a longer-acting depot may cause extrapyramidal side effects and decreased mood.[5] When the Cochrane Collaboration evaluated the depot fluphenazine, it was found to have equivalent effects as the oral high potency antipsychotics in terms of efficacy and side effects.[5] The only clear advantage of the depot identified in this review is that this form of medication may potentially improve patient compliance.[5]

To properly evaluate therapeutic responses, researchers and providers must appreciate pharmacokinetic properties. Fluphenazine is one such drug whose pharmacokinetic properties have been thoroughly examined. In the Dysken, et al. 1981 study, the average half-life of oral fluphenazine was 16.4 hours when measured in a group of twenty-nine individuals.[6] The plasma fluphenazine level peaked at 6 ng/ml, which occurred two hours after a dose of 20 mg of oral fluphenazine hydrochloride was given.[6] The therapeutic window based on fluphenazine plasma levels ranged from approximately 0.2 ng/ml to 2.8 ng/ml.[6]

Tardive dyskinesia is an irreversible movement disorder that can occur using any antipsychotic medication.[7] In the Csernansky et al. study, researchers found a significant correlation between the dose of fluphenazine in the decanoate depot form and abnormal involuntary movement scale (AIMS) scores.[7] When the decanoate form was compared to an oral form of fluphenazine, the decanoate form was found to independently increase AIMs scores.[7] When the dose of the oral form was kept constant, increasing doses of the decanoate fluphenazine increased AIMs scores.[7] However, when the dose for the decanoate form was kept constant, the AIMs scores were reduced.[7] High AIMs scores correlated with an increased risk of developing tardive dyskinesia.[7] In this study, the decanoate formulation of fluphenazine was correlated with the development of tardive dyskinesia and was responsible for 36% of the difference between these AIMs scores.[7]

Prochlorperazine is a phenothiazine that can reduce nausea and vomiting related to chemotherapy.[8] However, this medication has had limited evaluation for safety in children relative to adults.[8] In the Lin et al. 2016 review, 4% of children evaluated developed extrapyramidal symptoms with multiple doses of prochlorperazine, while 10% of children had sedation.[8] When examining single-dose studies, 9% of children were found to have extrapyramidal symptoms develop after a single dose of prochlorperazine.[8] Sedation and extrapyramidal symptoms were the most reported adverse events for children in all reviewed studies.[8] Of note, most children recovered completely after discontinuation of prochlorperazine.[8] With these side effects and others in mind, parents should be educated about the drug before their child is administered prochlorperazine.[8]

Chlorpromazine was originally developed in 1951 as an antihistamine. Still, its ability to induce a state of artificial hibernation and reduce psychotic symptoms eventually led researchers to use the drug to treat schizophrenia.[9,10] Early trials of the drug compared to placebo indicated that it hastened clinical recovery, facilitated improvements in social functioning, and effectively prevented relapse.[11] However, the drug has many known side effects including impaired vision, a dry mouth, tremors or uncontrolled shaking, sadness, muscular stiffness, and restlessness may occur.[11] Chlorpromazine is considered a 'benchmark' drug and is often used as a control drug instead of a placebo when a new treatment is being evaluated.[11] Considering this, chlorpromazine was re-evaluated by the Cochrane Schizophrenia Group in a systematic review of randomized controlled trials (RCTs) to review the drug's effects and provide quantification to support clinical impression. Adams et al. reported evidence suggesting that chlorpromazine reduces relapse and improves people's mental health, symptoms, and functioning.[11] The reported side effects include sleepiness and sedation, abnormalities of movement (such as tremors and uncontrolled shaking), significant weight gain, and hypotension with concomitant dizziness.[11] Of note, the evidence was rated by the review authors as low quality. The review authors ultimately concluded that chlorpromazine's position as a 'benchmark' treatment for schizophrenia was not threatened by the review results.[11]

Perphenazine is another antipsychotic that has been used in the treatment of schizophrenia and other psychotic disorders for over 50 years. It was first available as an oral preparation in late 1957 and later became available for intravenous injection in the 1970s.[12] In a double-blind study published in 1957, 20 male patients were divided into a control group (Group I) and a group treated with perphenazine (Group II). The control group was given a combination of a placebo and chlorpromazine. Each group consisted of nine patients with chronic schizophrenia and one patient suffering from epilepsy with psychosis. The drug dosages for both groups ranged from 8 mg to 20 mg twice a day over 12 weeks. The study found that Group I had no significant changes, and Group II showed marked improvement. Notably, this study reported a striking finding that perphenazine was relatively free from side effects and that its only side effects were mild parkinsonian features in two cases. Furthermore, the researchers found that adding Artane and/or a decrease in dosage caused a disappearance of the parkinsonian features.[13] This is interesting because more recent research suggests there are quite a few side effects caused by perphenazine.

Decades later, in a systematic review performed in 2015, the Cochrane Schizophrenia Group sought to examine per-

phenazine's clinical effects and safety compared to placebo and/or other treatments. It was not possible to draw any clear conclusions related to low-quality evidence presented by the RCTs that were reviewed. However, Hartung's review found that perphenazine was no better or worse than other older antipsychotic drugs in treating the symptoms of schizophrenia. Like other older antipsychotic drugs, the side effects of perphenazine included tremors, uncontrollable shaking, the inability to sit still, and restlessness.[14]

PHENOTHIAZINE: OTHER CLINICAL USES

Phenothiazines have been demonstrated to be reliable therapy for intractable hiccups and acute migraines in adults. Additionally, phenothiazine derivatives are potentially useful as antiviral drugs and have also been researched as analgesics.

Hiccups are considered persistent if they last more than 48 hours and intractable if they last more than a month. In either case, hiccups are uncomfortable and even painful. Many treatments and remedies exist for hiccups, but chlorpromazine is the only medication approved by the Food and Drug Administration. Chlorpromazine uses a central mode of action through dopamine antagonism in the hypothalamus. However, related to its serious potential side effects, it is not recommended as the first line of defense. These side effects include hypotension, glaucoma, and delirium.[15] Additionally, Freidgood and Ripstein reported transient faintness, palpitation, and tachycardia as side effects of chlorpromazine.[16] Nevertheless, chlorpromazine's effectiveness in treating the intractable hiccup makes it a popular remedy. For example, Friedgood and Ripstein claimed that of 50 patients with a variety of medical and surgical diagnoses, 80% had a permanent cure and 10% had a transient benefit. Chlorpromazine has been found much more effective in treating hiccups when given intravenously than intramuscularly, especially after a single dose of 50 mg.[17] It is important to note that if the cause of hiccups is untreated, such as subphrenic abscess, the hiccupping may return. Furthermore, due to chlorpromazine's unpredictable effects, it is recommended that any patient receiving the drug should be monitored closely and observed for several hours post-injection or ingestion.[16]

Another phenothiazine drug, prochlorperazine, has been found useful in the treatment of acute migraines in adults. A systematic review examined 5 RCTs that compared prochlorperazine to a placebo. The findings of the RCTs concluded that prochlorperazine was more effective for controlling headaches than placebo. However, the studies also found that it was associated with an increased risk of adverse effects, such as extrapyramidal symptoms, compared to placebo. The review concluded that the risk of adverse effects should be considered when deciding whether to use prochlorperazine to treat migraines as safer options are available.[18]

The SARS-CoV-2 pandemic caused researchers to switch their focus to antiviral therapies, primarily to characterize potential antiviral activity of existing drugs. As reported by Otręba et al., chlorpromazine, fluphenazine, perphenazine, prochlorperazine, and thioridazine possess anti-viral activity towards different types of viruses. These drugs inhibit clathrin-dependent endocytosis, cell-cell fusion, infection, replication of the virus, decrease viral invasion, and suppress entry into the host cells.[19]

Lastly, phenothiazines have been studied in double-blind clinical trials for their potential use as analgesics or potentiators of analgesics. The study concluded a lack of supportive data of analgesic activity and noted the adverse reactions associated with phenothiazines. Therefore, phenothiazine derivatives are not recommended by this study as analgesics.[20]

In conclusion, the studies referenced in this discussion support the use of chlorpromazine to treat intractable hiccups and acute migraines. Furthermore, due to their method of action, phenothiazine derivatives are also potentially useful antiviral drugs. However, more research is warranted to confirm effectiveness and potential development of adverse side effects.

SIDE EFFECTS WITHIN ORGAN SYSTEMS

AUTONOMIC AND CARDIOVASCULAR

Autonomic and cardiovascular side effects are potentially the most dangerous and can include ileus, falls, arrhythmias, and seizures.[2] Cardiac effects may be caused by hypotension and anticholinergic-induced tachycardia.[2] In elderly patients given low-potency phenothiazines, postural hypotension can be a problem and may also contribute to hip fractures.[2]

In addition, changes can be seen on electrocardiographs, including QT prolongation, abnormal T-wave morphology, and widening of the QRS complex.[3] The QT interval measures the time it takes between the start of depolarization and the end of repolarization.[21] In some patients, QT prolongation can cause sudden death and has been reported in 1.5 to 1.8 persons per 1000 years of exposure to any antipsychotic drug.[22] QT prolongation can increase the risk for torsade de Pointes (TdP), which can degenerate into ventricular fibrillation, leading to sudden cardiac death.[21] Therefore, patients receiving phenothiazines are at particular risk for TdP arrhythmia, which can be lethal.[21] Among the phenothiazines, chlorpromazine and thioridazine are more likely to prolong the QT interval. They are, therefore, associated with a known risk of TdP, even when taken as recommended.[21]

ENDOCRINOLOGIC

Phenothiazine side effects affecting the endocrinologic system come from hyperprolactinemia, including amenorrhea, galactorrhea, gynecomastia, and impotence.[2] It was suggested by Marken et al.[19] that typical antipsychotics may block the dopamine receptors in prolactin-secreting cells, which prevents the reduction of prolactin release. Hyperprolactinemia can cause impotence in men and amenorrhea in women.[19] A study by Windgassen et al.[23] reported a prevalence rate of 19% for galactorrhea in 150 patients treated with fluphenazine, perphenazine, perazine, thior-

idazine, levomepromazine, and other antipsychotics. Patients taking antipsychotics were at greater risk for galactorrhea if they had a history of prior pregnancy or use of oral contraceptives.[23] Hyperprolactinemia can be a sign of pituitary adenoma in rare cases.[2]

METABOLIC

Weight gain is the most common metabolic effect caused by phenothiazines and is classified as an increase of more than 5 kg within two months.[2] Each phenothiazine has a different level of risk regarding weight gain. Chlorpromazine carries a relatively high risk of weight gain, whereas fluphenazine carries a low risk.[13] Excessive weight gain might put individuals at risk for a variety of complications. other obesity-associated side effects such as non-insulin-dependent diabetes and cardiovascular disease.[2]

HEMATOLOGIC

Phenothiazine side effects affecting the hematologic system include agranulocytosis, neutropenia, leukocytosis, and leukopenia (2; 9). These effects usually occur within 3 to 6 weeks after treatment.[2] There is some evidence that chlorpromazine, fluphenazine, perphenazine, thioridazine, and trifluoperazine carry a higher risk than other phenothiazines and typical antipsychotics.[9] The risk of agranulocytosis for chlorpromazine is 0.13 percent.[9]

HEPATIC

Liver function abnormalities have always been observed during antipsychotic treatment because the liver is responsible for the metabolization of most antipsychotics.[6] Chlorpromazine is the phenothiazine most associated with severe liver toxicity and should not be used for patients with pre-existing liver dysfunction.[6] Cholestatic jaundice is common and usually occurs in the first month of treatment.[6]

ALLERGIC/ DERMATOLOGIC

Allergic side effects of phenothiazines include maculopapular rash, erythema multiforme, angioedema, exfoliative dermatitis, and generalized urticaria.[2] Chlorpromazine treatment, in particular, has been reported to cause photo contact urticaria.[17] Photosensitivity and skin hyperpigmentation are side effects associated most commonly with the phenothiazine chlorpromazine when it is given long-term in high doses.[18] This side effect can be mitigated by avoiding sun exposure and applying sunscreen.[18]

OPHTHALMOLOGIC

Pigmentary retinopathy and deposits in the lens or cornea leading to cataracts are the main ocular issues found with antipsychotic medications. Phenothiazines generally carry the highest risk.[2] Out of the phenothiazines, Thioridazine has been most associated with pigmentary retinopathy.[13] It has been found that a higher dose of Thioridazone and other phenothiazines correlates with a higher risk of pigmentary retinopathy.[11] Corneal and lenticular pigmentation is predominantly a side-effect of chlorpromazine, although other low-potency drugs like thioridazine and fluphenazine have also been reported to cause pigmentary changes.[14] Ruigómez et al. wanted to determine whether schizophrenia or antipsychotic drugs were a risk factor for cataracts, so they compared the rate of clinical diagnosis of cataracts in patients with schizophrenia and compared it with the rate in the general population.[24] They found that, overall, antipsychotic drug treatment was not associated with the occurrence of cataracts. However, long-term uses of chlorpromazine at doses of 300 mg or more daily was associated with an increased risk of cataracts.[24]

ANTICHOLINERGIC EFFECTS

Anticholinergic effects of phenothiazines consist of blurred vision, constipation, delirium, dry mouth, tachycardia, and urinary difficulties.[25] For example, these symptoms are usually benign but can be clinically significant but people with a compromised cardiovascular system.[25] These effects would be why phenothiazines would not be a good medication to use in the elderly for agitation. Low-potency phenothiazines (e.g., chlorpromazine and thioridazine) commonly result in these symptoms.[25] Elderly people fair the worst with these side effects because they have slower or deficient drug metabolism and elimination, along with age-related deficits in cholinergic transmission.[25] Some clinical observations have suggested that treatment with phenothiazines over a long time can cause urinary retention and incontinence (8; 24). One study by Finkbeiner and Bissada investigated the action on the urinary bladder of two of the most commonly prescribed phenothiazines, chlorpromazine and prochlorperazine.[8] Their results showed that both drugs depressed the stimulatory effects of barium chloride, electric stimulation, acetylcholine, and bethanechol with the degree of depression relating to the dose of the phenothiazine.[8] They found that chlorpromazine and prochlorperazine depress smooth muscle activity in the bladder in vitro by a peripheral cholinergic blocking action and directly depressing it.[8] One study found that urinary incontinence has a reported prevalence of 3-6% and has been found with almost all typical antipsychotics given in various doses.[26] Urinary difficulties are rare adverse effects of antipsychotic agents. However, they can impact patient compliance.[26]

CENTRAL NERVOUS SYSTEM SIDE EFFECTS

EXTRAPYRAMIDAL SYMPTOMS

Antagonism of D2 receptors in the nigrostriatal pathway is associated with the potential development of extrapyramidal side effects.[27] Akathisia is characterized by a sense of inner restlessness and an urge to move. The inability to stand in one place and fidgety movement of the legs are the most observable symptoms.[2] In addition, women are twice as likely to experience akathisia.[2] A study was done to determine the incidence and severity of prochlorperazine-induced akathisia at 1 hour and 48 hours.[7] They

found that single-dose intravenous prochlorperazine frequently caused akathisia within 1 hour.[7]

Akinesia is associated with difficulty initiating and sustaining voluntary motor movement, depressed mood, and cognitive impairment.[2] Bradykinesia is very similar to akinesia. However, it is more so associated with slowed movement.[20] Tremors can also occur, which involve involuntary, rhythmic shaking movements.[28] Dystonia is another severe side effect that usually occurs during the first week of treatment and manifests as involuntary contractions or muscle spasms. These reactions are uncomfortable and can be life-threatening.[2] In one study, the occurrence of dystonia was measured in 1,152 psychiatric inpatients who were exposed to butyrophenone, phenothiazines, or thioxanthenes.[27] While all phenothiazines were associated with dystonia, the highest frequencies of dystonia occurred among recipients of long-acting injectable fluphenazines and another typical antipsychotic, haloperidol. Out of all the patients at risk, dystonia was most common in younger patients and men. Of those who received chlorpromazine, the risk of dystonia was positively associated with high dosage (300 mg or higher daily), male sex, and young age.[27] Compared to high-potency phenothiazines (e.g., fluphenazine and perphenazine), low-potency phenothiazines (e.g., chlorpromazine and thioridazine) are less likely to cause extrapyramidal symptoms.[13]

TARDIVE DYSKINESIA

Tardive Dyskinesia (TD) is a hyperkinetic movement disorder that occurs after the chronic use of antipsychotic medications, especially phenothiazines.[2] The most common expressions of TD are involuntary movements of the mouth and tongue. However, the arm, legs, and respiratory muscles can also be affected.[2] Types of perioral movements may include: protruding and twisting the tongue, pouting, smacking lips, retraction of the corners of the mouth, bulging of the cheeks, chewing movements, or blepharospasm.[1] Studies have indicated that elderly patients and people with diabetes are at greater risk for developing TD.[1]

In some cases, TD can be irreversible and a lifelong condition with major negative impacts on quality of life.[2] This is one of the most troubling side effects of phenothiazines because the disfiguring that it causes contributes to the stigma of schizophrenia. All phenothiazines have been found to carry a risk of TD, but higher risk has been attributed to fluphenazine and trifluoperazine.[13]

NEUROLEPTIC MALIGNANT SYNDROME

The characteristics of neuroleptic malignant syndrome (NMS) are fever, clouding of consciousness, muscle rigidity, and autonomic instability.[5] It is generally accompanied by creatine kinase elevation and rhabdomyolysis.[5] The occurrence of NMS ranges between .01% to 1%. However, it can be fatal.[5] No differences in risk have been reported for phenothiazines.[13]

SEIZURES

Seizures are a potential early complication in phenothiazine treatment because typical antipsychotics generally reduce the seizure threshold.[2] In 2015, case-control analysis of more than 60,000 patients found that the risk of seizure with typical antipsychotics was 49.4 per 10,000 person-years of taking chlorpromazine and thioridazine.[4] They also looked at the risk of seizure with exposure to trifluoperazine which was 59.1 per 10,000 person-years, compared with 11.7 for controls.[4]

SEDATION

All phenothiazines have sedating effects related to histamine blockade.[2] The lower-potency phenothiazines, specifically chlorpromazine and thioridazine, are highly sedating due to their high histaminic H1 receptor antagonism levels. In contrast, the higher potency drugs are less sedating (e.g., fluphenazine and trifluoperazine).[16] Sedation can often interfere with rehabilitation and can be mistaken for cognitive impairment.[5]

SEXUAL AND REPRODUCTIVE SIDE EFFECTS

SEXUAL DYSFUNCTION

All conventional antipsychotic medications are associated with impaired sexual function.[15] Men may experience ejaculatory disturbances, impotence, decreased libido, and changes in the quality of orgasm.[2] Women may suffer from orgasmic dysfunction and a decrease in desire.[2] La Torre et al. meta-analysis reported sexual dysfunction symptoms in 60 percent of thioridazine-treated patients.[15] In addition, prolonged erection, which can lead to priapism, is a possible side effect of all antipsychotic drugs, but especially for phenothiazines (chlorpromazine, fluphenazine, and thioridazine).[15] Sexual side effects can harm patient compliance throughout treatment.

TERATOGENICITY, RISK TO NEONATES AND BREASTFEEDING

Teratogenicity, the potential of a drug to cause fetal deformities, risk to neonates, and the risk from ingesting breast milk are all concerns of typical antipsychotics.[10] These medications cross the placenta and are secreted in breast milk.[2] One study observed a two-week-old infant girl with psychomotor disturbances and whose mother had been treated with intramuscular injections four times during the second and third trimester with perphenazine.[12] The symptoms of the infant resembled tardive dyskinesia.[12] In another study, Yoshida et al. studied 12 breastfeeding mothers who had been prescribed chlorpromazine, trifluoperazine, and another antipsychotic.[29] The researchers found that infants were ingesting up to 3% of the maternal dose per kg body weight.[29] Three of the infants of the mothers who were prescribed chlorpromazine showed a decline in their developmental scores between assessments at 12-18

months.[29] The researchers advised caution when taking these antipsychotics while pregnant and breastfeeding.

PATIENT COMPLIANCE

Along with affecting patients' quality of life, all of these side effects contribute to noncompliance. A review by Awad and Hogan reported that the subjective response to antipsychotics can predict compliance, suicidal behavior, and therapeutic outcome.[3] Side effects influence a patient's daily life in a multitude of ways varying from annoying to life-threatening. Some effects occur within the first few days of starting treatment, while others may not emerge for months or even years.[2] The subjectivity of these side effects can be a source of concern and a deterrent for patients.[3] Even the simply annoying side effects can interfere with patient compliance and, therefore, disrupt treatment. Table 1 summarizes the side effects and associated phenothiazines discussed in this section.

CONCLUSION

The present investigation outlines use, efficacy, and adverse effects of phenothiazines. Phenothiazines play an important role in the management of mental and physical illnesses. The value of this class of medications should not be understated as they were the first antipsychotic medications developed. Still, the side effects of these medications should also be taken into consideration because they can pose a significant health risk. Phenothiazines have been used for decades to treat mental illnesses, including schizophrenia, mania in bipolar disorder, and psychosis. Additionally, they offer relief for physical illnesses such as migraines, hiccups, nausea, and vomiting in both adults and children. Still, further research is warranted to evaluate efficacy of phenothiazines in many disease states.

Phenothiazines are available in a variety of forms, including oral medication and depot injections. By having the option to receive these medications in the depot form, patients may be more compliant with their medications and less likely to experience a relapse of their symptoms. Each phenothiazine drug has its own pharmacokinetic properties that differ based on the type of medication administered and the dose. Having this data available from various types of studies has allowed providers to select the most appropriate medication for an individual. However, these medications have a long list of potential side effects. The body systems affected by phenothiazines include the central nervous system, autonomic, cardiovascular, endocrine, reproductive, metabolic, hematologic, dermatologic, ocular, and hepatic, as well as the potential for allergic response. For this reason, patient education and follow-ups are critical to improving symptoms, preventing adverse effects, and ensuring patient compliance with these medications.

Although recommendations for antipsychotics have changed in the past few decades, phenothiazines remain important as a means of managing mental illnesses and many physical symptoms from a diverse list of medical conditions.

AUTHOR CONTRIBUTIONS

NE and AMK were responsible for the conceptualization of the manuscript. ANE, GA, CR, RP, and AA were responsible for the writing of the manuscript. ANE, EMC, ADK, and AMK were responsible for the editing of the manuscript.

FUNDING

This research received no external funding.

INSTITUTIONAL REVIEW BOARD STATEMENT

Not applicable.

INFORMED CONSENT STATEMENT

Not applicable

DATA AVAILABILITY STATEMENT

Data reported in this manuscript can be found on PubMed and is publically available.

CONFLICTS OF INTEREST

The authors have no conflict of interest to disclose.

Table 1. Side Effects Associated with most Phenothiazines

			Phenothiazines
Adverse Effects	**Autonomic, Cardiovascular, Endocrine, Metabolic**	QT prolongation, TdP, VF, SCD, postural hypotension, orthostasis, retrograde ejaculation, Illeus falls arrhythmias, seizures Hyperprolactinemia, amenorrhea, galactorrhea, gynecomastia, impotence, pituitary adenoma Weight gain/obesity Anticholinergic: xerostomia, constipation, dry mouth, blurred vision, delirium, tachycardia, and urinary retention, urinary incontinence	chlorpromazine levomepromazine cyamemazine thioridazine trifluoperazine mesoridazine promazine fluphenazine perphenazine pipotiazine pericyazine triflupromazine
	CNS	Tardive dyskinesia, extrapyramidal symptoms (akathisia, akinesia, bradykinesia, tremor, dystonia), neuroleptic malignant syndrome, seizures, sedation	chlorpromazine levomepromazine cyamemazine thioridazine trifluoperazine mesoridazine promazine fluphenazine perphenazine pipotiazine pericyazine triflupromazine prochlorperazine
	Sexual and Reproductive	Sexual dysfunction (ejaculatory disturbances, impotence, decreased libido, change in quality of orgasm, priapism) Teratogenicity (nonspecific congenital defects) Risk to neonates (Neonatal hepatic dysfunction, anticholinergic side effects, extrapyramidal side effects, complicated childbirth) Breastfeeding (neurologic and other side effects)	chlorpromazine levomepromazine cyamemazine thioridazine trifluoperazine mesoridazine promazine fluphenazine perphenazine pipotiazine pericyazine triflupromazine prochlorperazine
	Hematologic, Hepatic, Allergic, Dermatologic, Ocular	Leukocytosis, leukopenia, agranulocytosis, neutropenia Cholestatic-like jaundice Maculopapular rash, erythema multiforme, generalized urticaria, angioedema, exfoliative dermatitis Photosensitivity, skin hyperpigmentation Corneal/lenticular changes, granular deposits, pigmentary retinopathy	chlorpromazine levomepromazine cyamemazine thioridazine trifluoperazine mesoridazine promazine fluphenazine triflupromazine perphenazine pericyazine pipotiazine

REFERENCES

1. Kidron A, Nguyen H. Phenothiazine. In: *StatPearls*. StatPearls Publishing; 2022. Accessed February 26, 2022. http://www.ncbi.nlm.nih.gov/books/NBK556113/

2. Muench J, Hamer AM. Adverse effects of antipsychotic medications. *Am Fam Physician*. 2010;81(5):617-622.

3. Vermeulen J, van Rooijen G, Doedens P, Numminen E, van Tricht M, de Haan L. Antipsychotic medication and long-term mortality risk in patients with schizophrenia; a systematic review and meta-analysis. *Psychol Med*. 2017;47(13):2217-2228. doi:10.1017/s0033291717000873

4. Bergman H, Rathbone J, Agarwal V, Soares-Weiser K. Antipsychotic reduction and/or cessation and antipsychotics as specific treatments for tardive dyskinesia. *Cochrane Database Syst Rev*. 2018;(2):CD000459. doi:10.1002/14651858.cd000459.pub3

5. Adams CE, Eisenbruch M. Depot fluphenazine for schizophrenia. *Cochrane Database Syst Rev*. 2000;(2):CD000307. doi:10.1002/14651858.cd000307

6. Dysken MW, Javaid JI, Chang SS, Schaffer C, Shahid A, Davis JM. Fluphenazine pharmacokinetics and therapeutic response. *Psychopharmacology*. 1981;73(3):205-210. doi:10.1007/bf00422403

7. Csernansky JG, Grabowski K, Cervantes J, Kaplan J, Yesavage JA. Fluphenazine decanoate and tardive dyskinesia: a possible association. *Am J Psychiatry*. 1981;138(10):1362-1365. doi:10.1176/ajp.138.10.1362

8. Lau Moon Lin M, Robinson PD, Flank J, Sung L, Dupuis LL. The Safety of Prochlorperazine in Children: A Systematic Review and Meta-Analysis. *Drug Saf*. 2016;39(6):509-516. doi:10.1007/s40264-016-0398-9

9. Laborit H, Huguenard P. Artificial hibernation by pharmacodynamical and physical means. *Presse Med*. 1951;59(64):1329.

10. Davis JM, Garver DL. Neuroleptics: Clinical Use in Psychiatry. In: Iversen LL, Iversen SD, Snyder SH, eds. *Handbook of Psychopharmacology*. Vol 10. Springer US; 1978:129-164. doi:10.1007/978-1-4613-4042-3_4

11. Adams CE, Awad GA, Rathbone J, Thornley B, Soares-Weiser K. Chlorpromazine versus placebo for schizophrenia. *Cochrane Database Syst Rev*. 2014;(1):CD000284. doi:10.1002/14651858.cd000284.pub3

12. Martindale W, Parfitt K. *The Complete Drug Reference*. Pharmaceutical Press; 1999. Accessed May 27, 2021. http://archive.org/details/martindale00kath

13. O'Reilly PO, Wojcicki HM, Hrychuk W, Keogh RP. Perphenazine (Trilafon) Treatment of Psychoses. *Can Med Assoc J*. 1957;77(10):952-955.

14. Hartung B, Sampson S, Leucht S. Perphenazine for schizophrenia. *Cochrane Database Syst Rev*. 2015;(3):CD003443. doi:10.1002/14651858.cd003443.pub3

15. Woelk CJ. Managing hiccups. *Can Fam Physician*. 2011;57(6):672-675.

16. Friedgood CE, Ripstein CB. Chlorpromazine (thorazine) in the treatment of intractable hiccups. *J Am Med Assoc*. 1955;157(4):309-310. doi:10.1001/jama.1955.02950210005002

17. Williamson BW, MacIntyre IM. Management of intractable hiccup. *Br Med J*. 1977;2(6085):501-503. doi:10.1136/bmj.2.6085.501

18. Long B, Koyfman A, Gottlieb M. Prochlorperazine for Treatment of Acute Migraines in Adults. *Acad Emerg Med*. 2020;27(3):243-244. doi:10.1111/acem.13864

19. Otręba M, Kośmider L, Rzepecka-Stojko A. Antiviral activity of chlorpromazine, fluphenazine, perphenazine, prochlorperazine, and thioridazine towards RNA-viruses. A review. *Eur J Pharmacol*. 2020;887:173553. doi:10.1016/j.ejphar.2020.173553

20. McGee JL, Alexander MR. Phenothiazine analgesia--fact or fantasy? *Am J Hosp Pharm*. 1979;36(5):633-640.

21. Windgassen KW, Wesselmann U, Schulze Mönking H. Galactorrhea and hyperprolactinemia in schizophrenic patients on neuroleptics: frequency and etiology. *Neuropsychobiology*. 1996;33(3):142-146. doi:10.1159/000119265

22. Arana GW. An overview of side effects caused by typical antipsychotics. *J Clin Psychiatry*. 2000;61(Suppl 8):5-11; discussion 12-13.

23. Diogo Telles-Correia A, nio Barbosa HCP, Machado R. Psychotropic drugs and liver disease: A critical review of pharmacokinetics and liver toxicity. *World J Gastrointest Pharmacol Ther*. 2017;8(1):26-38. doi:10.4292/wjgpt.v8.i1.26

24. Nielsen J, Graff C, Kanters JK, Toft E, Taylor D, Meyer JM. Assessing QT interval prolongation and its associated risks with antipsychotics. *CNS Drugs*. 2011;25(6):473-490. doi:10.2165/11587800-000000000-00000

25. Sicouri S, Antzelevitch C, Lankenau Institute for Medical Research, Wynnewood, PA, USA, Lankenau Institute for Medical Research, Wynnewood, PA, USA, Lankenau Heart Institute, Wynnewood, PA, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA, USA. Mechanisms Underlying the Actions of Antidepressant and Antipsychotic Drugs That Cause Sudden Cardiac Arrest. *Arrhythmia Electrophysiol Rev*. 2018;7(3):199. doi:10.15420/aer.2018.29.2

26. Marken PA, Haykal RF, Fisher JN. Management of psychotropic-induced hyperprolactinemia. *Clin Pharm*. 1992;11(10):851-856.

27. Jibson MD. First-generation antipsychotic medications: Pharmacology, administration, and comparative side effects. *UpToDate*. Published online June 2021.

28. Flanagan RJ, Dunk L. Haematological toxicity of drugs used in psychiatry. *Hum Psychopharmacol Clin Exp*. 2008;23(S1):S27-S41. doi:10.1002/hup.917

29. Lovell CR, Cronin E, Rhodes EL. Photocontact urticaria from chlorpromazine. *Contact Dermatitis*. 1986;14(5):290-291. doi:10.1111/j.1600-0536.1986.tb05278.x