Module 2.5

CLINICAL OVERVIEW

Promazine hydrochloride 25mg/5ml Oral syrup and 50mg/5ml Oral Syrup

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List of Abbreviations

5-HT	5-hydroxytryptamine
BAC	blood alcohol concentrations
BDZs	benzodiazepines
CNS	Central nervous system
CPZ	Chlorpromazine
CPZ	chlorpromazine
CVAE	Cerebrovascular events
CYP	Cytochrome P450 isoforms
D	Dopamine
DP	Delusional parasitosis
ECT	Electroconvulsive treatments
EPS	Extrapyramidal side effects
FDA	Food and Drug Administration
FGAs	first-generation antipsychotics
H1	Histamine 1
HERG	Human ether-à-go-go-related gene
HPLC	High Performance Liquid Chromatography
IC_{50}	half maximal inhibitory concentration
IM	intramuscular
MAE	Movement after effect
Mtb	*Mycobacterium tuberculosis*
Ndh	NADH:quinone oxidoreductase
SGOP	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SSRIs	selective serotonin reuptake inhibitors
TADs	tricyclic antidepressants
TdP	torsade de pointes arrhythmia

2.5.1 Product Development Rationale

The aim of this report is to provide an overview of the clinical pharmacology, efficacy, safety and risk/benefit balance of *Promazine hydrochloride 25mg/5ml Oral syrup and 50mg/5ml Oral Syrup*.

Promazine hydrochloride is a well-known active substance that has been authorised as a medicinal product and marketed under the requested indications in numerous European countries for many years, including doses comparable to that being applied for. This is an abridged application made under section 10.a of European Directive 2001/83/EC; no non-clinical or clinical studies have been undertaken in support of this application.
As the application is a bibliographical application, the application references the pharmacological and clinical profile of promazine hydrochloride that is sufficiently described in published articles as well as in pharmacological clinical textbooks.
In compliance with the Notice to Applicants Medicinal products for human use presentation and format of the dossier Common Technical Document (CTD) Volume 2B from May 2008 relating to bibliographical applications, non-clinical/clinical overviews should demonstrate that the constituent(s) of the medicinal product have a well-established use, with an acceptable level of safety and/or efficacy, as outlined in Annex I to Directive 2001/83/EC.
The safety and efficacy of promazine hydrochloride is supported by several studies and evidenced by its long use in medical practice worldwide.
In order to establish the time over which promazine hydrochloride has been used in the European Union (EU), the date of first authorisation of promazine hydrochloride in the EU countries was considered, as well as the studies published in literature. Promazine hydrochloride 25mg/5ml Oral syrup and 50mg/5ml Oral Syrup were authorized for the first time in 1982 and 1985, respectively. The EURD of promazine was set on 13th April 1956, thus documenting its clinical use for more than 60 years.
Therefore, we can consider that a proposed "well established use" is possible since the minimum required period of 10 years of systematic use is met and well documented in the European Community. Promazine hydrochloride meets all the claims of well-established medicinal use according to Directive 2001/83/EC, as amended, with long-term history on the market worldwide with an acceptable level of safety and efficacy, as outlined in Part II.1 of Annex I to Directive 2001/83/EC. This approach can be considered acceptable, taking into account the long period of use of the active substance and its well-characterised properties.

Current Regulatory Status

Promazine is a phenothiazine introduced into clinical practice since 1956 as Sparine [redacted].
Promazine is reported as an active ingredient of medicinal products marketed in the following countries: Italy (Talofen); Germany (Protactyl; Sinophenin); Luxemburg, Swiss, Belgium, Croatia, (Prazine); United Kingdom, Ireland, Australia, Denmark, Finland, Sweden (Sparine); United States (Sparine, Prozine); Poland (Promazin)[redacted]

Legal Basis of Submission

Promazine hydrochloride is a well-established active ingredient of *Promazine hydrochloride 25mg/5ml Oral syrup and 50mg/5ml Oral Syrup* and no clinical studies have been undertaken in the support of the abridged licence application. The application is a bibliographical application which cites the scientific literature, and clinical guidelines to demonstrate the safety and efficacy of the product.

Therefore, the present application is submitted according to Article 10(a) of the European Directive 2001/83/EC and seeks to demonstrate that this formulation of promazine is suitable for authorisation within the EU.

Search Strategy

The submitted clinical overview is being based on data available in published literature. The [redacted] were used for searching of the relevant publication as well as relevant renowned medical textbooks. The exhaustive bibliographic search was carried out in December 2024.

The search performed in all databases used the key word "promazine" in combination with "pharmacodynamics", "pharmacokinetics", "mechanism of action", "efficacy", "safety" and "adverse events, being "human" the only limit applied. A secondary search included terms such as "psychomotor agitation", "first-generation antipsychotics", "psychomotor agitation management".

Publications were considered relevant if they were related to the indications and route of administration, as well as the efficacy and safety of the product, or when they reported relevant data for clinical pharmacology or mechanism of action of promazine. Both favourable and unfavourable data have been reported.

2.5.1.1 *Pharmacological Class of the Medicinal Product*

Drugs in the phenothiazine group share the same three-ring structure with different side chains joined at the nitrogen atom of the middle ring. The activity of the group can be affected by substitutions at position 2 or 10. The phenothiazines are the largest chemical group, comprising more than 40 compounds [redacted]

Promazine is an aliphatic phenothiazine antipsychotic agent, with a low-potency antidopaminergic action, α1-adrenergic antagonism and anticholinergic properties [redacted] Promazine is an antagonist of dopamine, serotonin, alpha-1 adrenergic, histamine H-1, and muscarinic receptors. Its chemical name is 10-(3-dimethylaminopropyl) phenothiazine; N,N-dimethyl-10Hphenothiazine-10-propanamine [redacted]

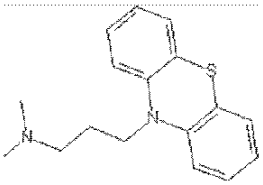

Figure 1. Chemical structure of promazine [redacted]

Promazine is used in the treatment of schizophrenia, paranoid states, mania, toxic psychosis (caused by amphetamines, lysergide, cocaine), mental organic disorders with delirium, severe anxiety refractory to benzodiazepines, and depression associated with psychomotor agitation and delusions. In elderly demented patients it is usually administered when behavioural disturbances occur. On the other hand, it may increase the sedative effects of benzodiazepines, hypnotics, anaesthetics and antihistaminic agents [redacted] The general properties and therapeutic uses of promazine are similar to chlorpromazine. It has pronounced sedative effects and moderate antimuscarinic and extrapyramidal side effects. Promazine is a relatively weak antipsychotic. Furthermore, promazine is a major metabolite of the group 1 phenothiazine, chlorpromazine [redacted] The comparison between the chemical structure of promazine and chlorpromazine is presented in Figure 2.

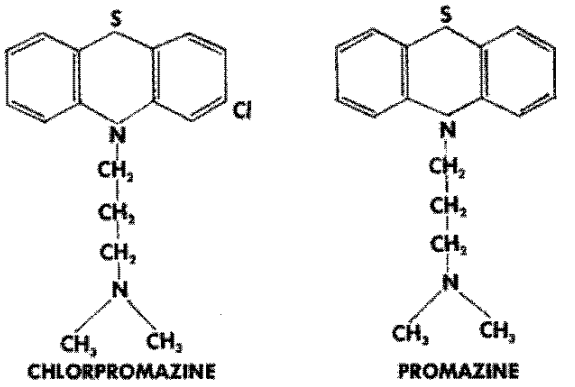

Figure 2. Comparison between the chemical structure of promazine and chlorpromazine [redacted]

Promazine hydrochloride is a white or almost white, slightly hygroscopic, crystalline powder. It oxidizes with prolonged exposure to air and develops a blue or pink color. Promazine hydrochloride is very soluble in water, in ethanol (96%) and in methylene chloride. Promazine is a major metabolite of the group 1 phenothiazine, chlorpromazine [redacted]

2.5.1.2 *Target Indications*

The proposed indication for Promazine hydrochloride 25mg/5ml Oral syrup and 50mg/5ml Oral Syrup, solution are:
As an adjunct non-pharmacological interventions in the short-term management of moderate to severe agitation and restlessness where there is a risk of harm to the individual or to others.

The term psychosis refers to a non-specific syndrome characterized by delusions (false beliefs), hallucinations (false sensory perceptions not shared by others), loss of contact with reality and bizarre behaviour. This syndrome can result from a wide range of conditions, including both primary psychiatric disorders (schizophrenia and schizophrenia-related disorders), medical disorders (physical trauma, temporal lobe epilepsy, dementia, neurologic and endocrine disease, metabolic abnormalities) and substance abuse disorders (particularly amphetamines and hallucinogens) [redacted]
Psychoses are common in the elderly, because events they can be either the expression of a disease that had its onset at a young age or the complications of some organic diseases beginning in later life (e.g. dementia). Psychoses prevalence varies from 6% to 10% in the elderly population [redacted]

Psychomotor agitation (PMA) is a challenging symptom observed in various psychiatric and medical conditions, often necessitating prompt intervention to ensure the safety and well-being of the individual. Characterized by motor restlessness, anxiety, irritability and increased psychomotor activity, PMA presents with emotional activation and heightened sensitivity to both internal and external stimuli, which may lead to impaired cognitive performance [redacted]

Psychomotor agitation is a disturbance of movement and behaviour associated with psychiatric or physical conditions. Agitation is included, with retardation, as one of the criteria for diagnosis of Major Depressive Episode in DSM-IV and of the somatic syndrome of depressive disorder in ICD-10. Agitation is described in a wide range of psychiatric syndromes: these include mood disorders, schizophrenia, drug intoxication and withdrawal states delirium and dementia. It is also particularly associated in depression with psychosis, melancholia, hypothalamic-pituitary-adrenal dysfunction and suggested as an outcome measure of treatment [redacted]

Agitation and restlessness are poorly understood in older adults, but are generally considered to have multifactorial etiology, including genetics, physical disease, changes in the brain, unmet needs, and unaddressed pain [redacted] Agitation and psychosis are common among older adults with dementia, with 80% of patients presenting with neuropsychiatric symptoms. Agitation and psychosis are important clinical problems as they decrease patient and caregiver quality of life and are a frequent contributor to caregiver's decisions to admit older adults with dementia to long-term care facilities [redacted] Symptoms of agitation and restlessness are also difficult for health care providers to manage. These symptoms commonly co-exist with acute or chronic pain in older adults and may present in response to an underlying, uncomfortable condition. It may be difficult for nurses and providers to identify the cause of an elderly patient's agitation. As older persons with dementia have fewer skills to communicate, they may exhibit signs of agitation, restlessness, and aggression in response to a host of underlying factors and frustrations that are not easily differentiated [redacted]

Management strategies for PMA typically progress from non-pharmacological intervention to pharmacological treatment based on the severity of the symptoms [redacted]

Non-pharmacological approaches, which address the contextual or psychosocial aspects of agitation, include techniques such as music therapy, aromatherapy, sensory interventions, light therapy, and various forms of cognitive and behavioural therapies. These interventions have demonstrated efficacy in reducing agitation, and are often the first line of treatment, especially in the early stages of PMA. When non-pharmacological methods prove ineffective, pharmacological management becomes necessary. Antipsychotics are the cornerstone of pharmacological treatment for PMA. The choice of antipsychotics depends on factors such as the severity of PMA, patient characteristics, pharmacokinetics and pharmacodynamics of the drug, patient preferences regarding route of administration, and age. The goal is to achieve rapid and effective control of symptoms whilst minimizing adverse effects [redacted]

Pharmacologic treatments for psychomotor agitation and aggressive behaviour with documented efficacy in children and adult populations include antipsychotics [redacted] The antipsychotic agents were introduced in 1954. The use of antipsychotic agents has provided for rapid treatment and rehabilitation of many patients who formerly would have been hospitalised for long periods and suffered prolonged or lifelong difficulty [redacted] Of all the psychotropic drugs, the neuroleptic agents are the most important in psychiatry. Major chemical classes of neuroleptic agents are the phenothiazines, butyrophenones, and thioxanthenes, and there are miscellaneous agents such as loxapine, molindone, and clozapine [redacted] The phenothiazines evolved from the aniline dyes and antihistamines, and the butyrophenones evolved from the meperidine-like analgesics. These agents are used primarily to treat psychotic disorders in adults in children. They are called neuroleptic agents because of their ability to cause a change in affect, with emotional quieting, psychomotor slowing, disinterest in surroundings, and decreased aggression and impulsivity. These drugs have a marked effect on thought disturbances associated with paranoid ideation, delusions, anxiety, and agitation. These drugs do not sedate or calm patients, they exert a selective antischizophrenic action [redacted]

Liquid antipsychotics in the management of psychomotor agitation

Liquid formulations of antipsychotic drugs have emerged as a preferred choice in managing PMA due to their ease of administration, better bioavailability and lower production costs [redacted] In emergency care settings, an effective treatment strategy for acute PMA should include medications that are easy to administer, have quick onset of action, lead to minimal sedation and have predictable pharmacokinetics [redacted]

Oral treatment of the psychotic with medication in tablet form may fail because of the propensity of the patient to conceal the dose in the mouth and later to expel it secretly [redacted] Liquid formulations of antipsychotics, including promazine, have been developed to improve clinical outcomes and treatment adherence, particularly in populations with swallowing difficulties, cognitive impairment or those requiring supervised administration. Liquid antipsychotics offer several advantages over traditional tablets and capsules, including easier administration, faster absorption and potentially higher bioavailability, which can lead to quicker therapeutic effects. The availability of liquid formulations is particularly beneficial in emergency settings, where rapid control of symptoms is required, and in long-term care settings, where patients may have difficulty swallowing or

may be uncooperative. By providing a more manageable and less invasive option, liquid formulations help ensure that patients receive timely and effective treatment, thereby reducing the need for more coercive measures such as physical restraint or involuntary medication administration [redacted]

Promazine as a treatment option for PMA

Promazine is included among the currently marketed first-generation antipsychotics available in liquid formulation [redacted] Promazine is a phenothiazine neuroleptic agent with strong anticholinergic, hypotensive and sedative effects and moderate antiemetic effects. It is used mainly as an antipsychotic and antiemetic agent and additionally as an adjunct agent in the management of severe pain [redacted] The action of promazine helps reduce the severity of psychotic-related symptoms, although it is also associated with extrapyramidal side-effects at higher doses. Unlike some other antipsychotics, promazine has lower propensity to induce hyperprolactinaemia, making it a preferred option in certain clinical scenarios. Promazine's pharmacokinetic profile also contributes to its clinical utility. The drug is efficiently absorbed from the gastrointestinal tract. Its effects are typically noticeable within 20 min, making it a valuable option for rapid symptom control. The drug's half-life of approximately 6 h allows for sustained therapeutic effects, although multiple daily doses may be required in some patients to maintain symptom control. Promazine undergoes extensive hepatic metabolism, producing several metabolites that are excreted in the urine. In clinical practice, promazine has been shown to be effective in managing psychotic agitation [redacted] The use of liquid formulation of promazine in clinical practice has been documented since many years. Early studies showed that promazine liquid concentrate may be preferable for treatment of such cases because the patient actually ingests every dose, and earlier blood levels are produced as a result of more rapid absorption of the fluid compound [redacted] Promazine is licensed in psychomotor agitation and agitation or restlessness in the elderly. A recent study identified that, while promazine is barely used by most clinicians, it makes up a substantial proportion of all antipsychotic prescribing in two small geographic regions in England. However, it should be mentioned that promazine is not reported in any NICE guideline [redacted] An Italian study on the use and misuse of antipsychotic drugs in patients with dementia in Alzheimer special care units, showed that promazine was included among the most frequently prescribed antipsychotics [redacted]

Before starting antipsychotic therapy, it is generally recommended to check weight and blood pressure. Other suggested monitoring includes electrocardiogram (mandatory in some countries for specific antipsychotics, for example haloperidol), full blood count, urea and electrolytes, creatinine phosphokinase, liver function tests, blood glucose, lipid pattern and prolactin. If these laboratory examinations are not feasible, health care providers should ask the patient and/or family member about the existence of cardiovascular, renal or hepatic abnormalities, and whether drug therapies for these medical conditions have been prescribed and taken [redacted]

It is generally suggested to start with low doses, and to increase gradually. The minimum effective dosage should be prescribed [redacted]

The proposed posology for PROMAZINE HYDROCHLORIDE 25MG/5ML ORAL SYRUP AND 50MG/5ML ORAL SYRUP is presented below:

Agitation and restlessness
Adults: 100mg to 200mg, up to four times daily.
Elderly: 25 mg initially, up to 50 mg four times daily.
The lowest effective dose for the shortest period possible should be used.

Paediatric population
Children: Promazine is not recommended for children.

2.5.1.3 *Brief Description of Clinical Development Programme*

A clinical development programme has not been conducted by the applicant to support this application for marketing authorisation.
The submitted clinical overview is being based on data available in published literature. The [redacted] were used for searching of the relevant publication as well as relevant renowned medical textbooks. The pharmacological and toxicological profiles of promazine are sufficiently described in published articles as well as in pharmacological textbooks.

The pharmacological and toxicological profiles of promazine is sufficiently described in published articles as well as in pharmacological textbooks. *Promazine hydrochloride 25mg/5ml Oral syrup and 50mg/5ml Oral Syrup* meets all the claims of well-established medicinal use according to Directive 2001/83/EC, as amended, with long-term history on the market worldwide with an acceptable level of safety and efficacy, as outlined in Part II.I of Annex I to Directive 2001/83/EC. This approach can be considered acceptable taking into account long period of use of the active substance and its well-characterised properties.

2.5.2 Overview of Biopharmaceutics

2.5.2.1 *Overview of formulation*

Table 1. Composition of Promazine Promazine hydrochloride 25mg/5ml Oral syrup

Table 2 Composition of Promazine Promazine hydrochloride 50mg/5ml Oral Syrup

All excipients present in Promazine hydrochloride 25mg/5ml Oral syrup and 50mg/5ml Oral Syrup are widely used in pharmaceutical products and are well-characterised. There are no safety or clinical concerns regarding the presence of any of these excipients in this formulation.

2.5.2.2 *Overview of biorelevant in-vitro and bioavailability data*

No clinical studies were necessary for this application made under section 10(a) of European Directive 2001/83/EC, which is acceptable given that this is a bibliographic application for a product containing active substance of well-established use. Bioequivalence studies are not necessary to support this bibliographic application.

2.5.3 Overview of Clinical Pharmacology

The first-generation antipsychotics (FGAs) also known as, typical antipsychotics, dopamine antagonists, neuroleptics, traditional, old generation and classic antipsychotics represent the first group of effective agents for schizophrenia and other psychotic illnesses. They include all of the antipsychotics in the following groups: phenothiazines, butyrophenones, thioxanthenes, dibenzoxazepines, dihydroindoles, and diphenylbutylpiperidines. The FGAs represent the first group of effective agents for schizophrenia and other psychotic illnesses. Typical antipsychotics (sometimes referred to as Dopamine antagonists, first generation antipsychotics, conventional

antipsychotics, classical neuroleptics, traditional antipsychotics, or major tranquilizers) are a class of antipsychotic drugs first developed in the 1950s and used to treat psychosis (in particular, schizophrenia). Typical antipsychotics may also be used for the treatment of acute mania, agitation, and other conditions.

All antipsychotics are considered equally effective. Rationale for determining which medication to use is based on side effect profile. First-generation antipsychotics are well absorbed when they are administered orally or parentally. As with most drugs, oral administration leads to less predictable absorption than parenteral administration. Plasma concentrations of the drugs usually reach peak levels 1 to 4 hours after ingestion and 30 to 60 minutes after intramuscular (IM) administration. They are metabolized in the liver by CYP450 enzymes. Three of the CYP450 enzymes such as CYP1A2, CYP2D6 and CYP3A4 are involved in metabolism of first generation antipsychotics [redacted]

2.5.3.1 Overview of Pharmacokinetics

Variability in the outcome of treatment with antipsychotic drugs may be due to differences in compliance and to variations in pharmacokinetics and concentration-response relationships at the receptor level. Among the various chemical classes of neuroleptics, the butyrophenones, the phenothiazines, and the thioxanthenes have similar pharmacokinetics, and show larger inter-individual variations in plasma drug levels after oral than after intramuscular doses [redacted]

2.5.3.1.1 Absorption, bioavailability and distribution

Plasma concentrations of these drugs usually reach a peak 2-3 h after oral doses and 1/2- 1 h after conventional intramuscular dosage. The rate of absorption from intramuscular depot preparations is slower, and may depend on the ester form. Significantly smaller inter-individual variations in plasma level:dose ratios have been observed after intramuscular than after oral doses of phenothiazines, which indicates that variation in presystemic metabolism may be important after oral administration [redacted]

Promazine is rapidly absorbed after oral administration. Peak plasma concentrations occur at between 2 and 4 hours and its plasma half-life is about 6 hours [redacted]

The apparent volumes of distribution of these drugs are usually in the 10-40 l/kg range, and the plasma levels are in the nanomolar range after therapeutic doses, except for thioridazine which attains plasma levels in the lower micromolar range [redacted]

Basic lipophilic drugs are characterized by extensive accumulation in tissues, which leads to a high volume of distribution. Nonspecific binding to cellular membranes and uptake by acidic compartments (mainly lysosomes) are responsible for such a distribution pattern. Lysosomal trapping is an important mechanism of distribution of basic psychotropic drugs; however, the tissue distribution of the aliphatic-type phenothiazine neuroleptic promazine, tricyclic antidepressants (TADs) and selective serotonin reuptake inhibitors (SSRIs) depends more on phospholipid binding than on lysosomal trapping, whereas in other cases, lysosomal trapping is as important for the tissue uptake as is phospholipid binding. In a literature review, the brain was found to contain several times more phospholipids than other tissues, but a lower amount of lysosomes, showing moderate accumulation of basic lipophilic psychotropics [redacted]

The plasma concentrations of promazine are very low, it is widely distributed especially in the brain. It crosses the blood-brain barrier to achieve higher concentrations in the brain than in the plasma [redacted] A study designed to examine the total uptake of psychotropic drugs by vertically cut slices of rat whole brain, the grey (cerebral cortex) and the white (corpus callosum, internal capsule) matters of the brain, as well as by primary neuronal and astroglial cell cultures. When analysing the total drug uptake between the grey and the white matter of the brain, total uptake by the grey matter was 1.5–2 times higher than uptake by white matter, and that by neurons was 4–10 times greater than by astrocytes. Unlike the majority of psychotropic drugs, promazine does not show lysosomotropism in the grey matter [redacted]

- **Protein binding**

Over 90% promazine is bound to plasma protein [redacted] Promazine is highly bound to plasma proteins, especially albumin [redacted]

2.5.3.1.2 Metabolism and excretion

Promazine is extensively metabolized in the liver. Promazine had been found to be a major plasma metabolite of CPZ in a population of chronic schizophrenics [redacted]
Among the phenothiazine neuroleptics, promazine is the weakest blocker of dopamine D2 and serotonin 5-HT2 receptors, but it is a relatively strong antagonist of adrenergic α1 and histamine H1 receptors. According to the above drug-interactions, promazine is one of the mildest neuroleptics, displaying a relatively sedative profile of action that markedly surpasses its antischizophrenic potency. Therefore, promazine is recommended for the treatment of psychoses in elderly patients, as well as for the therapy of somatogenic psychoses with the symptoms of anxiety and fear [redacted]
Paths of metabolism of promazine include hydroxylation and conjugation with glucuronic acid, N-oxidation, oxidation of a sulfur atom, and dealkylation [redacted] During phase I of metabolism, neuroleptics that are phenothiazine derivatives, for example promazine (Figure 3), undergo mainly S-oxidation in the thiazine ring in position 5 and N-demethylation in a side chain, as well as aromatic hydroxylation and N-oxidation. In man, N-demethylation and sulphoxidation were reported to be the dominant pathways of promazine biotransformation. Similar promazine metabolism was observed in animals [redacted]

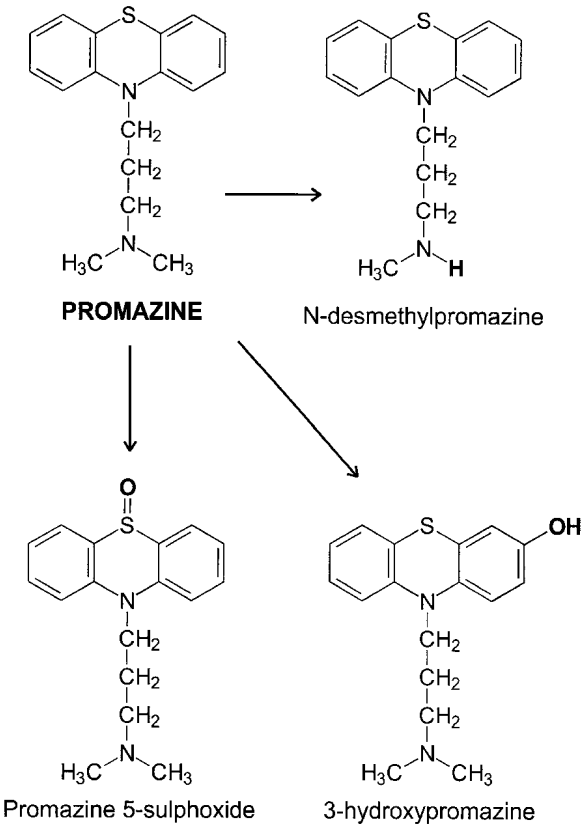

Figure 3. Metabolic pathways of promazine [redacted]

The contribution of human CYPs to the 5-sulphoxidation and N-demethylation of promazine, an aliphatic-type derivative and the chemically simplest phenothiazine neuroleptic was investigated by [redacted]. The *in vitro* study aimed to identify human cytochrome P-450 isoforms (CYPs) involved in 5-sulphoxidation and N-demethylation of the simplest phenothiazine neuroleptic promazine in human liver. As results, the authors concluded that CYP1A2 and CYP3A4 are the main isoforms responsible for its 5-sulphoxidation, while CYP1A2 and CYP2C19 are the basic isoforms that catalyse N-demethylation of promazine in the human liver. Of the other isoforms studied, CYP2C9 and CYP3A4 contribute to a lesser degree to promazine 5-sulphoxidation and N-demethylation, respectively. The role of CYP2A6, CYP2B6, CYP2D6 and CYP2E1 in the investigated metabolic pathways of promazine seems negligible[redacted]

In a more recent study, [redacted], studied the metabolism of phenothiazine neuroleptics (promazine, perazine) in a primary culture of human hepatocytes after pretreatment of cells with those neuroleptics. After the results, the authors suggested that phenothiazine neuroleptics may stimulate their own metabolism by inducing CYP1A2, CYP3A4 and CYP2C19. By inducing CYP isoforms (e.g. during a long-term neuroleptic therapy of psychiatric patients), phenothiazines may increase their elimination and thus attenuate the desired pharmacological effect. Moreover, phenothiazine neuroleptics are administered for months or even years, also to patients treated simultaneously with other clinically important drugs that are substrates of CYP1A2 (e.g., caffeine, theophylline, phenacetin, imipramine, propranolol, clozapine, melatonin), CYP3A4 (e.g., carbamazepine, cyclosporine A, calcium channel antagonists, macrolide antibiotics, benzodiazepines) or CYP2C19 (e.g., tricyclic antidepressants, S-mephenytoin, omeprazole). They may enhance metabolism of the co-

administered drugs, leading to the diminution of their pharmacological effect. On the other hand, hepatic CYP3A4 induction by phenothiazine neuroleptics may alter metabolism of endogenous substrates (e.g., steroid hormones), while the induction of CYP1A2 may increase the metabolic transformation of heterocyclic aromatic amines into reactive intermediates, resulting in toxicity and cancer. Hence, the induction of CYP enzymes by phenothiazines may be of physiological, pharmacological and toxicological importance [redacted]

Less than 1 per cent of a dose of promazine is excreted in urine [redacted] The elimination half-lives are usually in the range of 10-30 h, and steady-state plasma concentrations are reached after 2-5 days of treatment. Extreme half-life values far above this range have been observed in the occasional elderly patient, in whom it is to be expected that concentrations of drug are accumulating during a proportionally longer period before a steady-state plateau is reached. Substantial variation in plasma drug levels between patients seems to be the rule after oral administration, especially of phenothiazines [redacted]

Promazine and its metabolites also cross the placenta and are distributed into breast milk [redacted]

2.5.3.1.3 Pharmacokinetic interactions

Phenothiazine neuroleptics are administered to patients for months or years -very often in combination with antidepressants, antimanic or antianxiety drugs, to treat severe complex or 'treatment-resistant' psychiatric disorders. Such situations raise a possibility of pharmacokinetic interactions. Therefore, it is essential to know the potential drug-drug interactions between these agents.

Neuroleptics and antidepressants mutually inhibit their lysosomal uptake. A decrease in the intralysosomal drug concentrations *in vivo* leads to a shift of the drug from organs abundant in lysosomes (lungs, liver and kidneys) to those poor in these organella, e.g., the heart, which may be of clinical importance (cardiotoxicity) [redacted]

Promazine may compete with tricyclic antidepressants for the active centres of CYP1A2, CYP3A4 and CYP2C19. Moreover, its metabolism via CYP1A2 may be inhibited by fluvoxamine, and that via CYP2C19 and CYP3A4 by fluvoxamine and fluoxetine. On the other hand, metabolism of promazine mediated by CYP3A4 may be induced by carbamazepine. Interactions of this type between promazine and antidepressant drugs or carbamazepine have been observed in the rat. It is also important to note that the metabolism of promazine may be dependent on the known CYP2C19 polymorphism occurring at the highest rate in Oriental populations [redacted]

The possible impact of three selective serotonin reuptake inhibitors (SSRIs) fluoxetine, fluvoxamine and sertraline on the pharmacokinetics of promazine in a steady state was studied in rats, and the implications for humans were considered in the study carried out by [redacted]. Promazine was administered twice a day for 2 weeks, alone or jointly with one of the antidepressants. Concentrations of promazine and its two main metabolites (*N*-desmethylpromazine and sulfoxide) in the plasma and brain were measured at 30 min and 6 and 12 h after the last dose of the drugs. All the investigated SSRIs increased the

plasma and brain concentrations of promazine up to 300% of the control value, their effect being most pronounced after 30 min and 6 h. Moreover, simultaneous increases in the promazine metabolites' concentrations and in the promazine–metabolite concentration ratios were observed. *In vitro* studies with liver microsomes of rats treated chronically with promazine, SSRIs or their combination did not show any significant changes in the concentrations of cytochromes P-450 and b-5. However, treatment with fluoxetine, alone or in a combination with promazine, decreased the rates of promazine *N*-demethylation and sulfoxidation. A similar effect was observed in the case of promazine and fluvoxamine combination. Kinetic studies into promazine metabolism, carried out on control liver microsomes in the absence or presence of SSRIs added *in vitro*, demonstrated competitive inhibition of both *N*-demethylation and sulfoxidation by the antidepressants. The results of *in vivo* and *in vitro* studies indicate the following mechanisms of the observed interactions: (a) competition for an active site of promazine *N*-demethylase and sulfoxidase; (b) adaptive changes in cytochrome P-450, produced by chronic treatment with fluoxetine or fluvoxamine; (c) additionally, increases in the sum of concentrations of promazine+ metabolites, produced by fluoxetine and sertraline *in vivo*, suggest simultaneous inhibition of another, not investigated in this study, metabolic pathway of promazine, e.g. hydroxylation.

The authors concluded that all the three SSRIs administered chronically in pharmacological doses, increase the concentrations of promazine in the blood plasma and brain of rats by inhibiting different metabolic pathways of the neuroleptic. Assuming that similar interactions occur in humans, reduced doses of phenotiazines should be considered when one of the above antidepressants is to be given jointly [redacted]

In the study conducted by [redacted] to examine the intracellular distribution of psychotropic drugs in the grey and white matter of the brain, the authors found a decrease (via a pharmacokinetic interaction) in the concentration of psychotropics in lysosomes (depot), which may lead to an increase in their level in membranes and tissue fluids (i.e. in concentrations relevant to their pharmacological action) and, in consequence, to enhancement of the drug binding to neurotransmitter receptors and/or transporters. As a conclusion, the interactions described may be of clinical importance, since antidepressants and neuroleptics are used jointly in the treatment of complex or 'resistant' psychiatric illnesses [redacted]

Promazine may increase the sedative effects of benzodiazepines, hypnotics, anaesthetics and antihistaminic agents [redacted]

Certain materials used as pharmaceutic adjuncts and intestinal adsorbents can adsorb significant amounts of various phenothiazine derivatives. Calculations show that one-half of a 50 mg. dose of promazine could be adsorbed by 3.6 Gm of kaolin, by 1.7 Gm of talc, or by 0.55 Gm of activated charcoal. Effects on the rate and extent of absorption of promazine from the gastrointestinal tract produced by a mixture with either activated attapulgite or activated charcoal were studied in humans using urinary excretion measurements. The initial rate of appearance of drug in the urine was slowed, but there was little decrease in total availability when promazine was administered in mixtures containing activated attapulgite. Activated charcoal decreased both the rate and extent of absorption. It was concluded that the forces

through which the adsorption interaction is mediated are important to the effect obtained in vivo [redacted]

- **Interactions with alcohol**

Fatal drug poisonings often involve alcohol, benzodiazepines (BDZs), or both, and additive or synergistic interaction may occur between some of the components. Fatal drug and alcohol concentrations found in autopsies in Finland from 1995 to 2002 at the Forensic Toxicology Division of the University of Helsinki, have been analysed by [redacted], including a discussion on the most important agent in fatal drug-alcohol intoxications. The study was carried out on the most common agents in fatal drug poisonings in Finland: amitriptyline, propoxyphene or promazine alone; (2) one of these drugs with alcohol present; or (3) alcohol (ethanol) with one of these drugs detected at or above the upper limit of the corresponding therapeutic range, which was 0.2 mg/L for amitriptyline, 0.75 mg/L for propoxyphene and 0.4 mg/L for promazine. As results, for promazine, the median drug concentrations in drug poisonings and drug-alcohol poisonings were 6.9 and 6.3 mg/L (Table 2).

Table 3. Blood drug concentrations, blood alcohol concentrations (BAC) and manner of death in fatal drug-alcohol poisonings sorted by the most important finding [redacted]

Most important finding	n *(%)*	*Median drug concentration (mg/L)*	*Median BAC (mg/g)*	*Manner of death*	
				Accident (%)	*Suicide (%)*
Amitriptyline + alcohol					
Amitriptyline	65 (83)	1.7	1.7	23 (35)	31 (48)
Alcohol	13 (17)	0.3	3.0	13 (100)	
Propoxyphene + alcohol					
Propoxyphene	86 (99)	4.7	1.6	19 (22)	52 (60)
Alcohol	1 (1)	1.0	2.3	1 (100)	
Promazine + alcohol					
Promazine	57 (92)	6.7	1.0	12 (21)	38 (67)
Alcohol	5 (8)	0.5	3.5	5 (100)	

In the single-drug poisonings without alcohol or BDZ detected, 80% of the poisonings occurred within the following drug concentration ranges (10th-90th percentiles): 1.1-15.2 mg/L for amitriptyline, 2.1-40mg/L for propoxyphene and 2.3-17 mg/L for promazine (Figure 4). Concerning the alcohol concentrations, median BACs in drug-alcohol poisonings (BDZ-positive) were 1.0 mg/g (1.4 mg/g) respectively in promazine-related poisonings. In clean alcohol poisonings, it was 3.3 mg/g, significantly higher [redacted]

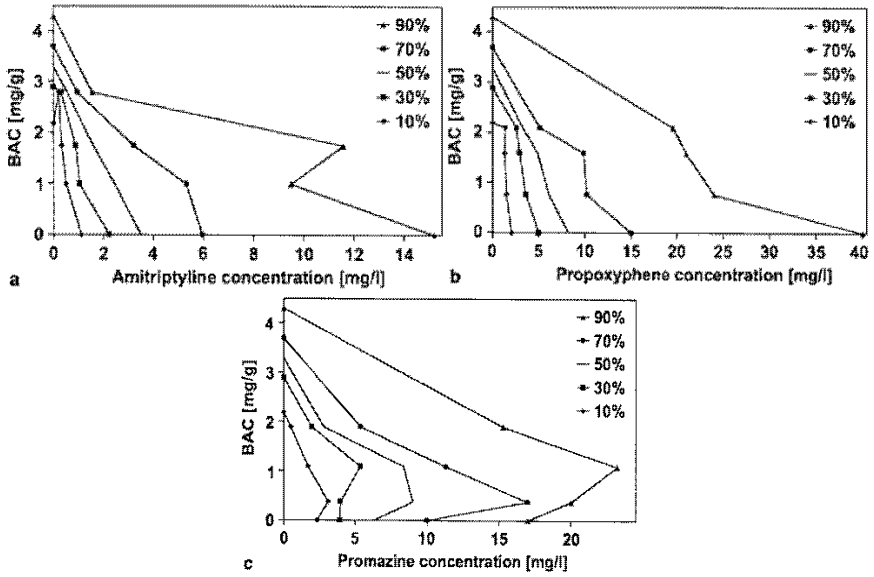

Figure 4. Combined drug-alcohol concentration curves in fatal poisonings caused by (a) amitriptyline, (b) propoxyphene and (c) promazine alone (x-axis), alcohol alone (y-axis) or both. Concentration pairs in the areas under the curves would account for 10, 30, 50, 70 and 90% of cases. BAC=blood alcohol concentration [redacted]

In an earlier study, in Finnish data from 1995-2000, 1006 fatal poisonings due to alcohol (ethanol), a single drug or both were statistically analysed in retrospect to evaluate the interaction between alcohol and drugs. In 53% of these cases, low concentrations of some common benzodiazepines were present. The median postmortem blood alcohol concentration (BAC) was 3.3 percent per thousand (w/w) in the 615 alcohol poisonings, but significantly lower, ranging from 1.3 to 1.7 percent per thousand, when promazine, doxepin, amitriptyline or propoxyphene were found together with alcohol. When levomepromazine, temazepam or zopiclone were present, the median BAC was also significantly lower, 2.5-2.7 percent per thousand. Citalopram and diltiazem did not exhibit a significant effect. The median BAC was significantly lower in cases with high concentrations than in those with low concentrations of a drug (excluding citalopram), suggesting a positive concentration-effect relationship. Fatal toxicity indices (FTIs) were calculated by relating the number of deaths caused by a drug to the corresponding sales figures. Promazine had an extremely high FTI, followed by levomepromazine, propoxyphene, doxepin and amitriptyline. The other drugs had relatively low FTIs [redacted]

The study of [redacted] describes the case of a 36- year-old man who repeatedly misused zopiclone, in daily doses of 60 - 90 mg. He used also trimiprarnine and promazine. Furthermore, the patient suffered from convulsion on two occasions following abrupt withdrawal of zopiclone. The concomitant use of alcohol, trimiprarnine, and promazine may have contributed to the development of convulsions.

2.5.3.1.4 Special population

Elderly patients

A systematic review carried out by [redacted] on psychotropic drugs in the elderly, summarises key pharmacological issues of these drugs in this population subset. Since adipose mass increases with aging, whereas total body water is reduced, the volume of distribution is

less for water-soluble drugs and greater for lipid soluble ones, such as promazine. Therefore, these lipid soluble drugs tend to accumulate in adipose tissue, resulting in increases in their plasma half-lives and their duration of action, thus increasing the risk of iatrogenic effects in elderly persons. Accordingly, the mean dosage in the elderly is 60-200 mg/day for schizophrenia, and reduced to 15–60 mg/day for dementia, or 10-15 mg/day for Parkinson's disease [redacted]

Pediatric patients

Specific pharmacokinetic data for oral administration of promazine and chlorpromazine in children are limited.

[redacted] studied the pharmacokinetics of chlorpromazine intravenous infusion in 25 children. The findings revealed significant differences in pharmacokinetic parameters compared to adults, with a clear relationship between age, serum terminal half-life, and systemic clearance. Specifically, younger children exhibited a shorter serum terminal half-life and higher systemic clearance, indicating a more rapid pharmacokinetic profile than in adults. These results suggest that children metabolize and eliminate chlorpromazine faster than adults, which has important implications for dosing regimens in pediatric patients to ensure therapeutic efficacy while minimizing potential adverse effects.

Promazine has limited pharmacokinetic data available for pediatric populations. In adults, after oral administration, promazine undergoes hepatic metabolism and is excreted primarily in the urine. The pharmacokinetic profile in children may differ due to developmental variations in drug metabolism and clearance.

Given the lack of specific pediatric pharmacokinetic studies, dosing in children is generally extrapolated from adult data, with careful consideration of age, weight, and clinical response. Healthcare providers should exercise caution, consider alternative therapies, and closely monitor any pediatric patients receiving promazine.

Hepatic disease

Alterations in the disposition of promazine as a consequence of hepatic disease could be expected taking account that is extensively metabolised in the liver. However, the pharmacokinetic parameters of promazine did not change as a consequence of viral hepatitis, according to the results of an investigation of the disposition of promazine in patients during and after recovery from the acute phase of infection with viral hepatitis B carried out by [redacted] The study was conducted with six male subjects with clinical evidence of the acute phase of viral hepatitis, in two study periods, separated by 5 months minimum. Each participant was given two 50 mg promazine tablets with 240 ml of water following an overnight fast. Immediately before the dose, and at approximately 15, 25, 40, and 60 min, and at 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 36, 48, 60, and 72 h thereafter, or until no drug was detected in the plasma. Concentrations of promazine in plasma, plasma water, red blood cells, and urine were measured after oral administration of the drug to six patients during and after apparent recovery from the acute phase of viral hepatitis B. As results, none of the promazine pharmacokinetic parameters were significantly different during and after the acute phase; these parameters included clearance, free drug clearance, metabolic clearance, volume of distribution, distribution and elimination half-life values, plasma protein binding,

and percent excreted in the urine (Table 3). No significant change was observed in the unbound fraction of promazine in plasma during the two phases of the study. This study suggests that promazine disposition was not significantly altered as a consequence of viral hepatitis [redacted]

Later on [redacted], following a similar methodology, presented the results of an investigation of the pharmacokinetics of promazine in normal subjects and patients with liver cirrhosis. The authors examined promazine pharmacokinetics in nine patients with hepatic cirrhosis and in six healthy subjects. A specific and sensitive HPLC method was used to measure promazine concentrations in plasma, plasma water (free drug), red blood cells, and urine after oral administration of promazine (2 x 50 mg tablet). There were highly significant reductions in total plasma clearance ($p < 0.01$), free drug total plasma clearance ($p < 0.01$), metabolic clearance ($p < 0.01$), metabolic clearance of free drug ($p < 0.01$), and fraction bound ($p < 0.01$) in the cirrhotic patients. The elimination half-life and the area under the plasma concentration-time curve were significantly increased ($p< 0.001$ and $p< 0.05$, respectively) in the cirrhotic patients. However, the overall excreted promazine in urine, time to the promazine peak concentration, distribution half-life, renal clearance, apparent volume of distribution, and the promazine concentration ratio between plasma and red blood cells were not different. This implies that the rate of promazine absorption was not affected. In this study, free total drug clearance was identified as a major parameter for adjusting the dose for patient. Since over 95% of promazine is metabolized, free metabolic clearance is another major parameter. In summary, the pharmacokinetic properties of promazine were significantly altered in patients with hepatic cirrhosis (Table 4). Thus, caution is needed in using promazine for patients with hepatic cirrhosis [redacted]

Table 4. Pharmacokinetic parameters during and after recovery from acute phase of viral hepatitis [redacted]

Pharmacokinetic parameters	Acute viral hepatitis (mean ± s.e.)	After recovery (mean ± s.e.)
α (1 min)	0·015 ± 0·0025	0·027 ± 0·015
β (1 min)	0·018 ± 0·0003	0·0014 ± 0·0003
k_{12} (1 min)	0·0053 ± 0·0007	0·0015 ± 0·011
k_{21} (1 min)	0·0054 ± 0·0014	0·0040 ± 0·0021
k_{10} (1 min)	0·0060 ± 0·0018	0·0095 ± 0·0022
$t_{1/2}$ (α) (min)	61 ± 19	55 ± 17
$t_{1/2}$ (β) (min)	613 ± 279	759 ± 281
V_c/F (l)	1135 ± 276	928 ± 250
V_{dss}/F (l)	2416 ± 544	3613 ± 1073
Cl_t/F (ml min^{-1}) (D_g/AUC_∞)	4725 ± 1222	6687 ± 1781
Cl_r (ml min^{-1}) ($\Sigma U_\infty/AUC_\infty$)	21 ± 12	6·3 ± 1·33
Cl_m/F (ml min^{-1}) ($Cl_t/F - Cl_r$)	4704 ± 1211	6681 ± 1780
f_u %	16 ± 2·9	17 ± 3·8
Cl_t'/F (l min$_{-1}$)	51 ± 26	45 ± 12
Cl_r' (ml min^{-1})	181 ± 87	49 ± 1·8
P/C	1·4 ± 0·13	2·0 ± 0·35
T_{max} (min)	137 ± 275	90·0 ± 13
C_{max} (ng ml)	71·1 ± 13	137 ± 62
ΣU_{∞} (%)	0·36 ± 0·11	0·13 ± 0·05

α, β: distribution and elimination rate constants.
k_{12}, k_{21}: microscopic rate constants between compartments.
k_{10}: elimination rate constant from the central compartment.
$t_{1/2}$ (α), $t_{1/2}$ (β): distribution and elimination half-lives.
V_c/F, V_{dss}/F: apparent volume of distribution for central compartment and at steady state.
Cl_t/F, Cl_r, Cl_m/F: total body clearance, renal clearance, metabolic clearance.
f_u %: per cent unbound in plasma.
Cl_t'/F, Cl_r': free drug total body clearance and renal clearance.
P/C: plasma/rbc concentration ratio.
T_{max}: time to plasma peak concentration.
C_{max}: plasma peak concentration.
ΣU_∞: total amount of drug excreted in the urine.

Table 5. Pharmacokinetic parameters of promazine in normal healthy volunteers and cirrhotic patients[a] [redacted]

Parameters	Normal	Cirrhosis	Statistics (t-test)
α (1/min)	0.0286 ± 0.0087	0.0174 ± 0.0044	ns
β (1/min)	0.00146 ± 0.00028	0.00063 ± 0.00006	$p < 0.01$
$t_{1/2(\alpha)}$ (min)	59.8 ± 11.0	66.7 ± 15.2	ns
$t_{1/2(\beta)}$ (min)	558 ± 111	1163 ± 89	$p < 0.001$
k_{21} (L/min)	0.0111 ± 0.0016	0.00394 ± 0.00066	$p < 0.001$
Vd(β)/F (L)	2540.2 ± 870.0	1499.3 ± 231.8	ns
AUC$_\infty$ (min μg/mL)	45.7 ± 14.4	132.2 ± 20.9	$p < 0.05$
Cl/F (L/min)	3.87 ± 1.24	0.94 ± 0.15	$p < 0.01$
Cl/F (mL/min)	21.5 ± 11.1	46.8 ± 23.7	ns
Cl$_m$/F (L/min)	3.60 ± 1.14	0.89 ± 0.15	$p < 0.01$
fu (%)	10.4 ± 1.1	35.5 ± 7.0	$p < 0.01$
P/C	1.17 ± 0.26	1.05 ± 0.28	ns
Cl$_t$/F (L/min)	37.2 ± 11.9	3.98 ± 1.24	$p < 0.01$
Cl$'_m$/F (L/min)	34.5 ± 11.0	3.85 ± 1.25	$p < 0.01$
ΣU_∞ (%)	3.53 ± 1.61	4.87 ± 2.15	ns
T_{max} (min)	71.4 ± 9.4	95.6 ± 15.1	ns

[a] ns: nonsignificant ($p > 0.05$) means are expressed ± one standard deviation.

Renal impairment

It is known that promazine is extensively metabolized in the liver and that less than 1 per cent of a dose of promazine is excreted in urine [redacted] Specific pharmacokinetic studies

of promazine in patients with renal impairment are limited. However, general guidelines for antipsychotic use in such populations can be informative.

Promazine pharmacokinetics appear to be generally similar to those of chlorpromazine [redacted] Chlorpromazine, a phenothiazine antipsychotic, promazine derivative, undergoes extensive hepatic metabolism, with renal excretion accounting for approximately 10–15% of its elimination. The drug exhibits a volume of distribution ranging from 5.9 to 9.1 L/kg and has a half-life of about 18 hours [redacted]

In patients with renal impairment, the pharmacokinetics of chlorpromazine are not well-defined. However, given its primary hepatic metabolism, significant alterations in drug clearance due to renal dysfunction are not anticipated [redacted].

Nonetheless, caution is advised when prescribing chlorpromazine to individuals with renal impairment, as they may have increased sensitivity to the drug's effects [redacted]

For patients with severe renal impairment (glomerular filtration rate [GFR] <10 mL/min), it is recommended to initiate chlorpromazine at lower doses and titrate slowly based on clinical response. This approach helps mitigate potential adverse effects due to altered drug handling in this population [redacted]

In summary, while renal impairment may not substantially impact the pharmacokinetics of chlorpromazine, careful dosing and monitoring are essential to ensure safe and effective use in this patient group.

2.5.3.2 Overview of Pharmacodynamics

Promazine belongs to a group of medications known as the phenothiazine antipsychotics. It acts by blocking a variety of receptors in the brain, particularly dopamine receptors. Dopamine is involved in transmitting signals between brain cells. When there is an excess amount of dopamine in the brain it causes over-stimulation of dopamine receptors. These receptors normally act to modify behaviour and over-stimulation may result in psychotic illness. Promazine hydrochloride blocks these receptors and stops them becoming over-stimulated, thereby helping to control psychotic illness. Promazine has weak extrapyramidal and autonomic side effects, which lead to its use in the elderly, for restless or psychotic patients.

The pharmacodynamic effects of promazine were changed significantly in patients with acute phase of viral hepatitis B. During the acute period of the illness, SGOP, SGPT, alkaline phosphatase, and total bilirubin were increased in all patients; they returned to within or near the upper limits or normal after recovery. Statistically significant correlations were observed during and after the acute phase of illness for alkaline phosphatase, and bilirubin. Also, the correlation coefficients for alkaline phosphatase with total body clearance and metabolic clearance during the acute phase were significant ($r = +0.9740$, $p < 0\text{-}01$ and $r = +0.9737$, $p < 0.01$, respectively). After recovery from the illness, the correlation coefficients for albumin with central compartment volume and total body volume of distribution were significant ($Y = +0.9172$, $p < 0.01$ and $r = +0.9040$, $p < 0.01$, respectively) (Table 5). Therefore, the authors of the study advised caution with patients who are taking promazine during the acute phase of viral hepatitis B [redacted]

Table 6. Results of biomedical function tests during and after recovery from the acute phase of viral hepatitis [redacted]

Subject no.	Phase	SGOT ($IU\,l^{-1}$)	SGPT ($IU\,l^{-1}$)	Alkaline phosphatase ($g\,dl^{-1}$)	Albumin ($g\,dl^{-1}$)	Total bilirubin ($g\,dl^{-1}$)
1	Acute	300	107	107	4·0	1·1
	Recovery	17	17	65	4·2	0·7
2	Acute	145	192	128	4·8	1·9
	Recovery	14	12	56	4·5	0·6
3	Acute	165	423	240	4·8	2·4
	Recovery	18	23	60	4·0	0·3
4	Acute	411	826	134	4·0	1·4
	Recovery	52	186	36·9	4·6	0·8
5	Acute	399	255	126	4·5	1·6
	Recovery	76·6	230	51·5	4·0	0·9
6	Acute	195	336	116	4·0	0·6
	Recovery	15·6	17·8	50·3	4·4	0·8

2.5.3.2.1 Mechanism of action

The primary mechanism of action of first-generation antipsychotics (FGAs) is postsynaptic blockade of the dopamine receptor (D-2 receptor). As a result, they reduce dopaminergic neurotransmission in dopamine pathways [redacted] The neuroleptic agents are antidopaminergics to varying degrees. Dopamine is one of the two principal chatecholamines in the brain. Receptors for dopamine occur most prominently in the reticular formation of the brainstem, the hypothalamus, the limbic system, and the basal ganglia. Blocking of the postsynaptic dopamine receptor site in the limbic system and the basal ganglia is thought to account for the antipsychotic activity of the neuroleptic agents. Receptor blockade results in decreased enzyme activity with decreased cell firing and increased production rate of dopamine metabolites. At least two different dopamine antagonist receptors have been identified, D_1 and D_2. Some of the D_1 receptors are linked to adenylate cyclase, and haloperidol binding preferentially labels D_2 receptor. Both receptors are thought to be blocked by antipsychotics. Some hypotheses suggest that D_1 receptors are primarily responsible for efficacy whereas D_2 receptors are responsible for extrapyramidal symptoms and efficacy. Although the inhibitory effect of the neuroleptics on classical D_2 receptors appears to correlate very well with antipsychotic dosage, this effect alone cannot explain all the clinically relevant differences between these drugs. It is possible that atypical antipsychotics may preferentially interact with different isoforms of the D_2 receptor [redacted]

Promazine is an aliphatic phenothiazine neuroleptic agent, part of the sedative antipsychotic class. It has low-potency antidopaminergic action, α_1-adrenergic antagonism and anticholinergic properties [redacted] Other importance psychologic properties of the neuroleptics are peripheral cholinergic blockade (antimuscarinic), α-adrenergic blockade, membrane-stabilizing activity, blocking of the reuptake of norepinephrine in the peripheral synapses, serotonergic action, and antihistaminic (H_1 receptor) action. Each of the neuroleptic agents differs in the degree of pharmacologic activity. The effects of the neuroleptics on the autonomic nervous system are therefore complex and unpredictable because the drugs exert varying degrees of effects on many areas of the autonomic nervous system [redacted]

Antidopaminergic
Greater effects on D_2 receptors
Results in excess cholinergic stimulation
Antimuscarinic
α-Adrenergic blockade
Antihistaminic (H_1 receptor)
Antiemetic
Central depression of chemoreceptor trigger zone
Blockade of reuptake of norepinephrine
Lowers seizure threshold
Membrane stabilization
Serotonergic

Table 7. Pharmacologic actions of neurolepte agents [redacted]

Compound	Antiemetic	Antimuscarinic	Extrapyramidal	Hypotensive	Sedative
Aliphatic					
Chlorpromazine	+++	+++	++	+++	+++
Promazine	++	+++	++	+++	+++
Triflupromazine	+++	+++	++	++	++
Piperidine					
Mesoridazine	+	++	+	++	+++
Piperacetazine	+	+	++	++	+
Thioridazine	+	+++	+	++	+++
Piperazine					
Acetophenazine	+	+	++	+	++
Carphenazine	+	+	+++	+	++
Fluphenazine	+	+	+++	+	+
Perphenazine	+++	++	+++	+	+
Prochlorperazine	+++	+	+++	+	++
Trifluoperazine	+++	+	+++	+	+

Table 8. Comparison of effects of phenothiazines [redacted]

Promazine does not appear to block dopamine within the tubero-infundibular tract, explaining the lower incidence of hyperprolactinemia than with typical antipsychotic agents or risperidone. Antagonism at muscarinic receptors, H1-receptors, and α_1-receptors also occurs with promazine [redacted]

2.5.3.2.2 Receptors and signalling pathways

Dopamine Inhibition

The principal brain target of all antipsychotic drugs is the dopamine D2 receptor. Traditional antipsychotics bind more tightly than dopamine itself to the D2 receptor, with dissociation constants that are lower than that of dopamine. Promazine shows high H1 histaminergic-receptor affinity, which may explain its potent sedative effect. On the other hand, it shows low affinity for D2 dopaminergic receptors, 5-HT serotoninergic receptors, α_1-adrenergic and muscarinic receptors, which is a similar behaviour when compared to other sedative antipsychotics (Figure 5) [redacted]

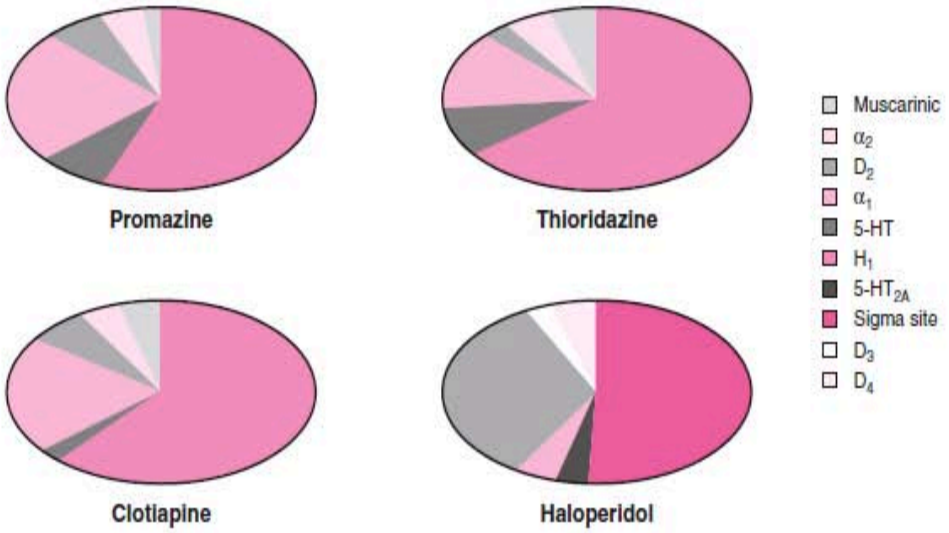

Figure 5. Receptor-binding profile of some antipsychotic agents. D = dopaminergic; H = histaminergic; 5-HT = 5-hydroxytryptamine (serotonergic) [redacted]

Promazine's antagonism at D2 receptors in the mesolimbic pathway is believed to alleviate positive symptoms of schizophrenia, such as hallucinations and delusions. This receptor blockade diminishes the overactivity of dopamine pathways implicated in the positive symptoms of psychosis [redacted] However, this same antagonistic action in the nigrostriatal pathway can lead to extrapyramidal side effects, underscoring the importance of receptor-specific interactions in both therapeutic and adverse outcomes [redacted] Promazine as well as traditional antipsychotics induces extrapyramidal signs and symptoms and elevate serum prolactin [redacted]

Studies of dopamine pathways in the brain, such as those conducted by [redacted] established foundational knowledge of dopamine neuron distribution, further supporting the mechanisms through which dopamine receptor antagonists like promazine exert their effects.

[redacted] conducted a comprehensive analysis of neuroleptic drugs, including promazine, assessing their affinities for various neurotransmitter receptors. Their findings indicated that promazine exhibits significant binding to dopamine receptors, correlating with its clinical antipsychotic potency.

promazine's antagonism of dopamine receptors leads to increased dopamine turnover in the brain, aligning with the established pharmacodynamics of phenothiazine antipsychotics [redacted] By blocking postsynaptic dopamine receptors, particularly the D2 subtype, promazine disrupts normal dopaminergic neurotransmission. This blockade leads to a compensatory increase in dopamine synthesis and release, thereby elevating dopamine turnover in the brain. This mechanism is consistent with the pharmacological profile of phenothiazines, which are known to enhance dopamine turnover as a result of receptor antagonism. For instance, studies on chlorpromazine, a closely related phenothiazine, have demonstrated accelerated dopamine synthesis and metabolism following receptor blockade. Given the structural and functional similarities between promazine and chlorpromazine, it is reasonable to infer that promazine induces a comparable increase in dopamine turnover.

Research comparing promazine to other phenothiazines, such as chlorpromazine, has demonstrated that promazine binds to multiple dopamine receptor subtypes, including D1, D2,

D3, and D4. This broad receptor interaction profile contributes to its antipsychotic efficacy [redacted]

These studies collectively underscore promazine's role as a dopamine receptor antagonist, elucidating its mechanism in the management of psychotic disorders.

Inhibition of prolactin release-inhibitory factor

Promazine, a phenothiazine antipsychotic, functions as a dopamine receptor antagonist. By inhibiting dopamine's action, promazine disrupts the suppression of prolactin secretion, leading to elevated prolactin levels. This mechanism is consistent across antipsychotics that block dopamine receptors.

Dopamine Antagonists and Prolactin Levels: A study published in [redacted] investigated the association between dopamine antagonist use and breast cancer development. The research found that women exposed to dopamine antagonists, including phenothiazines like promazine, had an increased risk of breast cancer, potentially due to elevated prolactin levels induced by these medications. This suggests that dopamine antagonists can lead to increased prolactin secretion [redacted]

Chlorpromazine and Prolactin Elevation: Research in the [redacted] examined plasma drug and prolactin levels during acute chlorpromazine treatment. The study observed that higher plasma levels of chlorpromazine were associated with increased prolactin levels. Given the pharmacological similarities between chlorpromazine and promazine, it is reasonable to infer that promazine may have similar effects on prolactin secretion [redacted].

In summary, while direct studies on promazine's impact on prolactin levels are limited, evidence from related antipsychotics and their shared mechanisms indicates that promazine likely increases prolactin secretion by inhibiting dopamine's regulatory effect on the anterior pituitary.

2.5.3.2.3 Secondary pharmacodynamics

Anticholinergic activity

Promazine, a phenothiazine antipsychotic, exhibits anticholinergic effects, though these are generally less pronounced compared to other phenothiazines. While direct comparative clinical studies are limited, available literature provides some insights:

Anticholinergic Cognitive Burden (ACB) Scale: This scale evaluates the anticholinergic potential of medications, assigning scores based on their impact on cognition. Drugs with possible anticholinergic effects receive a score of 1, while those with more significant cognitive impacts score higher. Although promazine is not explicitly mentioned, phenothiazines as a class are recognized for their anticholinergic properties [redacted]

Clinical Observations: In clinical practice, promazine's anticholinergic side effects, such as dry mouth, constipation, and blurred vision, are observed to be milder compared to other phenothiazines. This characteristic makes it a potential option for patients who are sensitive to anticholinergic adverse effects [redacted]

In summary, while specific clinical studies directly comparing the anticholinergic effects of promazine to other phenothiazines are scarce, existing literature indicates that promazine's

anticholinergic side effects are generally less pronounced. This profile may influence its side effect spectrum and tolerability in patients.

Alpha-Adrenergic Blocking Activity

Promazine exhibits alpha-adrenergic blocking activity, contributing to its pharmacological profile. This action leads to vasodilation and a potential decrease in blood pressure, enhancing its sedative and tranquilizing effects, resulting in orthostatic hypotension. This side effect is particularly significant in clinical settings, especially among the elderly or those with preexisting cardiovascular conditions [redacted]

Chlorpromazine, a closely related phenothiazine, has been shown to block alpha-adrenergic receptors, leading to vasodilation and decreased blood pressure. Given the structural and functional similarities between promazine and chlorpromazine, it is reasonable to infer that promazine exhibits comparable alpha-adrenergic blocking activity [redacted]

The combined antagonism of alpha-adrenergic and histamine H1 receptors by phenothiazines contributes to their sedative properties, which are utilized therapeutically in managing agitation and anxiety.

CNS Depression

Promazine is recognized for its central nervous system (CNS) depressant effects, which contribute to its sedative and tranquilizing properties. Several clinical studies have investigated these effects:

Influence on Cerebral Hemodynamics and Metabolism: A study of [redacted] examined the impact of promazine on cerebral hemodynamics and metabolism. The research indicated that promazine effectively controls patients with increased psychomotor activity, suggesting its CNS depressant capabilities.

Clinical Trial in Chronic Schizophrenic Patients: A clinical trial reported by [redacted] evaluated the efficacy of promazine hydrochloride in chronic schizophrenic patients. The study found that promazine exhibited sedative effects, which were beneficial in managing agitation and psychotic symptoms, highlighting its CNS depressant action.

Effects on MMPI Performance: Research of [redacted] assessed the effects of promazine on the Minnesota Multiphasic Personality Inventory (MMPI) performance in chronic psychiatric patients. The findings suggested that promazine's sedative properties influenced patients' test performances, reflecting its CNS depressant effects.

These studies collectively demonstrate promazine's CNS depressant effects, which are integral to its therapeutic applications in managing conditions like schizophrenia and agitation.

Sedative Effects via the Reticular Activating System

Promazine's sedative action is primarily attributed to its antagonism of central histamine H1 receptors. This antagonism affects the tuberomammillary nucleus (TMN), a component of the brain's reticular activating system (RAS), which plays a crucial role in maintaining wakefulness. By inhibiting histaminergic activity within the TMN, promazine reduces arousal levels, leading to sedation. Additionally, this inhibition can modulate the processing of internal stimuli, contributing to its calming effects [redacted]

Influence on Gastrointestinal Activity

Promazine acts peripherally by blocking the vagus nerve in the gastrointestinal tract. The vagus nerve is integral to GI function, coordinating activities such as peristalsis and secretion. While promazine's direct action on the vagus nerve in the GI tract is not extensively documented, its anticholinergic properties can influence parasympathetic activity, potentially affecting GI motility and secretions. However, specific clinical studies detailing promazine's impact on vagal activity within the GI system are scarce [redacted]

Other

Phenothiazines, including promazine have been shown to exhibit in vitro and in vivo activity against *Mycobacterium tuberculosis* (Mtb) and multidrug-resistant Mtb. They are predicted to target the genetically validated respiratory chain component type II NADH:quinone oxidoreductase (Ndh). Using a set of compounds containing the phenothiazine pharmacophore, [redacted] investigated whether chemical validation data support the molecular target and evaluated pharmacophore tractability for further drug development. Pharmacodynamic profiling of the phenothiazines, including antitubercular efficacy in aerobic and O_2-limited conditions, time–kill assays and isobole analyses against first-line antituberculars, was performed. Potential mitochondrial toxicity was assessed in a modified HepG2 cell-line assay and against bovine cytochrome bc1.

The IC_{50} values ranged between 10 and 160 μM, with a rank order of potency of thioridazine>trifluoperazine>flupenthixol>perphenazine>fluphenazine>chlorpromazine>promethazine>promazine. Against Mtb under aerobic and anaerobic growth conditions (validated by an idiosyncratic improvement in metronidazole activity), the phenothiazines exhibited significant concentration dependent activity (Figure 6). Additionally, phenothiazines exhibit rapid bactericidal activity in time–kill studies all of the phenothiazines caused significant reductions in cfu/mL within the first 48 h and by day 4 no viable organisms remained. The order in which the phenothiazines reduced cfu/mL to zero was established as chlorpromazine=perphenazine (1 day) > trifluoperazine = thioridazine (2 days) > promethazine = promazine = flupenthixol = fluphenazine (4 days).

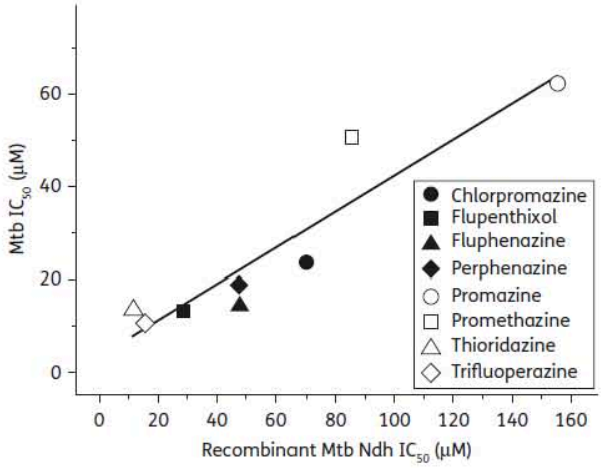

Figure 6. Scatterplot of the IC_{50}s of eight phenothiazine-like compounds against recombinant Mtb Ndh and aerobically cultured Mtb. The data demonstrate a strong positive correlation between enzyme inhibition and in

vitro antitubercular activity. Data for phenothiazine are not included, as accurate IC_{50} determinations could not be made [redacted]

The results support the hypothesis that Ndh is the molecular target of phenothiazines. The favourable pharmacodynamic properties of the phenothiazines are consistent with a target product profile that includes activity against dormant/persistent bacilli, rapid bactericidal activity and activity against drug-resistant Mtb by a previously unexploited mode of action. These properties warrant further medicinal chemistry to improve potency and safety [redacted]

Promazine is also human ether-à-go-go-related gene (HERG) potassium channel blockers. HERG-blockade can lead to QT prolongation with increased risk of potentially life-threatening torsade de pointes arrhythmia (TdP) [redacted]

2.5.4 Overview of Efficacy

Promazine is used in the treatment of schizophrenia, toxic psychosis, mental organic disorders with delirium, behavioural and psychological symptoms of dementia, and depression associated with psychomotor agitation and delusions [redacted]

In clinical practice, promazine has been shown to be effective in managing psychotic agitation. Several studies have highlighted its efficacy in both short-term and long-term treatment scenarios [redacted] In a study conducted by [redacted] on 259 patients with acute psychiatric syndromes, promazine was effective in reducing symptoms of agitation with minimal extrapyramidal side-effects when compared to chlorpromazine [redacted] Another study by [redacted] explored the use of liquid promazine in hospitalized patients with psychotic agitation. The results showed that 74% of patients treated with liquid promazine experienced marked improvement, and the study emphasized the benefits of the liquid formulation, noting its rapid onset of action and ease of administration, which are particularly advantageous in managing highly agitated patients. Further evidence of promazine's efficacy comes from a study conducted by [redacted] over a 3-year period. This study involved 180 patients with chronic psychosis who were hospitalized and treated with different formulations of promazine, including tablets, liquid form and intramuscular injections. The study demonstrated marked improvement in 26% of patients and moderate improvement in 48%, indicating that promazine was effective in modifying disturbed behaviour patterns. This allowed for successful psychotherapy, which ultimately led to the discharge of 26 patients from the hospital. Lastly, an 18-month prospective, observational study by [redacted] provided additional evidence for the efficacy of promazine [redacted] This study included 349 older patients (aged ≥65 years) with dementia residing in 35 Alzheimer disease special care units in Italy. The study focused on the use of antipsychotics, including promazine, to manage behavioural and psychological symptoms of dementia. The results showed that promazine was frequently prescribed by healthcare professionals for managing agitation in patients with Alzheimer disease, with a significant reduction in agitation symptoms observed amongst the treated patients. It is important to highlight that promazine has also been associated with withdrawal symptoms when abruptly discontinued, necessitating a

gradual tapering over 3–4 weeks. [redacted] determined which antipsychotic are currently in use, to establish which doses are administrated to patients, to find out is there a practice of proscribing simultaneously more then one antipsychotic drug, to determine whether antipsychotic are proscribed in divided doses, to establish whether there is, besides antipsychotics, treatment with other medicaments (co-administration), especially with antiparkinsonics. The research (study) is epidemiological-clinical prospective, descriptive and analytical and it was conducted at University hospitals in [redacted] Criteria for inclusion, non-inclusion and exclusion from the study were precisely defined as a mean for formation of sample. Based on this hypothesis were established, zero and alterative. According to zero hypothesis in the treatment of schizophrenia at University hospitals in F/BiH new antipsychotic drugs are in use, small doses are proscribed (up to 20 mg), not more then one antipsychotic drug is used simultaneously, antipsychotics are administrated once a day and alongside with antipsychotics other medicaments are not co-administrated, especially antiparkinsons. The results of our study are showing that majority of patients are treated with classical antipsychotics. Minority of patients is treated with atypical neurolepics like olanzapine, which is proscribed only in [redacted] Use of risperidone and ziprasidone is registered also only in [redacted] but only small number of patients is treated with these drugs. Most frequent antipsychotics were promazine and haloperidol. Further, they studied polypharmacy in the treatment of schizophrenic patients in three University Centers in the [redacted] The sample consisted of 216 patients: 85 from [redacted] and 44 and 87 respectively from [redacted] All schizophrenic patients who were hospitalised in three University Centers of [redacted] on a particular day are included in the study. This included patients of both sexes (131 (60.65%) males and 85 females (39.35%)), 20-60 ages, who were on antipsychotic treatment with an established diagnosis of schizophrenia by the treating psychiatrist. The research was performed in the year 2004. The census of patients was conducted simultaneously in all three Centers, using a questionnaire in which all routine prescribed antipsychotics were registered, as the common method of the administration, and the doses as well saving as data for other medications that were simultaneously prescribed to the patients that day. Within the total sample the most frequently applied classical antipsychotics were haloperidol, promazine and from the group of new antipsychotics clozapine. The most frequently used other medications were biperidine and diazepam. The administration of all medication was followed through recording of individual doses, daily doses and frequency of administration. There are statistically significant differences regarding the frequency of biperidine use between the centers (p=0.008) [redacted]. [redacted] assessed the effects of earthquake that occurred on April 6, 2009 on the use of antidepressant and antipsychotic drugs in the province of [redacted]. In a retrospective, drug utilization study all the persons who received at least one dispensing of antidepressant and/or antipsychotic drugs during the period April 1st, 2008–March 31st, 2010 were identified. The monthly prevalence of use of these drugs, 1 year prior and after the date of earthquake in [redacted] was compared between the two provinces, [redacted] All the analyses were stratified by age groups, gender and drug classes. An increase in the use of anti-psychotic drugs and, to lesser extent, of antidepressant agents (mostly typicals and tryciclics, respectively) in the first 2 months after the earthquake in [redacted] but not in [redacted] was observed. The earthquake determined a short-term increase in

the use of antipsychotics (mostly haloperidol and promazine) and, to lesser extent, of antidepressants (i.e. tryciclics), especially in older women of [redacted].
The *in vitro* ability of promazine to modulate dopaminergic neurotransmission in a dose-dependent manner aligns with its observed clinical benefits in reducing the severity of agitation and psychotic symptoms. This combination of *in vitro* and clinical evidence underscores the efficacy of promazine, particularly in situations where controlling excessive dopamine activity is essential [redacted]

Promazine has been effectively used in clinical practice since the 1950s. Numerous clinical studies have evaluated the efficacy of promazine to reduce agitation and restlessness in comparison with placebo or other antipsychotics. A selection of the available studies is presented in the present overview. Both adults, elderly and children were included in the provided trials.
A number of clinical trials investigated the efficacy of promazine in various psychotic disorders. Promazine had a very satisfactory range of safety, the effectiveness has been proved, and the complications or side effects are negligible. Promazine significantly alleviated the secondary symptoms of the psychoses such as agitation and restlessness and permits greater amenability to psychotherapy. Drug habituation to promazine was not evident from clinical studies. The general properties and therapeutic uses of promazine are similar to chlorpromazine but promazine shows less toxicity. This drug can be used effectively in patients in whom chlorpromazine or other antipsychotics must be discontinued because of severe complications [redacted]
Promazine was also evaluated as a therapeutical option in the treatment of behavioural and psychological symptoms in dementia, of the symptoms of mental deficiency and schizofrenia [redacted]
Furthermore, promazine can be useful in controlling alcohol withdrawal symptoms such as tremor, anxiety and agitation [redacted]
Additionally, some studies evaluated the use of promazine in combination with other agents in the management of psychotic disorders [redacted] The use of promazine combined with imipramine has proved to be effective in various types of depression, with overall good response of the entire pattern of target symptoms [redacted]
The studies described in this overview are presented in order to demonstrate the efficacy of promazine and to confirm its safety profile. These studies included both adults and elderly. However a special attention has been paid to elderly in section 2.5.5.7.

2.5.4.1 Promazine in the relief of agitation and restlessness

Agitation and restlessness related to psychotic disorders
A study was made over a 3-year period of 180 chronic hospitalized psychotic patients, 95 men and 85 women, for whom promazine hydrochloride therapy was prescribed. The patients ranged

in age from 16 to 88 years and the duration of their mental illness varied from 1 to 62 years with an average of 15 years. The patients came from two groups: those in whom complications developed as a result of chlorpromazine therapy (58 patients), and those who received promazine therapy during the initial evaluation studies (122 patients). The dose of promazine administered varied from 50 mg. given at bedtime to 400 mg. q.i.d. The initial dose of promazine hydrochloride was administered according to the psychokinetic activity of the individual. If the symptoms of restlessness, agitation, or proneness to get into difficulties with other patients were mild, 100 mg of promazine, two or three times daily, usually were prescribed. When the behavior of the patient was severe, 400 mg of promazine, t.i.d., were prescribed. One patient in the group received 1600 mg. of promazine daily for a period of approximately 15 months. When patients accepted the tablets only to collect them or to eject them later, liquid promazine concentrate in equal doses in aromatic (glucose) solution was substituted for the tablets. When the liquid form of medication was refused, one-half the prescribed dose was given intramuscularly. Statistically, 47 (26%) of the 180 patients showed marked improvement in behavior, and 82 (46%) showed moderate improvement. There was not any improvement in 51 (28%) of the patients; however their behavior did not become worse. Improvement in their psychosis was also noted; marked improvement occurred in 23 patients (13%) and moderate improvement occurred in 54 patients (30%). In 98 (54%) patients there was not any psychotic improvement and, in 5 (3%), there was some indication of mild regressive trends. Promazine adequately modified the formerly disturbed behavior pattern of the chronic schizophrenic patients so that psychotherapy was facilitated and, as a result, made it possible for 26 patients to be released from the hospital. Two patients returned from convalescent care because they did not take the promazine as directed. The results of this study confirm the conclusions of other authors of the need for adequate medication, but within the prescribed limits of the medication and in the range up to 1200 mg divided equally into three doses given daily. Promazine has a very satisfactory range of safety, the effectiveness has been proved, and the complications or side effects are negligible [redacted]

An investigation was carried out to determine the efficacy of promazine hydrochloride in the management of mentally ill patients suffering from tuberculosis. Ninety-seven patients who had either active or "arrested" tuberculosis concomitant with various acute and chronic mental disturbances received promazine therapy. Symptoms included agitation. Of the 97 patients (23-73 years), 74 also received standard therapy for tuberculosis, and 14 received additional adjunctive medication in the form of methylphenidate hydrochloride, chlorpromazine, diphenylhydantoin sodium, phenobarbital, prochlorperazine, iproniazid, or reserpine. In the whole group, the response to medication was excellent in six, good in 19, and moderate in 45. Twenty-seven patients did not respond to therapy. In this study, promazine appeared to be a very useful drug in the management of tuberculous, mentally-ill patients [redacted]

A study evaluated the beneficial effects of promazine in mentally ill patients. Two hundred patients received promazine in dosages of 50 mg to 1.5 gm daily for two to six months. They ranged in age from 22 to 72 years and had been mentally ill from one to 15 years. Promazine diminished violence and acute overactivity, and reduced combativeness and distortion of sense perceptions. Relapses were common on cessation of treatment. Promazine alleviated insomnia, including patients in whom sleeplessness was believed to be the result of arteriosclerosis. It increased emotional control, improved interpersonal relationships, reduced active antagonism,

but left fixed paranoid delusional ideation mostly unaffected. There was less constraint, and there was increased verbalization among the withdrawn, intellectually preserved types of patient. Little change was seen in moderately deteriorated patients with apathy and defective judgment. The deeply regressed, severely disturbed or vegetative patients showed some improvement, particularly in bladder and bowel control. Of the 200 patients treated, 15 (7.5 per cent) were released; none had returned after three months. There were no side effects detected on clinical or laboratory examination. Drug habituation to promazine was not evident [redacted]

The efficacy of promazine was investigated in chronically psychotic subjects. Diagnoses included paranoid, hebephrenic, catatonic or simple schizophrenia (152 patients); manic-depressive psychosis (4 patients), psychoneurosis (7 patients), psychosis with mental deficiency (5 patients), and psychosis resulting from alcoholism (32 patients). All had been ill 1 to 15 years. Twenty-two had been repeatedly treated unsuccessfully with electro or insulin shock, or had received psychosurgery; other ataraxics had been used for 41 without improvement. Promazine was administered, in total daily doses of 300 mg to 1.5 Gm for 2 to 13 months, to 200 ward patients 22 to 70 years old. Optimal dosage with promazine was determined cautiously by individual trial, with adjustment and change in route of administration as indicated. The violently disturbed received 100 or 200 mg intravenously, twice daily for 3 to 6 days; others, 50 mg intramuscularly twice a day for 3 days. On control of behavior abnormalities, medication was continued by mouth in doses of boo to 500 mg three times daily. Blood counts, serum bilirubin and serum alkaline phosphatase tests were performed at the start and at about monthly intervals throughout treatment. Since no precise methods exist for screening the effects of the ataraxics in the human, conclusions were based, not on statistical calculations, but on evaluation of the clinical responses obtained. Promazine medication had the following effects: 1) Reduced violence, combativeness and overactivity; and alleviated insomnia, even in the aged and arteriosclerotic. 2) Controlled anxiety, irritability and emotional tension in interpersonal relationships. 3) Acute hallucinations and delusions usually were relieved in a few days; fixed paranoid delusional ideation, however, generally remained unaffected. Patient with distortions in sense perception of fairly recent onset showed improvement earlier than did those in the more chronic cases (two years duration or more). 4) Withdrawn but intellectually preserved patients became less constrained and capable of freer verbalization. 5) The negativistic and catatonic occasionally exhibited progress. 6) Deeply regressed, severely disturbed or vegetative patients also showed some improvement, particularly in bladder and bowel control. 7) Capacity for readjustment was seldom increased in the nonviolent or moderately deteriorated with impoverishment of initiative; apathy and defectiveness in judgment were little altered. 8) All tended to relapse or regress soon after medication was stopped or reduced. About I9% (37 patients) have been released; only 2 (alcoholics) have returned in the subsequent 3 to 10 months. About 21% (41 patients) have shown such sustained improvement that they have been transferred to open wards, received maximum privileges and been assigned to work. One third of this group (14 patients) now receive no medication; the rest are maintained on 100 to 300 mg daily. Of the total series, 3% (6 patients) regressed after initial improvement on 1.5 mg daily; later, 4 of these improved and tolerated reduction of daily dosage to 6oo mg. No convulsions or other untoward effects have developed, and no signs of habituation, even in the alcoholics. Promazine significantly alleviates the secondary symptoms of the psychoses and

permits greater amenability to psychotherapy. A larger percentage of the chronically psychotic are showing improvement; there is less destructiveness and need of mechanical restraint. A protective environment is still necessary, however, in advanced cases [redacted]

Ninety chronically psychotic patients, 96 per cent of whom had been ill for one to 16 years, were treated with promazine, at first in a short course by the parenteral route, which was later replaced by oral medication. Treatment was continued for three to 13 months; there were no complications or side effects. All patients were discharged from hospital or clinic and maintained subsequently on smaller doses by mouth. The diagnoses were as follows: schizophrenia (n= 24); depressive reaction (n= 33); manic-depressive psychosis (n = 20); schizo-affective disorders (n= 11); chronic anxiety (n= 2). Psychotic manifestations were eliminated in the great majority, and considerably alleviated in the remainder. Associated somatic symptoms, including excessive hyperactivity and restlessness, showed a noticeable improvement. Seventy-one per cent have resumed household duties, school work or have returned to or are seeking gainful employment [redacted]

	Patients no.	Symptoms eliminated no. patients	Symptoms alleviated but still present no. patients
Psychotic Manifestations			
Insomnia	46	43	3
Delusions of persecution, fear, suspicion and bizarre ideas	41	30	11
Crying	29	23	6
Extreme hyperactivity and restlessness	17	10	7
Despondency, moroseness and unsociability	14	11	3
Belligerence, combativeness and destructiveness	11	9	2
Irritability	9	7	2
Memory defects	8	7	1
Overtalkativeness, noisiness	6	5	1
Inappropriate or flattened affect	6	3	3
Unkemptness	6	4	2
Impaired insight or judgment	2	1	1
Guilt feelings	2	2	0
Hallucinations—auditory, 13; haptic, 8; visual, 5; olfactory, 1; gustatory, 1	28	20	8
Somatic Symptoms			
Anorexia and weight loss	49	44	5
Headache	25	22	3
Dizziness	14	12	2
Fatigue and inertia	13	11	2
Disorders of vision	7	7	0
Functional cardiac disturbances choking sensations and shortness of breath	15	11	4
Gastrointestinal distress (ulcer symptoms, vomiting, diarrhea, belching)	10	8	2
Nervousness, trembling, profuse perspiration	8	6	2
Urinary frequency and urgency	4	4	0
Hypertension, with or without pedal edema	7	0	7
Neurodermatitis	1	0	1
Paresthesias	1	1	0
Stuffy nose	1	1	0

Table 9. Response of psychotic and somatic symptomis in 90 patients treated with promazine [redacted]

A study investigated whether promazine hydrochloride was equal or superior to chlorpromazine as a tranquillizer in psychiatric patients and whether it had fewer adverse side effects than chlorpromazine. Fifty psychiatric patients treated with promazine hydrochloride. As to diagnoses, 22 had schizophrenia, 15 had agitated depressions, II had psychoneuroses, and 2 severe, acute organic mental reactions. The duration of illness varied from 20 hours to 21 years, the vast majority being less than 4 months. All patients were treated with promazine hydrochloride for more than 2 weeks. The longest period of treatment has been 4 months. The majority of patients had had therapy with other ataraxic drugs prior to starting on promazine. Of the 50 patients studied 17 (34 %) were considered as presenting excellent or good results. The remaining group obtained very slight benefit or none at all. In other words, the drug was effective in one-third of the patients treated. Promazine hydrochloride was most effective in patients with marked anxiety, particularly those in whom there was a great deal of motor activity as part of the anxiety. Adverse side-effects are mild and relatively uncommon as compared with those produced by chlorpromazine. Promazine appeared to be as effective as chlorpromazine as a tranquillizer in psychiatric practice. Promazine hydrochloride appears to have great advantages over chlorpromazine because the adverse side-effects produced by the drug have,

thus far, been minimal as compared with those caused by chlorpromazine. Promazine can be used effectively in patients in whom chlorpromazine must be discontinued because of severe complications. The authors were impressed with the tranquillizing effects of the drug in agitated patients [redacted] compared the effects on mental syndromes of thioridazine versus chlorpromazine and promazine in a single-blind study. Thioridazine was administered to 75 patients, 25 women and 50 men. Forty patients of the above 75 were selected for comparison with two other groups of 40 patients, who received chlorpromazine and promazine respectively. Diagnostically in each of the three groups there were 16 schizophrenics (one hebephrenic and 15 paranoids), 13 manic depressives (5 manic and 8 depressive), 2 organic psychotics and 9 neurotics (8 anxiety states and one character neurosis). The average age of the patients was about 40 in all groups. Thioridazine was administered orally in all patients with an average dose of 400 mg daily (minimum of 150 mg. and maximum of 2000 mg daily), for an average period of three weeks in the acute cases and three months in chronic cases. The starting dosage was 100 mg. daily. It was increased by approximately 100 mg. every 3-5 days, until the appearance of adequate therapeutic effect. It should be noted that the maintenance dose of the drug for the chronic patients appeared to be about 800 mg daily. In the two groups of patients receiving chlorpromazine and promazine for comparative purposes, both of these cirugs were administered with the same routine as thioridazine. The effects of thioridazine were compared with chlorpromazine and promazine in two different conditions: similar syndromes in different patients, and in the same patients longitudinally. In the latter case only chlorpromazine and thioridazine were compared. The three drugs showed similar effect from the point of view of symptomatic relief, including reduction of agitation. The average daily dose was lowest with chlorpromazine (200 mg) and highest with promazine (600 mg). Thioridazine dosage was closer to that of chlorpromazine (250 mg). The general impression of different observers was that, dose for dose, chlorpromazine seemed to be slightly more effective. This came out more clearly in the chronic patients receiving both drugs longitudinally. Because of the unavailability of intramuscular thioridazine, manic patients and agitated schizophrenics with marked suspiciousness could be controlled faster and more smoothly with intramuscular chlorpromazine or promazine. Thioridazine and promazine produced less "knocked out" feeling and indifference than chlorpromazine [redacted]

[redacted] compared promazine versus chlorpromazine. The drugs were administered to a total of 259 patients, divided into three categories:

1) The first group consisted of 200 non-selected patients in an open psychiatric setting, or from an out-patient clinic, manifesting acute or recently apparent psychiatric syndromes. The first 100 patients received chlorpromazine in an average daily dose of 200 mg, for an average period of three to four weeks. The second 100 patients received promazine in an average daily dose of 300 mg. for an average period of four weeks. Except for five patients, the drugs were administered orally. The sex distribution in the two groups was similar and consisted of 65% female and 35% male patients, with an average age of 40 years. The syndrome distribution for the chlorpromazine group consisted of 28 cases of schizophrenia, 25 of manic-depressive states, 44 of neurotic states and 3 of organic psychoses; and for the promazine group, 23 cases of

schizophrenia, 29 of maniac-depressive states, 45 of neurotic states, and 3 of organic psychoses.

2) The second group consisted of 30 patients with the same characteristics as the first group, who received chlorpromazine and promazine in two different periods for the purpose of comparing the effects of two drugs in the same individual. In 13 cases of this group the switch from chlorpromazine to promazine was made because side-effects appeared. The group as a whole consisted of nine schizophrenics, seven manic-depressives and 14 neurotics.
3) The third group consisted of 29 male chronic schizophrenics from a closed psychiatric setting, with an average age of 38 years. They received chlorpromazine and promazine in two different periods for an average of three months.

Promazine and chlorpromazine had a similar effect on the overt behaviour and symptoms of patients with mental disorders. There was a relatively identical result in improvement ratings in both instances, particularly in agitated, tense and anxious patients. To obtain this similar clinical response the daily dosage of promazine should be from 30 to 100 mg higher (per dose) than chlorpromazine in acute or recently appearing psychiatric cases, and from 100 to 400 mg (per dose) higher in chronic psychiatric cases. Regardless of the clinical response, promazine produces much less drowsiness and knocked-out feeling than chlorpromazine. There was a relative absence of liver dysfunction, as assessed by the tests used in this study, with promazine (4%) in comparison with chlorpromazine (25%). Extrapyramidal complications occurred in about 4% of chlorpromazine-treated cases, but not with promazine. According to the authors, a shift from chlorpromazine to promazine could be instituted if serious complications occur with the former substance without their reappearance with the latter drug. The impression was reached that the therapeutic locale par excellence for promazine is the outpatient clinic and private practice, where the appearance of complications and undue drowsiness is socially and individually more important [redacted] Table 9 presents the comparison of promazine and chlorpromazione in similar clinical syndromes.

Diagnosis	*No. of cases*		*Improvement* *Marked*		*Moderate*		*Slight*		*None*	
	P	*C*	*P*	*C*	*P*	*C*	*P*	*C*	*P*	*C*
1. Schizophrenias.										
Paranoid agit.	10	10	5	5	5	5				
Paranoid non-agit.	5	15			2				3	15
Hebephrenia	2	3			1				1	3
Borderline	6		4		1		1			
2. Manic-depressive psychosis.										
Manic	10	5	6	3	3		1	2		
Depression agit.	8	5		1	6	4	2			
Depression, non-agit.	11	15			1	1		2	10	12
3. Neuroses.										
Anxiety neuroses	23	27		4	12	12	9		2	11
Anxiety hysteria	6				1		3		2	
Hysteria	4	5					1	1	3	4
Obsession	3	5							3	5
Addiction	6	4			4	4	1		1	
Character neuroses	3	3							3	3
4. Organic psychoses	2	3			1	2	1			1
Post-lobotomy agit.	1				1					
Total	100	100	15%	13%	38%	28%	19%	5%	28%	54%

P—Promazine. C—Chlorpromazine.

Table 10. Comparison of promazine and chlorpromazione in similar clinical syndromes [redacted]

A clinical trial was carried out to evaluate the gross clinical effects of promazine in mental syndromes, and to compare it with chlorpromazine. Promazine was administered to two groups

of patients: (1) 100 unselected patients suffering from what are called acute or recently apparent psychotic or neurotic states, in an open psychiatric setting; and (2) 26 so-called chronic schizophrenics in a closed psychiatric setting. The first group consisted of 40 male patients with an average age of 39 years, and 60 female patients averaging 45 years. The group as a whole comprised 20 schizophrenics, 29 manic-depressives, 45 neurotics, and three organic cases. Except for three manic patients who received the drug initially intramuscularly, all patients received it by mouth for an average period of three weeks. The dosage ranged from 100 to 1500 mg, with an average of 400 mg per day. All patients received' concomitantly some kind of supportive psychotherapy. The second group consisted of 26 male patients with an average age of 38 years. They received promazine for an average period of eight weeks, with an average dose of 800 mg per day. In 23 recent schizophrenics the best results were obtained in agitated paranoids (10 cases), and in borderline states (five out of six cases). In 26 chronic schizophrenics improvement in ward management was noted in 14 cases. Nine out of 10 manic patients showed considerable improvement, and eight agitated depressives benefited moderately from promazine therapy. Non-agitated depressed patients showed no change. Thirty-one out of 45 neurotics showed some symptomatic relief, and three agitated organic cases responded favourably. Complications were few and consisted of allergic responses in 4% of patients and a rise in alkaline phosphatase level in 4% of cases. There was no jaundice or extrapyramidal change. In a relatively small number of cases the clinical and biochemical effects of promazine and chlorpromazine were compared. The 26 chronic schizophrenics in group 2 of the present study had previously received chlorpromazine for an average period of three months and an average daily dose of 500 mg. The clinical effects of promazine are similar to those of chlorpromazine, but to obtain a similar clinical response higher doses of promazine are necessary. This difference on the basis of daily dosage appeared to be between 30 and 100 mg. in acute psychotic states, and between 100 and 400 mg. in chronic psychotic states. Also there was a greater time lag between the administration of the drug and the clinical response to promazine than to chlorpromazine. This time lag was of the order of 24-48 hours. The incidence of hepatic changes was about six times higher in chlorpromazine-treated cases than with promazine [redacted] A summary of the results of promazine therapy is presented in Table 10.

Diagnosis	*No. of cases*	*Improvement* — *Marked*	*Moderate*	*Slight*	*None*
(1) Schizophrenia					
Paranoid, agitated	10	5	5		
Paranoid, non-agitated	5		2		3
Hebephrenia	2		1		1
Borderline	6	4	1	1	
(2) Manic Depressives:					
Manic	10	6	3	1	
Depression, agitated	8		6	2	
Depression, non-agitated	11		1		10
(3) Neuroses:					
Anxiety neuroses	23		12	9	2
Anxiety hysteria	6		1	3	2
Hysteria	4			1	3
Obsession	3				3
Addiction	6		4	1	1
Character neuroses	3				3
(4) Organic Psychoses:	2		1	1	
Post-lobotomy agitated	1		1		
Total	100	15%	38%	19%	28%

Table 11. Summary of the results of promazine therapy [redacted]

[redacted] performed a clinical evaluation of the two phenothiazines promazine and mepazine on the same groups of psychotic patients. Fifteen acute patients (8 men, 21-53 years of age, and 7 women, 26-51 years of age) were given these drugs. In addition, approximately 50 chronically ill psychotic patients, almost equally divided according to sex, were tested; the majority were between 40-70 years of age with long histories of residence averaging 19 years in state hospitals. All the chronic patients were sufficiently disturbed to require closed ward therapy and maximum hospital security. The schedule of oral medication was an initial placebo period of 2 weeks followed by 4 weeks of one of these drugs, then a placebo period before the alternate one was employed. Authors found promazine and mepazine to be of value in the treatment of psychotic patients with acute and chronic symptomatology. In the acute patients both promazine and mepazine yielded social recoveries as well as lesser degrees of improvement. The degrees of improvement included "definite improvement"-a change of the psychotic picture including an attenuation of all psychotic symptoms, but referring chiefly to the secondary ones, such as diminution of psychomotor hyperactivity. One patient in 15 remained unchanged with promazine as did 2 in 10 with mepazine. Of the chronic patients 50% of those on mepazine revealed various grades of improvement, while 71% exhibited similar improvements with promazine. The best type of marked improvement was shown in 3 patients (6%) with mepazine, 7 (13%) with promazine, and 9 (24%) with chlorpromazine. Side-reactions with mepazine were constipation, dizziness, dry mouth, and dermatitis. In some instances the use of promazine was associated with constipation, dry mouth, dizziness, and Parkinsonian tremor. Two patients exhibited grand mal seizures. In general, for the chronic patients, the dosage employed with promazine was greater than that used with mepazine [redacted]

Promazine was administered either orally or parenterally to 407 acutely disturbed patients. The series consisted of 103 agitated or confused psychotic patients (95 exhibited increased psychomotor activity), 42 addicts experiencing withdrawal symptoms, and 262 alcoholics. The last group included 110 patients with full-blown delirium tremens, 55 with acute inebriation, and 97 with acute tremulousness and/or hallucinosis. The initial dose of promazine, ranging from 50 to 400 mg, was effective in inducing sleep in these disturbed subjects. A maintenance dose every four to six hours in most instances kept these patients in a quiescent, detached state, from which they could be easily aroused to care for their personal needs. In the agitated psychotic patients the induction of sleep was frequently associated with a dramatic return toward normal of both blood pressure and heart rate. Orthostatic hypotensive phenomena observed most frequently in the alcoholic group were not serious. Neither acute vascular collapse nor pain from intramuscular injection has been noted. Promazine appeared to potentiate the action of barbiturates and to have an antiemetic effect. During the relatively short period of treatment in these acutely disturbed patients, none of the complications reported after the use of other phenothiazine derivatives were noted. In summary, the drug, in doses of 50 to 200 mg, was effective in inducing sleep and maintaining these subjects in a quiescent detached state. They were easily aroused from sleep to care for their personal needs, thus reducing considerably the work load of the medical, nursing, and attending staff. The drug appeared to

have other desirable properties, such as potentiation of the action of barbiturates and an antiemetic effect [redacted]

Agitation and restlessness related to schizophrenia

A study evaluated the psychiatric effects of promazine and reserpine on schizophrenic out-patients. Specifically, it was sought to determine whether these drugs achieved control of pathological symptoms and whether they would induce behavioral toxicity, that is, diminished activity, drive level, or range of interest. Thirty-five patients, 20 on promazine and 15 on reserpine, who had from two and one-half to seven and one-half months of ataractic treatment were studied. Both promazine and reserpine are effective in the care of chronic schizophrenic out-patients in the context of a supportive doctor-patient relationship. Statistically significant changes in the patients' psychiatric condition occurred during drug treatment and were not observed during an initial placebo period. Patients treated with promazine and reserpine showed significant declines in pathological thinking, particularly in the area of paranoid projectivity. Promazine and reserpine patients gave evidence of decreased withdrawal and apathy. The median dosage levels at which these changes were observed were 150 mg daily for promazine, and 2 mg daily for reserpine. These relatively low doses may be responsible for the type of improvement observed. This improvement includes both the control of pathological thinking and the facilitation of greater social responsiveness. However, for patients with symptoms of agitation or strong aggressive urges initially higher doses may be necessary. The effect achieved at these lower dosages appears qualitatively different from that achieved at a higher dosage. In comparison with reserpine, promazine appears to be a fast acting drug. This speed may contribute to holding the patient in treatment, that is, preventing drop-out and cementing the doctor patient relationship. After six weeks of treatment had elapsed, however, the holding and therapeutic action of reserpine was equal to that of promazine. The quality and timing of somatic side reactions in this study are related to the effectiveness of promazine treatment. Transient side reactions specific to the drug (rather than to a placebo) were associated with eventual psychiatric improvement. No serious side reactions were observed with promazine or reserpine [redacted]

The effects of the tranquilizing drug Sparine (promazine) was evaluated on forty-six chronic schizophrenic patients. Forty-six patients (33 female and 13 male) were given Sparine orally. They all suffered from a chronic schizophrenic illness, three being basically oligophrenic in addition. Their present stay in hospital ranged from 1 to 37 years with an average of 16 years. Ages ranged from 27 to 71 with an average of 47 years. The majority had previously had some form of physical treatment; 8 had undergone prefrontal leucotomy. The case material was therefore the least promising available, as all the patients were suffering from a very chronic illness and many showed a deterioration. However, a considerable number of this group when previously treated by other tranquillizing drugs had shown a minimal or temporary improvement. Treatment was commenced with 150 mg. daily for one week, then it was increased to 300 mg. daily for a further two weeks after which a dose of 600 mg was maintained for five weeks. The drug was administered in a divided dosage three times daily. For the final three weeks of the investigation placebo tablets identical in appearance to the active drug were given. The full course of treatment thus occupied thirteen weeks. Sparine was found to be of no value in the treatment of this series of chronic schizophrenic patients. Thirteen per cent. of the

patients benefited to a limited extent from the drug, 11 per cent. became worse and 76 per cent. showed no change. Table 13 shows a more detailed analysis of the effects of Sparine on various signs and symptoms, including overactivity Sparine had little significant effect on any of these. Aggression was improved in eight patients (21 per cent.), but it could only be said to have been abolished in one case and in the other seven the diminution in its intensity could not be considered striking. There was an average increase in the pulse rate of five beats per minute. In 32 patients, the pulse became faster during treatment and in 11 patients it became slower. There was no significant change in weight or in the systolic and diastolic blood pressures. Reported side effects following the short term use of sparine have been few and not serious in nature or degree [redacted]

Symptoms and Signs	Present at Onset	Improved	No Change	Worse
Aggression	38	8	28	2
Delusions	36	3	32	1
Hallucinations	41	1	38	2
Severe withdrawal	18	3	13	2
Retardation	21	4	15	2
Overactivity	12	2	9	1*
Depression	5	2	2	1
Tension	14	3	9	2
Elation	5	0	4	1
Confusion	30	2	25	3
Impulsiveness	38	4	32	2
Faulty habits	9	0	9	0

* An additional two patients who had not previously shown overactive tendencies became overactive.

Table 12. Analysis of the Effects of Sparine on Certain Signs and Symptoms [redacted]

The effect of schizophrenia is to increase movement after effect (MAE) duration, and this is not due to some peripheral artefact. Longer MAEs in the illness could result from enhanced neurally signaled contrast and/or from the increased adaptability of cortical neurons. Various visual aftereffects have been reported to be abnormal in schizophrenia. The MAE is the apparent movement of a stationary field which follows prolonged inspection of a moving display. The effect is negative; that is, the apparent motion is in the opposite direction to the real movement to which the subject adapted. [redacted] measured the effects on the visual aftereffects of tilt and motion after intramuscular injections of chlorpromazine, promazine and saline in a series of experiments. They found that, compared with saline, both drugs significantly reduced MAE duration, but chlorpromazine produced a significantly greater reduction than did promazine. Although both drugs increased self-reported drowsiness, compared with saline, the difference in their effects was not significant [redacted]

Agitation related to mental deficiency

Promazine was evaluated in mental deficiency in male in-patients divided by intelligence levels, into three groups: Group I- 46 patients, aged 8 to 14 years, with IQ's of 50 to 80; Group II--7 patients, aged 8 to 14 years, with IQ's of 20 to 49; Group III-13 patients, aged 25 to 50 years, with IQ's of 13 to 49. Promazine was given over a 10-month period to 76 patients. It produced marked or moderate improvement in 53 patients. It was effective with patients in an age range from 8 to 50 years, and an IQ range from 13 to 80. The only side effect observed was occasional drowsiness, which was easily counteracted. In this study, promazine has proved to be an effective drug for the treatment of mentally defective patients. It has given good results, both

with severely retarded children who are hyperactive and excited and with higher-grade defectives who suffer from severe disturbances of behavior. It has also given favorable results with a small group of severely retarded older patients who are hyperactive and excited. The majority of these patients had been previously treated with chlorpromazine without appreciable benefit. For this reason, their improvement on promazine is the more impressive. The greatest improvement occurred in the more intelligent group of boys. Although they regressed to bad behavior when the drug was temporarily discontinued, it is possible that permanent improvement may be effected with some children. Calming them and relieving their anxieties make them more accessible to other forms of therapy, and remove some of the hindrances to their natural development, both physical and psychological [redacted] Results of promazine administration are presented in Table 16.

	GROUP I IQ — 50-80		GROUP II IQ — 20-49		GROUP III IQ — 13-49	
	No.	Per cent	No.	Per cent	No.	Per cent
Marked improvement	16	34.8	1	5.9	0	0
Moderate improvement	25	54.3	8	47.0	3	23.0
Slight improvement	3	6.5	5	29.4	6	46.2
No improvement	2	4.4	3	17.6	4	30.8
Totals	46	100.0	17	100.0	13	100.0

Table 13. Results of promazine administration [redacted]

Agitation related to psychosis due to alcohol withdrawal

Promazine can be useful in controlling alcohol withdrawal symptoms. Some controlled studies suggested that chlorpromazine and promazine are essentially indistinguishable in performance, but that both of these are superior to reserpine and meprobamate in controlling alcohol withdrawal symptoms. Patients without delirium tremens treated with promazine showed a short duration of anxiety and agitation [redacted]

A double-blind comparative evaluation was made of placebo, chlordiazepoxide, and promazine for the treatment of withdrawal symptoms in 58 male alcoholics admitted to hospital within 24 hours of their last drink. The principal sources of discomfort due to alcohol withdrawal were sleeplessness, agitation, tremor, sweating, anorexia, nausea, and vomiting. Chlordiazepoxide was given in total daily doses of 200 and 400 mg, and promazine in doses of 400 and 800 mg. The five treatment groups were compared with respect to hours of sleep, blood-pressure, pulse rate, spontaneous and intention tremor (measured photoelectrically), electrical resistance of the skin, and calorie intake. Observations were made before the start of treatment and twice daily for three days on treatment. Both promazine and chlordiazepoxide were more effective than the placebo in promoting sleep (Table 17; Figure 7) and diminishing sweating, but tolerance developed quickly to promazine while chlordiazepoxide remained effective. Promazine reduced tremor significantly, while chlordiazepoxide did not, or even increased it (Table 18; Figure 7). Promazine rapidly produced a marked postural hypotension and compensatory tachycardia, while chlordiazepoxide caused a more gradual onset of hypotension. Neither drug improved the appetite compared with the placebo. Grand-mal seizures or delirium tremens occurred in five patients on promazine, one on placebo, and none on chlordiazepoxide.

Chlordiazepoxide appeared to be the better drug for the treatment of alcohol-withdrawal symptoms, but the total benefit produced by it constituted a relatively small addition to the placebo effect [redacted]

Treatment*	% Time Slept	P Values for Between-Group Differences				
		Plac	Chl 50	Chl 100	Pro 100	Pro 200
Day 1						
Plac	10·6	—				
Chl 50	22·5	N.S.	—			
Chl 100	35·9	< 0·01	N.S.	—		
Pro 100	37·7	< 0·003	< 0·05	N.S.	—	
Pro 200	39·5	< 0·001	< 0·001	< 0·02	< 0·02	—
Day 2						
Plac	4·7	—				
Chl 50	15·5	< 0·02	—			
Chl 100	26·6	< 0·02	N.S.	—		
Pro 100	19·7	< 0·01	N.S.	N.S.	—	
Pro 200	31·6	< 0·001	< 0·01	N.S.	N.S.	—
Day 3						
Plac	6·0	—				
Chl 50	12·4	N.S.	—			
Chl 100	27·9	< 0·01	< 0·01	—		
Pro 100	12·7	N.S.	N.S.	< 0·02	—	
Pro 200	15·9	N.S.	N.S.	N.S.	N.S.	—

* The following abbreviations are employed in all tables to designate the various treatment groups: Plac = Placebo. Chl 50 = Chlordiazepoxide, 50-mg. dose. Chl 100 = Chlordiazepoxide, 100-mg. dose. Pro 100 = Promazine, 100-mg. dose. Pro 200 = Promazine, 200-mg. dose.

Table 14. Comparison of Treatment Effects on Percentage of Time Spent Sleeping [redacted]

Treatment	% of Group Showing Increased Frequency	P Values for Group Comparisons				
		Plac	Chl 50	Chl 100	Pro 100	Pro 200
Plac	100	—				
Chl 50	90	N.S.	—			
Chl 100 ..	89	N.S.	N.S.	—		
Pro 100 ..	72	N.S.	N.S.	N.S.	—	
Pro 200 ..	44	< 0·01	< 0·04	< 0·04	N.S.	—

6th Observation

Treatment	Mean Change (beats/min.)	P Values for Group Comparisons				
		Plac	Chl 50	Chl 100	Pro 100	Pro 200
Plac	+14	—				
Chl 50	+10	N.S.	—			
Chl 100 ..	+24	N.S.	< 0·025	—		
Pro 100 ..	−1	N.S.	N.S.	< 0·025	—	
Pro 200 ..	+1	< 0·05	< 0·025	< 0·001	N.S.	—

Table 15. Change in Frequency of Spontaneous Tremor from Admission Values [redacted]

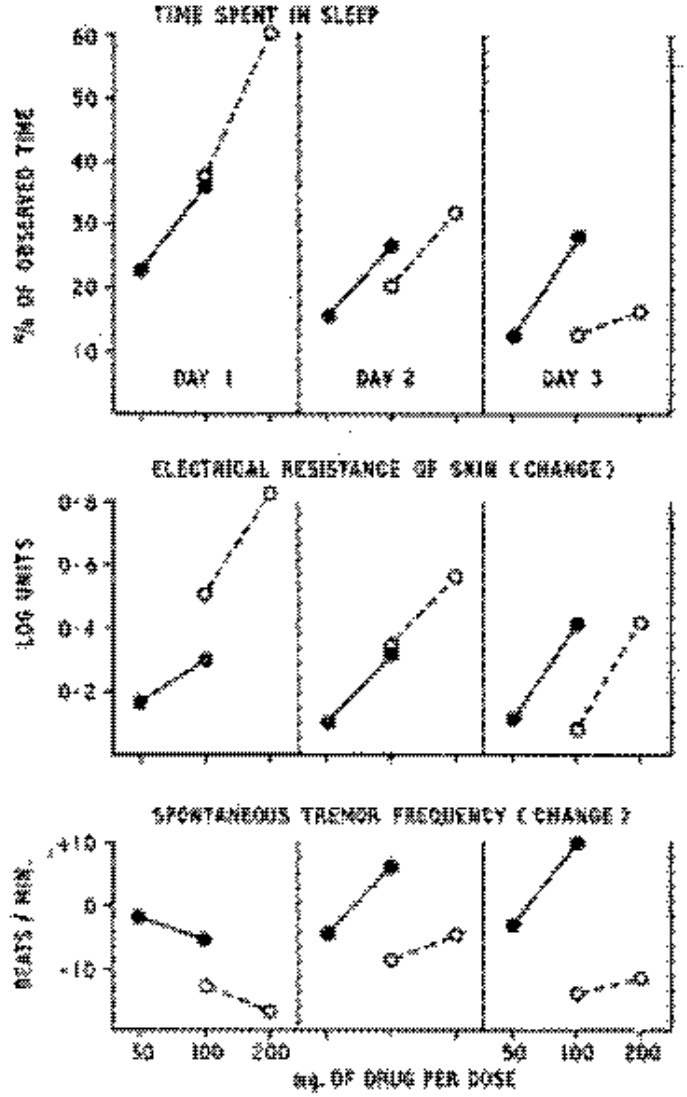

Figure 7. Comparative dose-response lines for chrodiazepoxide ●——● and promazine ○- - -○. A. Percentage of time spent in sleep. B. Elcetrical resistance of skin, as change from admission values, corrected for change in placebo group. C. Spontaneous tremor frequency, as change from admission values, corrected for change in

placebo group. Comparative potencies of the two drugs with respect to a given criterion on a given day can be assessed roughly by reading the doses corresponding to the same level of effect. In some cases this requires extrapolation of one of the dose-response lines [redacted]

[redacted] carried out a trial in order to compare promazine versus paraldehyde in the treatment of the symptoms due to alcohol withdrawal. Patients were divided in two groups. In Group 1, subjects were given promazine hydrochloride orally in a dosage of 200 mg every four to six hours. In Group 2, subjects were given paraldehyde orally in a dosage of 10 ml every four to six hours. The treatments were given routinely and not as circumstances required. The rating schedule recorded tremulousness, disorientation, hallucinations, fear, agitation, eating and sleeping, pulse rate, temperature, sweating, blood pressure, vomiting, convulsions, and awareness of reality. The dosage of promazine used in this trial was larger than is usually prescribed. In this series of 106 alcohol-withdrawal patients, significantly more deaths occurred in those treated with promazine hydrochloride than in those treated with paraldehyde. For most patients with mild withdrawal, symptoms cleared more rapidly with promazine. Paraldehyde was more efficacious in the delerium tremens group. A classification of severity on admission, based on autonomie and behavioral measures, proved a reliable prognostic tool [redacted]

A comparison was made of the treatment of the alcohol withdrawal syndrome with either promazine, paraldehyde or promazine-paraldehyde combined. 175 patients, 136 without delirium tremens and 39 with delirium tremens, were studied. Promazine was found to be better than either paraldehyde or promazine-paraldehyde combined, in the categories of early discharge from the hospital, decreased agitation and anxiety, and return to normal eating and sleeping patterns. When the delirium tremens group treated with promazine was compared with the group treated with paraldehyde, there was not a significant difference. Vomiting was approximately the same in all groups. Convulsions were more frequent in the groups treated with promazine, but not significantly so. Postural hypotension was a frequent complication of promazine therapy. Ward management of the patients who did not receive paraldehyde was easier than of those who did receive it. It appeared that with the use of promazine many of the patients could have been managed in a general hospital [redacted]

Promazine was used for treatment of 141 patients hospitalized for acute alcoholic intoxication. In addition to alcoholism, 70% were also suffering from various complications, including Laennec's cirrhosis. Withdrawal symptoms were satisfactorily controlled in all who remained in the hospital for the complete course of treatment, which usually required three to five days. Nausea and vomiting were promptly checked in most patients, and, with few exceptions, fluids and oral feedings could be administered immediately after initiation of drug therapy. No serious complications developed throughout the entire series. Dizziness and postural hypotension were the only side-effects encountered. Results were more satisfactory than in a similar group treated with chlorpromazine; minimal hypotensive effect was seen, and there were fewer cases of compensatory tachycardia than after chlorpromazine therapy. Promazine could be given intramuscularly with little pain or local tissue reaction [redacted]

The effects of promazine on reduction of mortality and morbidity in delirium tremens, was evaluated in 180 patients. In 173 the onset occurred while the patient was actively drinking; in 7 it occurred 1 to 48 hours after admission to the hospital. This fact conflicts with the teaching that delirium tremens is a withdrawal syndrome. Treatment in uncomplicated cases consisted of the complete withdrawal of alcohol and the administration of promazine hydrochloride.

Experience led to a program consisting of an initial intramuscular injection of 200 or 300 mg, a second injection of 100 mg within four or less hours, and oral administration of 100 mg four times a day for maintenance thereafter. In the last 87 cases there have been no deaths. The prompt control of delirium, shortened period of hospitalization, and lowered mortality contrast sharply with the prolonged illness and mortality of 10% associated with older methods of treatment [redacted]

Other conditions

The use of imipramine combined with promazine has proved to be most effective in various types of depression, with overall good response of the entire pattern of target symptoms. This drug combination was used in the treatment of 35 patients (24 females and 11 males). One patient was a schizophrenic and the others had some form of depression. All patients were from private practice and the majority were in the 40- to 80-year age group. They were under therapy for periods ranging from 1 to 7 months. Most patients were started on a 1 : 2 ratio (25 mg imipramine plus 50 mg promazine per capsule) with one capsule q.i.d. In the more serious cases this was rapidly increased to 6 to 8 capsules, and in a few instances to 12 capsules per day. Several patients received a 1: 1 ratio (25 mg imipramine plus 25 mg promazine per capsule) or a 1: 2.5 ratio (10 mg imiprainine plus 25 mg promazine per capsule). With one exception, the latter group consisted of those patients who after improvement were placed on maintenance dosage. More than half the patients received small supplementary doses of a phenothiazine, usually chiorpromazine, at night to overcome sleep disturbances. In cases of pronounced agitation or anxiety, a small amount of phenothiazine was also given with each meal. Most patients felt much more relaxed and were able to continue their normal routine at work or at home. Remarkably few side effects were observed. A few complaints of morning lethargy or drowsiness were usually controlled by small doses of methyiphenidate. Imipramine-promazine therapy resulted in an overall good clinical response in 80% of a group of patients with depressive syndromes. Response of symptoms of anxiety alone was over 90%. Patients were treated privately, and received intensive psychotherapy, which included other members of the family. Most patients were very comfortable on the mixture. Serious side effects were few and blood pressure changes were minimal. Additional dosage of phenothiazine was necessary in some cases, especially at night, to induce sleep. The imipramine-promazine combination appears to be highly effective, and would seem to be particularly useful in this new capsule form for the general practitioner and in outpatient clinics [redacted]

	COMPLETE		MODERATE		SLIGHT		NONE OR WORSE		
DIAGNOSIS	NO.	%	NO.	%	NO.	%	NO.	%	TOTAL
Involutional depression	2	33.3	3	50.0			1	16.7	6
Manic-depr. depression	7	46.7	5	33.3	1	6.7	2	13.3	15
Reactive depression			1	50.0	1	50.0			2
Depression of organic origin			1	100.0					1
Neurotic depression	2	22.2	6	66.7			1	11.1	9
Schizo-affective depression			1	100.0					1
Schizophrenia					1	100.0			1
Total	11	31.4	17	48.6	3	8.6	4	11.4	35

* Satisfactory Clinical Response = 80%.

Table 16. Response To Imipramine-Promazine Therapy Overall Response [redacted]

DIAGNOSIS	COMPLETE NO.	%	MODERATE NO.	%	SLIGHT NO.	%	NONE OR WORSE NO.	%	TOTAL
Involutional depression			4	80.0	1	20.0			5
Manic-depr. depression	2	16.7	9	75.0	1	8.3			12
Reactive depression	1	50.0	1	50.0					2
Depression of organic origin			1	100.0					1
Neurotic depression			8	88.9			1	11.1	9
Schizo-affective depression			1	100.0					1
Schizophrenia			1	100.0					1
Total	3	9.7	25	80.6	2	6.5	1	3.2	31

* Satisfactory Clinical Response = 90.5%.

Table 17. Response To Imipramine-Promazine Therapy Anxiety Response [redacted]

In 216 patients with various types of depression, imipramine was administered: (1) alone; (2) with small amounts of ataractic drugs; or (3) with promazine. Duration of drug administration ranged from two weeks to two years. The initial oral or parenteral imipramine dose of 75 to 100 mg daily was gradually increased in most cases to 150 mg and then decreased to 50 mg for maintenance. Imipramine + promazine was started with a 1: 1 ratio (100 mg each daily) and increased or decreased as necessary. A ratio of 1:2.5 (40 mg. imipramine+ l00 mg promazine) was used for the daily maintenance dose. Occasionally within one week, and more often within three weeks, over-all satisfactory clinical response was observed in 78 per cent of patients treated with imipramine as the major drug, and in 82 per cent receiving imipramine+promazine. With imipramine alone, excellent response was obtained in every case of manic depression. The imipramine+promazine combination was more effective in depressions associated with marked anxiety, agitation or insomnia. The majority of patients, previously unresponsive to treatment with a variety of ataraxic drugs, responded well to imipramine or imipramine -+- promazine. In some patients the latter drugs reduced the number of electroconvulsive treatments (ECT) required and eased the course of psychotherapy. A few cases refractory to ECT also did well. Most side effects were usually controlled by reduction of dosage, and serious reactions were few. Imipramine appears to be an effective antidepressant for the treatment of many types of depressive syndromes, while the combination of imipramine and promazine would seem to be more useful in cases associated with intense agitation, anxiety or insomnia. The high percentage of patients who were able to return to normal habits of work and daily living indicates that this mode of therapy may be used in many patients to replace ECT or previously ineffective drugs [redacted]

In patients with complex partial seizures without sleep deprivation, sleep was induced by 2mg/kg body weight of Protactyl (promazine hydrochloride) given orally. After sleep deprivation most patients fell asleep spontaneously [redacted]

2.5.4.2 ***The alfentanil/promazine and meperidine/promazine sedation in patient undergoing cataract surgery resulted excellent sedation, excellent peri-operative condition and few anaesthetic and other side effects*** [redacted] ***Elderly***

A number of the efficacy studies, presented in the previous section supported the use of promazine in elderly and they included patients up to 88 years of age [redacted]

[redacted]

An Italian study of the pattern of medication prescription for the treatment of agitation in elderly patients among consultant psychiatrists practicing in Tuscany, showed that promazine was the most frequently used drug when treating agitated elderly patients, regardless of their diagnosis. When treating elderly agitated patients affected by psychiatric disorders, the most frequently prescribed drug was promazine, 4 g/100 ml oral solution and prometazine 50 mg injection [redacted] Table 16 shows the percentage of using of drugs according to the four conditions: psychiatric disorder, delirium, dementia, medical disease.

	Psychiatric disorders	Delirium	Dementia	Medical disease
Promazine 4g/100 ml oral solution	53,1%	50%	70%	58%
Promazine 25 mg injection	Lower than 50%	65,6%	56,2%	51,6%
Prometazine 50 mg injection	51,6%	Lower than 50%	Lower than 50%	Lower than 50%

Table 18. Percentage of using of drugs according to the four conditions: psychiatric disorder, delirium, dementia, medical disease [redacted]

A preliminary study was carried out to determine the efficacy of the combined medication of meprobamate plus promazine in the treatment, of geriatric patients who had chronic brain syndrome associated with cerebral arteriosclerosis with psychotic and behavioral reactions. Twenty-six male geriatric patients ranging in age from 65 to 85 years were selected for this study. Seventeen had been hospitalized for periods ranging from four months to ten years; 9 were on convalescent leave and were seen on an outpatient basis. All 26 were classified as having chronic brain syndrome associated with cerebral arteriosclerosis, with psychotic and behavioral reaction. Symptoms included anxiety, agitation, restlessness, tension, apprehension and occasional unpredictable behavior. The combined medication was administered in capsule form. Each capsule contained 200 mg of meprobamate and 25 mg. of promazine hydrochloride. The initial dosage of the medication was limited to 3 capsules daily. The dosage was gradually increased according to the condition and requirements of the patient, and his response to the medication. The amount of medication prescribed daily did not exceed 6 capsules. When the desired response was obtained, the amount of medication administered was gradually decreased to the original dosage level. No other medication, i.e., tranquilizers or sedatives, was administered in conjunction with the meprobamate-promazine combination. A placebo control study was established with 21 patients in the same diagnostic and age categories. At the end of five weeks. not, even slight improvement was noted in the patients receiving placebos. In the three months of this continuing study, 21 of the 26 patients (81 per cent) in the treatment group have shown marked improvement. The remaining 5 patients (19 per cent) have shown some improvement in that they have become more calm, more quiet, and more cooperative. For 11 of the 26 patients, it was necessary to increase the dosage of medication to 2 capsules three

times daily. The dosage was continued at this level for two weeks until a satisfactory response was obtained (improvement in behavior and in attitudes), and then decreased gradually to 1 capsule three times daily. A good response was noted on the third day of treatment. Fourteen of the 16 patients who were hallucinating in both the auditory and visual spheres showed no signs of hallucinations after the sixth day of treatment. In 20 of the 26 patients, signs of anxiety and agitated behavior disappeared. In the remaining 6 patients, there were occasional signs of mild restlessness, but all were fairly cooperative. Most of the patients slept for longer periods of time and their appetites improved. Only a slight increase in weight, from 5 to 8 pounds, was noted during treatment. Results of the laboratory tests performed every tenth day were within normal limits. In none were there any severe side-effects. In conclusion, the combined medication facilitated the control and management, of these patients, made them more amenable to psychotherapeutic and rehabilitation programs, and was an excellent adjunct to psychotherapy [redacted] evaluated the use of promazine as premedications must be to diminish apprehension and anxiety, and give sufficient sedation without endangering the patient's well-being in elderly patients (n=64; average age above 60 years) undergoing intraocular surgery. Patients were premedicated with a combination of promazine 50 mg and meperidine 50 mg. Superior sedation and a smoother postoperative course were noted as compared to a control group premedicated with the usual high dosages of opiates and barbiturates. The incidence of nausea and vomiting, urinary retention, and postoperative disorientation was less than 20%. Hypotension was not a problem. Promazine was found to potentiate the action of opiates and barbiturates given in smaller dosages, thus permitting surgical procedures to be carried out with safety in an older population prone to the complications of opiate and barbiturate administration [redacted]

2.5.4.3 *Paediatric population*

A number of the efficacy studies, presented in the previous section supported the use of promazine in paediatric patients, aged above 12 years, with chronic psychosis [redacted] and in patients, aged above 8 years, with mental deficiency [redacted] However, there is a lack of evidence on the use of the proposed product in paediatric population. A double blind study was carried out in psychiatrically disturbed (n= 58, autistic or symbiotic childhood psychosis) and normal (n=13) children (1-15 years) during promazine sedation in order to evaluate EEC abnormalities in early childhood schizofrenia. Each individual had one or more EEC's at least one of which was done after the administration of promazine, 1 to 1.5 mg./lb. intramuscularly. Any medication the child had been taking was discontinued at least a week prior to the EEC. Among the 149 patients 51% had abnormal records. None of the psychiatrically normal children had EEC abnormalities. Except for the neurotics, the EEC abnormalities were qualitatively and quantitatively similar in the psychiatric patients. The most frequent abnormalities were irregular paroxysmal spike and wave complexes, often best seen during the transition from wake to sleep. Of the 149 patients, 33% had this complex, either alone or with independent spikes. Although these complexes were most frequent in the autistic symbiotic group, the incidence was not statistically significantly different from the higher performing, chronic undifferentiated schizophrenics who had communicative speech or the non-psychotic children with acting-out behavior disorders. Large doses of promazine do cause

EEC changes, but within the dose range employed, 1 to 1.5 mg. per pound, the literature indicates that promazine has little effect on the EEC except to induce sleep. The fact that none of 13 control subjects had abnormal records after being given promazine supports this conclusion. Perhaps the major point is that promazine permits the electroencephalographer to read the record reliably. Many of pre-promazine records were unreadable. Under promazine sedation, the child, who may have been combative, crying, and hyperventilating, soon becomes quiet and drowsy, and the EEC becomes free of muscle or movement artefact [redacted] described a case of promazine modification of reflex rigidity in a decerebrate child. Gross cerebral failure was initiated in a 19-month-old girl by convulsive phenomena following a mild gastrointestinal disorder. The over-all picture was that of a child in decerebrate condition, with release of diencephalic and brain-stem function resulting in continuous automatic activity and decerebrate spasticity. The central excitatory state was suppressed below the diencephalic level with promazine, in an initial dose of 25 mg. intramuscularly, followed by four intramuscular injections of 12.5 mg per day for two days. The fluid form of the compound was then administered by mouth in the same dosage. After the patient's discharge from the hospital, maintenance doses of 7.5 mg. were administered orally. Reflex excitability was inhibited with promazine. Decerebrate spasticity was relaxed. Mechanical crying was controlled. The child was enabled to sleep naturally, probably by attenuation of the impulses that had been stimulating the alerting mechanism in the reticular formation [redacted]

2.5.4.4 Pregnancy and breastfeeding

If possible, antipsychotics should be avoided during pregnancy, particularly during the first trimester [redacted]
Efficacy studies of promazine during pregnancy and breastfeeding are insufficient to provide information of the effects on pregnancy and/or embryo/foetal development and/or postnatal development and on the baby.

2.5.5 Overview of Safety

2.5.5.1 Phenotiazines safety profile

The adverse effect profile of an individual phenothiazine agent may relate to its relative affinities for the different neurotransmitter receptors responsible for its pharmacological action. All phenothiazines have associated anticholinergic adverse effects because of their binding at muscarinic receptor sites. Anticholinergic signs and symptoms include sedation, dry mouth, mydriasis, urinary retention, ileus, delirium and hallucinations. Phenothiazines all lower the seizure threshold in a dose-related fashion. In all patients, including adults and those patients with psychiatric indications, phenothiazine use is associated with seizures at an incidence of 1.2%. Phenothiazines have quinidine-like effects on the cardiac conduction system, causing nodal conduction delays through and delayed ventricular repolarisation, which is manifest as prolonged PR intervals, prolonged QTc intervals, flattened or biphasic T waves, and attendant dysrhythmias in patients who have overdosed on these medications. Postural hypotension is frequently seen as a adverse effect of phenothiazine use. More serious life-threatening

cardiotoxicity associated with phenothiazine use includes ventricular arrhythmias. Phenotiazines may cause dystonic reactions and extrapyramidal dyskinesias and in rare cases potentially fatal neuroleptic malignant syndrome. Other less common adverse effects of phenothiazines in susceptible individuals include photosensitivity reactions (dermatitis, urticaria, purple-grey discolouration of the skin) and other rashes. Hepatitis with cholestasis, bile duct damage and fibrosis has been described; other gastrointestinal symptoms including nausea, vomiting and gastritis are sometimes seen. Marrow suppression with severe but reversible neutropenia and blood dyscrasias have also been observed. Galactorrhoea, menstrual difficulties and bodyweight gain have been reported. Priapism in an adult taking fluphenazine was reversed using intravenous diphenhydramine. Pigmentary retinopathy has been described in patients on thioridazine, and lenticular deposits were associated in rare cases with aliphatic phenothiazine use. A case of a lupus-like syndrome also has been reported after aliphatic phenothiazine use [redacted] Phenotiazines may cause hyperglycemia, hypoglycemia, glycosuria, high or prolonged glucose tolerance, eosinophilia, thrombocytopenia, aplastic anemia with pancytopenia, purpura, or granulocytopenia; and hemolytic anemia [redacted] Furthermore, venous thromboembolism, corneal and lens opacities, weight gain may, interference with temperature regulation (dose related) can occur with phenotiazines [redacted]
As for all antipsychotics, caution should be used in patients with blood dyscrasias, cardiovascular disease, conditions predisposing to seizures, depression, epilepsy, history of jaundice, myasthenia gravis, Parkinson's disease (may be exacerbated), photosensitisation (may occur with higher dosages), prostatic hypertrophy, severe respiratory disease, susceptibility to angle-closure glaucoma [redacted]

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death, mostly from cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) causes. A causal relationship with antipsychotic use has not been established. In controlled trials, treatment with some atypical antipsychotic drugs was also associated with an increased risk of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in elderly patients with dementia- related psychosis. These agents are not approved for the treatment of patients with dementia- related psychosis [redacted]

According to the publicly available information on similar products on the market the following drug interactions have been reported for promazine:

- The concomitant administration of this product with other medication such as central nervous system depressants (including alcohol and anaesthetics) or antihypertensives, opioids, anticholinergic or dopaminergic drugs may result in accentuation of their effects, while potentiation of action may also occur with monoamine oxidase inhibitors, antidepressants and analgesics. Promazine may impair the effects of anticonvulsants. Promazine may affect the control of diabetes and possibly antagonises the hypoglycaemic effect of sulfonylureas. Undesirable anticholinergic effects can be enhanced by anti-parkinson or other anticholinergic drugs.

- The concomitant administration of this product with myelosuppressive drugs (carbamazepine, co-trimoxazole, chloramphenicol, sulphonamides, pyralizone analgesics (e.g. azapropazone), penicillamine and cytotoxics) increases the risk of toxicity.
- Lithium administration will result in an increased risk of extrapyramidal effects and the possibility of neurotoxicity.
- Coadministration of phenothiazines with metoclopramide or tetrabenazine increases the risk of extrapyramidal effects.
- An increase in plasma concentration of antipsychotic drugs may occur if taken with ritonavir.
- There is an increased risk of convulsions when promazine is coadministered with tramadol
- Antipsychotic drugs antagonize the pressor effects of sympathomimetics.
- The effects of antipsychotic drugs may be enhanced by cimetidine and reduced by memantine.
- Antacids and kaolin may reduce absorption of phenothiazines.
- Caution should be used when using antipsychotics with reboxetine.
- Sotalol administration will result in an increased risk of ventricular arrhythmia.
- Concomitant use of promazine with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias, including torsade de pointes. Therefore concomitant use of these products is not recommended. Examples include certain antiarrhythmics, such as those of Class 1A (such as quinidine, disopyramide and procainamide) and Class III (such as amiodarone, sotalol and dofetilide), certain antimicrobials (sparfloxacin, moxifloxacin, erythromycin IV), tricyclic antidepressants (such as amitriptyline), certain tetracyclic antidepressants (such as maprotiline), other neuroleptics (e.g. phenothiazines, pimozide, sertindole and haloperidol), certain antihistamines (such as terfenadine), cisapride, bretylium and certain antimalarials such as quinine and mefloquine. This list is not comprehensive.
- Concurrent use of drugs causing electrolyte imbalance is not recommended. Diuretics, in particular those causing hypokalemia, should be avoided but, if necessary, potassium-sparing diuretics are preferred [SPC Promazine 25mg/5ml Oral Syrup, 2020].

2.5.5.2 Promazine safety profile

Promazine has been used in clinical practice since the late ‘50s and its safety profile is well characterized.

Promazine is a group 1 phenothiazine, characterized by pronounced sedative effects and moderate extrapyramidal and antimuscarinic adverse effects. Promazine had a very satisfactory range of safety, the effectiveness has been proved, and the complications or side effects are negligible. Drug habituation to promazine was not evident from clinical studies. The general properties and therapeutic uses of promazine are similar to chlorpromazine but promazine shows less toxicity. Promazine use is not recommended in the following cases: previous known hypersensitivity, depressed level of consciousness, hepatic or renal impairment, cardiovascular disease, Parkinson’s disease, epilepsy, hypothyroidism, prostatic hypertrophy, narrow angle

glaucoma, pheochromocytoma, and myasthenia gravis. Special precautions include elderly, pregnancy, lactation, and cerebral arteriosclerosis [redacted]
The main adverse effects recorded with promazine are sedation, somnolence, insomnia, anxiety, agitation, seizures, various anticholinergic effects (caution is required in association with anticholinergic drugs), EPS, dizziness, hypotension, orthostatic hypotension, sinus tachycardia, syncope, leucopenia, agranulocytosis, thrombocytopenia, hyperprolactinaemia, cholestatic jaundice and neuroleptic malignant syndrome. Commonly other reported physical side effects of the psychotropic promazine are weight gain, constipation, dry mouth, tardive dyskinesia, urinary retention. The incidence of sedation is very high with promazine while the incidence of weight gain, anticholinergic, hypotension and prolactin elevation is moderate. Extrapyramidal effects can occur with a low frequency [redacted]

2.5.5.3 Analysis of adverse effects

Nervous system
Nervous system side effects with promazine are common and include drowsiness, dystonia, akathisia, athetoid movements and other extrapyramidal effects. Mutism has also been reported [redacted] Involuntary rhythmical movements of the tongue, face and mouth characterize tardive dyskinesia. Early recognition of premonitory symptoms of tardive dyskinesia (like hyperkinetic dysarthria and fine vermiform movements of the tongue) may allow discontinuation of promazine before irreversible dyskinesia ensues [redacted] Fever, altered consciousness, autonomic dysfunction and muscle rigidity are the hallmarks of the neuroleptic malignant syndrome. The neuroleptic malignant syndrome is associated with a case fatality rate of about 20%. Immediate discontinuation of neuroleptic therapy and intensive monitoring and supportive care are indicated. Other side effects including tardive dyskinesia have been reported after administration of other phenothiazines and may be irreversible. The neuroleptic malignant syndrome has been reported to occur in as many as 0.5 to 1% of patients taking other neuroleptic agents [redacted] Two case reports with clinical presentation of three consecutive neuroleptic malignant syndrome. One patient developed neuroleptic malignant syndrome while he was taking combination of drugs: first time haloperidol, promazine and fluphenazine, second time fluphenazine and perazine and third time clozapine, promazine and valproic acid consecutively. The other patient developed neuroleptic malignant syndrome while taking following combination of drugs: first time haloperidol and lithium carbonate, second time risperidone and third time clozapine consecutively [redacted]
Promazine has antiemetic properties and it may mask sign of drug overdsage, symptoms of brain tumor or intestinal obstruction [redacted]

Skin reactions
Potential skin reactions associated to the use of promazine are: dermatitis, edema, exanthems, hypohidrosis, photoreactions, photosensitivity [redacted] photoxicity, pigmentation, purpura, rash, urticarial, xerosis [redacted] erythema [redacted]
Gastrointestinal tract
Gastrointestinal side effects of promazine including nausea, vomiting, constipation, excessive salivation, and dry mouth have been reported [redacted]

Endocrine side effects

Endocrine side effects including hyperprolactinemia, galactorrhea, amenorrhea, gynecomastia, and (less frequently) hyponatremia have been reported with other neuroleptics [redacted]

Hematologic reactions

Hematologic side effects including agranulocytosis have been reported rarely with promazine [redacted]. Disseminated intravascular coagulation, anaemia and neutropenia have been reported in patient taking promazine [redacted]

Genitourinary tract

Genitourinary side effects including priapism, urinary incontinence, urinary retention nocturnal enuresis, and spontaneous ejaculation have been reported with other neuroleptics [redacted]

Immunologic system

Immunologic side effects including Raynaud's phenomenon and a lupus-like syndrome have been reported with other neuroleptics [redacted]

Cardiovascular system

Cardiovascular side effects including nonspecific EKG changes of uncertain clinical significance, orthostatic hypotension, tachycardia, and syncope have been reported with other neuroleptics [redacted] Promazine has an established link with a number of adverse cardiovascular effects (hypotension, tachycardia/arrhythmia and QTc prolongation). Relative incidence and severity of side effects is higher than other antipsychotics [redacted]

Oncologic side effects

Oncologic side effects including endometrial adenocarcinoma has been reported in association with neuroleptic induced hyperprolactinemia. Some investigators have suggested that endometrial sampling be performed in women taking neuroleptics if warranted by clinical suspicion [redacted]

Withdrawal reactions

Withdrawal symptoms have included sweating, hypotension, insomnia, nausea, vomiting, constipation and diarrhea. Withdrawal symptoms after abrupt discontinuation of promazine and other neuroleptics have been reported [redacted]

Musculoskeletal and connective tissue disorders

Promazine may induce rhabdomyolysis [redacted] Increased creatine phosphokinase levels in blood have been recorded with promazine [redacted]

Other

Increased body temperature and acute renal failure have been recorded with promazine [redacted]

2.5.5.4 Clinical safety studies and case reports

Relatively few and transient complications have been reported in clinical studies of promazine. The following table summarizes the main adverse events recorded with promazine during clinical trials.

Adverse Event	References
Allergic responses	
Skin reactions	
Extrapyramidal symptoms such as parkinsonism	
Alkaline phosatase rise	
Edema	
Dizziness, weakness, headache	
Seizures	
Collapse	
Drowsiness, fatigue	
Confusion, cognitive impairments	
Gastro-intestinal discomfort such as constipation, nausea, vomiting	
Jaundice	
Urinary retention	
Leucopenic reactions	
Agranulocitosis	
Hypotension, orthostatic hypotension	
Cardiac events such as sinus tachycardia	
Xerostomy, sweating	
Blurred vision	

Table 19. Main adverse events recorded with promazine during clinical trials.

Nervous system

Low potency antipsychotics such as promazine and chlorpromazine are associated to a lower incidence of seizure than antipsychotics with higher potency. Case reports of epileptiform seizures have been reported [redacted] However, it unlikely that the single dose of promazine (2 mg/kg body weight, given orally in syrup form) can have a provocative seizures effect [redacted].

Hematologic reactions

Case reports of agranulocytosis have been recorded during the course of promazine treatment [redacted].

Intravenous administration

Severe local reactions, such as burning, have occurred following the use of intravenous promazine [redacted].

Skin reactions

Isolated reports dermatitis have appeared [redacted]. According to the literature the group of phenothiazines is the category of drugs with rare appearances of skin reactions. Promazine has less frequent side effects in the leaflet states increased skin sensitivity to sun, skin rash-associated with contact dermatitis, allergic reactions, cholestatic icterus. [redacted] reported that the only reported dermatological side effect of promazine is its metabolites deposition in the cornea. Authors described a case of a forty-two years old female patient, admitted to the [redacted] because of suspected exanthema, undoubtedly caused by promazine as a medication for [redacted]

In addition, promazine is much less phototoxic than chlorpromazine both in vivo and in vitro as lacks a chlorine atom at the 2-position, to undergo homolytic fission to give the promazinyl radical, which is probably responsible for some of the observed in vitro phototoxic effects of this drug [redacted]

Phenothiazine-induced lupus with circulating anticoagulant has been reported infrequently, and is rarely associated with significant symptoms [redacted]

Cardiovascular events

Marked hypotension, which is more properly considered an anticipated pharmacologic effect, has been observed but is said to be "slight," "moderate," and, in fact, "not encountered". Though mention is made of a death following vasomotor collapse after use of promazine, hypotension is usually considered as a relatively benign side-effect of the use of this drug. Serious and even fatal hypotensive reactions have been observed following the administration of promazine. While lethal vascular collapse could not be unequivocally attributed to promazine, in as much as the patients were suffering from illnesses in themselves very profound, nevertheless the fact that irreversible collapse occurred immediately after the administration of the drug emphasizes the harmful potentialities in susceptible persons [redacted]

Hypovolaemic shock has been reported with promazine [redacted]

Withdrawal symptoms

[redacted] carried out a study to test withdrawal from meprobamate in patients treated with usual therapeutic doses, in patients receiving large doses, and in patients receiving large doses of meprobamatepromazine combination. Withdrawal reactions from large doses of meprobamate were frequent, though not related to initial plasma levels or electroencephalographic changes. Reactions similar in frequency and intensity were noted when promazine was combined with meprobamate. Symptoms from withdrawal at ordinary therapeutic doses were infrequent and mild, resembling recrudescence of symptoms being treated [redacted]

Safety in elderly patients

The study of [redacted] compared the short-term effects of incident use of typical and atypical antipsychotic agents on the risk for hospitalization in a community-dwelling elderly population. This retrospective data analysis involved a longitudinal cohort of

typical and atypical antipsychotic users and was based on data from the 1996–2004 Medical Expenditure Panel Survey. Typical antipsychotic agents included chlorpromazine, fluphenazine, haloperidol, levomepromazine, loxapine, mesoridazine, molindone, perphenazine, promazine, thioridazine, thiothixene, and trifluoperazine. Atypical antipsychotic agents included aripiprazole, cloza- pine, olanzapine, quetiapine, risperidone, and ziprasidone. Incident cases of antipsychotic use in community-dwelling elderly (aged ≥60 years) persons were selected for the assessment of risk for all-cause hospitalization within 60 days of exposure to antipsychotics. Bivariate analyses were used to compare baseline characteristics; multivariate logistic regression was used to compare hospitalization risk among users of typicals and atypicals after controlling for age, sex, race, income, insurance coverage, perceived general health, perceived mental health, and other concurrent psychotropic use. The analytical sample consisted of 124 community-dwelling elderly patients (atypicals, 75 patients; typicals, 49). A majority of the elderly study sample were women (63%), white (79%), and of middle/high income (57%). The mean (SD) age of the study sample was 74.37 (8.65) years. There were no significant differences in baseline characteristics between typical and atypical users, with the exception of perceived mental health status. After control- ling for other factors, the risk for hospitalization was nearly 4-fold higher with typical antipsychotic use than atypical use (odds ratio, 3.81; 95% CI, 1.12–12.99). In this population of community-dwelling elderly, use of typical agents was associated with an increased risk for hospitalization compared with atypical agents.

Two significant observational studies have investigated the association between antipsychotic use and increased mortality in elderly patients with dementia.

A retrospective cohort study was conducted involving 22,890 patients aged 65 years or older with drug insurance benefits in Pennsylvania, who began treatment with either a conventional or atypical antipsychotic medication between 1994 and 2003. Analyses of mortality rates and Cox proportional-hazards models were used to compare the risk of death within 180 days, less than 40 days, 40 to 79 days, and 80 to 180 days after the initiation of therapy with an antipsychotic medication. We controlled for potential confounding variables with the use of traditional multivariate Cox models, propensity-score adjustments, and an instrumental-variable analysis.

The results showed that conventional antipsychotic medications were associated with a significantly higher adjusted risk of death than were atypical antipsychotic medications at all intervals studied (≤180 days: relative risk, 1.37; 95 percent confidence interval, 1.27 to 1.49; <40 days: relative risk, 1.56; 95 percent confidence interval, 1.37 to 1.78; 40 to 79 days: relative risk, 1.37; 95 percent confidence interval, 1.19 to 1.59; and 80 to 180 days: relative risk, 1.27; 95 percent confidence interval, 1.14 to 1.41) and in all subgroups defined according to the presence or absence of dementia or nursing home residency. The greatest increases in risk occurred soon after therapy was initiated and with higher dosages of conventional antipsychotic medications. Increased risks associated with conventional as compared with atypical antipsychotic medications persisted in confirmatory analyses performed with the use of propensity-score adjustment and instrumental-variable estimation.

The authors concluded that these results suggest that conventional antipsychotic medications are at least as likely as atypical agents to increase the risk of death among elderly persons and that conventional drugs should not be used to replace atypical agents discontinued in response to the FDA warning [redacted]

A Population-based, retrospective cohort study was conducted to examine the association between treatment with antipsychotics (both conventional and atypical) and all-cause mortality in Canada. Older adults with dementia who were followed between 1 April 1997 and 31 March 2003.

The risk for death was determined at 30, 60, 120, and 180 days after the initial dispensing of antipsychotic medication.

Two pairwise comparisons were made: atypical versus no antipsychotic use and conventional versus atypical antipsychotic use. Groups were stratified by place of residence (community or long-term care). Propensity score matching was used to adjust for differences in baseline health status.

A total of 27 259 matched pairs were identified. New use of atypical antipsychotics was associated with a statistically significant increase in the risk for death at 30 days compared with non-use in both the community-dwelling cohort (adjusted hazard ratio, 1.31 [95% CI, 1.02 to 1.70]; absolute risk difference, 0.2 percentage point) and the long-term care cohort (adjusted hazard ratio, 1.55 [CI, 1.15 to 2.07]; absolute risk difference, 1.2 percentage points). Excess risk seemed to persist to 180 days, but unequal rates of censoring over time may have affected these results. Relative to atypical antipsychotic use, conventional antipsychotic use was associated with a higher risk for death at all time points.

Sensitivity analysis revealed that unmeasured confounders that increase the risk for death could diminish or eliminate the observed associations.

Information on causes of death was not available. Many patients did not continue their initial treatments after 1 month of therapy. Unmeasured confounders could affect associations. The authors concluded that atypical antipsychotic use is associated with an increased risk for death compared with nonuser among older adults with dementia. The risk for death may be greater with conventional antipsychotics than with atypical antipsychotics [redacted]

These studies underscore the importance of cautious antipsychotic use in elderly patients with dementia, considering the associated mortality risks. It is crucial to note that promazine is not licensed for managing dementia-related behavioural disturbances, and its use in such contexts should be carefully evaluated.

Others

Several case reports of antipsychotic-induced dysphagia have been described for both atypical and typical agents [redacted] investigated the incidence of dyslipidemia (hypertriglyceridemia and hypercholesterolemia) in patients treated with antipsychotics of new generation compared to conventional therapy. This retrospective study included 116 chronic psychiatric patients divided into two groups: a test group who were on treatment with antipsychotics of the new generation and a control group who were treated with classical antipsychotics. Laboratory and vital parameters were monitored in a group of patients who were treated with new generation antipsychotics (clozapine, olanzapine, risperidone), as well as in the group of patients who were treated with classical antipsychotics (promazine, levopromazin, haloperidol, fluphenazine). Mean triglyceride level in the test group was 3.13 mmol/L, and for the control group, 2.28 mmol/L, while the mean value for cholesterol test group was 6.12 mmol/L, and for the control group, 5.85 mmol/L. The average age of the test group was 49.6 years, while the control group was 51.47 years. There was a statistical significance in

triglycerides (p = 0.004), while the cholesterol (p = 0.239) and age (p = 0.356) had no statistical significance in the test group compared to the patients who were treated by the new generation of antipsychotics, and the control group of patients who were treated with antipsychotics. Dyslipidemia in the form of hypertriglyceridemia occurs more frequently in patients on therapy with the new generation of antipsychotics compared to patients treated with conventional therapy.

2.5.5.5 Post marketing experience

Data on suspected side-effects, also known as suspected adverse drug reactions, for promazine as authorised medicine in the European Economic Area (EEA) has been found in Eudravigilance web-site and are reported in the following figure [redacted]

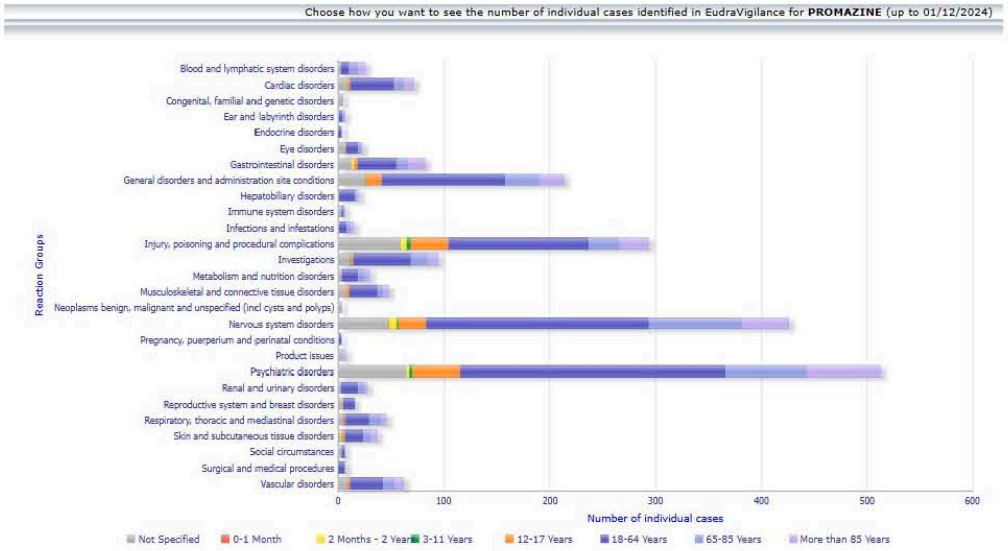

Figure 8. Number of individual cases of promazine by reaction groups and age groups in Europe, up to December 2024

Figure 8 shows the distribution by reaction group and age group. It was noted that the reaction groups with a higher number of cases were Psychiatric disorders and Nervous system disorder [redacted]

A study was carried out to elucidate the differences in adverse events between pediatric, adult, and geriatric populations using the FDA's Adverse Events Reporting System (AERS), a database that has collected information about adverse events since 1998. AERS is the FDA's primary tool for post-marketing adverse event surveillance, with over 250,000 adverse event reports annually. Antipsychotics such as chlorpromazine and promazine were associated with a significant difference in the number of adverse events in the adult vs. geriatric populations [redacted] Furthermore, the study confirmed that promazine is associated to a lower toxicity than chlorpromazine. Table 23 and Table 24 show the main outcomes for the two drugs.

Generic Name	% of Adverse Events			p-value (vs. Adults)		Statistical Significance
	Pediatrics	Adults	Geriatrics	Pediatrics	Geriatrics	
Chlorpromazine	20.3	17.1	12.1	0.066	$3.31e^{-6}$	Geriatrics
Fluphenazine	0.3	5.1	2.4	$4.3e^{-5}$	$4.39e^{-6}$	Both
Haloperidol	64.9	56.3	72.8	0.0011	0	Both
Loxapine	2.8	2.7	1.9	0.46	0.043	--
Mesoridazine	0.0	0.2	0.1	0.20	0.27	--
Molindone	0.9	0.3	0.6	0.017	0.018	--
Perphenazine	0.3	2.7	2.3	0.0038	0.19	--
Pimozide	3.4	1.6	1.3	0.0082	0.17	--
Promazine	0.6	2.8	0.1	0.0095	$9.39e^{-10}$	Geriatrics
Thioridazine	5.5	3.9	3.4	0.070	0.20	--
Thiothixene	0.0	4.5	0.9	$4.9e^{-5}$	$1.24e^{-10}$	Both
Trifluoperazine	0.9	2.9	2.0	0.017	0.031	--
TOTALS	100.0	100.0	100.0			

Table 20. Comparison of the Number of Adverse Events in Each Population. Results were statistically significant either for pediatrics vs. adults, geriatrics vs. adults, or both. The significance threshold was 0.05/26 = 1.92 x 10-3. The p-values that R found to be extremely low are labeled as "0." [redacted].

Generic Name	Event Pediatrics	N	Event Adults	N	Event Geriatrics	N
Chlorpromazine	DRUG EXPOSURE DURING PREGNANCY	12	DIABETES MELLITUS	100	WEIGHT DECREASED	17
Chlorpromazine	SOMNOLENCE	9	VOMITING	59	DIARRHOEA	16
Chlorpromazine	AGGRESSION	7	NEUROLEPTIC MALIGNANT SYNDROME	52	DEHYDRATION	15
Chlorpromazine	DRUG INEFFECTIVE	6	CONVULSION	51	PNEUMONIA	14
Chlorpromazine	WEIGHT INCREASED	6	PYREXIA	50	SEPSIS	13
Promazine	NEONATAL DIABETES MELLITUS	1	DIABETES MELLITUS	33	DRUG INTERACTION	2
Promazine	PREMATURE BABY	1	PANCREATITIS	15	METHYLMALONIC ACIDURIA	1
Promazine	DEATH	1	MYOCARDIAL INFARCTION	15	MUSCLE RIGIDITY	1
Promazine	DIAPHRAGMATIC HERNIA	1	BLOOD PRESSURE DECREASED	14	CONFUSIONAL STATE	1
Promazine	PULMONARY HYPOPLASIA	1	MYOCARDITIS	14	PLATELET COUNT INCREASED	1

Table 21. Number and type of events in each population for chlorpromazine and promazine [redacted]

All the above mentioned studies and isolated reported cases are in accordance and corroborate the undesirable effects that can be found in the Summary of Product Characteristics from the already marketed Promazine 25mg/5ml Oral Syrup [SPC Promazine 25mg/5ml Oral Syrup, 2020].

2.5.5.6 Drug interactions

As other phenotiazines, promazine may increase the sedative effects of benzodiazepines, tricyclic antidepressants, hypnotics, anaesthetics, antihistaminic agents, opioids or other drugs with sedating characteristics [redacted] This may result in effects ranging from excessive sleepiness to respiratory depression. Drugs with anticholinergic effects, such as antihistamines and tricyclic antidepressants, may also have additive effects on the phenothiazines. Anticholinergic drugs may delay the absorption of phenothiazines as well as producing more anticholinergic symptoms. Tricyclic antidepressants may enhance the cardiotoxicity of phenothiazines such as thioridazine, resulting in cardiac dysrhythmias. The coadministration of lithium with a phenothiazine agent may predispose the patient to neuroleptic malignant syndrome. Phenothiazines, like all drugs with extensive hepatic metabolism, can compete with the sites of metabolism for other drugs such as anticonvulsants. Barbiturates, conversely, may lower blood phenothiazine concentrations by virtue of their induction of the cytochrome P450 enzyme complex [redacted] Table 25 summarizes potential promazine drug interactions.

Agent Name	Mode of Interaction
ACE inhibitors	Severe postural hypotension.
Angiotensin-II antagonists	Severe postural hypotension.
Alcohol	Enhanced sedative effect.
General Anesthetics	Enhanced hypotensive effect.
Analgesics	Enhanced sedative and hypotensive effect.
Antacids and adsorbents	Reduced absorption of phenothiazines.
Antiarrhythmics	Increased risk of ventricular arrhythmias due to prolonged QT interval.
Antidepressants	Increased risk of ventricular arrhythmias with tricyclic antidepressants. Co-administration increases plasma concentration and enhances antimuscarinic effects. Monoamine oxidase inhibitors may enhance hypotensive effects.
Antidiabetics	Hypoglycaemic effect of sulphonylureas antagonized.
Antiepileptics	Reduce seizure threshold and reduce efficacy of anticonvulsants.
Antihypertensives	Enhanced hypotensive effect.
Antimuscarinics	Antimuscarinic side effects increased, but plasma concentration decreased.
Antivirals	May increase plasma concentration of antipsychotics.
Anxiolytics and hypnotics	Enhanced sedative effect.
Beta-blockers	Increase risk of ventricular arrhythmias.
Calcium-channel blockers	Enhanced hypotensive effect.
Cocaine	Increased risk of antipsychotic-induced dystonic reactions.
Diuretics	Hypokalaemia increases risk of ventricular arrhythmias.
Dopamine receptor agents	Antagonism of hypoprolactinaemic and antiparkinsonian effects of bromocriptine and cabergoline. Antagonism of effect of apomorphine, levodopa, lisuride, and pergolide.
Lithium	Increased extrapyramidal effects and neurotoxicity.
Sympathomimetics	Antagonize pressor action.
Tetrabenazine	Increased extrapyramidal effects.
Tobacco smoking	Clearance of phenothiazine may be increased.
Ulcer-healing drugs	Cimetidine may enhance antipsychotic effects.

Table 22. Promazine drug interactions [redacted]

Propafenone and promazine are also human ether-à-go-go-related gene (HERG) potassium channel blockers. HERG-blockade can lead to QT prolongation with increased risk of potentially life-threatening torsade de pointes arrhythmia. The worsening of preexisting congestive heart failure with propafenone or new-onset congestive heart failure was also

observed. Antipsychotic, often used to control agitation in a context of dementia, is responsible for drug-induced arrhythmias, ranging from QTc lengthening to torsade, which can cause increased mortality in elderly patients treated for dementia. Regarding to this issue, a case of widened QRS interval and left ventricular systolic depression due to propafenone therapy for atrial fibrillation, co-administered with the antipsychotic drug promazine in demented 90 year old Italian women has been reported [redacted]

An increase in the risk of ventricular arrhythmias has been reported with concomitant use of moxifloxacin and phenothiazines [redacted]

The concomitant administration of levodopa and phenothiazines should be avoided since this can lead to precipitation or exacerbation of Parkinson's disease [redacted]

The association of metrizamide and phenothiazines may cause seizures [redacted]

Concurrent use /of alcohol or other central nervous system (CNS) depression-producing medications/ with phenothiazines may result in increased CNS and respiratory depression and increased hypotensive effects; dosage reductions of either drug may be necessary during concurrent use or when sequence of use enhances CNS effects. Alcohol may increase the risk of heat stroke when taken concurrently with phenothiazines [redacted]

Phenothiazines can cause the appearance of dark colouration of the urine [redacted]

Phenothiazine compounds, which are known to produce false positive biological pregnancy tests, may also induce a false positive result in immunological tests for pregnancy [redacted]

Antacids. Studies in 6 patients showed that chlorpromazine plasma concentrations were significantly lower after giving chlorpromazine with an aluminium hydroxide and magnesium trisilicate antacid gel (Gelusil) than after chlorpromazine alone. In-vitro studies indicated that chlorpromazine was highly bound to the gel [redacted]

Antiarrhythmics. There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of droperidol, pimozide, or thioridazine with antiarrhythrnics (especially amiodarone, disopyramide, procain-amide, and quinidine) should be avoided. Use of haloperidol with amiodarone is also not recommended. A study in healthy subjects has suggested that quinidine might increase plasma concentrations of haloperidol [redacted]

Antibacterials. Seven schizophrenic patients whose antitubercular therapy included rifampicin (in addition to isoniazid, and in some cases also ethambutol) had lower serum concentrations of haloperidol compared with tuberculotic schizophrenic patients receiving no antimycobacterials and with non-tuberculotic schizophrenics [redacted]

Pharmacokinetic studies involving some of these patients indicated accelerated haloperidol clearance in the presence of rifampicin. Abnormally high serum-haloperidol concentrations occurred in 3 of 18 patients treated with isoniazid alone.

Black galactorrhoea occurred in a patient receiving minocycline, perphenazine, amitriptyline hydrochloride, and diphenhydramine hydrochloride [redacted] Simultaneous occurrence of phenothiazine-induced galactorrhoea and tetracycline-induced pigmentation was considered responsible.

Sudden cardiac deaths have been reported [redacted] in patients given clarithromycin and pimozide. Elevated pimozide plasma concentrations were recorded after pretreatment with clarithromycin [redacted]

Antidepressants. Interactions between antipsychotics and tricyclic antidepressants are generally of two forms: additive pharmacological effects such as antimuscarinic effects or hypotension; or pharmacokinetic interactions. Although not commonly reported in the literature, additive antimuscarinic activity may be a significant risk especially in the elderly. Careful drug selection might help to prevent the development of serious adverse effects. Mutual inhibition of liver enzymes involved in the metabolism of both the antipsychotic and the tricyclic antidepressant might result in increased plasma concentrations of either drug. In one study [redacted] addition of nortriptyline to chlorpromazine therapy produced an increase in plasma concentrations of chlorpromazine but this resulted in a paradoxical increase in agitation and tension.

There is an increased risk of arrhythmias when tricyclic antidepressants are given with other drugs that prolong the QT interval. It has been recommended that the use of droperidol, pimozide, or thioridazine with tricyclic antidepressants should be avoided. Increased serum concentrations of haloperidol have occurred when patients were also given fluoxetine, fluvoxamine, or nefazodone [redacted] Isolated reports [redacted] of extrapyramidal symptoms, psychoneuromotor syndrome, stupor, bradycardia, and urinary retention associated with use of fluoxetine "With antipsychotics suggest that fluoxetine might exacerbate the adverse effects of antipsychotics or produce additive toxicity. Similar CNS effects have been noted in subjects given perphenazine and paroxetine [redacted] There has also been an isolated report of a patient who complained of amenorrhoea and galactorrhoea after fiuvoxamine was added to loxapine therapy [redacted] Significant increases in the plasma concentrations of thioridazine have occurred after use with fluvoxamine [redacted] Paroxetine may also inhibit the metabolism of thioridazine, resulting in increased thioridazine plasma concentrations; UK licensed product information for paroxetine contra-indicates their concomitant use. The US licensed product information for paroxetine states that giving paroxetine with pimozide was associated with a mean increase of 1 5 1 % in the area under the concentration-time curve of pimozide and 62% in its mean peak plasma concentration. Due to the narrow therapeutic index of pimozide concomitant use of these 2 drugs is contra-indicated [redacted]

Combinations of antipsychotics and lithium should be used with care. Lithium can reduce plasma-chlorpromazine concentrations and there is a report of ventricular fibrillation on withdrawal of lithium from a patient also taking chlorpromazine. Chlorpromazine has also been reported to enhance the excretion of lithium. Neurotoxic or extrapyramidal symptoms have been reported rarely in patients taking antipsychotics and lithium; these may be atypical cases of lithium toxicity or neuroleptic malignant syndrome [redacted].

A patient o n long-term trifluoperazine treatment developed neuroleptic malignant syndrome after a single dose of venlafaxine [redacted] The authors noted that the manufacturers of venlafaxine have received a small number of similar reports after introduction of venlafaxine in patients receiving antipsychotics including molindone.

There have been occasional reports of sexual disinhibition in patients taking tryptophan with phenothiazines [redacted]

Other Phenothiazines. Combining promazine with other phenothiazines or central nervous system depressants can enhance sedative effects, increasing the risk of profound sedation or

respiratory depression. Additionally, concurrent use may elevate the risk of extrapyramidal symptoms and other neurological adverse effects.

Combining chlorpromazine with other phenothiazines can amplify adverse effects. [redacted] investigated the antidepressant effects of combining chlorpromazine with diethazine, another phenothiazine derivative. The results indicated a significant antidepressant effect in neurotic depressions. The study also highlighted the importance of monitoring for adverse effects when using such combinations.

Promazine is effective in managing certain psychiatric conditions; however, its use, especially in combination with other phenothiazines, requires careful monitoring and patient education to mitigate the risk of adverse effects.

Antidiabetic drugs. Since chlorpromazine may cause hyperglycaemia or impair glucose tolerance the dose of oral hypoglycaemics or of insulin may need to be increased in diabetics [redacted]

Antiepileptics. Carbamazepine. phenobarbital, and phenytoin are potent enzyme inducers and may decrease plasma concentrations of antipsychotics or their active metabolites when used together [redacted] The clinical effect of any interaction has not been consistent; worsening, improvement, or no change in psychotic symptoms have all been noted. Delirium has been reported in a patient given haloperidol and carbamazepine [redacted]. Phenytoin might also exacerbate antipsychotic-induced dyskinesia. Care should be taken when withdrawing enzyme-inducing antiepileptics as this may result in a rise in antipsychotic serum concentrations [redacted].

Antihistamines. There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of droperidol, pimozide, or thioridazine with antihistamines such as astemizole or terfenadine should be avoided [redacted]

Antimalarials. Pretreatment with single doses of chloroquine sulfate, amodiaquine hydrochloride, or sulfadoxine with pyrimethamine increased the plasma concentrations of chlorpromazine and 7-hydroxychlorpromazine, but not of chlorpromazine sulfoxide, in schizophrenic patients maintained on chlorpromazine. The raised plasma concentrations appeared to be associated Virith a greater level of sedation [redacted]

There is an increased risk of arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. It has been recommended that the use of antipsychotics, and pimozide in particular, with antimalarials such as halofantrine, mefloquine, or quinine should be avoided [redacted]

Antimigraine drugs. A report [redacted] of a patient receiving loxapine who had a dystonic reaction within 15 minutes of subcutaneous sumatriptan suggests that these two drugs might interact or potentiate each other's adverse effects. However, the patient had a history of dystonic reactions associated with haloperidol and was receiving benzatropine prophylactically. Furthermore, the dose of loxapine had been increased 2 days before the event and this may have predisposed the patient to dystonia.

Antiparkinsonian drugs. Antiparkinsonian drugs are sometimes given with antipsychotics for the management of antipsychotic-induced adverse effects including extrapyramidal disorder. Theoretically, dopaminergics such as levodopa and bromocriptine might induce or exacerbate psychotic symptoms. A study in 18 subjects and review of the literature suggested that

bromocriptine can be used safely in patients at risk of psychotic illness provided they are clinically stable and maintained on antipsychotics. Conversely, antipsychotics might antagonise the effects of dopaminergics; diminished therapeutic effects of levodopa have been noted with several antipsychotics and thioridazine has been reported to oppose the prolactin-lowering action of bromocriptine [redacted]

Additive antimuscarinic adverse effects are obviously a risk when antimuscarinic antiparkinsonian drugs are given with antipsychotics. Although these are generally mild, serious reactions have occurred. Trihexyphenidy [redacted] and orphenadrine [redacted] have both been reported to decrease plasma concentrations of chlorpromazine, possibly by interfering with absorption from the gastrointestinal tract.

Antipsychotics. Elevated plasma levels of haloperidol were reported [redacted] in a patient being treated for schizophrenia when chlorpromazine or clozapine were also given.

Antivirals. Ritonavir may increase the plasma concentration of some antipsychotics. The increases expected for pimozide were considered in licensed product information for ritonavir to be large enough to recommend that these drugs should not be used together. Other classical antipsychotics predicted to have increases include haloperidol, perphenazine, and thioridazine; it was recommended that monitoring of drug concentrations and/or adverse effects were required when used with ritonavir [redacted].

Beta blockers. Chlorpromazine and propranolol may mutually inhibit each other's hepatic metabolism. Propranolol has been reported to increase plasma concentrations of chiorpromazine and thioridazine, and pindolol to increase plasma-thioridazine concentrations [redacted] Neither beta blocker tested had a significant effect on haloperidol concentrations, although there is a report of severe hypotension or cardiopulmonary arrest occurring on occasions in a schizophrenic patient given haloperidol with propranolol [redacted] The clinical significance of antipsychotic-beta blocker interactions is unclear [redacted]

There is a n increased risk o f arrhythmias when antipsychotics are given with other drugs that prolong the QT interval. The use of antipsychotics, and pimozide in particular, with sotalol should be avoided [redacted]

Buspirone. The use of haloperidol with buspirone has resulted in increased serum haloperidol concentrations. However, while some [redacted] found the mean rise in serum-haloperidol concentrations to be 26%, that seen by others [redacted] was not statistically significant.

Cimetidine. Despite expectations that cimetidine might reduce the metabolism of chlorpromazine, mean steady-state plasma concentrations of chlorpromazine fell rather than rose in 8 patients given cimetidine for 7 days in addition to regular chlorpromazine therapy [redacted] The explanation was probably that cimetidine interfered with chlorpromazine absorption. Excessive sedation, necessitating a reduction in chlorpromazine dosage, has been reported [redacted] after addition of cimetidine to the drug therapy of 2 chronic schizophrenics.

Cocaine. The risk of antipsychotic-induced dystonic reactions may be increased in cocaine abusers. Dystonia occurred in 6 of 7 cocaine abusers treated with haloperidol [redacted]

Desferrioxamine. Loss of consciousness lasting 48 to 72 hours occurred in 2 patients given prochlorperazine during desferrioxamine therapy [redacted]. Prochlorperazine may enhance the removal of transition metals from brain cells by desferrioxamine.

Disulfiram. A psychotic patient, previously maintained with plasma-perphenazine concentrations of 2 to 3 nanomol/mL on an oral dose of 8 mg twice daily, was read-mitted with subtherapeutic plasma-perphenazine concentrations of less than 1 nanomol/mL, despite unchanged dosage, after disulfiram therapy [redacted] The concentration of the sulfoxide metabolite of perphenazine was much increased. After a change from oral to intramuscular perphenazine therapy there was a substantial clinical improvement associated with a return to therapeutic plasma concentrations of perphenazine and a fall in concentration of the metabolite. Disulfiram appears to greatly enhance biotransformation of oral perphenazine to inactive metabolites, but parenteral administration avoids the 'first-pass' effect in the liver.

General anaesthetics. A schizophrenic patient without a history of epilepsy who was receiving oral chlorpromazine and flupentixol depot injection had a convulsive seizure when given enflurane anaesthesia [redacted]

Piperazine. There has been an isolated report [redacted] of convulsions associated with the use of chlorpromazine in a child who had received piperazine several days earlier. Subsequent animal [redacted] studies produced conflicting evidence for an interaction and it was suggested that an interaction would only be clinically significant when high concentrations of piperazine were reached in the body.

Sympathomimetics. A 27-year-old woman with schizophrenia and T-wave abnormality of the heart, receiving thioridazine 100mg daily with procyclidine 5 mg twice daily, died from ventricular fibrillation within 2 hours of also taking a single dose of a preparation reported to contain chlorphenamine maleate 4mg with phenylpropanolamine hydrochloride 50mg (Contac C) [redacted]

Myelosuppressives. While promazine is not classified as a myelosuppressive agent, it has been associated with hematologic adverse effects, including agranulocytosis, leukopenia, and thrombocytopenia. These effects are rare but can be serious. Regarding interactions with myelosuppressive drugs, specific studies are limited. However, combining promazine with other agents known to suppress bone marrow function could potentially increase the risk of hematologic toxicity. Therefore, caution is advised when co-administering promazine with myelosuppressive drugs, and regular monitoring of blood cell counts is recommended to detect any adverse effects promptly.

Metoclopramide. Both phenothiazines and metoclopramide act as dopamine antagonists. Their concurrent use can potentiate dopamine blockade, elevating the risk of EPS. A study published reported that metoclopramide-induced extrapyramidal reactions are more common in patients under 30 years old, especially females, and can occur even at standard doses. The study emphasizes caution when prescribing metoclopramide, particularly in combination with other dopamine antagonists like phenothiazines [redacted].

Tetrabenazine. Combining phenothiazines with metoclopramide or tetrabenazine can significantly increase the risk of extrapyramidal side effects due to their synergistic effects on dopamine pathways. Healthcare providers should exercise caution, monitor patients closely, and consider alternative treatments when appropriate [redacted]

Tramadol. Co-administration of promazine, a phenothiazine antipsychotic, with tramadol, an analgesic, may increase the risk of seizures. This potential interaction arises from their individual effects on the central nervous system and seizure thresholds.
The concurrent use of tramadol and promazine may result in an additive effect on lowering the seizure threshold, thereby elevating the risk of seizures. While specific studies directly examining the interaction between promazine and tramadol are limited, the individual seizure risks associated with each drug suggest that their combination could potentiate this adverse effect.
Tramadol is known to lower the seizure threshold, leading to an increased risk of seizures, even at therapeutic doses. A systematic review and meta-analysis reported that seizures occurred in approximately 3% of patients taking therapeutic doses of tramadol [redacted].
An observational study involving patients treated with first-generation antipsychotics reported that 1.2% of those receiving phenothiazines experienced seizures. The study identified two main factors that increased seizure probability: high dosages and the period around the initiation or escalation of the phenothiazine dose. Specifically, seizures occurred in 9% of patients treated with high doses (equivalent to 1,000 mg/day of chlorpromazine), compared to 0.7% with moderate doses and 0.3% with low doses (200 mg/day chlorpromazine equivalent) [redacted]
Reboxetine. Phenothiazines can cause orthostatic hypotension [redacted] Phenothiazines possess anticholinergic properties, leading to side effects such as dry mouth, constipation, and urinary retention.
Reboxetine has been reported to cause mild anticholinergic effects. Reboxetine has been shown to increase heart rate and blood pressure [redacted].
The co-administration of phenothiazines, such as promazine, with reboxetine may result in additive cardiovascular effects due to their individual side effect profiles and could also increase the risk of anticholinergic side effects.

2.5.5.7 Special populations

Elderly

According to guidelines, antipsychotics should be used in the elderly only for disturbances such as schizophrenia, mania with psychosis, agitated dementia with delusions, psychotic major depression and delusional disorders [redacted] and aggression in elderly people is a common issue and physicians may have to deal with this condition during their medical practice. It may be due to several causes such as mental disorders or medical conditions. A recent study showed that the drug mostly used in the treatment of agitation and aggression, regardless of the etiology, was Promazine followed by Chlorpromazine. These drugs were primarily administrated by injection, with slightly differences depending on the causes of agitation and aggression. The choice of the drug appeared to be mostly moved by its safety profile. Promazine (oral or via injection) was the most frequently administered drug in patients with agitation due to psychiatric disorders, with a slight preference for the oral route of administration (57.8% vs 50.6%). In case of delirium, the 60.7% of physicians preferred promazine via injection, while for dementia both the oral and the intravenous/intramuscular formulations received more preferences (52,4% and 52,3% respectively). In addition, promazine was preferred for agitation associated with organic diseases. Second generation

antipsychotics were barely preferred, in spite of current guidelines suggest [redacted]

Sudden unexplained death has been reported in patients taking antipsychotics, including promazine. It is relatively rare, although it is more common in older patients and males. Clinical characteristics and risk factors associated with sudden unexplained death in the psychiatric population are unclear [redacted]

In April 2005, the US Food and Drug Administration issued a warning about the increased risk of all-cause mortality associated with atypical antipsychotic use in elderly patients with dementia. Pneumonia was one of the most frequently reported causes of death. Extrapyramidal adverse events, dysphagia, and sedation as a result of dopamine, cholinergic receptors, and H1 receptors may all play a role in antipsychotic-induced pneumonia [redacted]

In 2003, the FDA warned of an association between risperidone and cerebrovascular events (CVAE), including stroke, in elderly patients with dementia. Additional clinical trials showed similar risks for other antipsychotics and the FDA warning now applies to all atypical neuroleptics. Atypical and conventional antipsychotics seem to be associated with a similarly increased risk for CVAE [redacted]

In elderly patients with behavioural symptoms that may be associated with cognitive impairment or dementia antipsychotics should be prescribed with caution. In general, one half to one third the adult dose is recommended in the elderly, who may be more susceptible to parkinsonian and anticholinergic side-effects. Phenothiazines should be used with caution given the risk of hypotension, and thioridazine may not be considered a first-choice medicine if other antipsychotics are available [redacted].

Promazine has an established link with a number of adverse cardiovascular effects such as QTc prolongation [redacted]]. QTc increased in duration with increasing age. The range of values for the QT interval in apparently normal older men or women, when combined with the range of expected QT interval changes induced by antipsychotic drugs, can readily be associated with prolonged QTc. Individuals with QTc at the 99th percentile may have serious QTc prolongation with antipsychotic drugs even those that are not usually associated with QTc prolongation [redacted]

Promazine is used in the treatment of schizophrenia, toxic psychosis, mental organic disorders with delirium, behavioural and psychological symptoms of dementia, and depression associated with psychomotor agitation and delusions. The mean dosage in the elderly is 15–60 mg/day increasing up to 200mg/day in schizophrenia treatment. The treatment dose in the elderly is reached according to the clinical response, surveillance of adverse effects and a careful evaluation of the patient's general medical condition. Promazine doses in the elderly population exceeding 200 mg/day are not recommended. Promazine demonstrated its safety along with efficacy in an elderly patient suffering from delusional parasitosis. The medication was administered under supervision due to the possibility of drug-associated hypotensive side effects. No side effects were noticed. It appears as an adequate alternative to atypical antipsychotic agents which may be associated with the increased risk of cerebrovascular events along with weight gain in the elderly population [redacted].

Paediatric population

No serious adverse events have been reported in children from clinical studies [redacted]

Nevertheless, reports of sudden infant death syndrome in children receiving a phenothiazine-containing syrup for symptoms of upper respiratory infection have been described. It means that the outpatient use of these compounds in very young infants is not recommended [redacted]

Pregnancy and breastfeeding

Safety studies of promazine in pregnant or breastfeeding women are insufficient to show the safety of this drug.

[redacted] evaluated promazine for fear and anxiety during labour. Three consecutive controlled clinical trials of promazine (sparine) were carried out on 1,565 maternity cases in the same unit. The first, a retrospective toxicity study of 993 consecutive cases, confirmed the safety of promazine suggested by the literature, despite a tendency towards maternal tachycardia. The reduction in vomiting from 5% to 1% and a corresponding reduction in the need for intravenous fluids suggested a powerful anti-emetic effect in the promazine group. In the first double-blind trial of 280 cases subjective relief was assessed by the average condition of the patient at various stages of labour. This method failed to demonstrate any significant difference between placebo and promazine groups. In a second double-blind trial of 292 cases subjective relief was assessed at a fixed time after each drug administration. The results showed a significant difference between the promazine and placebo groups. Taking all dosage levels, 58.5% of promazine cases and 36.1 % of placebo cases showed marked improvement in pain. The corresponding figures for "mental state" were 63.2% for promazine cases and 36.2% for placebo cases. Promazine has not been found to increase the length of labour when given intramuscularly or intravenously in toxicological studies. Evaluation of the effect of promazine on the foetus showed no evidence of foetal respiratory depression. The only deleterious effects of promazine were maternal tachycardia, occasional foetal tachycardia, and maternal hypotension, but these appeared to be less frequent with intramuscular administration. In order to confirm the apparent safety of intramuscular and oral promazine, a retrospective comparison was made between 500 consecutive cases admitted to the unit before promazine was used and a similar group of 500 mothers given promazine to allay fear and anxiety. In the first group, pethidine, chloral, dichloralphenazone, and –methylpentynol were used, according to the individual preference of the attendant. In the second group, promazine was administered for fear and anxiety according to the patients' requirements, the usual dose being 50 to 100 mg. intramuscularly. The other drugs given were pethidine for pain and promethazine for insomnia. The results of this retrospective study (Table X) confirmed the safety of promazine suggested by the literature. They also show the greater tendency towards maternal tachycardia (120 per minute and over) with promazine, and the drug's anti-emetic effect [redacted].

Group	Total Patients	Surgical Induction	Episiotomy	Lacerations	Forceps	Caesarean Sections
Control	498	58	147	120	49	21
Promazine	495	41	155	113	42	23

Duration of Labour

Group	1st Stage (Hours)					2nd Stage (mins.)				3rd Stage (mins.)		
	<5	5–	10–	20–	40+	<15	15–	60–	120+	<15	15–	60+
Control ..	70	153	166	77	32	127	252	83	15	429	37	11
Promazine	60	150	171	85	29	102	261	87	22	433	33	6

Complications

Group	Maternal Tachycardia	Foetal Distress	Post-partum Blood Loss (oz.)			Manual Removal of Placenta	Vomiting	Intravenous Fluids	Fresh Stillbirths
			<10	10–	20+				
Control ..	18	41	367	78	32	14	27	15	6
Promazine	32	42	368	78	26	10	5	3	5

Table 23. Results of Retrospective Comparison Delivery [redacted].

Hepatic impairment

In the study conducted on the pharmacokinetics of promazine in patients with acute viral hepatitis B, during the acute period of the illness, SGOP, SGPT, alkaline phosphatase, and total: bilirubin were increased in all patients; they returned to within or near the upper limits or normal after recovery. Despite the unchanged promazine disposition, four out of six patients had more severe promazine side-effects, such as sedation, postural hypotension, and dizziness during the acute phase of the illness than later [redacted]

Subject no.		Side-effects Sedation	Postural Hypotension	Dizziness
1	D	++	–	++
	R	+	–	–
2	D	++	++	++
	R	–	–	–
3	D	++	++	++
	R	–	–	+
4	D	+	–	+
	R	–	–	–
5	D	+	++	++
	R	–	–	–
6	D	–	–	–
	R	–	–	–

D, R: During and after recovery from acute phase of viral hepatitis respectively.
++: Severe: in the case of postural hypotension, patient fell down while standing up; whereas on sedation, patient fell asleep for more than 4 h.
+: Not severe: patient fell asleep less than 4 h.
–: No response was observed.

Table 24. Occurrence and severity of promazine side-effects during and after recovery from the acute phase of viral hepatitis after receiving two 50 mg promazine tablets [redacted]

Renal impairment

There are no safety data of promazine in patients with renal impairment.

2.5.5.8 Overdosage

One of the risks with any sedative is the potential for poisoning, either by iatrogenic errors in the hospital setting or unintentional or intentional poisonings occurring at home. Phenothiazines have a sufficiently narrow therapeutic: toxic dose ratio to make the potential for severe, life-threatening overdoses a valid concern, especially among young children who may have an exaggerated toxic response to these compounds [redacted].
[redacted] discussed that compilations found in fatal poisonings, often associate promazine concentrations >5 mg/L with fatalities and those >1 mg/L with toxicity. In comparison, concentrations > 2.3 mg/L of promazine were found in whole blood in 90% of our clean promazine poisonings. The authors concluded that promazine is rather uncommon worldwide as a drug. Nevertheless, it was frequently found in fatal poisonings, particularly associated to alcohol. Promazine concentrations tend to be the highest when 0.5-1.0 mg/g of alcohol is involved in the fatalities [redacted]
Signs and symptoms of phenotiazines overdose are sedation, coma, tachycardia, arrhythmia, pulmonary oedema, hypotension, QT prolongation, seizures, dystonia, NMS [redacted]
A case of lethal suicidal intoxication by promazine was reported in a patient who had been treated following several prior suicide attempts. The administered dose of promazine exceeded 100 tablets, each containing 100 mg. The determined blood concentration of promazine immediately after hospitalization was 8.4 mg/L [redacted].
A case report of acute intoxication by triazolam and promazine has been described by [redacted] The authors presented the case of a 76-year-old woman who was found deceased and the cause of death was determined to be acute intoxication due to the effect of triazolam and promazine and the manner of suicide. The triazolam concentration in each specimen was as follows: blood 1100 ng/ml; gastric content 1300 ng/ml; the promazine concentration in blood and in gastric content was 3450 ng/ml and 5800 ng/ml respectively [redacted] reported a case of a young woman who according to ECG, enzyme release, and echocardiography, developed transient acute myocardial ischemia and minimal myocardial damage following self-poisoning with promazine hydrochloride. The total dose of promazine ingested by our patient (600 mg) might still be considered within the therapeutic range, even if suggested doses in the case of psychomotor agitation are 100±200 mg four times daily.
Forty-eight cases of phenothiazine poisoning were analyzed by [redacted] Of these 48 cases, 34 were attributed to suicide attempts, nine to accidental ingestion, and five to drug reactions. As outpatient treatment of schizophrenia increases, cases of overdose with phenothiazine drugs may be expected to increase also. The prescribing of multiple phenothiazines and antidepressants is probably contributory to the occurrence of mixed drug ingestions. The symptoms and signs of phenothiazine poisoning are largely predictable if the atropine-like, alpha-blocking, quinidine-like, and extrapyramidal actions of phenothiazines are appreciated. Phenothiazine poisoning is characterized by a tendency toward hypothermia, tachyeardia, tachypnea, and decreased diastolic blood pressure. A clear tendency toward greater obtundation was noted in cases of mixed drug overdoses. Unexplainable tachypnea and paradoxical miosis were noted in severe cases. In one case in the study phenothiazine intoxication was present in the newborn infant of a schizophrenic mother. Treatment included administration of ipecac (15

cases), gastric lavage (nine cases), intravenous hydration (25 cases), and intravenous diphenylhydramine in three cases. Methylphenidate had been given to two children at other hospitals before they were transferred to hospital. Interestingly intubation was not needed in any case in which only phenothiazine was ingested, but it was required in six cases of mixed overdose [redacted]

The study of [redacted] examined the trend and role of antipsychotics as a method of self-poisoning suicide. During the 23-year follow-up period, second-generation antipsychotics (SGAs) overtook first-generation antipsychotics (FGAs) as a suicide method. Female victims, compared to males, had more commonly used quetiapine (17.5% vs. 6.1%, p 1⁄4 .016), while suicides using promazine were more common in males compared to females (36.5% vs. 22.2%, p = .049). People with unipolar depression had more frequently used SGAs (40.0%) or a combination of SGAs and FGAs (12.5%) than FGAs (19.2%) (p = .019) in their suicides.

The outcome of antipsychotic overdose is generally favourable unless other central nervous system depressants, such as alcohol and benzodiazepines, have been ingested. Overdosage of phenothiazines may cause more severe symptomatology than other antipsychotic classes. Antipsychotic overdose is characterized by hypotension, tachycardia, hypothermia, arrhythmia, drowsiness, dystonias and seizures. If antipsychotic overdosage of antipsychotics is suspected, referral to acute medical facility is recommended [redacted].

A recent retrospective review of single-substance acute oral overdoses with promazine in adults and children (<16 years) analysed cases reported in a poison centre by physicians and with a high causality assessment from 1997–2021. Promazine displays an acute toxicity profile similar to other phenothiazine neuroleptics. In adults, severe courses occurred only with doses 2.5-times above the maximum recommended dose. Accidental ingestions by toddlers may be of concern [redacted]

2.5.5.9 Dosage and administration

The choice of this antipsychotic drug should be made jointly by the individual and the clinician based on informed discussion on the relative benefits and side effects which is recorded in the notes. A risk assessment should be performed by the clinician responsible for treatment and the multidisciplinary team regarding compliance with medication [redacted].

Before starting antipsychotic therapy, it is generally recommended to check weight and blood pressure. Other suggested monitoring includes electrocardiogram, full blood count, urea and electrolytes, creatinine phosphokinase, liver function tests, blood glucose, lipid pattern and prolactin. If these laboratory examinations are not feasible, health care providers should ask the patient and/or family member about the existence of cardiovascular, renal or hepatic abnormalities, and whether drug therapies for these medical conditions have been prescribed and taken [redacted]

It is generally suggested to use one antipsychotic at a time. The concurrent use of two or more antipsychotics do not provide additional benefit, while it produces additional adverse reactions and may interfere with treatment adherence. High doses of antipsychotics increase the risk of adverse reactions without providing additional benefit. It is generally suggested to start with

low doses, and to increase gradually. The minimum effective dosage should be prescribed [redacted]

The recommended daily dose of oral promazine is 100 mg with a range from 50 to 200 mg per day [redacted].

Dosage in elderly

Lipid-soluble drugs, such as promazine, tend to accumulate in adipose tissue, resulting in increases in their plasma half lives and their duration of action, thus increasing the risk of iatrogenic effects in elderly persons. The treatment dose in the elderly is reached according to the clinical response, surveillance of adverse effects and a careful evaluation of the patient's general medical condition. Promazine doses in the elderly population exceeding 200 mg/day are not recommended [redacted]

Approved posology of similar products on the market

Psychomotor Agitation

Adults: 100mg to 200mg, four times daily.

Elderly: Half the normal starting dose may be sufficient for a therapeutic response.

Agitation and Restlessness

Elderly: 25mg initially, increasing, if necessary, up to 50mg, four times a day [SPC Promazine 25mg/5ml Oral Syrup, 2020].

Paediatric population

Children: Promazine is not recommended for children.

Proposed posology

The proposed posology has been reported below and is based on all the above mentioned information.

Agitation and Restlessness

Adults: 100mg to 200mg, up to four times daily.

Elderly: 25 mg initially, up to 50 mg four times daily.

The lowest effective dose for the shortest period possible should be used.

Paediatric population

Children: Promazine is not recommended for children.

2.5.6 Benefits and Risks Conclusions

Promazine has been used as an antipsychotic for more than 60 years, in the treatment of schizophrenia, paranoid states, mania, toxic psychosis, mental organic disorders with delirium, severe anxiety refractory to benzodiazepines, and depression associated with psychomotor agitation and delusions. The general properties and therapeutic uses of promazine are similar to chlorpromazine. It has pronounced sedative effects and moderate antimuscarinic and extrapyramidal side effects. Promazine is a relatively weak antipsychotic.
The pharmacology of promazine is well described. Promazine is rapidly absorbed after oral administration. It's mainly distributed in the brain, mostly bound to plasma proteins, extensively metabolised in the liver and excreted in urine. Promazine may increase the sedative effects of benzodiazepines, hypnotics, anaesthetics and antihistaminic agents. Synergistic interaction with alcohol is also described.
Promazine is an aliphatic phenothiazine antipsychotic agent, with a low-potency antidopaminergic action, α1-adrenergic antagonism and anticholinergic properties. Promazine is an antagonist at dopamine, serotonin, alpha-1 adrenergic, histamine H-1, and muscarinic receptors.
A number of clinical trials investigated the efficacy of promazine in psychomotor agitation or restlessness associated with psychotic disorders such as schizophrenia and others in adults and elderly. Promazine had a very satisfactory range of safety, the effectiveness has been proved, and the complications or side effects are negligible. Promazine significantly alleviated the above-mentioned symptoms of the psychoses and permits greater amenability to psychotherapy. Drug habituation to promazine was not evident from clinical studies. The general properties and therapeutic uses of promazine are similar to chlorpromazine but promazine shows less toxicity. This drug can be used effectively in patients in whom chlorpromazine or other antipsychotics must be discontinued because of severe complications.

The safety profile of promazine is well characterized. The incidence of sedation is very high with promazine while the incidence of weight gain, anticholinergic, hypotension and prolactin elevation is moderate. Extrapyramidal effects can occur with a low frequency.

The efficacy and safety profile of promazine have been proven in clinical trials and during its clinical use for more than 60 years. Therefore, it meets the requirements for well-established medicinal use. The Summary of Product Characteristics is in keeping with the information available on this product and with the promazine products already authorised in the European Union.

Overall, the benefit/risk ratio for Promazine hydrochloride 25mg/5ml Oral syrup and 50mg/5ml Oral Syrup is favourable and the indication and precautions for the use of this drug are justified by its pharmacological properties. Its efficacy and safety profile indicate that it is a recognised useful medication as an adjunct to short-term management of moderate to severe psychomotor agitation and in the treatment of agitation and restlessness in the elderly.

2.5.7 References