Summary and Conclusions

Reading epilepsy is a new syndrome characterized by unconsciousness and a generalized grand-mal seizure precipitated only by reading. The patient typically experiences a feeling of movement of the jaw, or actual observable single twitches of the jaw, before the seizure occurs. If reading is discontinued the jaw jerking stops, and the seizure is cut short.

The electroencephalogram is normal, but if the patient reads during the tracing dysrhythmia develops.

The diagnosis is based on the history of reading, usually prolonged, provoking the attack, and by the jaw jerking.

Primary reading epilepsy is to be distinguished from the secondary type. Two cases of the latter and 1 of the former are described.

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MEDICAL PROGRESS

COMPLICATIONS FROM THE USE OF TRANQUILIZING DRUGS*

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TRANQUILIZING drugs, for better or worse, have established a place in medical therapy. Within less than four years after their introduction in general use in this country, many reports have concerned their beneficial effects in a wide variety of emotional and physical disorders. A smaller but rapidly growing number of reports has been concerned with some of their ill effects. The increasing realization of the possible adverse effects of these agents has confirmed the need for close medical supervision of their use.

Excellent reviews have already appeared on the complications of chlorpromazine[1-3] or both chlorpromazine and reserpine.[4,5] This paper reviews the clinically important complications of chlorpromazine, reserpine and meprobamate. These three most widely used tranquilizing drugs have also been the prototypes of other agents of possible clinical usefulness. For purposes of convenience, complications are classified according to general type of pharmacologic effect represented.

Adverse Behavioral Effects

Tranquilizing drugs usually improve disturbed behavior, but occasionally behavior is made worse (Table 1). Somnolence, lethargy and mental retardation are often observed when high doses of any tranquilizing drug are used. More serious symptoms, such as restlessness, insomnia, bizarre dreams and social withdrawal, are usually associated with chlorpromazine or reserpine. In some cases such symptoms precede the appearance of marked excitement, mental depression, feelings of unreality or depersonalization, delusions or hallucinations.[5] These psychotic states should be distinguished from a toxic-confusional state occasionally produced by high-dose regimens of chlorpromazine[1] or reserpine.[5] Increased confusion in arteriosclerotic patients on chlorpromazine has been explained on the basis of diminished cerebral blood flow.[2]

Mental depression has been the most serious adverse effect on behavior because of suicidal attempts or prolonged duration. Reserpine has been most often incriminated as causing mental depression, hypertensive patients being the most commonly affected.[6] Frequently, no previous history of mental or emotional instability can be obtained. Some depressions have been so severe as to require electroconvulsive therapy or prolonged psychiatric treatment. In the present studies, 7 of 19 normal subjects who received daily doses of 1 mg. of reserpine for brief periods reported mental depressions as one of the effects of the drug.

Table 1. *Adverse Behavioral Effects of Tranquilizing Drugs.*

Symptom Group	Agent	Determining Factor
Somnolence Lethargy Mental retardation	Any tranquilizing drug	Dose
Restlessness Insomnia Bizarre dreams Social withdrawal	Chlorpromazine; reserpine.	(?) Patients's personality
Excitement Depression Unreality feelings Delusions Hallucinations	Chlorpromazine; reserpine.	(?) Patients's personality
Toxic-confusional state	Chlorpromazine; reserpine.	Dose
Withdrawal reaction Habituation	Meprobamate	Dose; duration; patient's personality.
?Impaired psychotherapy		

This high prevalence of mental depression in normal subjects and hypertensive patients on small doses of reserpine stands in contrast to the comparatively infrequent reports of depression in schizophrenic patients treated with large doses of the drug.[7] This difference suggests that mental depression may be a

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somatopsychologic phenomenon, contingent upon misinterpretation of disturbed bodily sensations produced by the drug.

Chlorpromazine has been reported as causing mental depression in psychiatric patients or as aggravating existing depressions. However, this drug is rarely used for long periods in the type of relatively normal patients who, on reserpine, may experience mental symptoms for the first time. In this regard, the present experience in the treatment of a group of nonpsychotic tuberculous patients with chlorpromazine has been most illuminating. Ten of 70 patients given daily doses of 300 mg. had appreciable mental changes. In 4, the changes were severe, 2 patients becoming depressed, and 2 becoming agitated. Since the study used a double-blind crossover design, several of these patients did not exhibit symptoms until they had received a prior dose of placebo for three months before starting on the active drug. Except for the changes in mood or psychomotor activity, no psychotic manifestations were present.

The mental confusion produced by high doses of chlorpromazine is found to a lesser degree with small doses. Twenty of 80 normal subjects given 50-mg. doses of the drug by mouth as compared with inert placebos complained of inability to think clearly as well as statistically significant differences in symptoms of tiredness, sleepiness and generally unpleasant feelings.[8] Acute doses of 200 mg. of chlorpromazine in double-blind trials in normal subjects produced as much mental impairment as an equal dose of secobarbital.[9] These findings cast some doubt on the common belief that sedation from chlorpromazine is associated with less impairment of function than that observed with barbiturates. It should be emphasized that with chronic dosage the comparison between the two drugs might have been considerably different.

Such altered states of awareness under tranquilizing drugs raise the question of their interfering with rather than helping psychotherapy. If one regards psychotherapy as a learning process, it is of some interest that both new maze learning and retention of previously learned material were significantly decreased in chlorpromazine-treated rats as compared with untreated controls.[10] On the other hand, normal subjects given meprobamate in 800-mg. doses showed no significant impairment of laboratory measures of ability to drive an automobile.[11] Rats in a maze and normal subjects in a laboratory experiment may have little relevance to psychiatric patients undergoing psychotherapy or driving an automobile. A great need still remains for more studies of possible impairment of nervous and mental functions in patients treated with tranquilizing drugs.

Neither chlorpromazine nor reserpine has proved to be addicting, despite the fact that many patients have received high doses of each drug for prolonged periods. On the contrary, both these drugs have been highly effective in relieving withdrawal symptoms of addiction to alcohol, opiates and barbiturates. Meprobamate given in large doses for prolonged periods has produced withdrawal symptoms in a few cases. This withdrawal syndrome is manifested by tremulousness, gastrointestinal symptoms, mental depression and in some cases convulsions.[12] Such withdrawal reactions occur rarely and have not been observed after administration of the drug in the usual daily doses of 1200 to 2400 mg. Since many patients being treated with meprobamate have past histories of habituation to alcohol or other drugs, care must be exercised not to supplant one kind of addiction with another.

TABLE 2. *Toxic Effects of Tranquilizing Drugs on the Central Nervous System.*

MANIFESTATION	AGENT	DETERMINING FACTOR
Extrapyramidal syndrome	Chlorpromazine; reserpine; proclorperazine.	Dose; duration of therapy; age of patient; type of psychosis.
Seizures	Chlorpromazine; reserpine; promazine.	Dose
Dystonic syndrome (difficulty in swallowing, standing & talking, with bizarre motor signs)	Chlorpromazine; reserpine.	?
Spasms of neck, tongue & pharyngeal muscles	Chlorpromazine; proclorperazine.	Dose
Hyperthermia	Chlorpromazine	Environmental temperature
Hypothermia	Chlorpromazine; reserpine.	?
Central respiratory depression	Chlorpromazine; reserpine.	Electroconvulsive therapy
Myasthenia-gravis-like syndrome Pseudotabes Bulbar-palsy-like syndrome	Chlorpromazine	?
Hyperpyrexia, ocular palsies & decerebrate movements	Reserpine	Previous brain damage
Acute choreo-athetosis	Reserpine	?Previous brain damage
Cerebellar signs	Reserpine	Dose

TOXIC EFFECTS ON THE CENTRAL NERVOUS SYSTEM

The extrapyramidal syndrome produced by both chlorpromazine and reserpine is manifested by the classic signs of the Parkinson syndrome: rigidity; resting tremor; and loss of associated movements, often accompanied by masklike facies, increased salivation and seborrhea (Table 2). Stimulation of the reticular formation in the midbrain by the drugs is the commonly mentioned cause of this syndrome. This neurologic effect appears to be related to dosage, seldom appearing at a dose of less than 300 mg. daily of chlorpromazine or 2 mg. daily of reserpine. Long treatment and advanced age of patients also

predispose toward its occurrence. Patients prone to the syndrome with one drug also manifest it with the other. Combinations of the drugs also increase the appearance of the syndrome. The reported frequency varies considerably, depending on what criteria are used for diagnosis and how carefully the changes are observed.

Many investigators have contended that the extrapyramidal syndrome is positively correlated with psychiatric improvement. They prefer to treat it by adding other drugs (usually benztropine methanesulfonate) without altering the dose of tranquilizing drug. However, no such correlation with psychiatric improvement was noted in a study that found a high rate (40 per cent) of extrapyramidal syndrome but a low prevalence of psychiatric improvement.[13] These observers reported that this syndrome was apparently more frequent in hebephrenic schizophrenic patients, a group ordinarily responding poorly to treatment.

What is most important is the question, Can this toxic sign be harmful? So far, no reports have appeared of permanent neurologic disability, although some patients have taken several months to recover after the drugs were stopped. Neuropathological studies in 2 fatal cases of toxic confusional state from chlorpromazine have revealed neuronal degeneration in the hypothalamus, globus pallidus, subthalamic body and amygdaloid nucleus.[14] Neither patient had clinically manifested an extrapyramidal syndrome. Perhaps there is a point when physiologic changes become pathologic. Since toxic effects on the central nervous system may quickly become permanent, long continuation of these effects can hardly be justified.

Rapid, generalized tremors resembling shivering occur early in the course of reserpine therapy and should not be confused with the extrapyramidal syndrome. However, single case reports of unusual neurotoxic effects have appeared. These include an acute choreo-athetoid syndrome that began after three days of relatively low doses of reserpine for hypertensive brain disease and cleared within two weeks after the drug was stopped and 1 case of transient cerebellar signs after heavy parenteral doses of reserpine. A midbrain syndrome of hyperpyrexia, ocular palsies and decerebrate signs has been described in patients with previous brain damage treated with reserpine.[5] Inability to swallow or speak clearly, inability to walk or stand and occasional choreiform or bizarre movements were noted in approximately 5 per cent of reserpine-treated patients and 4 per cent of those receiving chlorpromazine.[4]

A peculiar motor disorder associated with chlorpromazine therapy is tonic spasms of the neck, tongue and pharyngeal muscles.[2] Syndromes resembling myasthenia gravis, tabes and bulbar palsy have also been observed. In the latter case, jaundice also appeared. However, the efforts to link the extrapyramidal syndrome and chlorpromazine jaundice to hepatolenticular degeneration appear to be on shaky ground. Neither of these complications of chlorpromazine tends to appear together, nor has either much clinical resemblance to Wilson's disease. In fact, the pathologic changes in the liver are considerably different (as pointed out below).

In view of the wide use of chlorpromazine, reports of such bizarre motor effects have been exceedingly rare. I have seen 3 patients with spasms of the muscles of the shoulder girdle and perioral area, spastic torticollis and athetoid movements of the tongue soon after the administration of proclorperazine parenterally in high dosage. It seems probable that this drug is more likely to produce these motor syndromes than chlorpromazine.

Seizures, often occurring for the first time, have frequently been reported in patients receiving reserpine[4,7] or chlorpromazine.[3,4] Like the extrapyramidal syndrome, this complication is directly related to high dosage and is more frequent when the drugs are combined. Eleven of 21 patients receiving high doses of chlorpromazine had seizures, some for the first time.[15] Promazine appears to be even more likely to produce seizures on the basis of early reports.

Hyperthermia, sometimes resembling heat stroke, has been reported as a complication of chlorpromazine therapy, especially during warm weather.[2-4] Neuropathological examination in 1 fatal case showed swelling of neuronal cells, especially in the thalamus and hypothalamus, capillary congestion and distention and petechial hemorrhages.[16] A toxic action on the hypothalamus, perhaps accentuated by environmental temperatures, has been postulated as the mechanism. Hypothermia from chlorpromazine is less common. A severe hypothermic reaction associated with circulatory collapse has been reported on the second day of intramuscular treatment with reserpine. The body temperature dropped to 93-93.8°F., where it remained for several hours.

Untoward reactions have occasionally been reported from a combination of reserpine or chlorpromazine with electroconvulsive therapy. Six cases of prolonged apnea or shock, 1 fatal, followed electroconvulsive therapy given in conjunction with reserpine.[17] Another fatal reaction due to respiratory arrest followed the fourth of a series of electroconvulsions while the patient was on large doses (as high as 15 mg. daily) of reserpine. A prolonged fall in blood pressure was noted in 1 patient given electroconvulsive therapy while receiving chlorpromazine. Speculations about the cause of such reactions include lowered convulsive threshold, central respiratory depression or abolition of compensatory blood-pressure reflexes. It should be remembered that similar reactions were associated with electroconvulsive therapy long before tranquilizing drugs appeared.

A large number of patients have been treated with the combined somatic therapies without ill-effect.

Toxic Effects on the Autonomic Nervous System

Chlorpromazine, reserpine and their congeners differ from previous sedative drugs in their pharmacologic actions on the autonomic nervous system (Table 3). Chlorpromazine has both an anticholinergic action and an adrenergic blocking action. Reserpine, by virtue of its central sympathetic depression, has cholinergiclike effects. Meprobamate has no effect on the autonomic nervous system.

Both chlorpromazine and reserpine reduce blood pressure in most patients receiving large doses. Hypotension usually occurs early in treatment, especially with the parenteral route. Syncope is uncommon, and prolonged shocklike states are rare. Such severe hypotensive states are most often associated with parenteral administration of the drugs in old or debilitated patients. One death after 15 mg. of parenterally administered reserpine was associated with the electrocardiographic demonstration of alternate ectopic beats from multiple foci.[18] Another death that followed chlorpromazine administration appeared to be due to acute renal failure associated with prolonged circulatory collapse.[19] Even as little as four

Table 3. *Toxic Effects of Tranquilizing Drugs on the Autonomic Nervous System.*

Manifestation	Agent	Determining Factor
Hypotensive crises	Chlorpromazine; reserpine.	Parenteral route; age; alcohol.
Activation of peptic ulcer Hematemesis & melena	Reserpine	Increased gastric acid secretion
Fecal impaction	Chlorpromazine	Age; neglect.
Tachycardia Dry mouth Blurred vision Pallor Constipation	Chlorpromazine	Predominantly anticholinergic effect
Nasal congestion	Chlorpromazine; reserpine.	Sympathetic depression
Bradycardia Excessive salivation Cutaneous flushing Vomiting Diarrhea	Reserpine	Predominantly cholinergic-like effect

oral doses of 25 mg. of chlorpromazine to a seventy-one-year-old woman produced a severe hypotensive episode that lasted for thirty-six hours and required intravenous l-nor-epinephrine for effective treatment. Whenever possible, parenteral doses, especially intravenous doses of drug, should be avoided. Likewise, care should be taken when the drugs are administered to elderly patients or those under the influence of unknown amounts of alcohol.

Effects on the autonomic nervous system account for many of the frequent but minor side reactions to chlorpromazine and reserpine. Both drugs produce nasal congestion, but in many other respects, their autonomic effects appear to be opposite. Chlorpromazine causes dry mouth, tachycardia, blurred vision, pallor and constipation, presumably anticholinergic effects. Reserpine causes excessive salivation, bradycardia, generalized cutaneous and mucous-membrane flushing, vomiting and diarrhea, presumably cholinergic effects. The infrequent nausea, heartburn and vomiting produced by chlorpromazine are more probably due to local irritation than to an autonomic action.

Constipation during chlorpromazine therapy may lead to massive fecal impactions. At times, these impactions may be confused with gastroenteritis (vomiting and diarrhea), intestinal obstruction (cramping pain, vomiting and abdominal distention), an obstructed or bleeding ulcer (acute gastric dilatation with coffee-grounds vomitus) or cardiorespiratory affections (aspiration of vomitus, with noisy respirations and some circulatory collapse). This complication must be guarded against by vigilant attention to the patient's bowel movements and frequent digital examinations of the rectum in cases of doubt.

Reserpine appears definitely to activate peptic ulcers.[7] The reasons are clear: the drug increases both the volume and acidity of gastric secretion.[20] For practical purposes, reserpine is contraindicated in patients with a known ulcer history. Patients who complain of recurring digestive symptoms while on the drug merit additional treatment with nonabsorbable alkali and anticholinergic drugs. Hematemesis and melena may also occur during reserpine therapy.[20,21] In some cases this complication has been associated with a demonstrable peptic ulcer. In others, it has been postulated that the source of bleeding had been acute gastric erosions.

Allergic or Toxic Reactions

Obstructive jaundice may occur in 1 or 2 per cent of patients receiving chlorpromazine for a week or more, the great majority occurring in the second to the fourth week of treatment (Table 4). The dose of drug is not related to the frequency or severity of this complication, tending to rule out a toxic origin. Fever, malaise and gastrointestinal symptoms herald the appearance of clinical jaundice, which may be accompanied by pruritus and liver enlargement or tenderness. Numerous histologic studies of liver biopsies taken during the course of jaundice have established a fairly typical histologic picture of periportal infiltration with inflammatory cells (chiefly lymphocytes and sometimes eosinophils), bile plugs in the biliary canaliculi and little or no hepatocellular damage.[22] Occasionally, biliary surgery has been performed on these patients mistakenly. Follow-up liver biopsies of recovered patients have raised the possibility of permanent parenchymatous

liver damage,[23] but examinations of livers of patients who have died from other causes after chlorpromazine jaundice have indicated a course toward healing.[24] Deaths directly attributable to this complication have been rare, most of the fatal cases being complicated by other conditions such as agranulocytosis, heart failure, possible viral hepatitis or cirrhosis and recent surgery.

TABLE 4. *Allergic or Toxic Reactions to Tranquilizing Drugs.*

MANIFESTATION	AGENT	PRINICIPAL CLINICAL FEATURES
Jaundice	Chlorpromazine	1-2% of patients treated for 7 days or more; 80% in 2d-4th wk. of treatment. Prodromal symptoms: fever, malaise & gastrointestinal disturbances. Histologic picture of "allergic cholangiolitis" Self-limited course; usually no residual damage; deaths rare. Successful challenge test (9 of 11) No cross-sensitivity with promazine Hepatocellular damage when treatment continued through jaundice
Agranulocytosis	Chlorpromazine; promazine.	Rare; about 50 cases. Predilection for elderly women 1st-11th wk. of treatment; most in 6th-8th wk. Fever, sore throat & necrotic ulcers Granulocytic arrest of bone marrow ⅓ of cases fatal Challenge test successful (1 case)
Purpura	Chlorpromazine	1 case only Positive capillary fragility; no other bleeding abnormality. Challenge test successful
Dermatitis: Systemic	Chlorpromazine	Itching maculopapular, urticarial petechial, edematous, bullous, & other descriptions 1st-6th wk. of treatment Challenge test usually not successful
Photosensitive		Exposed areas erythematous, edematous & vesicular Any time in course, on exposure to sunlight
Contact		Drug handlers affected Patch tests usually positive; no cross-sensitivity.
Dermatitis	Meprobamate	1-2% of patients Usually immediate; may be delayed. Erythematous, petechial — over pelvic girdle, axillas & dependent parts Systemic symptoms (fever & nausea) Challenge test usually positive
Asthma	Chlorpromazine; reserpine.	Questionable allergy to reserpine
Angioneurotic	Reserpine	1 questionable case

Evidence for an allergic origin of this complication rests chiefly on the reappearance of jaundice on subsequent challenge doses of chlorpromazine. In my study, 9 of 11 patients challenged with the drug had evidence of retained sensitivity for as long as seventeen months after the original episode.[25] No cross-sensitivity with promazine could be demonstrated by the challenge test, suggesting that other phenothiazine derivatives may be used safely in patients with chlorpromazine jaundice.

Not all patients retain their sensitivity, and some may be continued on the drug through an attack of jaundice with no apparent ill-effects. In 2 of my patients treated through an attack of chlorpromazine jaundice (both had carcinoma), post-mortem examination gave definite histologic evidence of toxic hepatocellular changes, despite the fact that in both patients jaundice had cleared despite continuation of the drug. I consider the practice of continued treatment in the face of jaundice to be dangerous.

Serial determination of alkaline phosphatase activity has been proposed as a test for detecting latent or developing cases of jaundice, the findings becoming abnormal before the onset of clinical jaundice. Screening patients by this method is hardly suitable for widespread application. I prefer to rely on carefully taken daily temperature during the first month of treatment, with especially close attention to clinical signs and laboratory tests in patients in whom fever develops. In my experience, early detection of the complication has made for a relatively mild course of the disorder.

Probably no more than 50 cases of chlorpromazine agranulocytosis have appeared.[26] In a review of 28 reports, a number of clinical features have been noteworthy. With comparatively few exceptions, most of the patients have been women, usually past fifty years of age. Although cases have occurred as early as a week and as late as eleven weeks after the beginning of treatment, the vast majority occur in the sixth to the eighth week. Neither the daily dose (which has varied from 50 to 600 mg.) nor the total dose (from less than 3 gm. to more than 14 gm.) has been an important factor. Fever and sore throat have been almost uniformly present, occasionally with necrotic skin lesions. Other evidence of allergy, such as jaundice, urticaria or other skin eruption, was noted concomitantly or before the onset of agranulocytosis in several cases. Challenge with the drug reproduced agranulocytosis in 1 case, but not in another. Bone-marrow examinations have almost always shown maturation arrest of the granulocytic series, usually without other abnormality. About a third of the reported cases have been fatal. A single reported case of agranulocytosis due to promazine resembled that of chlorpromazine in most respects.

Careful clinical observations for untoward symptoms or signs and frequent leukocyte counts (at least once weekly) are usually recommended during the crucial first eight weeks of treatment. Since transient leukopenia that does not progress to agranulocytosis is sometimes observed early in treatment, decision about continuing may be difficult. Likewise, transient leukopenia may occur after several months of treatment. I have observed several such patients who

continued to receive the drug without progressing to agranulocytosis or who showed no depression of leukocyte count when the drug was resumed after interrupted treatment.

A single case of purpura from chlorpromazine has been reported.[27] This complication occurred on the twenty-seventh day of treatment and was associated with a positive capillary-fragility test. Platelet count, bone marrow and bleeding time were all normal. Purpura recurred thirty-three days after the drug was started again.

Dermatitis associated with chlorpromazine therapy may occur in 3 to 12 per cent of patients. Several types of reactions are observed: systemic sensitization manifested by generalized eruptions variously characterized as maculopapular, urticarial, petechial, edematous, bullous and others; photosensitivity, with actinic dermatitis; and contact sensitivity in handlers of the drug.

The systemic reaction usually occurs early in treatment, from the ninth to the thirty-seventh day.[28] Clearing promptly with cessation of therapy, it does not commonly recur when the drug is started again. Photosensitive dermatitis has been the most common in my experience in California. The diagnosis is easy: the rash is distributed over the scalp, face, neck, dorsa of the hands and other exposed parts. In its mildest form it resembles sunburn, but more severe cases are associated with much edema and vesicle formation or petechiae. The exposed portions of the conjunctivas are also reddened. The remedy is obvious. In most particulars, chlorpromazine-induced photosensitivity resembles that of phenothiazine. Contact dermatitis, usually on the hands of nurses or other hospital personnel dispensing the drug, is a bothersome problem. Remarkably little drug may produce eruptions, 1 case in a dentist being ascribed to the amount of drug in the saliva of his patients. Patch tests to chlorpromazine are usually positive, but no crossreactions with other phenothiazine derivatives have been found.[29]

Skin rashes from meprobamate occur in approximately 2 per cent of patients, usually from the initial doses of the drug. Urticarial eruptions may be associated with fever. Itching, erythematous, petechial eruptions may be associated with nausea and faintness, chills and fever and syncope. These eruptions show a predilection for the pelvic girdle, breast area, axillas and dependent parts. They are frequently reproduced by challenge doses of the drug.[30] Though most such reactions occur in response to a single dose, a few patients apparently acquire sensitivity after seven to sixteen days of treatment.

Reserpine is not highly allergenic. No cases of jaundice or agranulocytosis have been attributed to this drug. Only one report of questionable angioneurotic edema from reserpine has appeared. Reserpine and chlorpromazine may both cause exacerbation of asthma.[4] It is not certain that this symptom is truly an allergic manifestation of reserpine sensitivity; the drug may precipitate latent bronchial asthma by virtue of its cholinergiclike action.

Metabolic or Endocrine Effects

During treatment with chlorpromazine or reserpine, some patients show remarkable weight gains (Table 5). I have observed weight gains of as much as 18.1 to 27.2 kg. (40 to 60 pounds) within a few months of the beginning of treatment. In part, the increased weight results from increased appetite, probably a hypothalamic effect. In addition, patients are less active physically when large doses of the drugs are used.

Table 5. *Metabolic or Endocrine Effects of Tranquilizing Drugs.*

Manifestation	Agent	Mechanism
Weight gain	Chlorpromazine; reserpine.	Increased appetite; decreased activity.
Edema	Reserpine	Polydipsia; water retention.
Lactation Gynecomastia Menstrual irregularity Increased fertility	Chlorpromazine; reserpine.	Pituitary-gonadal effects?
Impotence (in men) Increased sexual desire (in women)	Chlorpromazine; reserpine.	?

Edema, usually transient, may occur early in the course of treatment with both drugs. As many as 20 per cent of psychiatric patients receiving reserpine are reported to show edema.[5] Reserpine or other Rauwolfia alkaloids used for the treatment of hypertension may produce enough fluid retention to precipitate frank congestive heart failure. Nine psychiatric patients treated with daily doses of reserpine up to 3.3 mg. for three weeks showed an increase in the plasma portion of the hematocrit, a fall in hemoglobin level and serum sodium and an increase in weight.[31] These observations suggest retention of water rather than salt. Polydipsia has been noted in patients on chlorpromazine and reserpine, but polyuria usually accompanied the increased fluid intake.[1,5]

Lactation has been reported in as many as 12 per cent of women during chlorpromazine therapy.[1] Both lactation and gynecomastia have been observed during reserpine therapy.[5] Other possible effects on the hypothalamicopituitary system are menstrual irregularity and increased fertility. Women are said to experience increased sexual desire whereas men complain of impotence. Either drug may have these effects.[1,5] Neither of these disquietingly disparate effects is easily explained on a physiologic or pharmacologic basis. In psychiatric patients, such complaints must be evaluated cautiously.

Miscellaneous Adverse Effects

Hypostatic pneumonia and formation of decubitus ulcers have been reported as complications of chlorpromazine and reserpine therapy (Table 6). Certainly, oversedation to the point of immobility can produce both complications. Their occurrence in quantity is more a reflection on the nursing care and therapeutic practices of the hospital than it is evidence of toxic effects of the drugs.

Table 6. *Miscellaneous Adverse Effects of Tranquilizing Drugs.*

Manifestation	Agent	Determining Factor
Hypostatic pneumonia Trophic ulcers	Chlorpromazine; reserpine.	Dose; age; neglect.
"Silent" myocardial infarctions	Chlorpromazine	Diminished pain sense Tachycardia Hypotension
Premature ventricular contractions	Reserpine	?
Complications during anesthesia	Chlorpromazine; reserpine.	Blocked pressor reflexes
Arthralgia	Chlorpromazine; reserpine.	?

Psychotic patients are notoriously stoical about pain. When one adds drugs that diminish perception of pain still further, diagnosis of some illnesses manifested by pain may be missed or delayed. I have been impressed with the lack of symptoms in some patients with myocardial infarctions during chlorpromazine therapy. These "silent" infarctions appear to be more common since the wide use of tranquilizing drugs. One report of a sudden fatal coronary thrombosis has raised the question of whether myocardial infarction may actually be precipitated by the hypotension and tachycardia resulting from chlorpromazine administration. On the other hand, cerebral infarcts appear to be no more frequent in patients on this drug than before.

Four cases of premature ventricular contractions during treatment with whole-root extracts of Rauwolfia suggested a potential danger of producing cardiac arrhythmias in some patients.[32] I have observed occasional patients with premature ventricular contractions during reserpine administration. In 1 case the contractions disappeared with continued treatment at slightly reduced doses. In another, short runs of ventricular tachycardia were demonstrated electrocardiographically. The arrhythmia was controlled by oral administration of procaine amide and did not return when the effect of reserpine had passed. More frequently, I have observed the opposite effect. Ventricular, nodal and supraventricular premature contractions occurring before reserpine therapy have subsided after treatment has begun. Paroxysmal supraventricular tachycardia and atrial fibrillation have also responded quickly to reserpine administration. Most of these responses were probably due to the combination of sedative and cholinergic actions of the drug. In patients with a known tendency to ventricular arrhythmias the drug should probably be used with some caution.

The danger of hypotensive reactions during surgical anesthesia has been emphasized in the use of both drugs. Sixteen of 50 patients on prolonged Rauwolfia therapy for hypertension became hypotensive during general anesthesia.[33] The recommendation was made that, whenever possible, Rauwolfia compounds be discontinued well in advance of elective surgical procedures. Nine severe hypotensive reactions, 1 fatal, occurred during the use of spinal, epidural and celiac-plexus block in patients receiving chlorpromazine.[34] These reactions have followed as little as two 25-mg. doses of the drug by mouth. It has been suggested that patients, their physicians and the records be consulted for possible chlorpromazine administration before any of these anesthetic procedures are undertaken.

Muscle aching and arthralgia have been noted from both drugs.[2,5] Since both chlorpromazine and reserpine seem to act on midbrain structures, analogy has been made to the early stages of the hydralazine syndrome, which is thought to be possibly the result of pharmacologically altered midbrain function. I have carefully studied patients with such arthralgic symptoms during drug administration. In every case in which systemic symptoms or objective joint findings accompanied the arthralgia, the disorder could be explained on the basis of acute gout or rheumatic fever, or chronic rheumatoid or degenerative arthritis. Preparations for demonstrating L.E. cells in these patients, and in asymptomatic patients who had received both drugs for long periods at high dosage levels, were uniformly negative.

One possible complication of tranquilizing drugs that has often been mentioned is the possibility of "brainwashing" or "will control." In none of the voluminous medical literature concerned with these drugs has such a proposal been seriously made, nor has any evidence for such a possibility been presented. For a long while, the classic story of a fallen woman has begun with an alcoholic episode. If the story is now changed to include a tranquilizing drug instead of gin, there is still no more reason than before to believe that either is the primary cause of the behavior. Social and psychologic influences on human behavior are still more potent than any tranquilizing drug currently known.

Discussion

Every potent pharmacologic agent may produce some complication. The mere fact that tranquilizing drugs may produce complications should be no deterrent to their proper use when indicated. In every case, the known risk of using the selected drug must be weighed against the expected benefit.

One chance in a thousand of agranulocytosis from chlorpromazine (certainly the highest possible risk for this complication) does not contraindicate this drug for the treatment of severely ill mental patients. However, one may hesitate to treat patients with mild anxiety or vomiting, especially since other effective agents with less risk are available. Nor is the risk of 2 cases of jaundice in 100 treated patients a deterrent to use of chlorpromazine in chronically hospitalized patients, but it is when one is treating the family breadwinner.

Likewise, the low risk of severe mental depressions in hypertensive patients treated with Rauwolfia alkaloids may be tolerable if a good therapeutic response has been maintained. If not, continuation of an inadequate treatment would not justify the hazard. The same reasoning may be applied to the risk of exacerbation of duodenal ulcer by these compounds.

To some extent, merely to be forewarned of the possibility of a complication is enough. Most of the allergic reactions to the drugs occur within a fairly narrow time range, indicating a period for particular caution to be exercised. To know ahead that some patients may become depressed, instead of experiencing the euphoria pictured in the drug advertisements, is a great aid in forestalling a serious depressive episode. The early recognition of most of the major complications of these drugs remains the best insurance against irreversible or fatal effects.

Many of the complications noted from one drug in a class (such as chlorpromazine among the phenothiazine derivatives) will appear to some extent in its congeners. Already some phenothiazine derivatives under investigation have been found to be as likely as or more likely than chlorpromazine to have extrapyramidal effects and to cause seizures, hypotensive crises and agranulocytosis. Some phenothiazines apparently are not as likely to produce jaundice or other allergic reactions. Still others may have completely unexpected effects, such as pigmentary degeneration of the retina.[35] Past experience with drugs of the same class may be helpful, but not entirely reliable, in indicating expected complications.

Conclusions

The tradition "to do no harm" has long dominated medical therapy, and it is well that it has. However, therapeutic paralysis has never done patients much good. Physicians will do less than they can if they are unwilling to ask their patients to take some treatment risks. What they must do is to know as much as they can about the risks and benefits of a given treatment. Only then will they be able to use the tranquilizing drugs (or any others) to their fullest potential.

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