THE PSYCHOPHARMACOLOGICAL TREATMENT OF SCHIZOPHRENIA

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Schizophrenia is the most destructive of all functional psychoses. Its lifetime incidence of 1 percent, the facts that its onset tends to be in young adulthood and its course chronic, all combine to make it one of the major mental health hazards of our time. The annual cost of schizophrenia to the United States has been estimated as being close to 20 billion. (Gunderson and Mosher, 1975). It is evident that its prevention and the treatment and rehabilitation of schizophrenic patients command high priority among all national and individual health problems.

Of all current therapeutic approaches to schizophrenia, pharmacotherapy of this disease can probably not be matched today by any other treatment in terms of effectiveness, reliability, availability and ease of administration, presenting at the same time a relatively low risk to the patient. There is also impressive evidence of the consensus of opinions on the indications for neuroleptic treatment of schizophrenic patients, a consensus that in one sample of British psychiatrists reached 96 percent. (Cawley, 1967; Willis and Bannister, 1965).

Need for Accurate Diagnosis

The appropriate pharmacotherapy of schizophrenic patients depends greatly on an accurate diagnosis. Only neuroleptic drugs (major tranquilizers) can successfully suppress truly schizophrenic symptoms. Minor tranquilizers are ineffective, and antidepressants may aggravate schizophrenic psychopathology. On the other hand, psychiatrists in North America often use an extended concept of schizophrenia in their diagnosis, including patients who would be diagnosed as suffering from affective

disorders in Great Britain and who might respond better to antidepressants or lithium than to neuroleptics. It is useful to remember that the mere presence of hallucinations or delusions in a patient does not spell a diagnosis of schizophrenia, since these symptoms also occur not infrequently in affective psychoses.

In recent years, Schneider's formulation of the first-rank symptoms, Feighner's operational criteria of the diagnosis of schizophrenia and the findings of the World Health Organization's International Pilot Study of Schizophrenia have contributed greatly toward making the diagnosis of schizophrenia a more reliable procedure, both for research purposes and for systematic treatment.

Three Different Types of Symptoms

The treating physician should remember that schizophrenic patients may present three different types of psychopathology, namely:

1. positive symptoms, e.g. hallucinations and delusions;
2. negative symptoms, e.g. apathy and cognitive impoverishment;
3. Disturbances of social interaction, e.g. withdrawal and general loss of social competence.

Pharmacotherapy is most effective in suppressing positive symptoms, much less effective in dealing with negative symptoms and almost ineffective against disturbances of social interaction.

Different Clinical Indications

There are three principal indications for the use of neuroleptics (or antipsychotics) in the treatment of schizophrenia:

1. as the main therapeutic agent in acute schizophrenic episodes;
2. as a major factor in the control and management of chronic schizophrenic conditions;
3. as maintenance treatment for schizophrenic patients in remission, in whom a potential relapse of the psychotic state must be prevented.

Prior to 1952 there were no drugs that could effectively control specific psychotic symptoms, such as hallucinations, delusions or disorders of thinking. Nor was there an effective way of preventing recurrences of psychosis in patients who were in remission. Today, clinicians have about 20 different neuroleptic drugs to choose from in the United States, and many more are under investigation. Besides reserpine, which is only rarely used as a neuroleptic today, the clinician can now select between 14 phenothiazines, 2 thioxanthenes, 1 butyrophenone, 1 dihydroindoline and 1 dibenzoxazepine. Altogether more than 10 different chemical structures with neuroleptic properties are presently under investigation.

Which, then, are the factors that determine the therapists' choice of any particular neuroleptic? They are mainly these: the types of side-effects each drug produces, its dose-related therapeutic potency, its mode of administration and its cost. In equivalent doses practically all neuroleptics produce the same therapeutic effects. Whatever slight differences in their therapeutic activity might exist, are only of statistical and not of clinical significance for the treatment of individual patients (Schooler et al, 1971; Galbrecht and Klett, 1968; Goldberg, 1968).

There is, for example, no good evidence that a "depressing" drug, like chlopromazine (Thorazine) produces better results in excited patients, while withdrawn or stuporous patients will respond better to a "stimulating" drug, like trifluoperazine (Stelazine) (Marks, 1963; Platz et al, 1967). Possible exceptions to this general rule of therapeutic equivalence of all neuroleptics may be the slight antidepressant effect of thioridazine (Mellaril) and the mild activating effect of thiothixene (Navane) that have been reported. (Gardos and Cole, 1973).

As in any area of therapeutics, there are always individual patients who respond better to one drug than to another, but these tend to be idiosyncratic exceptions. Of course, certain patients are more susceptible to one type of side effect than to another, and it is therefore recommended that every clinician familiarize himself with at least four different neuroleptic drugs. He may choose between the three types of phenothiazines, i.e. the aliphatic, the piperidine and the piperazine derivatives, two thioxanthenes, a butyrophenone, a dihydroindole and a dibenzoxazepine. If a patient develops a hypersensitivity to one neuroleptic drug, it should be replaced, preferably by a neuroleptic belonging to a different chemical class.

Different Pharmacological Effects

The typical side effects of the various neuroleptics can be briefly described as follows: aliphatic phenothiazines, e.g. chlorpromazine, (Thorazine), most frequently produce drowsiness and autonomic side effects; piperazine derives, like perphenazine (Trilafon), produce less drowsiness and fewer autonomic but more extrapyramidal side effects, and they are more potent, milligram per milligram; piperidine derivatives, like thioridazine (Mellaril), tend to produce

drowsiness and autonomic side effects, similar to the aliphatic phenothiazines, but fewer extrapyramidal effects. Of the thioxanthenes, chlorprothixene (Taractan) resembles chlorpromazine (Thorazine), and thiothixene (Navane) resembles piperazine phenothiazines chemically and in its effects. The butyrophenone haloperidol (Haldol) is very potent as far as dosage is concerned and causes few autonomic but intense extrapyramidal side effects. The dihydroindolone compound molindone (Moban) and the dibenzoxazepine loxapine (Loxitan) resemble the piperazine phenothiazines in action and dose requirements. (Lehmann, 1974).

Action Mechanisms

No definitive explanation for the antipsychotic effects of neuroleptic drugs is available at this time. However, there are several theories, and they are probably not far off the mark.

It has long been established that neuroleptic drugs reduce CNS arousal through inhibition of the ascending reticular formation. This action is either the result of or a condition for a restriction of perceptual input which in schizophrenic patients seems to be excessive, in that the patient is not capable of processing all incoming information. The resulting "jamming" of associational processes may then lead to psychotic decompensation (Lehmann, 1966).

The restriction of perceptual input and the partial deactivation of the CNS are probably related to the sympatholytic action of most neuroleptic drugs, an action that seems to be mediated through the blocking of catecholamine neurotransmitters. More specifically, it has recently been demonstrated that all drugs with established antipsychotic action block dopaminergic

receptor sites in neurons of ventral-tegmental areas in the brain that project to the limbic system. (Creese et al, 1976; Snyder, 1974; Sedvall et al, 1974; Matthysse, 1974; Bunney and Aghajamian, 1974; Crow and Gillbe, 1973; Carlsson and Lindquist, 1963).

In addition, neuroleptic drugs may have an energy-sparing action that manifests itself in increased levels of the high-energy phosphate ATP. The final common path of all these effects may be an interference with cell membranes (Guth, 1964) and thus with the exchange of electrolytes that are essential for neuronal functioning and nervous conduction.

Antipsychotic Effectiveness

Clinicians had realized quickly that the new neuroleptic drugs were in a pharmacological class by themselves and that they were uniquely effective in controlling psychotic symptoms, but it took about 10 years and several large-scale controlled studies to establish the antipsychotic effectiveness of the neuroleptic drugs beyond any reasonable doubt. The key studies were carried out by the Veterans Administration in 1960 (Casey et al) and by the National Institute of Mental Health in 1964.

Later, a survey of more than 100 studies revealed that phenothiazines had proved to be superior to placebo in practically all cases where they had been administered in adequate does, i.e. at least 500 mg/day of chlorpromazine or its dose equivalents. The few studies where the drug had been no better than placebo were early clinical trials, undertaken before adequate dose levels had been determined (Klein and Davis, 1969).

The superiority of neuroleptic pharmacotherapy over other physical treatments, e.g. insulin-induced coma and electroconvulsive therapy, has also been established by several investigators. (Heinrich et al, 1972; May, 1968; Kelly and Sargant, 1965).

Similarly, comparisons of the results of individual psychotherapy, group psychotherapy and milieu therapy as single treatments with those of neuroleptic drug treatment in schizophrenic patients demonstrated that the greatest sustained improvement occurred with pharmacotherapy (Grinspoon et al, 1968; May, 1968). However, there is also evidence that a combination of psychotherapy or other social therapies with pharmacotherapy may be more effective than pharmacotherapy alone, notably so during the rehabilitation and maintenance phases of treatment, after the acute psychotic symptoms have abated. (Hogarty et al, 1973; Borowski and Tolwinski, 1969).

Unfortunately, the dramatic success of the neuroleptic drugs in suppressing psychotic symptoms and in preventing their recurrence has misled many people - including physicians, and even psychiatrists - to believe that these substances could cure schizophrenia. Nothing could be farther from the truth than such a sanguine and simplistic belief. Neuroleptic drugs can no more cure schizophrenia than insulin can cure diabetes or digitalis heart disease. The facts are, of course, that no agent or procedure may be expected to cure any disease unless it removes its known cause - and the cause of schizophrenia is still unknown. As long as we do not know its cause, we may not reasonably expect to find a cure for it. Nevertheless, it is no small merit for a treatment to provide as valuable therapeutic control over a patient's symptoms as do insulin, digitalis or the neuroleptic drugs. Some day we may discover the primary cause or causes of the schizophrenias, and then we may have a good chance of finding a basic cure for them. In the meantime we will have to use the best combinations of

therapeutic approaches - of a symptomatic, corrective and compensatory nature - that we have available to combat schizophrenia; and the most powerful single factor in an integrated therapeutic program of this disease - particularly during its acute, florid stages - is today the pharmacotherapeutic approach.

Preventing Relapses

When a schizophrenic patient has recovered from his acute symptoms he remains at risk for a relapse. How great is this risk? Several reliable studies have indicated that it is at least twice as great for patients who do not continue to take neuroleptic medication after their symptoms have remitted than it is for those who continue on neuroleptic maintenance treatment. One of the best controlled recent studies reported a 72.5 percent relapse rate, after one year, in schizophrenic patients on placebo, but only 32.0 percent relapses in those remitted schizophrenics who were taking chlorpromazine, ~~(Thorazine)~~. Thirty percent of the patients on placebo did well for a period of 10 months and then suddenly relapsed without having given any warning. Had all the patients on active drug therapy really taken their medication regularly, the investigators felt that their relapse rate would have been even lower, perhaps 20 percent or less (Hogarty et al, 1973).

Other investigators have found no significant differences between drug and placebo groups of patients in the control of symptoms and prevention of relapse (Letemendia and Harris, 1967). It must be noted, however, that these patients were residing in a hospital, while the other study was carried out with patients living in the community where the individual is not shielded against life events and stresses. That environmental factors encountered in the community are important contributors to the risk of relapse has been demonstrated

by Brown et al (1972; 1968) who also showed that neuroleptic drugs in schizophrenic patients were among the most powerful protective agents against noxious social stresses.

While it is true that possibly 30 to 50 percent of former schizophrenic patients on maintenance treatment do not need to take their medication and would not relapse without it, there is unfortunately no way yet of telling which of the patients would remain well even without maintenance (Brown and Bleuler, 1972; Davis, 1975; Gardos and Cole, 1976) treatment. The clinician has to make a decision whether to embark on a maintenance regime of possibly indefinite duration, with its attendant risk of eventual toxic complications, or to accept the risk of letting the patient have another psychotic breakdown.

Non-Compliance

Non-compliance of patients on maintenance treatment is a troublesome problem with schizophrenic patients in remission, just as it is in patients suffering from affective disorders or from hypertension. A high proportion of patients, estimated to range from 30 to 50 percent, are unreliable drug takers. Socially isolated patients with a poor educational background, who are hostile in their attitude, are particularly high-risk defaulters. The physician can improve the situation if he maintains an interested, positive attitude, simplifies the treatment regime as much as possible, ~~e.g. by prescribing once a day medication,~~ and keeps the patient under close supervision by arranging for regular after-care visits to the clinic or office (Blackwell, 1973; DiMascio, 1970).

It is an old clinical experience that schizophrenic patients may show some deterioration after having suffered repeated relapses. Even if they again become symptomfree, they may develop personality defects, lose some of their social skills and begin to go down on the socio-economic ladder. This is only one of the reasons why one should take every

reasonable precaution against the recurrence of a schizophrenic attack.

Dosage and Mode of Administration

Ideally, plasma levels of neuroleptics should be used as indicators of the drugs' bioavailability and as guides to clinical treatment. But the determination of plasma levels of neuroleptic drugs is still so complicated that this procedure is not yet available for routine clinical purposes, and the reported correlations between plasma levels and clinical effectiveness of neuroleptic drugs have not been impressive until now. (Bergling, 1975; Rivera-Calimlim et al, 1973; Curry et al, 1970). It is known that wide inter-individual variations of plasma levels exist in response to identical doses. In connection with this, Curry (1976) has recently proposed an interesting explanation for the puzzling observations that schizophrenic patients treated in Europe required only a fraction of the dose required of the same neuroleptic for patients treated in North America. He points out that the plasma level yield of chlorpromazine of an oral dose given to patients in the U.K. was three times that of patients in the U.S.A. He thinks that this difference relates to differences in gastrointestinal functions, because the difference in plasma level yield disappears when the drug is administered parenterally.

One study has shown that schizophrenic patients who had not responded to oral chlorpromazine had significantly lower plasma levels of the unmetabolized drug following oral administration than after an intramuscular injection. (Adamson et al, 1973). Other investigators have found that poor responders to chlorpromazine had higher levels of the inactive metabolite chlorpromazine sulphoxide in their plasma and cerebrospinal fluid than good responders, who had higher levels of the active metabolite 7-hydroxychlorpromazine (Axelsson et al, 1975; Mackay et al, 1974; Sakalis et al, 1973; Sakalis et al, 1972).

For clinical purposes it may be assumed that parenterally administered neuroleptics are twice or three times as effective as the same dose given orally. Liquid oral medication is to be preferred over tablets when there is reason to believe that a patient may only pretend to swallow his pills, while he actually conceals them in his mouth until he can discard them when he is no longer observed.

It has already been mentioned that adequate daily doses of neuroleptics are in the range of 300-500 mg of chlorpromazine or its dose equivalent, at least for acute patients. If a patient does not respond well, his dose may have to be raised to 1000 mg/day or higher.

One review of schizophrenic patients' records admitted to a mental hospital over a 3-year period, revealed that most of the patients had been treated with doses of neuroleptic drugs below the optimal level, with the result that only those patients improved who would have been expected to remit spontaneously without treatment (Hartmann and Mueller, 1974).

Since the toxicity of neuroleptic drugs is low, it is a good rule of thumb in the early stages of treating a schizophrenic patient to exceed the minimal required dose rather than to remain below it. In the elderly, however, more caution is indicated, and doses in general, but particularly at the beginning of treatment, should be one half or one third of those used in younger adults.

The sequence of symptomatic responses to neuroleptic drugs may serve as a guide to dosage. When adequate doses are prescribed, the symptoms belonging into the category of <u>arousal</u> tend to improve first, and usually within two weeks, e.g. psychomotor excitement, irritability and insomnia. <u>Affective</u> symptoms, e.g. anxiety, depression, and social

withdrawal respond next, as a rule after two to four weeks. The last symptoms to disappear are those related to perception and cognition, e.g. hallucinations, delusions and thinking disorder; they may take six to eight weeks. If improvement in these areas of functioning has not occurred within the expected periods of time, the neuroleptic dose prescribed was probably inadequate. (Lehmann, 1966).

Dose requirements for the management of chronic patients are usually lower, and maintenance treatment is often successful with daily doses as low as 100 mg. or even less, of chlorpromazine or its equivalent.

One mode of administration that has unique and import features is the injection of long-acting neuroleptics e.g. fluphenazine (Prolixin) enanthate or decanoate. These preparations, once injected intramuscularly, remain active over a period of about two weeks and thus may circumvent a patient's non-compliance, since he has to come to the clinic or office only once every two weeks instead of having to take his medication himself every day. Other neuroleptic drugs that remain active for even longer periods of time, as well as long-acting drugs that may be taken orally once a week, are currently under investigation.

Polypharmacy

Most neuroleptics can be safely combined with other medications. One exception is the simultaneous administration of phenothiazines, tricyclic antidepressants and antiparkinsonism drugs. Any two of them might be given together, but combining all three may become dangerous for some patients because of the synergistic effects resulting from the anticholinergic action of each of these substances (Warnes et al, 1967).

Neuroleptics may safely be combined with tricyclic antidepressants when schizophrenic patients develop depressive symptoms, but there is rarely any reason for the simultaneous prescription of two or more neuroleptic drugs or of a neuroleptic with a minor tranquilizer, unless the latter is employed for its anticonvulsant properties.

There is at least one report that lithium in combination with haloperidol (Haldol) caused serious complications. (Cohen & Cohen, 1974). On the other hand, a recent controlled trial with a combination of lithium and various phenothiazines in 22 chronic schizophrenic patients who had not responded to the neuroleptics alone, was successful in 10 of these patients. (Small et al, 1975).

Adverse Reactions and Complications

Although the toxicity of neuroleptic drugs is low and their therapeutic margin wide, they have a broad range of side effects. Most of these are uncomfortable but not serious, and many can be successfully dealt with by simple reduction of the dose of the offending drug or, as in the case of extrapyramidal effects, by the added administration of other drugs.

The many side effects of neuroleptic drugs are so well known that they will not be described here, but they must always be carefully considered and discussed with the patient when they appear. It may be wise to warn the patient in anticipation of their possible occurrence, so that he may be reassured in advance.

Only 30-50 percent of patients on neuroleptic drugs develop extrapyramidal symptoms, and it has now been established that it is good practice <u>not</u> to prescribe antiparkinsonism medication routinely for patients on neuroleptics. Anti-parkinsonism drugs should only be given when extrapyramidal

symptoms have actually occurred. Even then they should be tentatively discontinued after one or two months, since in many cases extrapyramidal symptoms may not reappear once the antiparkinsonism drugs have been withdrawn. (Pecknold et al, 1971; DiMascio and Demirgian, 1970).

A serious complication of neuroleptic treatment is tardive dyskinesia. This extrapyramidal syndrome occurs in about 10-~~15~~ 20 percent of patients who have been exposed to long-term treatment with neuroleptics. (Hollister, 1967; Guttmacher et al, 1970; Simpson, 1975) It is most likely to occur in elderly patients who have received large cumulative doses of neuroleptics and is characterized by involuntary movements of the oral region of the face, mostly of lips and tongue, and may be associated with chorea-like movements of other muscle groups.

In contrast to the drug-induced extrapyramidal symptoms that often appear within the first two months of neuroleptic treatment, respond to antiparkinsonism drugs and disappear when the neuroleptic is withdrawn, tardive dyskinesia rarely develops before 1 year of neuroleptic therapy, does not respond to antiparkinsonism drugs and cannot be reversed by discontinuing the neuroleptic medication.

No reliable treatment for this condition is known at the present time,* ~~although~~ some relief may often be obtained by increasing the neuroleptic medication that is responsible for the complication, since the same drugs that cause the syndrome are also capable of masking its manifestations. There is some reason to believe that periodic interruptions of long continued neuroleptic treatment, for short periods of time, may be helpful in preventing or delaying the development of this complication. Such regular "drug holidays" are now recommended by most clinicians. Patients on long-term neuroleptic therapy may, for instance, stop the medication over the weekend.

* although experimental treatment with cholinergic drugs and, more recently, with l-Dopa have produced some promising results. (Cohen, 1975; Friedhoff, 1977)

H. In most cases this will not interfere with the drugs' therapeutic or preventive action, but it will reduce its cumulative dose.

Common Errors

Finally, here are the errors most commonly committed by physicians in the pharmacotherapy of schizophrenia:

1. Acute patients are treated with inadequate doses that are kept too low because the physician is afraid - without sufficient reason, except in the elderly - of toxic effects, and he mistakes ordinary side effects for toxic complications.

2. Antiparkinsonism drugs are prescribed routinely in order to prevent extrapyramidal symptoms, instead of waiting to see whether they will actually appear and prescribe them only when needed.

3. More than one neuroleptic drug is prescribed at one time. In almost every care this will be unnecessary polypharmacy.

4. If the patients' response is unsatisfactory, the neuroleptic drug is changed for another one instead of adjusting (usually increasing) the dose or simply waiting a little longer. It is unlikely that one neuroleptic will turn out to be significantly more effective than another.

5. In treating chronic patients the physician frequently fails to check periodically whether

the patients' dose is still optimal. The patient might require less or more medication; sometimes he may be doing just as well - or, at least, not any worse - without any medication. Such checks should be made every 6 months or, at least once a year.

6. The patients' medication is given in multiple daily doses instead of once or, at most, twice a day. Multiple daily doses are only justified in very acute or excited patients whose dose still needs to be titrated and in whom tissue saturation has not yet been achieved. As soon as possible one should always aim at once-a-day medication, preferably taken at bedtime.

7. Long-term medication, for instance during maintenance treatment, is prescribed for continuous use-instead of interspersing it with periodic short-term interruptions ("drug holidays")- thus increasing the risk of tardive dyskinesia.

BIBLIOGRAPHY

Adamson, L., Curry, S.H., Bridges, P.K. et al. Fluphenazine decanoate trial in chronic in-patient schizophrenics failing to absorb oral chlorpromazine. Dis. nerv. Syst. 34 (4): 181-191, 1973.

Axelsson, S., Jönsson, S., and Nordgren, L. Cerebrospinal fluid levels of chlorpromazine and its metabolites in schizophrenia. Arch. Psychiat. Nervenkr. 221 (2): 167-170, 1975.

Bergling,R., Mjörndal, T., Oreland, L. et al: Plasma levels and clinical effects of thioridazine and thiothixene. J. Clin. Pharmacol. 15(2): 178-186, 1975.

Blackwell, B. Drug deviation in psychiatric patients. In: Ayd, F.J., Jr. (ed.), The Future of Pharmacotherapy New Drug Delivery Systems. Baltimore: International Drug Therapy Newsletter, 1973, pp. 17-31.

Borowski, T., and Tolwinski, T. Treatment of paranoid schizophrenics with chlorpromazine and group therapy. Dis. nerv. Syst. 30: 201-202, 1969.

Brown, G.W., and Birley, J.L.T. Crises and life changes and the onset of schizophrenia. J. Health Soc. Beh. 9: 203, 1968.

Brown, G.W., Birley, J.L.T., and Wing, J.K.: Influence of family life on the course of schizophrenic disorders: a replication. Brit.J. Psychiat. 121: 241, Sept.1972.

Bunney, B.S., and Aghajanian, G.K.: Differentiation between neuroleptic antipsychotic properties and side effects by subgroups of dopaminergic neurons. Psychopharmacol. Bull. 10 (4): 17-18, October 1974.

Carlsson, A., and Lindquist, M. Effect of chlorpromazine and haloperidol on the formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol. Toxicol. 20: 140-144, 1963.

Casey, J.F., Bennett, I.F., Lindley, C.J. et al. Drug therapy in schizophrenia: a controlled study of the relative effectiveness of chlorpromazine, promazine, phenobarbital and placebo. Arch. Gen. Psychiat. 2: 210-220, 1960.

Cawley, R.H. The present status of physical methods of treatment of schizophrenia. In: Coppen A., and Walk, A. (eds.), Recent Developments in Schizophrenia. Ashford: Headley Brothers Ltd., 1967,

Cohen, W.J., and Cohen, N.H. Lithium carbonate, haloperidol, and irreversible brain damage. JAMA, 230(9): 1283-1287, December, 1974.

Creese, I., Burt, D.R., and Snyder, S.H. Dopamine receptor binding predicts clinical and pharmacological potencies of anti-schizophrenic drugs. Science, 192: 481-483, April, 1976.

Crow, T.J., and Gillbe, C. Dopamine antagonism and antischizophrenic potency of neuroleptic drugs. Nature (London) 245(140): 27-28, 1973.

Curry, S., Marshall, J., Davis, J., and Janowsky D. Chlorpromazine plasma levels and effects. Arch. Gen. Psychiat. 22(4): 289-296, 1970.

Curry, S.H. Plasma level studies in psychotropic drug evaluation. Br. J. Clin. Pharmac., Suppl.: 20-28, 1976.

DiMascio, A. Dosage scheduling. In: DiMascio, A., and Shader, R.I., (eds.), Clinical Handbook of Psychopharmacology. New York: Science House, 1970, pp. 289-295,

DiMascio, A., and Demirgian, E. Antiparkinsonian drug overuse. Psychosomatics, 11: 596-601, 1970.

Galbrecht, C.R., and Klett, C.J. Predicting response to phenothiazine: the right drug for the right patient. J. Nerv. Ment. Dis. 147: 173-183, 1968.

Gardos, G., and Cole, J.O. The dual action of thiothixene. Arch.Gen. Psychiat. 29: 222-225, 1973.

Goldberg, S.C. Prediction of response to antipsychotic drugs. In: Efron, D.H. (ed.), Psychopharmacology. A Review of of Progress 1957-1967. Washington: U.S. Government Printing Office, PHSP, No.1836, 1968, pp. 1107-1117.

Grinspoon, L., Ewalt, J.R., and Shader, R. Psychotherapy and pharmacotherapy in chronic schizophrenia. Am. J. Psychiat. 124(12): 1945-1952, 1968.

Gunderson, J.G., and Mosher, L.R. The cost of schizophrenia. Am.J. Psychiat. 132 (9): 901-906, September, 1975.

Guth, P. The mode of action of chlorpromazine (CPZ): a review. Bulletin Tulane University Medical Faculty, 24(1): 30-42, 1964.

Hartmann, W., and Mueller, P. The therapy of first time hospitalized schizophrenics. Fortschr. Neurol. Psychiat. 42(12): 601-614, 1974.

Heinrich, J.H., Kretschmar, J.H., and Kretschmar, C.M. Über die Ergebnisse verschiedener somatischer Therapie-Verfahren bei Schizophrenen. In: Ehrhardt, H.E. (ed.), Perspektiven der heutigen Psychiatrie. Frankfurt/M: Verlag Gerhards u. Co., 1972, pp. 377-382.

Hogarty, G.E., Goldberg, S.C., and the Collaborative Study Group (Baltimore). Drug and sociotherapy in the aftercare of schizophrenic patients. Arch. Gen. Psychiat. 28: 54-64, January 1973.

Kelly, D.N., and Sargant, W. Present treatment of schizophrenia - a controlled follow-up study. Br.Med. J. 1: 147-150, 1965.

Klein, D.F., and Davis, J.M. Diagnosis and Drug Treatment of Psychiatric Disorders. Baltimore: Williams & Wilkins, 1969.

Lehmann, H.E. Pharmacotherapy of schizophrenia. In: Hoch, P., and Zubin, J., (eds.), Psychopathology of Schizophrenia. New York: Grune & Stratton, 1966, pp. 18-41.

Lehmann, H.E. Physical therapies of schizophrenia. In: Arieti, S., and Brody, E.B. (eds.), American Handbook of Psychiatry, Second Edition, Vol.3 (Adult Clinical Psychiatry). New York: Basic Books, 1974, pp.652-675.

Letemendia, F.J.J., and Harris, A.D. Chlorpromazine and the untreated chronic schizophrenic: a long-term trial. Br.J. Psychiat. 113: 950-958, 1967.

Mackay, A.V.P., Healey, A.F., and Baker, J. The relationship of plasma chlorpromazine to its 7-hydroxy and sulphoxide metabolite in a large population of chronic schizophrenics. Br.J. Clin. Pharmac. 1: 425-430, 1974.

Marks, J. Predrug behavior as a predictor of response to phenothiazines among schizophrenics. J. Nerv. Ment.Dis. 137: 597-601, 1963.

Matthysse, S. Dopamine and the pharmacology of schizophrenia: the state of the evidence. J. Psychiat. Res. 11: 107-113, 1974.

May, P.R.A. Treatment of Schizophrenia: A Comparative Study of Five Treatment Methods. New York: Science House, 1968.

National Institute of Mental Health. Psychopharmacology Service Center Collaborative Study Group. Phenothiazines treatment in acute schizophrenia: effectiveness. Arch. Gen. Psychiat. 10: 246-261, 1964.

Pecknold, J.C., Ananth, J.V., Ban, T.A. and Lehmann, H.E. Lack of indication for the use of antiparkinson medication - A follow-up study. Dis. Nerv. Syst. 32: 538-541, 1971.

Platz, A.R., Flett, J., and Caffey, E.M., Jr. Selective drug action related to chronic schizophrenic subtype. (A comparative study of carphenazine, chlorpromazine and trifluoperazine). Dis. Nerv. Syst. 28: 601-605, 1967.

Rivera-Calimlim, L., Astaneda, L., and Lasagna, L. Effects of mode of management on plasma chlorpromazine in psychiatric patients. Clin. Pharmacol. Ther. 14(6): 978-986, November-December, 1973.

Sakalis, G., Curry, S.H., Mould, G.P., and Lader, M.H. Physiologic and clinical effects of chlorpromazine and their relationship to plasma level. Clin. Pharmacol. Therap. 13: 931-946, 1972.

Sakalis, G., Chan, T.L., and Gershon, S. CPZ metabolites and clinical response. Psychopharmacol. Bull. 9: 27, 1973.

Schooler, H.R., Boothe, H., Goldberg, S., and Chase, C. Life history and symptoms in schizophrenia: severity at hospitalization and response to phenothiazines. Arch.Gen. Psychiat. 25: 138-147, 1971.

Sedvall, G., Fyro, B., Hyback, H. et al. Mass fragmentometric determination of homovanillic acid in lumbar cerebrospinal fluid of schizophrenic patients during treatment with antipsychotic drugs. J. Psychiat. Res. 11: 75-80, 1974.

Small, Joyce, G., Kellams, J.J., Milstein, V., and Moore, J. A placebo-controlled study of lithium combined with neuroleptics in chronic schizophrenic patients. Am. J. Psychiat. 132: 1315-1317, December 1975.

Snyder, S.H. Drugs, neurotransmitters, and psychosis. Psychopharmacol Bull. 10(4): 4-5, October 1974.

Warnes, H., Lehmann, H.E., and Ban, T.A. Adynamic ileus during psychoactive medication: a report of three fatal and five severe cases. Canad. Med. Ass.J. 96: 1112-1113, 1967.

Willis, J.H., and Bannister, D. The diagnosis and treatment of schizophrenia. A questionnaire study of psychiatric opinion. Br. J. Psychiat. 111: 1165-1172, 1965.