Psychopharmacology of Schizophrenia: A European View

by Nenad Bohaček

In 1980 the Schizophrenia Bulletin (Vol. 6, No. 4) published a series of articles describing research on schizophrenia in the North European countries, Switzerland, and the United Kingdom. I wrote to the editor suggesting that it would be useful to add other articles so as to present a more comprehensive picture of the European contribution to knowledge about schizophrenia. The editor of the Bulletin accepted this suggestion and invited me to guest-edit these contributions. The present issue is thus complementary to the articles published earlier and contains reviews produced by authors from countries that were not included and on topics not covered in the 1980 issue—for example, epidemiology of schizophrenia and schizophrenia in children.

The two issues are complementary but do not cover all the contributions that European psychiatry has made to the solution of problems related to schizophrenia. It is therefore to be hoped that there will be further issues with contributions from European psychiatry and perhaps from psychiatry in other lands. The problem of schizophrenia is of tremendous proportions, and international and national collaboration in research and in exchange of information is a most promising avenue to its solution.

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Abstract

This article describes how psychopharmacological therapy is applied in Yugoslavia and other countries in Central Europe. The first part of the article summarizes experience and customary use of psychopharmacological substances in relation to clinical syndromes, course of disease, and dominant symptoms. In the second part of the article, the experience obtained in treatment with combinations of drugs and in prolonged pharmacotherapy of schizophrenia is described. Finally, the last section of the article addresses the social implications of psychopharmacological treatment and presents some of the problems and disadvantages that accompany this form of treatment.

This article is neither a theoretical treatise on psychopharmacotherapy nor an attempt to summarize psychopharmacological research in Europe. It describes Yugoslav practice and experience in treating people who suffer from the various forms of schizophrenia, and is thus not a comprehensive description of the practices of European psychiatrists. To aim at such a description would be a vain effort. There are at least twice as many schools of psychiatry as there are countries in Europe; and few of the practicing psychiatrists remain within their school's rules during their working life.

Even Yugoslav practice and teaching has changed considerably over the years. It will undoubtedly continue changing with new discoveries, and more experience. In spite of these limitations, I believe that what is described here would be accepted as the usual practice of treatment of schizophrenia in Europe. This belief is based on contacts with

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Psychopharmacological treatment
has assumed the central place in the
treatment of schizophrenia in all of
the European countries (Shepherd,
Lader, and Rodnight 1968). Psycho-
therapy and social measures are
recognized as important and used in
conjunction with medication. There
are clear variations in the social and
psychotherapeutic methods
employed, as well as in the degree of
importance attached to them.

Medications used in the
psychopharmacotherapy of schizo-
phrenia are usually divided into two
major groups (Angst 1969; Benkert
and Hippius 1974; Heinrich
1976): The first are basic (or
nonspecific) neuroleptics. They are
given in high doses, and have a
global influence on the majority of
symptoms seen in schizophrenia,
including agitation, insomnia,
restlessness, hallucinations, and
delusions. They tend to have fewer
extrapyramidal side effects and a
stronger sedative action than drugs in
the second group. The second group
comprises drugs that are given in
relatively small doses and appear to
be more specific in their action.

The following characteristics of
schizophrenia are generally
considered in decisions about
pharmacotherapy:

• Clinical form of schizophrenia
(simple, hebephrenic, catatonic, or
paranoid).
• Course of disease and phase in
which treatment is prescribed (acute
or chronic).
• Dominant symptoms (agitation,
stupor, apathy, or abulia).
• Balance between productive
(positive) and nonproductive
(negative) symptoms.

Psychopharmacotherapy in
Relation to Illness
Characteristics

Clinical Form.1 In simple and
hebephrenic schizophrenia, basic
neuroleptics are used first, and
specific neuroleptics may not be used
at all. If the latter are used, they will
be administered after treatment with
basic neuroleptics has been tried for
some time. In catatonic excitement,
both basic and specific drugs are
used, whereas in catatonic stupor,
specific drugs are prescribed. In
paranoid, hallucinatory forms of
schizophrenia, treatment begins
immediately with specific drugs;
later, and only occasionally, some of
the nonspecific symptoms (such as
insomnia) will be treated by basic
drugs.

The principle of using as few drugs
as possible is observed in most
settings. In addition to neuroleptic
treatment, a patient is usually also
given antiparkinsonian drugs and
sometimes antidepressants. As a rule,
these combinations are used with less
reluctance than the combination of
several neuroleptics, although there
are some clinics in which a large
number of neuroleptics are used at the
same time.

Course of Illness. The acuteness of
the disease plays a major role in
decisions concerning drug type and
dosage. In very acute cases, basic
neuroleptics such as chlorpromazine,
levomepromazine, and promazine
(reported to be well tolerated in the
elderly) are prescribed. Shortly there-
after, specific neuroleptics (such as
fluphenazine, trifluoperazine,
thioproperazine, clozapine, and
haloperidol) are added depending on
the clinical syndrome that dominates
the picture. In acute cases, the doses
are usually high—as much as 1,200
mg of chlorpromazine, 600 mg of
levomepromazine, or 600 mg (or
even more) of promazine. Fluphen-
azine, trifluoperazine, and thiopro-
perazine are given in doses > 30-60
mg/day. In chronic forms of schizo-
phrenia (and for the maintenance of
remission), thioridazine and
pimozide, as well as depot prepara-
tions (see below), are used. Doses of
thioridazine range from 200-600
mg/day; doses of pimotid, 4-12
mg/day.

Dominant Symptoms. A patient
with a dominant picture of psychomotor
excitement is given basic neuro-
leptics, whereas in a patient with
psychomotor stupor or retardation,
specific neuroleptics are preferred. In
a patient with paranoid or paranoid/
hallucinatory symptomatology,
specific neuroleptics are used from
the beginning. In the instance of
apathic or apathic/abulic syndromes,
most of the basic neuroleptics have
little effect. Specific neuroleptics do
seem to have some effect in such

1 In describing clinical syndromes and
assessing change of the patient's condition
in the course of treatment, a variety of
instruments have been used. The Present
State Examination (World Health Organ-
ization 1973, 1979) and the AMI System
(Association for Methodology and
Documentation in Psychiatry) (Angst et
al. 1969; Bobon 1978; Bohaček 1978) are
examples of some of the instruments used
in a number of countries.
recognized that such combinations fluphenazine even though it is widely often combined with a specific leptomics such as levomepromazine are exception than the rule. Basic neuro-
of only one neuroleptic is more the symptoms of schizophrenia, the use side effects, and so on.

Presence of Productive Symptoms. The balance of productive (positive) and nonproductive (negative) symptoms of schizophrenia is also a factor in decisions concerning the type and dosage of neuroleptics to be prescribed. Most neuroleptics are efficacious in treating positive symptoms (such as hallucinations or excitement), but their effects in treating negative symptoms (such as apathia-abulia) are far less dramatic. There have been attempts to use psychostimulants (amphetamines or sid nocarb) (Persic et al. 1972) and even hallucinogens (LSD-25 or Deanol) (Fouks et al. 1966) to deal with negative symptoms. It is hoped that such agents will precipitate positive symptoms, which will be more amenable to standard treatment with neuroleptics.

Drug Combinations Occasionally a single medication can be sufficient to achieve a full therapeuthic effect. In most instances, however, psychiatrists prescribe several medications simultaneously. For example, neuroleptics are used to treat the main symptoms, hypnotics to treat subsidiary symptoms, antiparkinsonian drugs to correct side effects, and so on.

Even in dealing with the main symptoms of schizophrenia, the use of only one neuroleptic is more the exception than the rule. Basic neuro-leptics such as levomepromazine are often combined with a specific "target" neuroleptic such as fluphenazine even though it is widely recognized that such combinations can potentiate side effects (e.g., extrapyramidal or hypotensive effects or transient delirious states). Occasionally a combination of neuroleptics with drugs such as diazepam is prescribed. The latter is usually given in high doses. Accessory symptoms (such as insomnia) sometimes warrant additional therapy with hypnotic drugs or levomepromazine. Benzodiazepines (e.g., nitrazepam and flurazepam) are also added in these cases (although this type of combination has been shown to cause tiredness and slowness) because of possible interactions of barbiturates with neuroleptics (e.g., the induction of microsomal liver enzymes, which in turn can lead to a decrease of the effectiveness or elimination of effects of psychopharmacological drugs). Combined treatment with several neuroleptics is also sometimes used to avoid side effects.

Management of Side Effects Early extrapyramidal side effects (e.g., tremor, rigidity, akathisia, and dyskinesia) are treated with antipar-kinsonian drugs such as biperidine, trihexyphenidyl, and ethybenz-tropine. Their administration is often stopped after a short time without a reappearance of extrapyramidal side effects, which may have been intense earlier in treatment.

In general, however, it is no longer considered necessary to continue giving antiparkinsonian drugs indefinitely, and they are not universally used to prevent extrapyramidal side effects. The earlier practice of providing antiparkinsonian drugs to all patients treated with neuroleptics was abandoned when it became clear that no more than half the patients treated with neuroleptics would experience extrapyramidal side effects, and when it was reported that antiparkinsonian drugs increased the risk of tardive dyskinesia (Gerlach 1979). There is also a possibility that combined treatment with neuroleptics and antiparkinsonian drugs decreases the concentration of neuroleptics in plasma and thus decreases their antipsychotic activity. Moreover, anticholinergic drugs (thus, also antiparkinsonian drugs), when combined with a pheno-thiazine, can lead to a disturbance of thermoregulatory centers and result in hyperpyrexia. More recently, reports of the serious nature of anticholinergic effects of antiparkinsonian drugs (e.g., dryness of mouth, disturbances of visual accommoda-tion, and micturition) and the fact that the use of some anticho-linergic drugs (such as trihexy-phenidyl) can lead to dependence further discouraged the routine use of antiparkinsonian drugs as preventive medicine (Vinar 1973; Cattabeni et al. 1980).

The most serious and treatment-refractory example of late extra-pyramidal side effects—tardive dyskinesia—has been reported in all European countries. In hospitalized patients, the reported incidence of tardive dyskinesia varies between 0.5 and 40 percent of all patients treated; most reports give a figure of about 15 percent. In chronic patients, the reported range (5 to 20 percent) is smaller. The reasons for these differences in the reported incidence of tardive dyskinesia are unclear and insufficiently investigated. Most reports state that dyskinesia will occur after long-term treatment with neuroleptic drugs (usually after 2 to 5 years), but cases occurring after 6 months of therapy have been described.

A variety of treatments have been tried but without much success. Since there is no effective therapy for
tardive dyskinesia, attempts are being made to prevent its occurrence by following these principles:

1. Every attempt should be made to achieve and maintain optimal effects with the smallest possible dose.
2. Very high doses should be avoided at all times.
3. Wherever possible, treatment with antiparkinsonian (anticholinergic) drugs should be avoided; if these drugs are considered necessary, their use should be interrupted at regular intervals.
4. "Drug holidays" should be employed when the patient's condition permits.
5. An intensive effort should be made to train practitioners to recognize tardive dyskinesia in its incipient stages.

Various psychological side effects of neuroleptic treatment have been described and linked to the dose of neuroleptics, combination of drugs used, and the premorbid personality structure and age of the patient. One such effect which requires immediate cessation of all treatment is the transient delirious state that is most often seen when neuroleptics are used together with antidepressant and/or antiparkinsonian drugs. Another side effect described in protracted treatment with neuroleptics is the "depressive shift": the occurrence of a depressive syndrome in the course of treatment with neuroleptic drugs, usually after the acute symptoms (especially in paranoid/hallucinatory forms of schizophrenia) have disappeared (Bohaček 1965; Müller 1981). Such a depressive shift (or postpsychotic depression) has been found in patients treated with all types of neuroleptics, from phenothiazines to butyrophenones. It can be seen in 15-20 percent of all those treated. If left unattended, this depressive syndrome can lead to suicide and attempted suicide. The condition responds well to tricyclic and tetracyclic antidepressants (e.g., imipramine, amitriptyline, and maprotiline), which can be given in combination with neuroleptic drugs. Some authors have argued that the syndrome of postpsychotic depression does not exist. If a depressive syndrome occurs in the course of treating schizophrenia, these authors believe that a mixed state in which schizophrenic and depressive syndromes were present must have existed before treatment began. Others believe that the depressive shift is, in fact, a syndrome of exhaustion that occurs after remission from schizophrenia (der "post remissive Erschöpfungszustand"; Heinrich 1967).

When physical disease occurs in patients with schizophrenia, it is generally agreed that it is essential to provide additional therapy for the concurrent diseases while maintaining neuroleptic treatment. Such combined therapy can lead, however, to untoward interaction between drugs and side effects. Among these, the following are the most frequently reported:

1. The combination of oral antidiabetic drugs (of sulfonylurea type) with neuroleptics of the phenothiazine type can decrease the effectiveness of phenothiazines.
2. Diuretics (thiazide and other saluretics), when given with phenothiazines, can potentiate hypotension.
3. Antibiotics such as cephalosporin, chloramphenicol, penicillin G, and tetracyclines can be inactivated or have their effects diminished.
4. Alcohol can potentiate the effect of chlorpromazine. (5) Neuroleptics increase the action of sedatives, alcohol, narcotics, and β-blockers, and decrease the effectiveness of anticonvulsants.

**Duration of Neuroleptic Therapy**

Neuroleptics are generally seen as symptomatic treatment. To be effective, neuroleptic treatment must coincide with the presence of manifest symptoms of the disease: in this sense, by pharmacological parallel, neuroleptic treatment could be called "psychostatic."

Up to 80 percent of schizophrenic psychoses in our experience follow a chronic course. In these patients permanent pharmacotherapy is necessary. Because it is impossible to predict with certainty whether recovery from an acute episode of schizophrenia will be followed by relapses, and whether schizophrenia will follow a chronic course, in our practice pharmacotherapy is continued for approximately 1 year after the first attack. At that point, if the patient's condition permits, neuroleptic treatment is stopped. If symptoms of the initial episode are still present, treatment is continued. If a patient has a relapse (i.e., a second episode of the disease), treatment is continued for 3 years from the time of the second episode. If a third attack occurs, it is generally considered that pharmacotherapy will have to be lifelong. These guidelines provide a general framework within which adjustments for the individual patient are necessary (Palmovic and Bohaček 1970).

**Maintenance Therapy**

After recovery from the acute phase of schizophrenia has occurred, drug dosages are gradually decreased to a minimum necessary to maintain an asymptomatic state. This decreased dose will be ¼, ½, or even ⅓ of the dose that was necessary during the acute phase.

Prolonged pharmacotherapy once required patients to take the neuroleptic in three or four daily doses—a difficult regimen to follow. Today,
however, a variety of depot neuroleptics is used: in the group of tricyclic phenothiazines, fluphenazine enanthate and decanoate, perphenazine enanthate, flupenthixol decanoate, pipotiazine undecilatester, and pipotiazine palmitinester (which can maintain the blood levels constant from 7 to 28 days); among butyrophenones, haloperidol decanoate (supposed to maintain the therapeutic action of haloperidol for a period of approximately 4 weeks); among diphenylbutyrylpiperidenes, pimozide (taken once every day or every 2 days), fluspirilene (once weekly), and penfluridol (once weekly when taken orally) (Doongaji et al. 1981).

There is general agreement about the advantages of treatment with depot preparations: they are easy to apply, there is a good local and general tolerance, and the patient feels less marked as a mentally disordered person when he can receive treatment in a general health facility. There are also numerous reports that this form of treatment leads to a better relationship and transference between the patient and the doctor. Greater possibilities for the use of other treatment methods (such as psychotherapy and sociopharmacology), fewer side effects (in particular, extrapyramidal side effects), and a reduced danger of suicide, which was a particular risk in countries where the scarcity of services made it necessary to prescribe medication in sufficient quantities to last a month and to give it to the patient in a health facility.

Social Implications of Psychopharmacological Treatment

Psychopharmacotherapy is undoubtedly an effective treatment for schizophrenia. It by far surpasses the effectiveness of previous biological treatments and poses considerably fewer risks. The improved treatment of schizophrenia has had numerous social consequences, ranging from changes in attitudes to changes in legislation and organization of health services.

Reports from various parts of Europe suggest that the attitudes of the patient, his family, lay personnel, and professionals toward the disease and its treatment are significantly more positive. Confidence in the efficacy of pharmacotherapy is constantly increasing.

The main social implication of the introduction of pharmacotherapy has been the possibility of outpatient treatment of a large number of schizophrenic patients who previously would have been institutionalized.

Although empirical observations were very important in establishing the efficacy of psychopharmacotherapy—the clinician's eye was the instrument that discovered the antipsychotic and antidepressive action of pharmacological drugs—psychopharmacological treatment led to the development of objective measurement techniques in psychiatry. These methodological advances have contributed to the scientific evidence about the value of different pharmacological drugs, so that results no longer rest only on clinical impressions. They have also made a contribution to the technology of assessment of complex human behavior. The pharmacotherapy of schizophrenic psychoses has also made it feasible to apply social and psychological therapeutic measures and to provide help for the schizophrenic and his family (Bohaček 1973).

There is much more agreement among psychiatric schools (regardless of their social, economic, political, and other differences) about the value of psychopharmacotherapy than there is similarity in the provision of treatment in different European countries. This is so for a variety of reasons. Pharmacotherapy, for example, is dependent on the social system, the philosophy of health care, and the organization of health services in general. In some European countries, health care is free and comprehensive; in others, health care is only free in part; and in others, much depends on the capacity of the patient and his family to pay the often exorbitant fees.

Conclusion

Much hope, and even more money and other resources are being invested in the search for new neuroleptics that will (1) be more effective and therefore applicable in smaller doses; (2) have an even more prolonged effect; (3) be more effective in dealing with nonproductive symptoms; and (4) have few or no side effects.

A question that psychopharmacology must resolve in the process of searching for new drugs is that of specificity of psychopharmacological substances. True specificity would mean that drugs used for the treatment of depression and schizophrenia were, in fact, specific for these diseases—which cannot today be affirmed for any one of the substances used.

In addition to these improvements in the psychopharmacological arsenal, most European countries are trying to improve the organization of services and other components of care. In this process the potential of different modes of treatment—with psychopharmacological, social, and biological means—has to be
reexamined, and ways to ensure the provision of treatment that will satisfy the patient, his family, and the community must be found.

References


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