

MODULE 3: TREATMENT

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This module is designed to give students an overview of the history of the development of somatic therapies for psychotic disorders, to review the basic pharmacology and mechanism of action for the medications that are commonly used, and to summarize the data supporting efficacy in acute psychosis and chronic maintenance therapy. The older "classical" or "typical" neuroleptics are described, and the relative advantages of the newer "atypical" or "second generation" neuroleptics are discussed. Practical issues are also discussed, such as the frequency and management of adverse effects, the use of oral versus depot compounds, and the pros and cons of discontinuing medications. Several different types of psychosocial therapies are also described. This module should provide some useful materials for students at all levels.

THE IMPORTANCE OF PROVIDING ADEQUATE TREATMENT FOR SCHIZOPHRENIA

Improving the treatment of schizophrenia will be an important goal during the 21st century. Schizophrenia is one of the leading causes of disability throughout the world. According to the World Health Organization study of the Global Burden of Disease, schizophrenia is the eighth leading illness in terms of disease burden for people between 15 and 45 worldwide. Furthermore, this same WHO study predicts that (unless some significant improvement in treatment is found) the disease burden will increase steadily during the time period between 1990 and 2020. As this discussion of the treatment of schizophrenia will demonstrate, significant advances have been made in improving the care of patients during the past decade; however, there is a clear and significant need for continuing the search for improved treatment methods. The optimal treatment for patients with schizophrenia should be integrative. That is, it should combine the best pharmacologic treatments with the best nonpharmacologic treatments. Particularly with the improvements in alertness that occur either with low dose treatments using older neuroleptics or the newer atypical neuroleptics, patients are increasingly able to participate in various kinds of psychosocial rehabilitative programs.

SOMATIC THERAPIES

Pharmacologic Background

The Introduction of Chlorpromazine

The era of effective pharmacological treatment of schizophrenia began with the introduction of chlorpromazine in the early 1950s. Before this the only drug with a claim to efficacy was reserpine. The active component of extracts of the plant *Rauwolfia serpentina* had been used in the treatment of mental illness in India for several centuries, but it was only with the isolation of the principal alkaloid reserpine by Bein and his colleagues in 1952 that its pharmacologic utility was fully clarified. Not long after this, it was demonstrated that the major actions of the drug depend upon its ability to deplete endogenous stores of the monoamines noradrenaline and 5-hydroxytryptamine (and later dopamine), findings that have been critical in the formulation of monoamine theories of affective illness and in the development of antidepressant medications. The tranquilizing properties of reserpine and its therapeutic effectiveness in schizophrenia are limited, however, and it has disadvantageous effects, including induction of hypotension. With the introduction of chlorpromazine, the use of reserpine as an antipsychotic agent was soon superseded.

The discovery of the antipsychotic effects of chlorpromazine is, like the introduction of a number of other treatments in psychiatry, a story of notable serendipity. Charpentier and colleagues of the Rhone-Poulenc Laboratories in France had been synthesizing phenothiazine compounds on account of their possible antihelminthic effects. Some were found to have antihistaminic actions. Laborit, a pharmacologist, was interested in compounds with actions on the central nervous system; he hoped to find an agent that produced "artificial hibernation." With chlorpromazine he produced a degree of hypothermia in animal experiments, and he also predicted that it might be useful in psychiatric practice. After some initial and discouraging attempts to use the drug in patients with hypomania, Delay and Deniker embarked upon a systematic study of what were initially considered relatively high doses (75 to 150 mg a day) in a group of agitated psychotic patients. In May of 1952 they reported their findings on 38 patients, describing how the drug reduced manic and psychotic agitation in patients who had been resistant to shock or sleep treatments. They also noted that chlorpromazine was effective in the treatment of confused patients, and in this respect it differed from sedative drugs, which made such patients worse. Agitation, aggressiveness, and delusional states in schizophrenic patients were improved.

The discovery of chlorpromazine launched the pharmacologic revolution in psychiatry. During the first fifty years of the twentieth century, the numbers of inpatients increased steadily, reaching a peak of nearly 150,000 in the United States at the time that chlorpromazine was introduced. After 1952, however, the numbers of patients began to drop precipitously, aided by the introduction of many additional neuroleptic drugs to the armamentarium. Interestingly, the discovery of chlorpromazine also helped launch the development of antidepressants. Its chemical structure is strikingly similar to that of the first antidepressant, imipramine, illustrating how difficult it is to predict the nature of a therapeutic effect based of chemical structure alone.

The Dopamine Hypothesis

There have been a number of biochemical theories of the underlying defect in schizophrenia. One theory - the dopamine hypothesis - has been remarkably successful in accounting for a number of observations concerning exacerbation and amelioration of symptoms.

With the development of techniques for studying catecholamines in the brain, high concentrations of dopamine were found to be present in the corpus striatum: a pathway of dopamine-containing neurons projecting from cell bodies in the substantia nigra to terminals in the corpus striatum was described. This system was discovered to be degenerated in Parkinson's disease by Hornykiewicz and colleagues, leading to the conclusion that the symptoms of that condition are attributable to a failure of dopaminergic transmission in the striatum. It had also been discovered by Carlsson and Lindqvist, in experiments on rats, that the drugs known at that time to be effective in the treatment of psychotic illness (e.g., chlorpromazine and haloperidol) caused an increase in accumulation of the dopamine metabolite homovanillic acid (HVA) in the brain. Arvid Carlsson proposed that this increase was a secondary feedback response of the presynaptic dopamine neuron to blockade of the postsynaptic dopamine receptor, an interpretation that is now generally accepted, and which forms the basis of "the dopamine hypothesis." He received the Nobel Prize in 2000 for his work on the dopamine system, along with Paul

Greengard (for his work on second messenger systems) and Eric Kandel (for his work on neural mechanisms of memory).

A second line of evidence for the dopamine hypothesis came from observations on the psychoses that were seen in individuals who had taken large doses of amphetamines and related compounds. Such psychoses were observed to include some of the features (e.g., Schneiderian first rank symptoms) of schizophrenic illnesses, to the extent that these illnesses were often misdiagnosed as schizophrenia. A key difference however is that the symptoms usually remit within a few days of discontinuing amphetamines, and negative symptoms are usually absent.

Based upon these clinical observations Randrup and Munkvad conducted a series of animal experiments to clarify the mechanism of action of the amphetamines. They described a syndrome of sniffing, licking, and gnawing in rats and related patterns of activity in a variety of other mammalian (and reptilian and avian) species. Repetitive and maladaptive ("stereotyped") behavior was in each case an important component of the amphetamine-induced syndrome. In pharmacological experiments they were able to show that the expression of this syndrome depended upon intact stores of dopamine; that is, if dopamine had been previously depleted, the behaviors were not seen following amphetamine administration. Furthermore, the behaviors were blocked by administration of neuroleptic drugs, and (importantly) at certain dose levels not only were the abnormal behaviors antagonized, but normal exploratory behavior returned. The chemical structure of dopamine and amphetamine are also very similar.

From this background the dopamine hypothesis was formulated: that psychosis is associated with an excess of dopaminergic transmission in the brain, and that this excess is corrected by the action of neuroleptic drugs acting at the level of the dopamine receptor. This hypothesis has stimulated much productive research both on psychosis and on the pharmacology of antipsychotic drugs.

There are two components to the dopamine hypothesis. The first component focuses on the nature of the disturbance in the brain in psychosis (that dopaminergic transmission is excessive). The second component concerns the mechanism of the antipsychotic effect (that it occurs by blockade of dopamine receptors).

The evidence for the first component, excessive dopamine transmission, is equivocal. Early studies of CSF and postmortem brain tissue established that, as reflected in levels of dopamine metabolites such as HVA and dihydroxyphenylacetic acid (DOPAC), turnover of dopamine is not increased. This appeared to rule out the possibility that dopamine neurons are overactive. For a time some evidence suggested that the numbers of dopamine receptors (particularly D2 receptors) in the brain might be increased. As studied by ligand binding methods, there is an apparent increase in numbers of receptors in the corpus striatum and nucleus accumbens (projection areas for dopaminergic neurons). However, the issue of whether this increase was secondary to neuroleptic medication, as has been observed in animal experiments, was unresolved. Recent studies with PET scan techniques suggest that, at least as studied by the most direct methods, dopamine receptor numbers in patients with acute psychotic illnesses untreated with neuroleptic medication are probably not increased.

The evidence for the second component, that neuroleptic drugs exert their therapeutic effects by blockade of dopamine receptors, remains strong. This aspect of the theory has also been able to accommodate a number of apparent anomalies. For example, the first available assay of dopamine receptor activity depended upon the ability of compounds to antagonize stimulation by dopamine of the enzyme adenylate cyclase in striatal tissue; whereas there was a good correlation in this system between antipsychotic and pharmacological activity for the phenothiazines, the butyrophenones were less effective than would have been expected from their clinical potency. With the introduction of a second form of assay, which depends upon binding of a butyrophenone label (e.g., spiperone) to striatal tissue, the relative activity of the butyrophenones was found to be increased and the discrepancy was resolved. It is now considered that the adenylate cyclase assay detects actions on the D1 receptor, and butyrophenone binding assesses activity at the D2 receptor; the latter may be more relevant to the antipsychotic effect. Working independently, both Seeman's group in Canada and Creese and Snyder in the U.S. have demonstrated a close correlation between clinical dose and D2 receptor binding.

Dopamine is relatively restricted in its location in the brain, although it has several components. The mesolimbic pathway runs from cell bodies more medially placed in the ventral midbrain and projects to the nucleus accumbens, olfactory tubercle, and some regions of the frontal cortex. This pathway is thought to be the focus for antipsychotic effects. The nigrostriatal pathway runs (as its name indicates) from the substantia nigra to the striatum. Blocking of this component leads to extrapyramidal side effects. In addition, classes of dopamine receptors differ in their locations. Five classes, which differ somewhat in

distribution, are now recognized. These are at present divided into the D1/D5 and D2/3/4 superfamilies. These differ in their distributions (e.g., D1 and D4 have more prominent cortical representation). The treatment implications of these various distributions are still under investigation, but the importance of dopamine—and of the D2 receptor—remains robust even in the faces of new advances, such as the development of “atypical” neuroleptics, which are described later.

Overview of Treatment Issues

The Older “Classical” Neuroleptics

The discovery of chlorpromazine led rapidly to the development of additional compounds, all of which shared the feature of producing dopamine blockade. Testing compounds for the ability to block amphetamine-induced stereotypies and other symptoms became a screening tool in the pharmaceutical industry. A number of classes of compounds were developed.

The phenothiazines, of which chlorpromazine was the prototype, have a three-ringed structure in which the side chain attached to the N in the thiazine (middle) ring accounts for the variations between compounds. In terms of side chain structure, the phenothiazines are usually sub-classified as follows:

aminoalkyl compounds such as chlorpromazine

piperazine compounds such as trifluoperazine and fluphenazine

piperidine compounds such as thioridazine

The butyrophenones are a group of compounds that were investigated and introduced specifically for their neuroleptic effects, and a number have proven effective and have high potency. Haloperidol is the reference structure. A closely related group of compounds is the diphenylbutyl-piperidine series of which pimozide and penfluridol are examples. A number of butyrophenones and diphenylbutyl piperidines are potent and relatively selective antagonists of the D2 receptor.

The benzisoxazole compound risperidone (an “atypical” or second generation neuroleptic described below) is a derivative of the butyrophenone class. Both haloperidol and risperidone were identified by Paul Janssen, a physician and neuropharmacologist who has been a major contributor to contemporary psychopharmacology.

The thioxanthenes differ from the phenothiazines in that they have a carbon atom in the place of the nitrogen in the central ring structure.

The benzamides include sulpiride and remoxipride. These compounds have a relatively low incidence of extrapyramidal effects. Since they are not potent anticholinergics, the basis for this is at present unclear.

The dibenzodiazapine clozapine is an older neuroleptic that is currently classed with the “new atypicals.” It is unusual both in its structure and its pharmacological profile of activity. It has relatively high anticholinergic activity, which may account for its lack of extrapyramidal effects. On the other hand, it is less effective as an antagonist at the D2 receptor, relative to its antipsychotic potency, than might be expected on the basis of a simple interpretation of the dopamine hypothesis. It has been noted to have a high affinity for the D4 dopamine receptor, an action that has excited interest in relation to its profile of antipsychotic activity. Clozapine was widely used for a time and then nearly abandoned, because of its tendency to produce agranulocytosis. It was revived again in the 1990s and is now again widely used. It is currently considered to be a prototype for the newer “atypicals” because of its broad pharmacologic profile.

What are the Target Symptoms for Neuroleptics?

The first issue that arises when we begin to consider the target symptoms for neuroleptics is: what shall we call the medications? When originally developed, these drugs were called “neuroleptics.” This term literally means “nerve-turner,” based on its Greek derivatives. As other classes of drugs were developed that also “turned the nerves,” they acquired names that were more specifically consistent with their target symptoms: antidepressants, angiolytics, or minor tranquilizers. For a time, the “neuroleptic” agents were also referred to as “major tranquilizers” and contrasted with the “minor tranquilizers” that were used more for anxiety symptoms. As time evolved, however, the “major” and “minor” terminology was abandoned, and these medications also became known as “antipsychotics.” The new terminology was chosen in recognition of the fact that a drug such as chlorpromazine or haloperidol was effective for psychotic symptoms, whether they occurred in schizophrenia, mania, dementia, or other psychiatric syndromes. Although these medications are almost never referred to as “anti-schizophrenic drugs,” the failure to use this term is somewhat ironic, in that all of these medications were first developed for the treatment for schizophrenia. Furthermore, most of the “neuroleptic” or “antipsychotic” medications

currently in use have been forced to demonstrate efficacy for the treatment of schizophrenia prior to initial registry. Typically, indications for usage in other conditions, such as mania or psychotic symptoms associated with depression or dementia, has come later.

The controversy surrounding the proper name for these medications is related to another important question about the treatment of schizophrenia: what are the target symptoms? For many years, both clinical practice and clinical drug trials emphasized evaluation and measurement of psychotic symptoms as the primary target symptoms. There are several reasons for this emphasis. First, psychotic symptoms are easy to measure reliably. Second, they are usually the most florid and attention-getting symptoms of the illness, and they are frequently the symptoms that cause a patient or family member to seek treatment. Third, they are also relatively responsive to neuroleptic/antipsychotic medications.

However, during the 1980s and 1990s psychiatrists throughout the world began to recognize the importance of other aspects of schizophrenia, particularly negative symptoms and related impairments in cognitive function. When neuroleptics were initially introduced, many psychiatrists hoped that rapid and effective treatment of acute psychotic episodes would reverse the previously deteriorating course that seemed to characterize schizophrenia from the time that it was initially identified by Emil Kraepelin. However, it soon became clear that this was a false hope. The new antipsychotics such as chlorpromazine and its later successors such as haloperidol did indeed reduce psychotic symptoms, but patients continued to have problems with their ability to think clearly, function effectively, or relate emotionally to others.

The recognition that other symptoms must be important led to a growing interest in negative symptoms, a development that has been described more extensively in module 1. In conjunction with the emerging interest in improving treatment for negative symptoms, psychiatrists also began to recognize the importance of an underlying cognitive impairment in schizophrenia. In many ways, the schizophrenia of the 21st century has returned to an emphasis on the components of schizophrenia that Bleuler found so important: problems in thinking (loosening of associations), impairments in attention, or “thought disorder.” In the 21st century, the bar for defining response for treatment has been raised considerably higher, with most psychiatrists and patients seeking a treatment that will ameliorate all the components of the illness, including negative symptoms and related cognitive impairments, in addition to psychotic symptoms.

Psychiatrists also began to note other problems with classical neuroleptics. Even for positive or psychotic symptoms, their efficacy in many patients is incomplete. Despite optimal doses of medications and good maintenance therapy, 10 to 20 percent of all patients continue to be nonresponders, even when positive psychotic symptoms are the only measure of clinical response. In addition, 50 percent of patients continue to suffer from residual symptoms when treated with classical neuroleptics. Furthermore, many patients resist taking classical neuroleptic medications and become noncompliant, due to the unpleasant nature of their side effects.

Adverse Effects

Neuroleptic drugs are relatively safe and have a high therapeutic index (i.e., ratio of therapeutic to toxic dosage). They are nevertheless associated with a wide range of side effects, particularly on the central and autonomic nervous systems, and these effects can limit compliance with treatment.

A number of side effects occur frequently as a consequence of treatment with neuroleptic compounds. These include the following:

Extrapyramidal effects resembling those seen in idiopathic Parkinson's disease, presumably secondary to blockade of dopaminergic transmission, including akinesia, rigidity, and tremor. Although these can be ameliorated with anticholinergic medication, a reduction in neuroleptic dosage should be considered as the first intervention. These symptoms are generally dose-related and may occur at any stage of treatment.

Dystonias presenting as abnormalities of posture and tone, commonly of the axial musculature (e.g., of the neck) may occur very early in treatment, but are also seen at other times. They can sometimes be confused with abnormalities of posture (e.g., mannerisms and catatonia) associated with the disease process. A particular subclass of dystonias, described as oculogyric crises, affects the extensor muscles of the neck and induces involuntary upward movements of the eyes, sometimes also affecting tongue and jaw muscles. Such symptoms may cause considerable anxiety in the patient and the unwary physician, but they are usually readily reversed by anticholinergic medication.

Akathisia (subjective and objective restlessness, particularly of the lower limbs) is common, often unrecognized, and apparently unrelated to the above. It can be among the most distressing of side

effects, and sometimes prevents achieving an adequate antipsychotic dose. There is some evidence that akathisia responds better to beta adrenergic antagonists than to anticholinergics, although it is sometimes resistant to both.

A number of other effects on the central and autonomic nervous systems may also occur in some patients. Such effects include orthostatic hypotension, drowsiness, dry mouth, constipation, and blurred vision. They may occur early in treatment and then diminish. Some of these effects may be due to antiadrenergic or anticholinergic actions, although the precise mechanism is often obscure and the effects in an individual patient unpredictable. If persistent and troublesome, a change to another compound may be required.

Seizures are occasionally seen, although these may also be a concomitant expression of the disease process.

Dyskinesia, a jerky or involuntary movement that is often seen in the perioral region but can occur also in the axial musculature and the extremities, is often attributed to neuroleptic medication. Tardive dyskinesia, or TD (so called because it emerges some time after treatment is initiated and tends to be persistent even after dose reductions), is one of the most distressing side effects of long-term treatment. It has now been conclusively established that the risk of developing TD increases significantly with greater years of neuroleptic exposure. After ten years of exposure to conventional neuroleptics, the cumulative incidence reaches 50%. While there is no doubt that TD is often caused by neuroleptic medication, dyskinesia may also be a primary symptom of schizophrenia in a small group of patients. Such abnormalities of movement were well described in patients before the neuroleptic era, and they are also reported in contemporary patients who have never received such medication.

Non-neurological side effects of neuroleptic drugs are also well-recognized. These include occasional cases of obstructive jaundice and aplastic anemia, which were described very early, for example, with chlorpromazine. Agranulocytosis is an acknowledged risk of clozapine administration, but may rarely occur with other drugs. Discontinuation of the particular drug is necessary in each of these cases, with a change to another class of agent.

Hyperthermia is an occasional occurrence in patients on neuroleptic medication. This is sometimes referred to as "neuroleptic malignant syndrome," although this term has been used to cover a variety of manifestations, some of which may relate to other effects of medication (e.g., Parkinsonism) or to components of the disease process (e.g., catatonia). Milder variants of this syndrome may be more common and less malignant than is generally thought and may not necessarily require discontinuation.

Skin sensitivities are also seen, among which photosensitivity (particularly with chlorpromazine) is the most common, followed by pruritus with this and other agents. These can often be managed by protection from sunlight or by administration of antihistamines, rather than drug withdrawal.

The most important among the **eye changes** that have been reported is central chorioretinopathy, an irreversible pigmentation of the retina, which has been associated with high (800 mg or more) doses of thioridazine.

The Newer "Atypical" or "Second Generation" Neuroleptics

Some patients do not respond adequately to treatment during their first episode of illness, and in others drug resistance emerges at a later stage. Because there was a suspicion that some patients who were not responding to other neuroleptic agents did better on the dibenzodiazepine clozapine, this compound was reintroduced into clinical practice in spite of its occasional ability to induce the serious effect of agranulocytosis.

In a landmark study Kane and colleagues investigated the potential efficacy of clozapine by selecting patients who had failed to respond to at least three different antipsychotic agents and initiating treatment in a single-blind fashion with haloperidol (mean dose 61 mg). Those patients whose condition remained unimproved were then randomly assigned to clozapine (up to 900 mg/day) or chlorpromazine (up to 1800 mg/day). A total of 268 patients entered the study, and 88% of the clozapine and 87% of the chlorpromazine treated patients completed the six-week treatment period. When *a priori* criteria for recovery were applied, 30% of the clozapine-treated patients were classified as responders, in comparison with only 4% of the chlorpromazine-treated patients. The benefits of clozapine for a subsample of seriously ill patients who are refractory or only partially responsive to treatment are now widely appreciated. However, clozapine has a serious risk of agranulocytosis, with an incidence of up to 4% of treated patients. Consequently, patients on clozapine must be closely monitored with weekly or bimonthly (after the first 18 months) white blood cell counts.

This study suggests that clozapine has therapeutic effects in patients who are resistant to other medications. Because clozapine is relatively less effective in antagonizing the D2 dopamine receptor, this conclusion challenges the view that D2 antagonist activity is the sole component of the antipsychotic effect.

The discovery of the efficacy of clozapine in treatment-refractory patients led to an extensive reappraisal of many previous assumptions about the treatment of schizophrenia: therapeutic pessimism that assumed there would always be a group of “nonresponders,” the emphasis on psychotic symptoms as the primary treatment target, and the belief that an ideal neuroleptic should be a potent D2 blocker. As clozapine became more widely used, psychiatrists recognized that it improved negative symptoms and cognitive function in addition to psychotic symptoms. Furthermore, apart from weight gain and the risk of agranulocytosis, it had few side effects. In addition, clozapine had very minimal extrapyramidal side effects, which caused patients to be more comfortable and therefore more compliant.

Ultimately, the pioneering clozapine studies ushered in a new era of neuroleptic treatment and a new class of drugs. These drugs have been given several different designations: atypical, novel, and second generation. The term “atypical” was chosen to imply an unusual mechanism of action – e.g. minimal dopamine blockade, or combined dopamine/serotonin blockade. Unlike most of the “classical” neuroleptics, the newer atypicals tend to have a broad pharmacologic profile, sometimes working minimally on dopamine, and frequently affecting multiple chemical systems in the brain. These drugs are also sometimes referred to as “novel neuroleptics,” since they were new at the time they were introduced in the late 20th century. By the early 21st century, a time when multiple atypical or novel neuroleptics were available, they were frequently referred to as “second generation” neuroleptics. This latter term is perhaps the most neutral, correct, and descriptive, but it is sometimes avoided because it sounds “wordy.”

Risperidone, a benzisoxazole, was the first of the new atypical second generation neuroleptics. It has a low incidence of extrapyramidal side effects within the therapeutic range of 2 to 6 mg per day. It has a stronger blockade of 5HT₂ (serotonergic) than D₂ receptors, and has weaker actions at alpha 1, alpha 2, and H₁ histaminergic receptors. It has been followed by several others, including olanzapine, quetiapine, ziprasidone, sertindole, and zodepin. By the end of the 20th century, psychiatrists had entered “the atypical era.” By 1999 nearly 60% of total prescriptions in the United States were for atypical or second generation neuroleptics. A survey of European psychiatrists has indicated that a majority would choose one of these medications as the preferred treatment for a member of their families. In general, they enjoy wide use throughout the world, although developing countries have found them less accessible due to their greater cost in comparison with the older classical medications.

The atypical neuroleptics have become a first-line treatment for a variety of reasons. Their broader pharmacologic profile has led to a broader therapeutic spectrum. They have therapeutic efficacy for positive symptoms, for refractory and residual symptoms, for negative symptoms, depressive symptoms, and cognitive deficits. In addition, depending on the specific drug or the dose used, they have minimal side effects. These include both objective side effects such as acute extrapyramidal symptoms and tardive dyskinesia, and object side effects such as dysphoria.

Their lower rate of side effects produces many additional advantages. Patients are more comfortable and therefore more compliant. They no longer stand out in society because they walk the “Thorazine shuffle,” and therefore they feel (and are) less stigmatized. Because of the reduced side effects, psychiatrists also feel more comfortable in prescribing medication earlier in the course of a psychotic illness, leading to more aggressive treatment in first episode patients, with the hope that early treatment may prevent a downhill course. The second generation neuroleptics also lead to earlier and better participation in psychosocial rehabilitation programs, a higher level of reintegration, and a better quality of life.

Psychiatrists now recognize a variety of reasons for switching from the older classical neuroleptics to the newer second generation medications. These include: inadequate response of positive symptoms, residual negative symptoms, associated mood symptoms such as depression, residual or unresponsive cognitive symptoms, relapse despite compliance, noncompliance due to adverse events or side effects, and a request from the patient or the patient’s family.

Switching to a second generation neuroleptic usually permits a reduction in the use of anticholinergic drugs for extrapyramidal side effects. For example, one study showed that 75 percent of patients required anticholinergic drugs when on conventional neuroleptics, while the percentage dropped to approximately 30 percent after the patients were switched to risperidone. Likewise, the incidence of

TD has been shown to be lower in patients treated with atypical neuroleptics as compared to conventional medications.

While the new atypical second-generation neuroleptics have many distinct advantages, they also have some disadvantages. The most significant of these is weight gain. This problem was noted quite early in the course of treatment with clozapine. As the newer atypical neuroleptics became available, it became clear that weight gain could potentially become a problem with these drugs. The various atypicals differ in their tendency to induce weight gain, with the problem being more severe with clozapine and olanzapine. If a pattern of weight gain begins to emerge, the clinician should consider strategies that will assist the patient in controlling weight gain, such as dieting or exercise. The possible negative consequences of weight gain are substantial. They include cardiovascular morbidity and mortality, psychosocial distress, and increased risk of diabetes. Furthermore, patients who know that they are gaining excessive amounts of weight may become noncompliant, thereby mitigating many of the positive effects of the newer medications.

Pharmacology of the “Second Generation” Neuroleptics

The second generation neuroleptics represent a significant departure from their predecessors in their basic pharmacology. These drugs are sometimes referred to affirmatively as having a “broad spectrum of action.” Only a decade or two earlier, they would have been called “dirty drugs,” due to this same pharmacologic profile. Because clozapine, the first of these second generation drugs, was noted to have a particularly potent blockade of the serotonin 5HT₂ receptor, initial interest in these drugs focused on their impact on the serotonin system. Unlike dopamine, which has a relatively specific anatomic distribution in nigrostriatal and limbic regions, the serotonin system is broadly distributed throughout the cerebral cortex, with much less associated activity in basal ganglia regions. The therapeutic efficacy of several of the earliest of the second generation neuroleptics was hypothesized to be due to their combined action on both serotonin and dopamine pathways. Both of these two early drugs, risperidone and olanzapine, had a similarly strong blocking effect on D₂ and 5HT₂ receptors. They shared their strong blockade of serotonin receptors with clozapine.

Subsequently, several other new second generation neuroleptic agents have joined the repertoire in countries throughout the world. Not all are registered as accepted drugs in all countries. In addition to clozapine, olanzapine, and risperidone, these new drugs include quetiapine, sertindole, and ziprasidone. Pharmacologists have developed “antipsychotic receptor pie charts” to illustrate their variable pharmacologic profiles. For example, quetiapine has a profile that is very similar to clozapine, in that it has modest D₂ blockade coupled with high 5HT₂ blockade. Both of these compounds also have a very high H₁ component. Several of these new compounds have very strong anti-serotonergic properties, including risperidone, ziprasidone, and sertindole. In comparison with haloperidol, which is a very potent D₂ blocker, all of these compounds have minimal D₂ blockade. The advent of these multiple new drugs had led to widespread discussion of the importance of serotonin blockade as a significant component of any “anti-schizophrenic” medication, as well as any antipsychotic medication.

However, it has been argued that the “receptor pie charts” are simply an abstract concept and may have minimal relevance to effective dosing strategies in human beings suffering from a specific mental illness such as schizophrenia. As described below, the tools of positron emission tomography (PET) imaging have been used to measure receptor blockade *in vivo*. These studies have established that in human beings who take any of these 5HT₂/D₂-blocking drugs, the degree of blockade (and D₂ blockade in particular) is a function of dose. That is, the higher the dose of the medication, the greater the D₂ blockade.

Using Imaging Tools to Develop Rational Dosing Strategies

The use of PET imaging to measure neuroreceptor density was pioneered by two groups working independently at Johns Hopkins University in the United States and at the Karolinska Institute in Stockholm. The Karolinska group used the ligand-binding method, coupled with scatchard plots, to develop a quantitative *in vivo* measure of D₂ blockade. They used the relatively specific D₂ blocker, ¹¹C raclopride, to obtain an image of the distribution of D₂ receptors in the brain, since these receptors were labeled by the ¹¹C raclopride ligand. This method was used originally to measure the numbers of D₂ receptors in patients with schizophrenia. However, it is also a powerful tool for looking at dose-response relationships.

In dose-response studies the ¹¹C-labeled raclopride ligand is injected prior to treatment, giving a picture of the distribution and number of D₂ receptors. The ¹¹C raclopride ligand binds to receptors that

are very specifically localized in the basal ganglia. The location of the receptors can be determined quite specifically by registering the PET scan on an anatomic MR scan. In studies that look at dose-response relationships, the next step is to do a PET study in which available D2 receptors are measured in patients who have been put on a specific drug commonly used for the treatment of schizophrenia. The effects of different doses of the same drug can also be compared. Studies of this type have demonstrated that a relatively low dose of haloperidol (e.g., 2 mg.) is a very potent D2 blocker. A 2 mg dose of haloperidol leads to 74 percent occupancy of available dopamine receptors.

These PET studies have yielded significant evidence about optimal dosing strategies and medication use in schizophrenia. They have demonstrated that, while serotonin blockade may provide an important component of atypical neuroleptic efficacy, D2 occupancy remains quite important. D2 occupancy can be used to predict clinical response. The optimal cutoff for D2 occupancy to yield a good clinical response appears to be approximately in the 65 percent range for improvement either in the Clinical Global Impression (CGI) or in severity of positive symptoms. These studies have also been used to look at the relationship between D2 occupancy and extrapyramidal side effects (EPS) or akathisia. In this instance, the cutoff point is somewhat different. Subjects begin to develop EPS/Akathisia at an occupancy level of approximately 78 percent. D2 occupancy can also predict another medication side effect that is relevant to treatment decisions: prolactin elevation. In this instance, the cutoff is 72 percent. Two out of fifteen subjects with occupancy below 72 percent show prolactin elevation, whereas five out of six show prolactin elevation above 72 percent occupancy.

Studies of this type have been used to determine the optimal dose range for several of the newer second generation medications. For example, the optimal dosage for risperidone is between 2 and 6 mgs, if the goal is to achieve adequate D2 occupancy without also producing EPS. The optimal dose for olanzapine appears to be between 10 and 20 mgs. Within these dose ranges, both of these drugs also produce 5HT2 occupancy in the 90 percent range. These studies validate standard clinical experience with both of these new second generation neuroleptic medications. That is, the appropriate dose for risperidone is in the 2 to 6 mg range (and preferably in the 2 to 4 range), while that for olanzapine is in the 10 to 20 mg range. If these dosing strategies are used, these two medications generally produce a good antipsychotic effect coupled with a low level of side effects.

Practical Aspects of Treatment

Dosage

Because of the increasing concern about side effects, including tardive dyskinesia, psychiatrists have had to find ways to safely reduce their patients' exposure to antipsychotic medication. Early treatment strategies tended to emphasize the use of higher doses. During more recent times, this strategy has been re-evaluated, and investigators have begun to stress the value of using the lowest possible dose.

Studies have shown that a dose of neuroleptics in the range of 4-5 mg/day of haloperidol is effective. For the acute phase of illness, no precise dosage can be arbitrarily recommended. The best strategy is probably to slowly titrate up the dose until target psychotic symptoms (e.g., delusions, hallucinations) begin to remit. Patient body size and gender should also be taken into consideration when prescribing medications, given that women have been shown to be more sensitive to the development of tardive dyskinesia.

For maintenance medication the lowest possible dose is also optimal, but it has not been determined with certainty how best to achieve this dose. Attempts have been made to reduce the average dose used during the acute phase by 50-90%. This strategy has been tested under randomized controlled conditions. One extensive low dose study by Kane and colleagues, involving 126 patients randomly allocated to continue to receive 12.5-50 mg of fluphenazine decanoate every two weeks in the control group, as compared to 1/10 their previous dose in the experimental group, revealed a 50% relapse rate in the dose reduction group and a 7% rate for those who were not reduced. In another setting, Johnson and colleagues found that if patients had their previous maintenance dose reduced by 50%, 32% relapsed in the first year, 56% relapsed in the second year, and 70% relapsed by the end of the third year. Thus there is overwhelming evidence that both withdrawal from long-term maintenance medication and dose reduction by 50% or more carries a significant risk of relapse.

Use of Anticholinergics

Anticholinergic compounds are widely used to reduce the side effects of neuroleptic medication. They are most effective against Parkinsonian effects (tremor, rigidity, akinesia) and the dystonias, but

less so against akathisia and the dyskinesias. While the use of anticholinergic compounds is of great benefit in the treatment of acute episodes of extrapyramidal symptoms, their long-term use is more questionable. They are associated with side effects of their own, principally those attributable to blockade of the parasympathetic system: failure of accommodation, dry mouth, constipation, and difficulty in micturition. They may also cause problems in memory and sleep. All of these effects are dose-related. Anticholinergics may also diminish the therapeutic effects of neuroleptic medication, particularly on positive symptoms.

A reasonable strategy to adopt in the management of extrapyramidal effects is to consider first whether the dose of neuroleptic medication can be reduced. Only if this cannot be done, or cannot be done immediately, should a regular course of anticholinergic medication be instituted.

Oral vs. Depot Neuroleptics

Long-acting depot injections are based on the principle that a decanoate ester of neuroleptics can be dissolved in sesame oil or a comparable lipid substance and will be slowly hydrolyzed after deep injection into muscle, thereby being released into the blood stream over a period of weeks. Fluphenazine and haloperidol decanoate can be routinely used on a monthly basis or more frequently. There are no consistent findings that one depot preparation is better than another or has less side effects, but almost every randomized controlled study has shown a marked advantage for patients who remain on continued medication. However, randomized studies of oral versus depot medication have been unable to demonstrate any difference in relapse rates, but many experts believe that depot medication is associated with a significantly lower risk of relapse, probably because covert noncompliance is prevented by the necessity for patients to report for depot injection at regular intervals. A new depot formulation of risperidone has recently become available. This formulation is the first depot "atypical," and it therefore may offer the advantages that are associated with the newer second generation drugs, in addition to the convenience and compliance advantages of a depot formulation.

Discontinuing Medication and Long-Term Outcome

Discontinuation of neuroleptic medication for patients who have been previously well controlled is associated with a significantly higher relapse rate than continuing medication, even among patients who have been maintained relapse-free for up to five years. Although long-term treatment with neuroleptics reduces the frequency and severity of relapse, most patients can expect to have a relapse at some time, even though they remain on medication. Follow-up studies by Hogarty and colleagues, when extrapolated beyond three-year results, predicted that 87% of patients would relapse on placebo and 65% would relapse on medication. A seven-to-eight year follow-up of 81 patients well maintained on neuroleptics reported that 83% had at least one relapse. Thus, whether patients are treated vigorously or not, relapse is very common among patients suffering from schizophrenia.

Can Antipsychotic Medication Prevent Deterioration?

Although prevention of schizophrenia has yet to be demonstrated, there is accumulating evidence that the prognosis for schizophrenia may be improved when effective treatment is started early in the course of the disorder. However, diagnosis at an early stage may be extremely difficult, particularly in cases where the onset is gradual. Early detection is further hampered by the stigma that is still attached to this disorder in most communities and the erroneous notion that this remains an incurable disorder. There is considerable need for updating the diagnostic skills of the professional community and improved public awareness of the benefits of modern treatment. Improved detection and early intervention with optimal combinations of biomedical and psychosocial treatment strategies offer hope of improved recovery rates, and reductions in long-term disability and handicap.

In working with schizophrenia, patients and their caregivers (including family practitioners, mental health professionals, and family members) may be trained to recognize the early signs of impending exacerbations so that delays in providing effective crisis management will be avoided.

PSYCHOSOCIAL TREATMENTS

The association between psychological factors and schizophrenia has a long history, dating back to the observations of Kraepelin and Bleuler. Both these pioneers noted the often adverse impact of environmental stresses on the course and outcome of this disorder. A series of systematic studies of environmental stress have associated persistent high stress with high morbidity in established cases.

Efforts to define a clear etiological role for stress and other psychosocial factors have been limited by the difficulty in conducting prospective studies in the general population. When such studies have been conducted in groups with a high familial risk for schizophrenia, the results have been equivocal.

The WHO pilot study on schizophrenia showed, however, that the outcome of schizophrenic patients in developing countries is better than in industrialized countries. This might be due to the importance of the familial ties in these countries, which are of help to the patient, by giving more support and therefore decreasing stress in daily life. This is usually less the case for the patients from Western countries. On the other hand, high levels of expressed emotion that represent criticism or overinvolvement can also be factors predisposing to relapse, since the coping abilities of the patient are overwhelmed.

Further, it is clear that the intrinsic nature of the illness process in schizophrenia usually leads to serious deficiencies in coping with interpersonal relationships. This is due to misperceptions of what is happening in the surroundings of the patient. It is also due to the fact that the answers of the schizophrenics are inappropriate towards familial and environmental members. Such misperceptions and inappropriate answers lead to misunderstandings, tense atmosphere, anxiety from both sides, and sometimes to increasing aggressiveness. The consequence of this impairment in communication and interpersonal relationships may ultimately be an exacerbation of symptoms or relapse.

Psychosocial interventions therefore aim at reinforcing the abilities of the patient to communicate in a positive manner with others and to become more adaptive and independent. They also may involve working with family members, who may also need additional psychological support in order to cope with the stress of living with an ill family member. Family members may also benefit from learning how to achieve greater tolerance for the patient's symptoms.

Although many kinds of therapeutic interventions have been shown to have a nonspecific positive impact on most mental illnesses, the types of psychosocial treatment used in schizophrenia need to be targeted to the specific nature of the illness. For example, insight-based therapies usually worsen the state of the schizophrenic patient, while supportive therapies are more beneficial. Not only is it of great importance for the therapist to be supportive to the patient, but to be also the "ambassador of reality" to him or her. This means that choices made by the patient, especially important ones, should take into account available resources and abilities, both internal and external, and should not be made only on the basis of the desires of the patient. Successful decision-making helps combat the social deterioration frequently seen in patients with schizophrenia. As a matter of fact, repetitive failures in desired goals or projects can lead the patient to become even more withdrawn, threatening further attempts to improve his or her social condition.

The combination of neuroleptic medications and psychosocial interventions has a better result than either of them alone. While antipsychotic medications are usually considered to be mandatory for the treatment of schizophrenia, clinicians sometimes overlook the fact that they may also enhance psychosocial interventions by improving the patient's insight and compliance.

Psychosocial research has led to the development of a model that postulates that episodes of schizophrenic symptoms are the result of interactions between biological vulnerability and psychosocial stress factors. While biomedical interventions may reduce vulnerability, psychosocial interventions may enhance a person's capacity to cope with the broad range of stresses that are encountered during the pursuit of personal accomplishments and when dealing with all forms of adversity. Some environmental stressors, such as those associated with social deprivation, are most effectively managed by social casework, which attempts to provide adequate housing, finances, and work and recreation opportunities. The role of specific psychological strategies is to strengthen the coping capacity of patients so that they may be able to maximize their personal abilities and minimize their functional disabilities within the constraints of the community they inhabit.

Psychosocial treatment strategies include:

- Facilitation of pharmacotherapy
- Psychosocial Treatment in the Inpatient Setting
- Specific treatments in the inpatient setting
- Caregiver-based stress management
- Living skills training
- Educational techniques and family therapy
- Social case management
- Specific cognitive-behavioral interventions

Facilitation of Pharmacotherapy

Neuroleptic drug therapy and a calm supportive environment are the basis for facilitating recovery from florid psychotic episodes. Three out of four cases derive substantial benefits from this regimen, although full remission of symptoms occurs in less than two-thirds, with a further third suffering persistent cognitive disturbance and associated deficits of mood, motivation and behavioral responses (i.e., "negative" symptoms).

The continuation of drug therapy once florid episodes have improved has halved the rate of recurrence in the first year after an episode. This prophylactic effect of pharmacotherapy necessitates high levels of adherence to drug regimens. Education about the relative benefits and "costs" (unwanted effects) of long-term drug treatment, combined with psychological strategies that involve active participation in coping with the problems encountered, particularly those likely to reduce compliance with taking medications, is crucial.

Almost all psychosocial strategies are based upon enhancing the understanding of the patient and his or her concerns about the nature of schizophrenia and its optimal clinical management. The cognitive impairments associated with the disorder reduce the effectiveness of this process, unless specific efforts are made to counter these deficits in each case. Some strategies that have been employed include simplifying the presentation of information, brief sessions, repetition, approaches to maximize attention, involving the patient as the "expert," clearly written handouts, visual aids, and ensuring that education is a continuing process. Studies of time-limited education, usually involving family or other caregivers as well as patients, have not shown any impact on reduction in acute episodes, but there is some evidence that continued education may contribute to enhance adherence to drug regimens.

Psychosocial Treatment in the Inpatient Setting

When hospitalized chronic psychotic patients become severely handicapped by the absence of activity and stimulation, the token-economy system can sometimes produce a remarkable improvement in the functioning of the patient, by rewarding daily activities with tokens which can be exchanged with pleasant items. This can represent a first step in the rehabilitation of chronically hospitalized schizophrenics.

Caregiver-Based Stress Management

Interventions that enhance coping with stress in households where people who are vulnerable to acute schizophrenic episodes reside have been shown to reduce the risk of exacerbation during the two years after a florid episode. These clinical benefits appear greatest where the interventions are combined with optimal drug strategies, are continued long-term, employ cognitive and behavioral strategies (e.g., patient education, interpersonal communication and problem solving training), and are integrated with effective case management procedures. Improved social functioning appears to be associated with interventions that aim not merely at reduction of environmental stress, but also encourage patients to increase their range of social activities, and that incorporate skills training procedures.

Living Skills Training

Although clinical remission and social recovery are closely associated, the aim of treatment should always be primarily to restore function. Psychosocial rehabilitation extends the benefits achieved by symptomatic treatment so that disability and handicap is minimized. A range of strategies has been effectively employed to assist persons who have suffered schizophrenia to return to a normal lifestyle, even when the impairments of the disorder persist. Social skills training is a widely-used form of behavioral therapy that aims to train people with deficits in interpersonal skills, such as making conversation, developing friendships, seeking employment, or expanding recreational pursuits. Patients rehearse interpersonal interactions that they find stressful in a group setting and receive supportive coaching from group leaders and fellow participants. Subsequent efforts to cope with similar situations in real-life are reviewed at the following sessions, with further practice and coaching where necessary.

The best evidence to support the efficacy of this approach comes from an outpatient study that compares the benefits of adding social skills training and family stress management to optimal drug therapy. Adding either social skills training or career-based stress management diminished by half the rate of florid episodes experienced with drug therapy alone during the first year of aftercare. The combination of social skills training and family management resulted in no episodes during the first year.

However, the benefits of social skills training were lost at two years. The focus on relapse prevention made assessment of social benefits difficult, but there was some evidence that social disability was reduced by the social skills training. Other studies have shown clinical and social benefits in severely disabled and institutionalized patients. Liberman and his colleagues have developed a series of workbooks and videotaped programs to facilitate training in a wide range of skills.

Social Case Management

The provision of adequate social supports, such as housing, day care, sheltered employment and vocational training, is an essential component of comprehensive long-term management of schizophrenia. When conducted by social workers in a systematic manner over an extended period, specific clinical and social benefits have been observed.

In the acute phase, no additional benefits have been demonstrated when psychosocial strategies have been added to optimal drug treatment. There is no evidence that efforts to enhance the hospital milieu adds to the effectiveness of specific drug treatment. Of course it is crucial that treatment is adequately supervised in a safe, and supportive environment. Alternatives to hospital environments have now been demonstrated as feasible locations for effective intensive care. These have included the provision of intensive care in community settings, including the person's home. Such approaches may reduce the social morbidity associated with under-stimulating residential care.

Educational Techniques and Family Therapy

One of the aims of educational and family therapy is to explain to the patient, as well as to family members, the nature and the course of schizophrenia. Both the patient and family members benefit from education about the types of treatments available and the importance of good compliance for a good outcome. This first explanatory approach is helpful in decreasing the level of stigma or embarrassment among the family members, as well as to increase the awareness of the patient about his illness. If the therapist succeeds in reducing expressed emotion in the family, the rate of relapse decreases sharply, even with less dosage of neuroleptics.

The family members, as well as the patient are taught to identify interpersonal problems, and can be given a systematized way of solving them. Avoiding negative feelings and emotions, and favoring positive ones, create a different climate in the family, which is less stressful to the patient, and which allows him to increase his level of interpersonal interactions within and outside the family.

This can also be achieved through group therapy, especially for the training aimed at increasing the social skills of the patient. Such training is given to enhance his survival abilities in an independent manner, as well as to increase his positive interpersonal relationships in the community. During the sessions, the patient plays a role that is usually difficult for him to cope with in reality. His behavior is analyzed in its various components: eye contact, intonation of voice, gesture, appropriateness of answers; the patient is then asked to change what seems to be an obstacle to a good communication process. The sessions can be video recorded and the tape analyzed with the patient. He or she is asked also to train at home and in the community in real situations, in order to strengthen the learned behaviors. It is obvious that such training should occur outside acute phases of the illness, since delusional thinking or experiences are likely to interfere with the therapy and divert a significant amount of energy. Searching for work is also important during the recovery phase of the illness. A self-help club (composed of patients in various stages of recovery) can be extremely helpful in this situation. Halfway houses and sheltered workshops may also provide important sources of support after inpatient treatment. Outpatient educational and family therapies require a substantial expenditure of personnel and time, although they are probably also more cost-effective than the traditional way of managing patients, especially the ones with numerous hospitalizations. The goal of such intervention is to lower as much as possible the number of these hospitalizations, by helping the patients and their families have better understanding and motivation and thereby to solve concrete daily problems.

Cognitive-Behavioral Interventions

A wide range of psychological strategies have been integrated into comprehensive long-term management of schizophrenia. In addition to skills training and compliance management, operant programs, anger management, anxiety and depression strategies, and sexual counseling, have all been applied to assist with specific problems. Their efficacy has been demonstrated in single case designs.

Recent applications of cognitive-behavioral interventions have focused on reducing the morbidity of psychotic symptoms that are refractory to optimal pharmacotherapy. Tarrier and his colleagues have

demonstrated the efficacy of an approach that aims to teach patients to enhance the coping strategies they employ to cope with persisting delusions and hallucinations.

Sustaining the Benefits

The combined benefits of drug prophylaxis and psychosocial management do not persist after the treatment is withdrawn, necessitating continued application. As already discussed in the Somatic Therapy section above, clinicians should explore the implementation of a "low dosage regimen" for psychosocial as well as somatic therapies after the first three to six months of care. But boosters of greater intensity may be needed to counter periods of major life stress, or other times when symptom exacerbation may emerge. There is some evidence that such an approach may facilitate clinical and social recovery when it is sustained for at least two years.

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