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Drugs That Affect Behavior

1. A 20-year-old single woman who works as a secretary complained of a severe headache. Another secretary working in the same office gave her two aspirin tablets. When her headaches returned in two hours, she bought a bottle of aspirin and took three tablets. She did not have lunch because she felt sick, but drank cup after cup of black coffee. Later, her supervisor advised her to go home and rest when she saw her taking another three aspirin tablets. At home, she continued to feel sick with both headache and nausea, but she could not rest because she had an important date with a new boyfriend. She took four more aspirins. She was brought to the hospital emergency room by her boyfriend when she developed severe nausea, abdominal pains, and dizziness in the evening.

*2. "A man with advanced lymphosarcoma was included in an experimental study of the since-discredited drug Krebiozen. After one administration, his tumors disappeared. When reports came out that the drug was ineffective, the doctor told the patient not to believe what he read and treated him with 'double strength' Krebiozen—actually an injection of water. The patient again experienced rapid remission. Then the AMA and FDA pronounced the drug worthless. The patient died within a few days."**

3. A 40-year-old housewife had been complaining for several years of shortness of breath and easy fatigability. She would not consult a doctor, however, and would demand attention from her husband and children. Eventually, her family treated her like an invalid, with a certain amount of contempt. She gained weight progressively and reduced her activity level. A few weeks ago, her dyspnea became so severe that she agreed to consult a physician. Rheumatic mitral valve disease was diagnosed, and she was placed on a

*From Holden (1978). Quoted with permission. The vignette is based on a case history reported by Klopfer (1957).

regimen of digitalis. Her dyspnea disappeared, and she lost weight dramatically. (The weight gain was largely edema—retention of fluids.) She again felt energetic and resumed her normal activities as an efficient housewife. Her relationship with family members improved and so did her sex life with her husband. She also became socially active again.

4. A 19-year-old single man was admitted to the psychiatric ward of the hospital. For the last several weeks, he had become increasingly withdrawn; he would stay up all night in his room, ostensibly listening to music, and sleep all day long. On the night of admission, his parents found him in his room, screaming at an imaginary person. He was quite incoherent and would not respond to his parents. On the psychiatric unit, he was given an intramuscular injection of chlorpromazine, after which he fell asleep. The following morning, the staff was able to converse with him rationally, although he would lapse into incoherent language from time to time. He was placed on a regular regimen of chlorpromazine.

5. A 60-year-old widow was admitted to the hospital because of severe low back pain. She appeared quite depressed and tearful on admission. History revealed that she had been diagnosed as having a depressive syndrome (see Chapter 6) three years ago, and antidepressant medication had been prescribed. She was "continued" on the antidepressant drug in the hospital. Within ten days, she was much brighter, her tearfulness and hopeless feelings abated, and she slept better. Subsequently, it was found that she had not been taking the antidepressant medication regularly at home because she felt that she needed to take the medication only when she felt extremely depressed. Thus, after receiving again a regular regimen of antidepressants in the hospital, she showed dramatic improvement.

These vignettes illustrate the multiple effects of drugs in the three major dimensions. For example, aspirin taken for the relief of headache (vignette 1) was probably associated with the following sequence of events:

1. Salicylate, by inhibiting prostaglandin synthesis, reduces stimulation of pain receptors and, in addition, acts directly on certain brain areas involved in the processing of pain sensation. These actions affect biological components of the pain and lead to. . . .
2. Relief from the experience of headache (personal dimension), which leads to. . . .
3. The patient's buying a full bottle of aspirin (environmental–interpersonal interaction) when the headache returns. The association of aspirin with relief from headaches is a learned behavior (personal dimension).
4. The patient takes more aspirin, which results in irritation and possible ulceration of the gastroduodenal mucosa (biological).

5. Increased consumption of coffee (personal), perhaps related to anxiety and discomfort associated with interpersonal stress (personal, environmental), contributes further to the gastrointestinal irritation (biological).
6. The observation by her supervisor of her illness behavior (personal) and the aspirin-taking leads to her going home early (environmental change).
7. The date with her boyfriend increases her anxiety (personal), perhaps aggravating the headache, which again leads to increased drug-taking, ultimately resulting in . . .
8. Acute gastrointestinal disturbance and mild salicylate toxicity (biological), leading to hospitalization (environmental).

DRUGS AFFECT ALL DIMENSIONS OF THE PATIENT

Drugs are usually administered with the intent of producing a particular effect in the biological or personal dimension. We may forget that drugs also have effects in dimensions other than those we have in mind. As illustrated in vignette 1, drug effects occur in many subsystems and in all dimensions: behavior of the person, of intracellular processes in neurons, and of other persons and systems in the environment.

The *pharmacological action* of a drug is usually mediated by effects in the biological subsystem, and these often lead to changes that are perceived in the personal dimension. The analgesic effect of aspirin is an example. Sometimes a drug may simultaneously cause desirable changes in the biological dimension and undesirable changes in the personal dimension. Such undesirable side effects may be due to the pharmacological effects of the drug on the central nervous system or to psychological responses to the drug's *symbolic meaning*. Patients with pain who do not respond to methadone, a potent analgesic, may ascribe conflictual symbolic meaning to this drug, which is also used for the management of addiction.

Most drugs have some pharmacological central nervous system action. The physician must keep informed about the central nervous system effects of medications that he prescribes; patients are often concerned about how a drug will make them feel.

As would be expected, there may be complex interactions between drug actions, drug-taking behavior, and the patient's personality (see Chapter 18). Certain patients (e.g., with dependent, demanding person-

alities) may consider drugs as tangible evidence of the doctor's caring, while others (e.g., with orderly, controlling personalities) may view the taking of drugs as a threat to their autonomy. Guarded, suspicious patients may become distrustful of prescribed drugs, suspecting that they might be harmful—even poisonous—especially if unexpected side effects occur and if the doctor–patient relationship is less than optimal. Sedating drugs may be especially threatening to patients who have concerns about autonomy. Patients with long-suffering, self-sacrificing personalities who are "addicted" to the sick role may feel threatened by drugs that promise "cure." Patients with impulsive personalities may be erratic in drug-taking and may unexpectedly abuse or overdose on drugs. Patients with chronic memory deficits may not be able to self-administer drugs because they forget the dosage and schedule and when the medication was last taken. Serious accidental overdosage may occur in these patients.

It is important to remember the *placebo effect* in prescribing any drug. Placebos may act as powerful agents, exerting their effects through as yet incompletely understood central nervous system mechanisms associated with the psychological phenomenon of expectancy. The effects of placebos attest to the powerful influence that the brain can sometimes exert on disease processes and the experience of illness (see vignette 2; see also Chapters 9 and 17 for further discussion of the placebo effect).

Drug effects that may be observed in the *environmental dimension* of the patient may be mediated in several ways. Some drugs cause changes in the *appearance* and *social attractiveness* of the patient, for example, staining of skin by tar ointments used in some dermatological conditions, hair loss caused by cytotoxic agents, and the smell of paraldehyde. The social relationships of patients receiving these drugs may become restricted. Some drugs are used primarily to change the *physical environment,* such as antiseptics in the operating room and insecticides in the home. Antibiotics used indiscriminately may foster the development of drug-resistant strains of bacteria that are dispersed into and contaminate the environment.

In addition to direct effects on the environment, social attitudes toward certain drugs may indirectly influence the behavior of the patient's family and friends. For example, a patient who requires methadone for pain may be stigmatized because of the social symbolic association of methadone with addiction. A patient under "chemotherapy" may be treated by his friends or relatives in accordance with their ideas of how a *cancer patient* should be treated (whether or not the chemotherapy is in fact being given for cancer).

Other indirect effects of drugs in the environmental dimension can be mediated by changes in the *patient's behavior.* A medication causing a depressive syndrome as a side effect may indirectly lead to isolation

of the patient from environmental supports because of social withdrawal; an antidepressant medication, on the other hand, may increase the patient's interaction with the environment.

To reiterate, any drug, no matter what its intended pharmacological action might be, can exert effects in all dimensions—directly, through specific pharmacological actions or symbolic meaning, and indirectly, through induced changes in behavior.

Another important consideration to bear in mind is that *prescription* (or ordering) of a drug does *not* ensure the taking of the drug. One quarter to one half of all outpatients do not take the prescribed medication at all (Blackwell, 1973)! Factors that influence patient compliance with a medication regimen include the patient's understanding of the need for the drug, the duration and schedule of administration, perceived effects and side effects, the symbolic meaning of the medication, the patient's personality, and the status of the doctor–patient relationship (see Chapter 17). In the presence of a good doctor–patient relationship, patients are willing to continue drugs even if they do not seem to have an immediate beneficial effect or despite uncomfortable side effects. Open, comfortable communication between the patient and the doctor will enable the patient to talk to the physician about side effects of the medication rather than to discontinue it without telling the doctor.

Even the *shape, size,* and *color* of medications have important effects on the likelihood of their being taken and on the safety of their use (Mazzullo, 1972). For example, pills of similar size and color can be confused, resulting in an overdosage of one of them. A larger pill often seems stronger to a patient than a smaller pill, regardless of its actual strength.

In the hospital, drugs are usually administered by a nurse in response to a physician's written order, and patients are generally not informed about the medication being given by the nurse. Even when the physician writes an order to continue the same medication the patient had been taking prior to admission, the hospital pharmacy may stock a different brand with a different shape and color. Difficulties and confusion can be avoided by discussing medications with the patient—those to be continued, whether the shape and color will be different, and whether new medications will be added.

PSYCHOTROPIC DRUGS

Some drugs are used primarily to change the patient's mood, thought processes, or behavior. Those medications that have their

primary pharmacological action on the central nervous system and that are used to produce changes in mood, thought processes, or behavior are called *psychotropic* drugs. It should already be obvious from the preceding section that psychotropic drugs are *not* the only medications that may have such effects. The psychotropic drugs, however, may be narrowly defined as a subset of drugs that act primarily and selectively on the central nervous system to produce relatively specific effects rather than general central nervous system stimulation or depression.

Psychotropic drugs may be broadly classified into (1) antianxiety drugs, (2) drugs that affect mood (antidepressants and lithium salts), (3) antipsychotic drugs, and (4) psychotomimetic drugs (those that cause psychosislike syndromes).

We will discuss very briefly general principles concerning the use of the first three classes of psychotropic drugs in clinical management. For detailed information, the reader should consult standard textbooks of pharmacology and psychiatry.

Antianxiety Drugs (Minor Tranquilizers)

As discussed in Chapter 4, anxiety is usually a signal of impending danger that may either be external or originate within the personality system of the patient. Ideally, the best treatment of anxiety is removing or avoiding the danger situation rather than decreasing the danger signal. Many anxiety situations are not amenable to relief by immediate intervention, but may subside or undergo resolution given adequate time. It may be necessary and desirable in such cases to reduce overwhelming anxiety and so reduce also the strength of associated physiological reactions that may themselves have pathogenic effects (see Chapter 4). Especially in hospitalized patients, excessive anxiety may interfere with recovery (e.g., in patients with myocardial infarction). As noted earlier, hospitalization and medical procedures in and of themselves almost always induce and aggravate anxiety.

Drugs commonly prescribed for their antianxiety effects include benzodiazepines, barbiturates, propanediol carbamates, antihistaminics, and antipsychotic medications in small doses.

Benzodiazepines such as chlordiazepoxide (Librium), diazepam (Valium), and alprazolam (Xanax) (see also p. 444) are the most commonly used and abused. Benzodiazepines bind to specific benzodiazepine receptors, which are functionally linked to the γ-aminobutyric acid (GABA) recognition sites, and form a GABA–benzodiazepine–chloride ionophore complex (Hoehn-Saric, 1982; Squires and Braestrup, 1977; Snyder *et al.*, 1977; Stein *et al.*, 1977). Benzodiazepines potentiate GABA, which in turn

Table 23. Commonly Prescribed Benzodiazepines in the United States[a]

Drug	Approximate dose equivalence (mg)	Relative rapidity of effect	Active metabolites	Half-life (hr)
Chlordiazepoxide (Librium)	10	Intermediate	Yes	5–30
Clorazepate (Tranxene)	7.5	Fast	Yes	30–200
Diazepam (Valium)	5	Fastest	Yes	20–100
Lorazepam (Ativan)	1	Intermediate	No	10–20
Oxazepam (Serax)	15	Slower	No	5–15
Prazepam (Centrax)	10	Slowest	Yes	30–200

[a]From Rosenbaum (1982). Reprinted with permission.

decreases neuronal activity by opening chloride channels that are directly linked to the GABA receptors. The resultant influx of chloride ions hyperpolarizes the cell and renders it less excitable.

Benzodiazepines are effective in reducing anxiety but may be habit-forming and, in some individuals, may produce paradoxical agitation, confusion, or fatigue. Benzodiazepines can also be used as hypnotics (to induce sleep); they do not affect REM but decrease stage 4 sleep. They also increase the seizure threshold. See Table 23 for a list of commonly used benzodiazepines.

Antipsychotic drugs (discussed below) also have antianxiety action and can be used in small doses (about one tenth of the antipsychotic dose) to treat anxiety in nonpsychotic patients. One should be aware of infrequent but serious side effects of antipsychotic agents, such as tardive dyskinesia, when one considers using them (see below).

Barbiturates and *propanediol carbamates* (e.g., tybamate and meprobamate) are similar in action to benzodiazepines, but perhaps more sedating and less specifically "anxiolytic." *Antihistaminics* are primarily sedating.

In addition to the drugs mentioned above, *narcotic analgesics* such as morphine are anxiolytic, especially in patients with severe pain or other physical distress such as shortness of breath. For such patients, adequate analgesia is also adequate treatment of anxiety.

A general principle in the use of antianxiety agents is that they should be used intermittently and for short periods of time because of their addictive potential. Concurrent comprehensive evaluation of the danger situation or a medical condition that may cause anxiety symptoms (Chapter 4) should be carried out, and the possibility of referral for counseling or psychotherapy should be considered. Self-control techniques of anxiety

reduction, such as self-hypnosis, relaxation exercises, and pursuing hobbies, are sometimes helpful and should also be considered.

Drugs That Affect Mood

Antidepressants. Drugs used in the treatment of the depressive syndrome are called antidepressants. When a depressed patient also shows signs of psychotic thought disorder (such as delusions), antipsychotic agents are often used in addition to antidepressants.

The antidepressants are not necessarily central nervous system stimulants. When an antidepressant is given to a normal person, the effect is usually sedation and drowsiness rather than euphoria. When it is administered to a patient with the depressive syndrome (see Chapter 6), in 80–90% of cases, there will be clear improvement, usually manifest in about two weeks' time, and often dramatic improvement by four to six weeks.

There are two major classes of antidepressants: the monoamine oxidase (MAO) inhibitors and the tricyclic antidepressants. Both classes of drugs ultimately seem to cause an increase in the functional levels of biogenic amines in the brain, especially norepinephrine and serotonin. The MAO inhibitors are believed to act by reducing the intraneuronal breakdown of biogenic amines by MAO.

The tricyclic antidepressants were initially thought to work primarily by inhibiting the reuptake of norepinephrine or serotonin or both at the nerve terminals, thus increasing their functional availability at the synapse. More recently, however, the modulating effect of tricyclic and other antidepressant drugs on the biogenic amine *receptor sensitivity* has received much attention. Long-term treatment with tricyclic antidepressants, MAO inhibitors, and electroshock therapy has consistently resulted in an enhancement of responses to serotonergic and (α_1-adrenergic stimulation through development of postsynaptic receptor supersensitivity and a reduction in the sensitivity of the β-adrenergic receptors (Charney *et al.*, 1981a). Charney *et al.* (1981b) proposed, on the basis of these findings, that the changes in postsynaptic receptor sensitivity may be the "final common pathway" of antidepressant action. It is generally believed currently that the ultimate effects of antidepressant therapy involve a normalization of the dysregulation of the various biogenic amine systems involved in mood modulation (see Figures 10 and 12 [Chapter 6]).

Tricyclic antidepressants. Imipramine, desipramine, amitriptyline, protriptyline, and doxepin are examples of tricyclic antidepressants. Imipramine (Tofranil) seems to have a greater effect on norepinephrine-containing neurons, while amitriptyline (Elavil) has a greater effect on serotonergic neurons in usual therapeutic doses (Maas, 1978).

Tricyclic antidepressants have a number of *side effects,* especially due to their *anticholinergic* effects. They include dry mouth, blurry vision, urinary retention, tachycardia, and orthostatic hypotension.

Tricyclic antidepressants do not seem to increase the risk of cardiac arrhythmias except in overdoses (Boston Collaborative Drug Surveillance Program, 1972). In fact, tricyclics seem to have quinidinelike antiarrhythmic effect (Kantor *et al.,* 1978). Amitriptyline has the most anticholinergic effect, desipramine the least.

Tricyclic antidepressants are also *sedating,* so that a hypnotic drug may not be necessary if the antidepressant is given at night. Tricyclics increase delta sleep and decrease REM. Amitriptyline appears to be more sedating than imipramine. Protriptyline seems to have little sedative property.

Tricyclic antidepressants interact with a number of other medications. For example, they reduce the potency of antihypertensive agents such as guanethidine by interfering with their uptake by the peripheral adrenergic neurons. Tricyclics should not be given with MAO inhibitors because of possible severe hypertensive crisis.

Tricyclic antidepressants are generally nonaddicting, and tolerance to the antidepressant effect does not develop, although the anticholinergic effects do become better tolerated.

Tricyclic antidepressants are toxic in large doses, primarily due to the anticholinergic effects and the cardiotoxic effect of an increase in the catecholamines in cardiac tissue. In prescribing tricyclic antidepressants, the possibility of overdose with suicidal intent should be considered.

In addition to treatment of depression, tricyclic antidepressants may be used to treat enuresis in childhood, severe obsessive-compulsive disorders, as well as phobic anxiety and panic states.

Maprotiline (Ludiomil) is a tetracyclic compound and trazodone (Desyrel) is a phenylpiperazine derivative. Both seem to have antidepressant actions and side effects similar to those of the tricyclics, except that their anticholinergic action seems to be less prominent (Hollister, 1981).

Alprazolam (Xanax) is a benzodiazepine that has both antianxiety and mild antidepressant action.

Newer nontricyclic antidepressants. Fluoxetine (Prozac) is a relatively new antidepressant that seems to influence the serotonergic system exclusively (inhibits serotonin reuptake). Its side effects are very different from tricyclics in that there is very little anticholinergic, sedating, or cardiovascular effects and an overdose of fluoxetine does not seem to be

lethal in most cases. Fluoxetine's side effects include anxiety, suppression of appetite, and insomnia (because of this, the drug should not be used at night).

Bupropion (Wellbutrin) is another relatively new antidepressant that seems to have dopaminergic activity. It also has fewer anticholinergic and sedative effects than tricyclics, and no weight gain or cardiovascular effects are reported. Grand mal seizures have been reported in approximately 0.4% of patients, however.

MAO inhibitors. Phenelzine (Nardil), tranylcypromine (Parnate), and isocarboxazid (Marplan) are examples of MAO inhibitors. Unlike tricyclic antidepressants, MAO inhibitors, especially tranylcypromine, may have amphetaminelike central-nervous-system-stimulating properties in addition to their antidepressant effect. The antidepressant effect of MAO inhibitors is considered to be related to the drug's entering into stable combination with the enzyme MAO, thereby irreversibly inhibiting its action.

MAO inhibitors are potent REM suppressants. They can also lower blood pressure, although their anticholinergic effects are much less potent than those of the tricyclic antidepressants (Snyder, 1977).

A major consideration in the use of MAO inhibitors is that they *interact* with a number of *foods* and *beverages,* as well as with other medications. In general, any sympathomimetic drugs and foods containing sympathomimetic amines, particularly *tyramine,* can cause a *hypertensive crisis* in conjunction with an MAO inhibitor. Cerebrovascular accidents may occur during the hypertensive crises. Foods containing tyramine include cheese, beer, wine, pickled herring, chicken liver, aged meats, sausage, broad-bean pods, coffee, yeast, and canned figs. Many nonprescription drugs contain sympathomimetic agents. MAO inhibitors potentiate the effects of biogenic amine precursors like L-dopa. *Meperidine* is *contraindicated* and can cause marked hyperpyrexia. MAO inhibitors can interfere with the detoxification mechanisms of many drugs, including barbiturates, alcohol, anticholinergics, and tricyclic antidepressants. Patients on MAO inhibitors should be cautioned not to take any other medication without consulting the physician and should be given a *list of foods and medications* that should not be taken concurrently.

There is some evidence that "atypical" depressives who do not show a classic depressive syndrome but whose depression is severe enough to warrant drug treatment may benefit from MAO inhibitors more than from tricyclic antidepressants. This population includes patients with depressive and hypochondriacal symptoms (Robinson *et al.,* 1978). In view of the myriad interactions with foods and other drugs, however, treatment with MAO inhibitors should be considered with extreme caution and used only when the physician is satisfied that there will be full compliance with the instructions.

In addition to treatment of depression, tricyclics and MAO inhibitors have been used to treat panic disorders, bulimia, and narcolepsy (utilizing the REM-suppressant action).

Lithium Salts. Lithium salts were used in the 1940s as a salt substitute for cardiac patients. Deaths occurred due to lithium poisoning, and the use of lithium salts was discontinued until the reintroduction of lithium as an antimanic drug in the 1960s. Lithium is currently used as a carbonate (Li_2CO_3). Lithium carbonate is effective in the *treatment of acute mania* (improvement in 70–80% of patients within 10–14 days) and as a maintenance drug in the *prevention* of manic attacks (Goodwin and Ebert, 1973). Lithium is also effective as a maintenance drug in reducing the number and intensity of recurrent unipolar depressive episodes (Baldessarini and Lipinski, 1975). This may be especially helpful in patients who have already shown recurrent episodes of depression (see Chapter 6).

Lithium carbonate may also be used to augment the antidepressant effect of a tricyclic or an MAO inhibitor drug in patients with refractory depression (De Montigny *et al.,* 1981). Dramatic improvements have been reported within two to three days of the initiation of lithium in patients who had been receiving an antidepressant drug without much effect.

The mechanism of action of lithium seems to be attributable to its being an "imperfect substitute" for other cations such as sodium and potassium and to its alteration of the intracellular microenvironment necessary for hormone action (Singer and Rotenberg, 1973). The latter involves interference with the hormone activation of adenyl cyclase or the action of cyclic AMP.

How lithium reverses and prevents mania and how it prevents depressive episodes are not completely known. Lithium may correct the tendency toward increased intracellular sodium concentration in affective disorders (see Chapter 6). There is evidence that lithium may exert antagonistic actions at catecholamine-mediated synapses in the brain. On a short-term basis, lithium increases serotonin turnover in the brain. With chronic administration, however, the turnover rate becomes normalized. Lithium initially increases norepinephrine turnover in rat brain, but on a long-term basis, the norepinephrine synthesis is normal. Lithium may increase the intraneuronal release of norepinephrine to be metabolized by MAO and decrease its extraneuronal release. Lithium inhibits basal and norepinephrine-activated adenyl cyclase (Gerbino *et al.,* 1978).

Lithium may also decrease the synthesis and release of acetylcholine and affect the metabolism of GABA and glutamates in the brain (Baldessarini and Lipinski, 1975). The overall clinical effect of lithium seems to be stabilization of moods.

In using lithium carbonate, it is necessary to *monitor* the plasma *lithium concentration* on a regular basis. The therapeutic range is 1.0–1.5 mEq/liter initially, and for maintenance, 0.6–1.0 mEq/liter. The plasma level of lithium should *never* exceed 2 mEq/liter! The blood level should be drawn preferably 12 hr after ingestion of the last dose. Lithium should be administered in divided doses to maintain, as much as possible, steady blood levels.

Lithium can cause fatigue and muscular weakness. Toxic signs include nausea, vomiting, diarrhea, slurred speech, and ataxia. Other side effects include nephrogenic diabetes insipidus, goiter with hypothyroidism, and EEG changes.

Lithium should be administered *with extreme caution* to patients on a sodium-restricted diet, because lithium excretion is slow and severe toxicity may occur. Lithium decreases the pressor effect of norepinephrine.

Carbamazepine (Tegretol) is an antiseizure drug that seems to be effective in acute mania, and may be used as a substitute for, or in combination with, lithium salts. Carbamazepine may cause agranulocytosis as a side effect.

Clonazepam (Clonopin) is a benzodiazepine that is primarily used as an antiseizure medication. Clonazepam is also effective in some cases of bipolar disorders.

Antipsychotic Drugs (Major Tranquilizers, Neuroleptics)

A number of drugs are now available for the treatment of psychotic states, including *schizophrenia.* They generally fall into one of the following categories: phenothiazines, butyrophenones, thioxanthines, dibenzodiazepines, and rauwolfia alkaloids.

The phenothiazines are representative of the antipsychotics. Synthesized in 1883, phenothiazine was first used in the 1930s as an anthelmintic, urinary antiseptic, and insecticide. Promethazine, a phenothiazine, was used as an antihistamine, sedative, and, in the early 1950s, as premedication for anesthesia. The introduction of chlorpromazine as an antipsychotic agent in the late 1950s and its wide acceptance in the 1960s revolutionized psychiatric treatment for schizophrenia.

All drugs that belong to the category of antipsychotic agents have, to a greater or lesser extent, certain features in common, as represented by chlorpromazine.

Central Nervous System Effects. All antipsychotics except rauwolfia alkaloids *block dopamine receptors* in the brain (see Figure 11 [Chapter 6]). The dopamine-receptor blockade in the dopaminergic mesolimbic system by the antipsychotics is considered to be the main mechanism of the antipsychotic effect. Dopaminergic blockade in the nigrostriatal tract by the antipsychotic agents can result in extrapyramidal symptoms, including parkinsonian features, dystonias, and the serious side effect of *tardive dyskinesia.* Tardive dyskinesia is a syndrome that is marked by characteristic involuntary movements of the mouth, tongue, and other parts of the body. It is considered to be due to the development of "receptor hypersensitivity" of the postsynaptic neurons (see the section on Behavioral Effects). Dopaminergic blockade is also probably responsible for the increase in prolactin levels in patients receiving antipsychotics, since dopamine normally inhibits prolactin release from the pituitary. Increased prolactin levels may cause gynecomastia and lactation. Rauwolfia alkaloids such as reserpine probably exert antipsychotic action through depletion of biogenic amines in the neurons, including dopamine, norepinephrine, and serotonin. Antipsychotic agents also block the reuptake of norepinephrine and serotonin in the brain, but do not affect GABA.

At the hypothalamic level, antipsychotic agents inhibit the release of growth hormone and may antagonize the release of the hypothalamic prolactin-release-inhibiting hormone. Hypothalamic temperature regulation may be interfered with by antipsychotics, and *hypothermia* may ensue.

Antipsychotics seem to increase the "filtering activity" of the reticular activating system in the brain stem, reducing the inflow of stimuli in a selective fashion (see Figure 7 [Chapter 4]). Antipsychotics have varying degrees of antiemetic action through an action on the chemoreceptor trigger zone. Chlorpromazine (Thorazine) and prochlorperazine (Compazine) have relatively high antiemetic action.

Antipsychotic agents slow the EEG pattern but also *lower the seizure threshold.* Drug-induced seizures are common among patients with preexisting seizure disorders or with a tendency to seizures.

Autonomic Nervous System Effects. Antipsychotic agents have varying degrees of *anticholinergic* activity, *anti-α-adrenergic* activity (direct receptor block), *adrenergic* activity (through blockade of reuptake of catecholamines), and *antihistaminic* activity. Chlorpromazine may reverse the pressor effects of epinephrine. Postural hypotension occurs more commonly with chlorpromazine than with more potent (and thus used in small doses) piperazine-ring phenothiazines such as fluphenazine or butyrophenones. Thioridazine (Mellaril) may cause ejaculatory

incompetence in male patients. In high doses, thioridazine may also cause retinitis pigmentosa.

Behavioral Effects. Antipsychotic drugs have a *specific effect* on psychotic individuals in reversing or reducing the psychotic symptomatology, including the thought disorder, autism, hallucinations, and paranoid ideations. Agitation or belligerence is also reduced. These effects tend to occur over the course of several weeks in schizophrenia. Psychotic states due to any disease process, including organic psychosis as well as schizophrenia, often respond to antipsychotics.

In addition to the specific antipsychotic effect, the antipsychotic agents also have varying degrees of *sedative action.* Characteristically, the sedation caused by antipsychotic agents is accompanied by a feeling of indifference to environmental events and psychomotor slowing. This phenomenon has been called the "neuroleptic syndrome," and the antipsychotics, *"neuroleptic drugs."* Antipsychotic drugs are also called "major tranquilizers," in comparison to the antianxiety agents like benzodiazepines, which are called "minor tranquilizers."

In experimental animals, antipsychotic agents impair *conditioned avoidance learning.* This test is often used for screening drugs that might possess antipsychotic effects. Minor tranquilizers do not have this effect. Sleep caused by a sedating antipsychotic drug such as chlorpromazine is easily arousable.

All antipsychotic agents reduce spontaneous *motor activity* in humans and animals. In large doses, this blends into the *parkinsonian* picture of rigidity, loss of associated movements, and tremors. Some patients may develop *catalepsy* ("waxy flexibility") with the administration of large doses of antipsychotics. *Akathisia* is an extrapyramidal symptom caused by some antipsychotics. It is characterized by a marked increase in motor activity and restlessness and a literal inability to sit still. This as well as other extrapyramidal symptoms can be effectively reversed with anticholinergic agents or antihistaminic agents such as benztropine (Cogentin) or diphenhydramine (Benadryl). A serious side effect with prolonged use is *tardive dyskinesia.* This syndrome is often irreversible.

The side effects of antipsychotics, in addition to those already mentioned, include hepatic microsomal enzyme induction, obstructive jaundice, cardiac arrhythmias, EEG changes, blood dyscrasias, photosensitivity, and skin rash. Clozapine (clorazil) is a newer neuroleptic that is effective for both the positive and negative symptoms of schizophrenia, has minimal extrapyramidal effects, but has a higher incidence of agranulocytosis and seizures.

Indications and Precautions. In the presence of a psychotic state, antipsychotic agents are indicated to control the psychotic symptoms. In psychosis associated with an underlying medical disease (see Tables 6 [Chapter 7] and 21 [Chapter 13]), treatment of the underlying disease should accompany symptomatic treatment of the psychosis with antipsychotic agents. The choice of drug depends, to a large extent, on the side effects to be avoided or taken advantage of. For example, an agitated patient might receive a more sedating phenothiazine such as chlorpromazine, while a psychomotor-retarded, depressed, psychotic patient might do better with a less sedating drug. For details concerning the side effects of individual antipsychotic drugs, the reader, as noted earlier, is referred to standard textbooks of psychiatry and pharmacology.

SUMMARY

Although drugs are usually administered to effect a particular change in the biological or personal dimension, all three dimensions, including the environmental–social dimension, are affected by drugs.

The pharmacological action of a drug is usually mediated by changes in the *biological dimension,* which may eventually cause changes in the *personal dimension* (e.g., analgesia). The personal dimension may be affected, additionally, by the *symbolic meaning* of the drug. The *placebo effect* is a potent and often beneficial effect that accompanies the use of any drug and may augment its action. The *environmental dimension* of the patient may be affected by drugs directly (e.g., foul odor of the breath of a patient taking paraldehyde) or indirectly (through the symbolic meaning of the drug to others or through the behavioral change of the patient).

Prescribing a drug is *not* equivalent to its actual administration. Up to one half of outpatients do not take prescribed drugs. The factors that affect *compliance* with a drug regimen include (1) the quality of the doctor–patient relationship, (2) the shape, size, and color of the drug, (3) the patient's information about the drug, and (4) the personality of the patient.

Psychotropic medications are drugs the primary pharmacological action of which is on the central nervous system to produce relatively selective changes in mood, thought processes, or behavior. They include *antianxiety drugs, drugs that affect mood, antipsychotic drugs,* and psychotomimetic *drugs.*

The *benzodiazepines* are the most commonly used *antianxiety* agents. While they are usually effective, they may produce paradoxical agitation in some individuals. They increase seizure threshold and reduce delta sleep. They are also sedating and may be used as hypnotics (especially flurazepam). The benzodiazepines are habit-forming with prolonged use. Antianxiety agents should be used judiciously and, generally, temporarily.

The *tricyclic* antidepressants *imipramine, amitriptyline,* and *fluoxetine* are the most commonly used antidepressants. They seem to block the reuptake by the presynaptic membrane of released norepinephrine or serotonin or both, which causes an increase in the functional levels of these amines at the synapse. In addition, their long-term effects include an enhanced sensitivity of postsynaptic serotonin and α_1-receptors and reduced sensitivity of β-receptors.

The antidepressants require time to work fully; usually, at least 10–14 days are necessary before the effects are manifested. The most common side effects of tricyclics are sedation and anticholinergic effects.

There are many drug interactions with *monoamine oxidase inhibitors,* and many foods, especially those containing the pressor amine tyramine, interact with the MAO inhibitors, causing serious hypertension. Meperidine is contraindicated in a patient receiving an MAO inhibitor.

Lithium carbonate is effective as an *antimanic* agent and also in preventing recurrent unipolar depressions. The plasma lithium level must be monitored in patients receiving lithium. The therapeutic range is 0.6–1.5 mEq/liter. Lithium should be administered with extreme caution to patients on sodium-restricted diets.

The *phenothiazines* and *butyrophenones* are representative *antipsychotic* agents. Their action seems to be the blockade of dopamine receptors, and they appear to increase the filtering activity of the reticular activating system. They tend to be sedating, and some have antiemetic action. They lower the seizure threshold and impair conditioned learning in animals. Autonomic side effects include orthostatic hypotension and anticholinergic effects. Neurological side effects include pseudoparkinsonism, akathisia, and tardive dyskinesia.

IMPLICATIONS

For the Patient

Properties other than the specific pharmacological action of a drug may be of primary importance to the patient, for example, the size, color, shape, and name of the drug as well as the price. The symbolic meaning of the medication also plays an important role in the patient's perception and expectations of a drug. Many patients do not comply with a drug regimen. This may be due to a number of reasons, the most important being the lack of a trusting doctor–patient relationship and associated lack of communication. The side effects of medications, although not alarming to the doctor, may be quite frightening to the patient if unexpected. Some patients attach extraordinary significance and importance to taking drugs and may become dependent on them.

For the Physician

Physicians should recognize that drugs affect all dimensions of the patient, regardless of the desired specific pharmacological action. In discussing and prescribing a medication, the physician should take into account the patient's personality type, previous experience with drugs, and expectations and symbolic meanings of the proposed drug. Specific questions must be asked to obtain such information. Good compliance with a drug regimen rests on a good doctor–patient relationship and an open channel of communication. The significance of the nonpharmacological aspects of drugs, such as the size, shape, and color of a pill, should be recognized and understood by the physician. Explanation concerning possible side effects of a medication is essential in reassuring the patient and maintaining a good doctor–patient relationship. The physician should be familiar with the effects of any planned medication in all dimensions of the patient and also with its interaction with other drugs and substances (e.g., tyramine-containing foods and MAO inhibitors).

For the Community and the Health-Care System

The community should be educated about the fact that drugs have many actions, some of which may be dangerous in themselves or in interaction with other drugs and substances. The public should learn to use medications only in consultation with a physician. Medical education should emphasize that any drug affects all three dimensions of the patient. Emphasis should also be placed on the nonpharmacological aspects of drugs, such as the shape, size, color, name, and symbolic meaning. Unrealistic and exaggerated claims by some pharmaceutical companies concerning their products should be regulated.

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RECOMMENDED READING

Goodman LS, Gilman A: *Goodman and Gilman's The Pharmacologic Basis of Therapeutics,* ed 8. Pergamon Press, New York, 1990. This is the standard textbook of pharmacology. We would especially suggest the chapter on drugs and the treatment of psychiatric disorders for a more detailed treatment of the subject. An excellent reference for all questions concerning drugs.

Hansten PD, Horn JR: *Drug Interactions: Clinical Significance of Drug-Drug Interactions,* ed 6. Philadelphia, Lea & Febiger, 1989. A very useful reference. Various drug interactions are presented in a tabular form.

Jarvik ME (ed): *Psychopharmacology in the Practice of Medicine.* New York, Appleton-Century-Crofts, 1977. A multiauthor volume. Unlike that edited by Lipton *et al.* (see below), this is oriented more toward the primary physician. Concise but comprehensive.

Meltzer HY (ed): *Psychopharmacology: The Third Generation of Progress* (in association with the American College of Neuropsychopharmacology). New York, Raven Press, 1987. A comprehensive and authoritative book on various aspects of the progress in psychopharmacology, including basic biochemistry, neurophysiology, and clinical psychopharmacology. An excellent reference.