American Handbook of Psychiatry

ADVANCES IN PSYCHO-PHARMACOLOGY

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Table of Contents

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The discovery of the therapeutic uses of the antipsychotic drugs, the tricyclics, the MAO inhibitors, lithium, and the benzodiazepines have revolutionized psychiatry. In this chapter, we provide an account of advances in psychopharmacology that have occurred since the appearance of the original section on psychopharmacology in volume V of the *American Handbook of Psychiatry.*

Before we proceed, let us review. Between 1949, when lithium was discovered, and the publication of the most recent chapter on psychopharmacology in the *American Handbook of Psychiatry,* various psychoactive drugs were introduced. The best way to review their status is to give an overall summary of their efficacy. For purposes of comparison and a general presentation, we have compiled summary data to show the efficacy of new treatment in comparison with the older placebo treatment. These are presented in the context of similar data for the classical antibiotics—streptomycin for tuberculosis and penicillin for pneumococcal pneumonia.

Summary: The Power of Psychoactive Drugs

The drug-placebo difference is a meaningful measurement of the overall

efficacy of a specific drug administered to patients with a specific disease. In terms of drug-placebo differences, the advance in psychotropic drugs is comparable to major innovations in chemotherapy.

Table 5-1 summarizes data from the National Institute of Mental Health (NIMH) Collaborative Study Number 1 on the efficacy of the treatment of acute schizophrenia with drugs and placebo and from studies by the British Medical Research Council on the efficacy of treatment for tuberculosis with streptomycin. Data on the treatment of pneumococcal pneumonia with penicillin and sulfonilamide and the use of drugs in surgery are also included. The drug-placebo difference is expressed as a product-moment correlation coefficient *R,* in which the higher the correlation, the bigger the difference.

Table 5-1 Percentage of Patients Who Do Well on Various Treatments

		WELL	POOR	R
Antipsychotic for treatment of	Drug	70%	25%	
acute schizophrenia	Placebo	30%	75%	.45
Maintenance antipsychotic for	Drug	80%	20%	
prophylaxis	Placebo	47%	53%	34
Imipramine acute depression	Drug	65%	35%	
	Placebo	32%	68%	.33
Tricyclic prophylaxis of	Drug	73%	27%	
depression	Placebo	48%	52%	.26

Lithium acute mania	Drug	73%	28%	
	Placebo	34%	66%	.38
Lithium prophylaxis of mania	Drug	63%	37%	
depression	Placebo	21%	79%	.43
Streptomycin for tuberculosis	Drug	69%	33%	
	Standard	31%	67%	.36
Penicillin for pneumococcal	Penicillin	93%	6%	
pneumonia	Sulfanilamide	88%	11%	.10
Drugs in surgery—1964-72	New	63%	37%	
	Old	57%	43%	.06

Although we caution against an overly concrete interpretation of such data, it appears that the discovery of effective psychotropic drugs is as much a breakthrough for psychiatry as the discovery of antibiotics was for medicine. Of course, no quantitative comparison can be made on the efficacy of different drugs for different disorders. However, the fourfold drug-placebo differences presented here facilitate qualitative comparisons between diseases treated and drug effects.

There have been many advances in psychopharmacology since the previous volumes of the *American Handbook.* More is known about plasma level and therapeutic efficacy and the dosages. Within the space limitations of this chapter, we shall discuss recent advances in psychopharmacology believed to be particularly significant. In the process of choosing studies to

review or topics to cover, we have, of necessity, been selective. There are some important problems that have been omitted because of few significant advances or a lack of firm knowledge.

Antipsychotic Drugs

Since the cause of schizophrenia is unknown, the exact mechanism by which the antipsychotic drugs biologically or psychologically benefit schizophrenics cannot be determined. We have previously examined the different symptoms that are ameliorated by antipsychotic drugs and find that these drugs lessen symptoms typical of schizophrenia, be they fundamental or accessory. If the antipsychotic drugs are, in essence, antianxiety agents, one would expect the greatest effect to be on anxiety and a lesser effect on symptoms more distinctly related to anxiety. This is not the case. All schizophrenic symptoms of abnormality appear to be benefitted by the antipsychotic drugs. Generally, schizophrenia is quantitated by rating scales which, in essence, are Kraepelin in orientation in that they evaluate the severity of symptoms and arrive at a total score as a summation of the severity of each of the individual symptoms. It is of psychological interest to find out whether the antipsychotic drugs relieve the thought disorders of schizophrenia as well as the other symptoms. Although Kraepelin discussed the typical thought disorder that occurs in schizophrenia, Bleuler was responsible for greater focusing and discussion of thought disorders, which

may be, in some sense, fundamental to schizophrenia. Holzman and Johnston have developed a psychological instrument to quantitate the degree of schizophrenic thought disorder and to verify that thought is disturbed in schizophrenia. It will be of interest to see if antipsychotic drugs have a beneficial effect on schizophrenic thought disorder, and, if so, whether this improvement is parallel to the extent and rate of the disappearance of the symptoms. Improvement in schizophrenic symptomatology as a function of drug treatment, was further assessed by the authors in collaboration with Holzman, Ericksen, and Hurt. Measures were obtained from patients suffering with thought disorder before and after drug administration. This was accomplished by means of a standard rating scale and responses to items from the Wechsler Adult Intelligence Scale and Rorschach cards. Blind assessments of the degree of thought disorder were performed by the psychologists. The most salient findings to emerge were the substantial reduction in psychotic symptoms among the study sample and the observation that the decrease in thought disorder occurred to the same degree and with the same time course as the schizophrenic symptomatology (see figure 5-1).

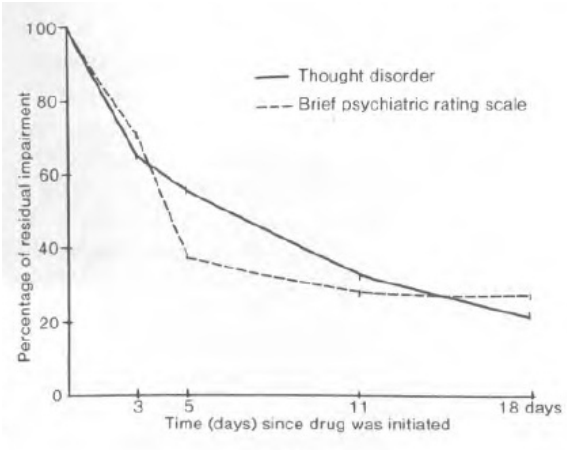


Figure 5-1.

Psychologists continue to speculate as to the underlying psychological and functional abnormalities of schizophrenia. It has been suggested that maintenance of a psychological set is problematic for such individuals, that is, they show poor concentration on certain tasks. Spohn and coworkers studied the effects of antipsychotics on the performance of chronic schizophrenic patients. Random assignment to chlorpromazine or placebo was arranged following a six-week washout period. Some of the patients (sixteen out of sixty-three) relapsed during this period, with a relapse rate of 17 percent per month. Forty patients in this study on placebo baseline were examined by means of a psychological test battery during the washout period, and again while on chlorpromazine or placebo at one, four, and eight weeks. Chlorpromazine proved to be more effective than placebo in bringing about

improvement, but due to the dropout of a quarter of the samples during the washout period, the drug-placebo differences were probably underestimated. The patients were also given an assortment of protocols aimed at assessing malfunctioning attentional, perceptual, and psychophysiological skills.

It was reported that chlorpromazine reduced overestimation and fixation time on a test of perception and increased verbal accuracy of perceptual judgment. Powers of attention and concentration were improved. The result common to these tests may be the ability to attend appropriately to the task in question. These results accord well with the normalization of symptoms and/or thought disorder just discussed.

In sum, the action of antipsychotic drugs suggests a normalizing effect. They reduce typical hallucinations and delusions. They speed up retarded schizophrenics and slow down the more excited ones. Yet, to classify these agents as antischizophrenic fails to do them justice as they are also effective in the treatment of psychotic depression, mania, and organic psychosis. It should be noted that those symptoms that are reduced by the phenothiazines are characteristics of psychosis, in general, and schizophrenia, in particular (see table 5-2). As such, the most judicious reference to them may be as antipsychotic drugs. The term tranquilizer is clearly inappropriate, since they do not produce a state of tranquility. Normal individuals often find their effects somewhat distasteful. If antipsychotic drugs produced their

therapeutic benefits through sedation, it would be expected that sedative drugs would be more efficacious than non-sedative antipsychotics. This is not the case. Furthermore, antipsychotics that are maximally stimulating are as potent as antipsychotics with maximal sedative properties. It is, therefore, an error to conceive of these drugs as a distinctive or special form of sedative.

Does Any Subtype of Schizophrenic Respond Best to Drugs?

Health Collaborative Study No. 1 has been examined to see which symptoms predict the greatest drug response (drug-placebo difference) and to discover in which subtype of patients (as defined by symptoms) the biggest drug response exists. In essence, there were few significant differences, and it would seem, at least within the limitations of this method of analysis, that there is no marked difference between subtypes of schizophrenics as defined by their response to drugs. Klein and coworkers report a better response to drugs in process schizophrenics. However, Judd and coworkers report that some reactive non-paranoid schizophrenics respond better to placebo. Since these results are apparently contradictory, more work is needed on this question.

Does Failure to Use Antipsychotics Cause Harm?

An important question is whether failure to treat with antipsychotic

drugs for an extended period of time will harm the patient permanently. May and Tuma, in an important study, randomly assigned first admission schizophrenics to receive drugs or no drugs and psychotherapy or no psychotherapy. Length of treatment was an essential methodological variable in this study. The experimental design called for six months to one year of treatment, either with or without drugs, which was unusual because most controlled studies last only four to six weeks. Patients who received drugs did substantially better on a number of variables than patients who did not receive drugs (see table 5-3). After the study ended, the patients were followed for the next three to five years. They were able to receive both indicated treatments during this time. It was then possible to determine if failure to treat with drugs resulted in permanent harm to the patient. The authors calculated the number of days in the hospital during the follow-up period, roughly equating many brief hospitalizations with fewer long hospitalizations (see figure 4-2). Patients who initially received drugs did much better in the follow-up period than those who did not. This indicates that withholding antipsychotics during a long hospitalization may result in some sort of permanent harm. The mechanism for this is unknown. Perhaps the disease does not progress so much with medication because the dopamine blockade of the antipsychotics somehow reduces the biological aspects of the psychosis. An alternative explanation is that long hospitalizations permanently sever social ties that are important to a patient's continuous

functioning. Whatever the answer to this, it does appear that drugs alter the natural history of schizophrenia.

Role of Psychological Intervention in Acute Treatment

Goldstein and coworkers emphasized a statistically significant effect on the prevention of relapse and rehospitalization due to family therapy. Patients were hospitalized initially for two weeks, at which time outpatient family therapy was introduced for six weeks thereafter. Since this was only a two-week (mean fourteen + six days) hospitalization, it may be expected that the patient's illness had not remitted completely by the time of discharge, making the psychological support, insight, family care, and patient psychotherapy essential to the treatment program.

Table 5-2. Effect of Phenothiannes on Symptoms in Schizophrenia

Blewer's Classification of Schizophrenic Symptoms	V.A. Study No. 1	V.A. Study No. 3	Kurland 1962	NIMH-PSC No. 1	Gornam and Pokorny, 1964 vs. Group Psychotherapy
Fundamental symptoms					
Thought disorder	++	++	++	++	++
Blunted affect-indifference				++	+
Withdrawal-retardation	++	++	o	++	++
Autistic behavior-mannerisms	++	++	o	++	+

Acessory symptoms					
Hallucinations	++	++	+	+	o
Paranoid ideation	o	++	o	+	+
Grandiosity	o	o	o	o	+
Hostility-belligerence	++	++	H.R.	+	+
Resistiveness-uncooperativeness	++	++	H.R.	++	++
Non schizophrenic symptoms					
Anxiety-tension-agitation	o	o	H.R.	+	o
Guilt-depression	++	o	o	o	o
Disorientation				o	
Somatization					o

++ Symptom areas showing marked drug-control group differences
+ those showing significant but less striking differences
o areas not sowing differential drug superiority
H.R. heterogeneity of regression found on analysis of covariance of the measures indicated (This invalidates this particular stastical procedure but does not mean that there was no drug effect (Cole et. al, 1966.)

Table 5-3. Assessment of Outcome in Schizophrenic Patients Treated With and Without Antipsychotic Drugs and Psychotherapy (May, 1978)

	No Drugs		Drug	
	No Psycho-therapy	Psycho-therapy	No Psycho-therapy	Psycho-therapy
Percent released	58.8	64.4	95.1	96.3

Nurses' rating MACC total	37.7	37.7	47.8	48.1
Menninger nurses' health-sickness rating	26	22.7	28.9	29.8
Nurses' idiosyncratic symptoms (125-X)	37.3	28.8	65.7	74.2
Therapists' rating on symptom rating sheet (50-X)	22.1	20.9	26.4	27.3
Analysis rating of insight	3.4	3.3	3.7	4.1

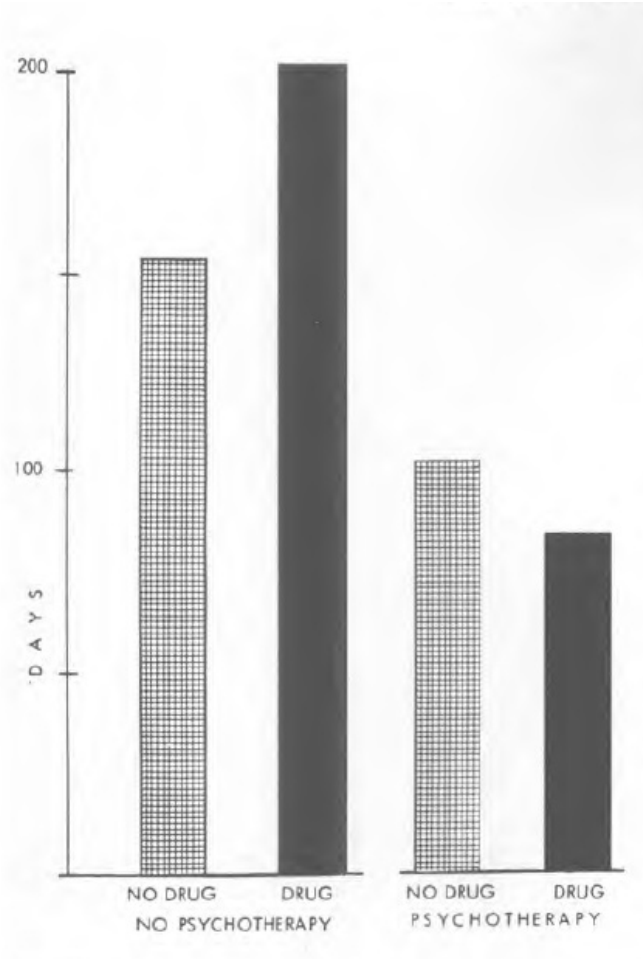


Figure 5-2.
Three years follow-up after first release.

Cost of Drug

The continuing rise of the cost of the drugs is an important issue in drug therapy. Cost is not a function of dosage (see table 5-4). For example, the cost of a 25 mg chlorpromazine tablet is comparable to that of a 100 mg tablet. Considerable savings in money and time, however, are to be derived from administering the largest available form once a day. Furthermore, a bedtime or evening dose may be less likely to be forgotten and easier to monitor than a three-times-a-day regimen. Spansules or other delayed release oral forms of some phenothiazines are available by prescription. However, these more expensive preparations have no discernible advantage over the standard tablet form. Since the cost of antipsychotic medication is measured generally in terms of cents per day, it is small in comparison to the amount paid for hospitalization. Costs of medications to the pharmacies are given in table 5-5.

High Dosage Phenothiazine Treatment

A broad range exists between effective dose and toxic overdose of antipsychotic agents. Patients who served as research subjects have been treated safely with ten to one hundred times the agreed-upon therapeutic dose (for example, 1,200 mg fluphenazine). While one should always exercise caution, it is safe to utilize substantially higher doses than those prescribed in the literature. Given reasonable clinical indications, dosage may be increased without great concern.

There is adequate evidence that the antipsychotic drugs help schizophrenia, but little is known about their effective use with respect to optimal load strategies, optimal plasma levels, and so forth. We will briefly review evidence relating both optimal doses and optimal plasma levels. Recently it has been suggested that a faster initial result and perhaps a better ultimate outcome could be achieved by giving a very high dose in the first few days of treatment. Such strategies have been called loading-dose strategies, rapid tranquilization, or high-dose strategies. Two different dimensions are involved. Too often, high doses are said to be better than low doses. We would like to disassociate two concepts, the concept of titration and the concept that a high dose is superior to a low dose. We believe that to say a high dose is better than a low dose is not an accurate representation of the problem. We would rather consider the dosage issue in terms of dose response.

If one is on the linear portion of the dose-response curve, a high dose is better than a low dose. If one is above the maximal point on the dose-response curve, a high dose is not better than a low dose (see figure 5-3). Indeed, it could be worse. Such patients may suffer more side effects. For theoretical reasons the dose-response curve is a better way to conceptualize the dosage issue than the nonspecific "high-dose-is-good" approach. There is a limited amount of evidence on dose-response relationship in psychiatry, and we will review some of the pertinent studies. In collaboration with Ericksen, Holzman, and Hurt, the authors have performed one study investigating

loading doses. The rapid-tranquilization question has also been investigated by Donlon and co-workers. Several groups have studied the use of very high doses in treating acute patients to establish if mega-doses achieve a better result than normal doses. With chronic patients or treatment-resistant patients, several groups have investigated whether higher doses are better than lower doses for sustained or maintenance treatment and these studies are also reviewed. It is curious that a certain subgroup of patients displays no significant benefit from any antipsychotic drug medication. The possibility of remission in these patients, had they been treated with higher than normal doses, remains an issue for research. We will, therefore, review the aforementioned studies that utilize a higher than normal dose.

Table 5-4 Comparative Costs of Antipsychotic Drugs

GENERIC NAME	TRADE NAME	AVERAGE DOSE*	WHOLESALE COST** A MONTH
		mg./day	
Fluphenazine	Permitil	9	$ 4.31
Fluphenazine HC1	Prolixin HC1	9	6.05
Chlorpromazine	Thorazine	734	6.80
Molindone	Moban	44	7.00
Trifluoperazine	Steiazine	20	7.84
Loxapine	Loxitane	64	903
Haloperodil	Haldol	12	919

Butaperazine	Repoise	66	9.93
Carphenazine	Proketazine	183	11.55
Acetophenazine	Tindal	169	11.93
Fluphenazine	Prolixin	5	12.34
decanoate	Decanoate		
Chlorprothixine	Taractan	323	13.08
Fluphenazine	Prolixin	5	14.18
enanthate	Enanthate		
Thiothixene	Navane	32	14.19
Piperacetazine	Quide	80	14.60
Prochlorperazine	Compazine	103	14.88
Perphenazine	Trilafon	66	15.76
Mesoridazine	Serentil	4	16.21
Thioridazine	Mellaril	712	19.30
Triflupromazine	Vesprin	205	26.03

*Empirically defined average dose for acute treatment (Davis, 1976).

**Cost to retailer for l-month supply of drug for average acute treatment, based on wholesale price of least expensive (largest) tablet or bottle purchased in largest quantity. Actual cost to the consumer is considerably greater because of physician's ordering of smaller-dose tablets.

Table 5-5 Cost per Milligram for Different Tablet Size as Percentage of Cost of Most Inexpensive Tablet Size

DRUG	200	100	50	25	16	125	10	8	5	4	25	2	1	0.5
Chlorpromazine	100	180	300	500			1060							
T riflupromazine			100	150			250							

Thioridazine	100	138	231	415			762									
Prochlorperazine				100			210		323							
Perphenazine					100			149		246		358				
Fluphenazine									100		154		270			
Trifluoperazine					100		153			353	553					
Carphenazine	100	165		277												
Butaperazine			100			197		310								
Mesoridazine	100	167	289			545										
Piperacetazine			100			167										
Haloperidol									100			178	238	332		
Chlorprothixene		100	165	271			494									
Thiothixene							100		151				291	450		

A study of this issue was carried out in our laboratory by means of a double-blind design. It was found that a five-day loading dose of 60 mg of haloperidol, administered intramuscularly, was no more effective than 15 mg orally four times a day, both at day five and at three weeks. This raises the question: Does an unusually high loading (digitalizing) dose encourage more rapid improvement during the initial treatment stages than does a normal dose? Given the assumption that this is true, it becomes important to ask if the patients in question maintain a better remission following gradual decrease of the dosage. In other words, is the patient's condition at three weeks more favorable than the condition that would have been achieved if a regular dose had been used? Patients who were acutely decompensated schizophrenics were randomly assigned to one of two groups. Fifteen mg of haloperidol given orally is approximately equivalent to 940 mg of chlorpromazine, a quantity which we consider to be a high-normal dose. Sixty mg given intramuscularly

would be the equivalent of 3,600 mg of chlorpromazine, or more, since the bioavailability of intramuscular haloperidol is superior to that which is administered orally. Thus, patients were given massive quantities of haloperidol (five day loading, high-dose group) and were subsequently compared to a group that was given more moderate amounts of the drug (normal dose group). Their medication was reduced to a normal dosage of 15 mg of haloperidol after five days of loading and a few days of tapering, while the normal dosage group received a constant dosage (15 mg) throughout the duration of the study. Between-group evaluation, administered on a double-blind basis, was made on the following measures: global scale, the Brief Psychiatric Rating Scale (BPRS), the New Haven Schizophrenia Index, and the Holzman-Johnston Thought Disorder Ratings. Analysis revealed that the therapeutic outcomes were identical at both points; however, the loading-dose group showed more side effects, in particular, dystonia. Thought disorder improved to the same degree among both patient populations. Such an estimate is imprecise but indicated only as an order of magnitude "guess."

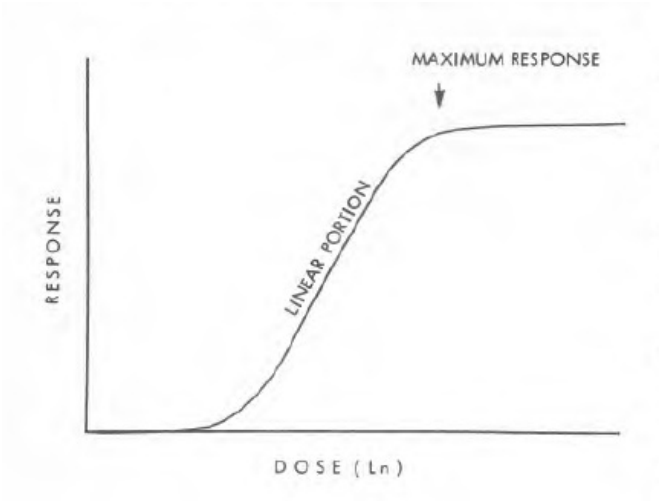


Figure 5-3.

Relevant to this discussion is another investigation, not unlike our own. Donlon and coworkers examined the influence of the rapid treatment of psychosis as compared to a standard dosage of 20 mg of fluphenazine. A maximum loading dosage of 80 mg per day was utilized. The decompensated schizophrenics were followed only a few days—seven days maximum. (During days two through seven of the study, the high-dose group actually underwent recurrent deterioration at a mean of 40 to 74 mg.) In sum, both dose strategies yielded similar results and are, therefore, consistent with our aforementioned findings. Twenty mg of fluphenazine for the standard dose is the equivalent to 1,667 mg chlorpromazine. The high-dose group received approximately 3,000 to 5,000 mg chlorpromazine equivalence.

Furthermore, Wijsenbeek, Steiner, and Goldberg completed a double-blind study in which they assessed the efficacy of 60 to 600 mg of Trifluoperazine given to newly admitted schizophrenic patients. Both treatments were found to be equally effective. As such, mega-doses do not appear to produce substantially greater improvement than regular doses, at least with newly admitted schizophrenics. One should recall that 60 mg of Trifluoperazine is equivalent to approximately 2,000 mg (60 X 100/2.8) of chlorpromazine per day. If a normal dose is equal to 700 mg per day, this amounts to thirty times the normal dose, while 600 mg of Trifluoperazine (or 20,000 mg chlorpromazine equivalence) is about thirty times the normal antipsychotic dose. Findings reported by Quitkin, Rifkin, and Klein further substantiate this. They showed that 1,200 mg per day fluphenazine (100,000 mg chlorpromazine equivalent) is no more effective than 30 mg /day (2,500 mg chlorpromazine equivalent).

Goldstein and coworkers divided a group of 196 acute first admission schizophrenics into four subgroups: low dose (6.25 mg q/2 wk) or high dose (25 mg q/2 wk) fluphenazine, family (FT +) therapy or no family (FT —) therapy, for an eight-week trial (two weeks inpatient, six weeks outpatient) using chlorpromazine equivalence of 73 versus 293. These assignments were arranged on a random basis. A clear-cut dose-response relationship emerged. High dose was associated with significantly fewer relapses ($p < .0002$, Fisher Exact Test). Additionally, the family therapy significantly and independently

prevented relapse, ($p < .05$). In sum, the numbers of relapses per sample size within the four subgroups were: high dose FT + =0/23; high dose FT— = 3/26; low dose FT+ 2/21: low dose FT— = 5/16. The six-month follow-up showed that both the dose-response drug effect and the family therapy effect endure, and actually become larger; outcome data for these same four groups were 0/23, 5/29, 5/23, and 10/21, respectively. It should be noted that 73 mg per day is less effective than 293 mg per day, given the conversion to chlorpromazine equivalents. This is further evidence that the dose range of 50 to 500 mg is located along the linear portion of the dose-response curve.

Furthermore, for acute patients, it is impossible to bracket precisely the optimal point on the dose-response curve. Very massive doses are no more effective than the equivalent of either 2,000 mg or 2,500 mg of chlorpromazine. A very high loading dose of haloperidol is no more effective than an oral dose of haloperidol, the equivalent of approximately 900 mg of chlorpromazine. It would seem that if one is in the range of 1 or 2 grams of chlorpromazine equivalence a day, a higher dose does not produce a better clinical response.

In addition to the studies of acute patients, there are a number of studies of antipsychotic treatments of more chronic patients. Prien and Cole performed a study comparing 2,000 mg of chlorpromazine versus 300 mg of chlorpromazine. The 2,000 mg dose was clearly superior to the 300 mg dose.

Gardose and coworkers compared 440 mg chlorpromazine with 1,760 mg chlorpromazine equivalence and found both doses to be essentially equal in effectiveness. A second study found 15 mg of Trifluoperazine (equivalent to 535 mg of chlorpromazine) to be as effective as 80 mg of Trifluoperazine (2,850 mg of chlorpromazine equivalence). This suggests that 535 mg closely approximates the maximal effective dose, and that an excessively high dose did not lead to additional improvement for this particular population. Clark and coworkers showed, however, that 300 mg or less of the drug is probably not an effective therapeutic dose for chronic patients—600 mg is better than 300, which is better than 150 mg.

Brotman and coworkers initiated a double-blind, non-crossover, random trial which included eighty patients. They were divided into groups receiving either placebo, or 15, 30, or 60 mg per day butaperazine in chlorpromazine equivalence of 167, 333, and 667 mg. The latter group showed a significantly better response on the uncooperative subscale of the BPRS. Analyses of items on the remaining five subscales yielded trends favorable to the high-dose group on the following: emotional withdrawal, tension, mannerism, posture, and flat affect. These differences were small with only one measure achieving statistical significance. However, they afford some limited evidence that 667 mg is better than 333 or less. These results were comparable to those described in the Clark study.

Another study compared 10 mg to 100 mg of Trifluoperazine (357 to 3,570 mg chlorpromazine equivalence) using a sample population composed of very chronic patients. No substantial differences emerged upon comparison of these doses. Given the chronic nature of these patients, this study addresses the topic of maintenance; 357 mg of chlorpromazine equivalence would probably constitute an adequate maintenance dose.

These various studies, when examined collectively, reveal considerable variation with regard to the nature of the sample and methodologies employed. However, despite these disparities, an approximate dose response curve can be drawn. Doses approaching either 300 mg or 150 mg of chlorpromazine are rather low for optimal treatment, at least for some patients. Entry of these numbers to the dose-response curve suggests that 150 and 300 mg (chlorpromazine equivalence) are, in a very rough sense, on the linear portion of the curve. More massive quantities are no more effective than those of approximately empirical range 357, 440, 535 mg (chlorpromazine equivalence). Clinically different patients require different doses and, in some cases, higher than normal doses become the treatment of choice. These dose-response considerations are intended as a statement of average dose to acquaint the reader with the nature and implications of the response relationship as a framework in which to evaluate these clinical phenomena. The dose-response curve is shifted to the right for patients who require high doses. Cases of increased sensitivity to the drug would

necessitate a shift to the left.

In considering relationships between dosage and therapeutic efficacy, attention should be directed toward the dose-response curve in figure 5-3. It can be observed that dosage increments along the linear portion of the curve are associated with a more favorable response. An inflection point is approached and diminishing clinical returns are apparent upon reaching the top of the linear portion of the dose-response curve. After this, as the dose is increased only a minimal increase is observed in the clinical response, with virtually no increases in clinical response as the dose is further increased. The inflection point, or the place at which the linear portion changes to "diminished returns," is often referred to as the optimal portion of the dose response curve. In essence, all of the clinical response that is potentially achievable occurs at this point. From the foregoing, it may be suggested that a 800 + 200 mg chlorpromazine equivalent is located at, or slightly above, the "optimal point."

Distinctions must be drawn between the use of moderately high doses, such as the double normal dose used by Prien and Cole, (not reviewed here) versus the mega-dose strategy used by Quitkin, Rifkin, and Klein, which was one hundred times the normal dose. As mentioned earlier, one must exercise discretion and guard against an overly enthusiastic attitude with regard to the potential of mega-dose antipsychotic drug treatment. A more modest increase

in dosage may clearly benefit some acute or subacute patients. In selective cases, perhaps, mega-dose treatment may be tried experimentally. Given the larger clinical literature on mega-dose fluphenazine therapy, these drugs may be more suitable for high dosage use. Also relevant is the general absence of undue toxicity resulting from larger doses of this drug, so that mega-therapy may be introduced without a great deal of concern. Patients who appear to resist treatment may receive at least a trial with a high dose. In sum, there is a grave lack of definitive research on dose levels and dosage response curves for the antipsychotic drugs. Continued efforts should yield information that will assist physicians who must arrive at decisions concerning individual drug treatment programs.

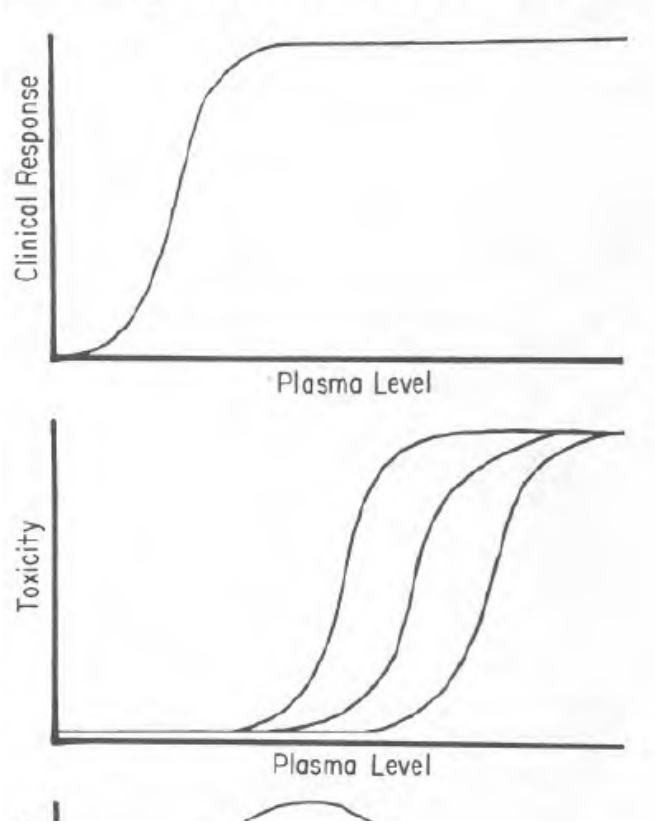
Chlorpromazine Blood Levels

There are reports of patients who respond only to relatively high doses of a given drug. In contrast, there are certain patients for whom only low doses have been beneficial. Studies that attempt to relate blood levels of chlorpromazine to therapeutic improvement and side effects are important in this regard.- Enormous variability in blood levels may occur with comparable doses. Some individuals receiving a moderate dose of chlorpromazine may show extremely high blood levels with excessive sedation, and striking improvement may be observed only upon dosage reduction. This type of patient may have a defective metabolism and, perhaps, have built up a high

toxic level of blood chlorpromazine. It is also possible to find patients with extremely low blood levels, despite their elevated doses. These patients may metabolize chlorpromazine so rapidly that, despite very high doses, the brain is deprived of adequate amounts of chlorpromazine.

A basic assumption underlying plasma level studies is that the rate of metabolism or other factors affect the amount of drug at the receptor site. As such, at a uniform dose, variable amounts of drug reach the receptor site because of individual differences in metabolism. It follows that the plasma level, clinical-response curve is essentially a dose-response curve. A possible plasma level, clinical-response curve is depicted in the classic sigmoid curve in figure 5-4. The first portion of the curve shows the relative lack of clinical response with small doses of drug. The linear portion of the curve represents a more favorable clinical response—when more drug reaches the receptor site. Beyond the linear part of the curve, as larger amounts of the drug are introduced, an area of diminishing returns is observed. A plasma level-toxicity relationship also occurs with various side effects (middle panel). If the clinical benefit is plotted for the patient against plasma level, it might be anticipated that as plasma levels increase, a better clinical response takes place. Leveling off of the curve indicates the region of optimal benefit. When plasma levels are notably elevated, the resulting detrimental side effects may cancel out any beneficial therapeutic effects. The inverted U-shaped curve, also pictured in figure 5-4, represents the so-called “therapeutic window.” In the area below

the therapeutic window, insufficient drug reaches the receptor site to produce the desired clinical response. The upper limit can be defined either by toxicity, by a paradoxical pharmacological response, or both. The description of information that indicates whether one or both effects may be occurring is important. Given that various conceptualizations of the upper end of the therapeutic window exist, it is critical that we achieve clarity as to the terms under discussion.



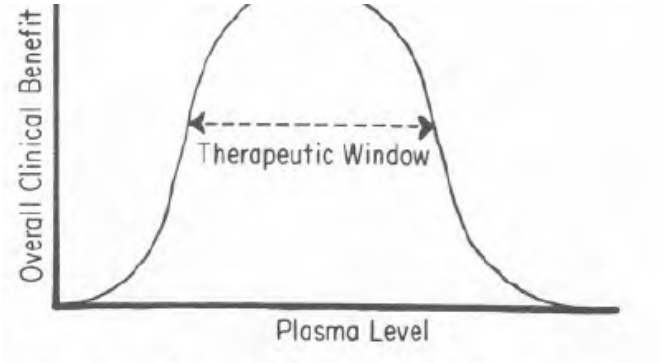


Figure 5-4.
Theoretical concept of therapeutic window.

By combining the therapeutic curve and the side effects curve, we can derive the inverted U-shaped curve. Increases in the plasma level, for some drugs, may be associated with a negative therapeutic effect or side effects. Certain agents may stimulate a receptor within a particular range of concentration but, at a higher range, inhibit the receptor. In other words, the therapeutic effectiveness of some drugs may diminish at high plasma levels. As a rule, the majority of drugs (but not all) show increasing side effects with increasing dosage. A drug that displays neither of these effects might be missing the downward portion of the inverted U-shaped curve. Expressed differently, the upper portion of the therapeutic window will be absent.

The concentration of the drug at the particular receptor site is the parameter that, ideally, should be assessed. This is often governed by factors that suggest that concentrations of the drug at these sites may be directly

proportional to the plasma levels. As such, plasma levels may constitute valid indices of this event.

Since psychotropic drugs are highly protein bound, it is possible that slight differences in binding could result in different amounts of drug reaching the brain. It is difficult to measure free drug in plasma, but if the same physicochemical properties govern how much drug passes into red cell that govern how much drug passes into the brain, perhaps red cell levels would be a better correlate to brain than plasma levels.

Data obtained from two controlled studies suggest that some non-responders have low red blood cell (RBC) levels and may be quick metabolizers (or poor distributors to tissue) and, hence, may show low brain levels of the drug. It is possible that such a state of affairs may be responsible, at least in part, for any failure of the drug treatment.

There were not enough subjects in these studies with high levels to prove that there are non-responders due to excessively high RBC and presumably central nervous system (CNS) levels, but there is some suggestion that it may be true. This aspect is clearly unproven. The majority of the patients did have low RBC levels, and this suggests that the most common clinical pharmacologic reason for nonresponse may be at the lower end of the therapeutic window. The most nonresponsive of all patients are certain

patients hospitalized in chronic state hospitals with a long history of failure to respond to drugs. Smith and his coworkers studied a population of extremely poor responders. These patients, treated in an identical protocol, had extremely low plasma and RBC levels. Similarly, patients in an acute hospital who showed no response and were scheduled for transfer to the state hospital or otherwise labeled as extreme non-responders also showed extremely low red blood cell and plasma levels. There are several studies utilizing low doses of chlorpromazine which found a slight tendency for a worse clinical response in those patients who had the lowest plasma levels. These differences were modest in direction but consistent with those previously mentioned.

In a pilot study in our laboratory, we have also found an inverted U-shaped relationship between plasma fluphenazine levels and clinical response. Although this result was statistically significant, the sample size was relatively small.

We should add that the proper methodology for plasma level studies requires a fixed dose or doses. If dose is varied with clinical response, then the experiment is meaningless. Such studies are difficult to do and there is limited literature on the subject. The limited data just reviewed indicate that variations in rate of metabolism and distribution may be one of the reasons the clinician should adjust the dose to clinical response. The question always

arises as to when a research finding is ready for clinical application. At this time, there is not enough evidence relating plasma or red blood cells to therapeutic efficacy to form definitive conclusions. Such conclusions as may be drawn provide preliminary support to the plasma and/or RBC level hypothesis; however, further research is clearly required for verification. The impressive variability in plasma and RBC levels may be one reason why different patients require different doses to achieve similar results. The sensitivity of end organs may also play a role. The clinician should adjust the dosage with regard to the therapeutic responses and side effects.

As an aside, brain sensitivity to drugs may be an inpatient variable. Maxwell and coworkers have illustrated the ability of chlorpromazine to produce central behavioral toxicity in hepatic coma to be an enhanced response of the brain to chlorpromazine's sedative properties. Plasma levels are normal so that such potentiation of hepatic coma does not reflect an impairment in drug metabolism. At present, the methods available for measuring blood levels of antipsychotic drugs remain highly technical and complex. It may be several years before it will be possible for psychiatrists routinely to examine unresponsive patients to make certain that appropriate antipsychotic drug blood levels have been achieved.

Maintenance Treatment with Antipsychotic Medication

The length of time that a patient should be maintained on antipsychotic drug treatment becomes a salient issue due to tardive dyskinesia. Not one single properly controlled double-blind study, among the thirty or so studies carried out, has failed to show that more patients relapsed on placebo than on continuous pharmacotherapy. The difference is significant with a *p* value of less than 10 when these studies are combined according to the method of Fleiss. Hogarty and Goldberg performed a particularly impressive study on this question. Three hundred and seventy-four schizophrenic patients who, after recovery, had been discharged from a state hospital were divided into two groups: one group received maintenance chlorpromazine treatment, while the second received placebos. In addition, half of each group received psychotherapy. The major finding was that patients receiving drugs and therapy fared better than those who received only drugs. Very few patients in the placebo group failed to relapse, despite their psychotherapy sessions. Thus, it would appear that maintenance phenothiazines are required for the prevention of relapse in most schizophrenic patients. Psychotherapy did increase the social adjustment, chiefly in the patients who also received a drug.

It is reasonable to ask the question: Are patients especially liable to relapse immediately upon the termination of antipsychotic drugs, or do they tend to relapse at a constant rate with the passage of time? If the latter holds true, then there would be an equal likelihood of patients relapsing during the

second month following discontinuance as during the eighth or the fifteenth month. A simple linear plot of patients relapsing is inadequate for the visual display of a constant relapse rate. This is due to the fact that the absolute number of patients relapsing depends upon the number of patients included in the clinical trial; as time goes by, the population in the trial (and at risk for relapse) decreases. To elaborate, we begin with 100 patients and assume a relapse rate of 10 percent per month. During month one, 10 percent of loo, or 10, would have relapsed, leaving 90. During month two, 10 percent of 90, or 9 patients, would have relapsed, leaving 81 patients in the trial. During month eight, 10 per cent of 81 would have relapsed, leaving approximately 72 patients in the trial. During the course of this entire period, the absolute number of patients relapsing per month progressively decreases, given the diminishing number of patients in the trial and the consistency of the relapse rate. These mathematical considerations are identical to those applying to the radioactive half-life *(T,/2)* or the *Tt/2* of drugs in plasma. Questions connected with this issue were first addressed in our laboratory. Data from several large collaborative studies were plotted to illustrate the most suitable fit to an exponential function, relative to a linear function (see figure 5-5). Replotting the data of Hogarty and Goldberg yielded a relapse rate of 10.7 percent for placebo for the first eighteen months. In the study by Caffey and coworkers (not reviewed here), we found a relapse rate of 15.7 per cent. These least squares analyses of the empirical data provide an excellent fit, with *r2* in the

vicinity of 0.96. We stress, however, that over an extended trial, some sort of ceiling effect may emerge. In other words, all the patients who were at risk for relapse would have relapsed, resulting in attenuation of the progressive nature of the relapse events. If a few patients in the trial do not show the recurrent form of the disease, they may never relapse; hence, they constitute a residual of unrelapsed patients. Empirically, the relapse occurred at a constant rate until about eighteen months in the study. There were so few patients remaining at this point that the empirically observed relapse rate might have been inaccurate; however, there is reason to believe that it may have changed then. Hogarty selected out those patients who had remained in the study for two years or more and examined their relapse rates more closely. Unfortunately, he was able to identify only a few patients in the placebo group who were still unrelapsed, certainly not enough to permit an effective study. In the drug-treated group, however, there remained a sufficient number of subjects available for investigation. Antipsychotic drug treatment had been discontinued for these individuals who did, in fact, relapse in an exponential fashion with a relapse rate similar to that observed initially. It is recognized that while relapse may be checked by drugs for a substantial period (two years), it may occur at approximately the same rate as with patients who are left drug-free after two months of maintenance medication.

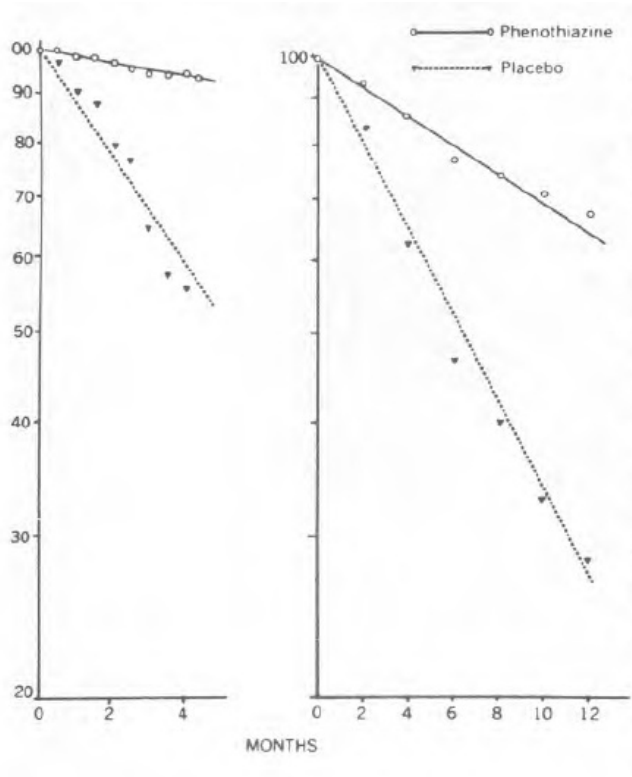


Figure 5-5.

Goldberg and his coworkers also examined which schizophrenics had relapses and which did not. Subjects were organized into four groups. It has been documented in the literature that patients with good prognostic signs may not require drugs. However, it was reported that patients with favorable signs appeared to profit the most from drug treatment. Patients who failed to take their medications regularly tended to do poorly. Results were also

influenced by psychotherapy. Patients who were asymptomatic with respect to schizophrenic symptomatology seemed to benefit most from psychotherapy, as compared with patients who showed a reasonable degree of psychosis and who seemed to do poorly in the psychotherapy group. It was hypothesized that psychotherapy may pose a stressful situation for patients in borderline compensation, as they fail to deal effectively with encouragement toward social responsibility.

In sum, decisions connected with long-term drug therapy should be derived clinically for each patient, based upon a thorough knowledge of his illness and life situation. It would seem reasonable to maintain the majority of patients on phenothiazines for six months to one year following a psychotic episode; however, over extended time periods, treatment may well require further individual tailoring. Since the so-called "reactive" schizophrenics may experience only a single episode during an entire lifetime, we do not recommend long-term maintenance medication for them.

Obviously, a history of relapse following discontinuation of antipsychotics is an indication for a prolonged period of such treatment. Evidence that antipsychotics may not have helped the patient originally or that the drug's prior discontinuation did not lead to relapse would be indications for the gradual reduction of dosage, leading to the termination of drug treatment. Psychotherapeutic and social interventions during the

recovery phase and throughout post-hospital care are very important in fostering improved social adjustment and may help to prevent relapse.

Several long-acting antipsychotic agents being studied offer a useful treatment approach for patients who fail to take their oral medication. Fluphenazine enanthate and fluphenazine decanoate are two intramuscular depot forms that are currently used in the United States. Open clinical trials investigating depot medication report evidence of patients who benefitted not only because they had previously failed to take oral medication, but also possibly due to the kinetics of the drugs—factors such as intramuscular versus oral absorption, distribution, and metabolism. Evidence from controlled studies finds depot fluphenazine to be as effective as oral fluphenazine, although the results are somewhat contradictory. Two double-blind studies showed the depot fluphenazine to be superior to the oral formulation, while three other studies found the two preparations to be equally effective. A recent NIMH collaborative double-blind study reported that the depot fluphenazine is essentially comparable to the oral medication. In addition, Rifkin and coworkers have presented data that demonstrate the equivalence of both preparations. Variable patient cooperation in taking the drugs routinely might be invoked as a partial explanation; compliance may have been greater in the latter series of studies. Regardless, it appears certain from anecdotal studies that the depot drug is particularly beneficial for patients who are somewhat negligent about taking their medication.

Simon and coworkers conducted an open maintenance (eighteen month) study in France to investigate the influence of standard neuroleptics, fluphenazine decanoate, and pipothiazine palmitate on chronic schizophrenia. Thirty psychiatrists were employed to assess the effects of these agents, which were administered at random to eighty-one patients from fifteen different wards. No significant differences in the efficacy of these drugs were found. It is worth noting that pipothiazine palmitate, like fluphenazine, is a long-acting neuroleptic that has demonstrated equal efficacy to depot or oral forms of antipsychotics. Quitkin and coworkers compared penfluridol to fluphenazine decanoate and found them both equally effective. Penfluridol, an antipsychotic, was administered once weekly.

As such, the depot intramuscular medication is a serious consideration in treating patients who fail to display optimal responses to oral medication or who show frequent relapses; these individuals are suspect for neglecting their medication schedules. In sum, depot phenothiazines are important supplements to our therapeutic armamentarium, for both outpatients and inpatients, although their particular benefit to the former is recognized. Furthermore, despite their propensity for inducing neurological side effects, depot fluphenazines can be useful in emergency room and home therapeutic regimens for the treatment of acutely psychotic patients, as the psychotic symptoms can be diminished without inpatient admission. This advantage in the emergency situation may outweigh their occasional disposition for

inducing neurological side effects.

It is worth determining if one of the two forms of this drug (fluphenazine enanthate and fluphenazine decanoate) may be preferable to the other. Given that these are both long-acting depot fluphenazine, it is anticipated that they would be approximately equal. Empirical studies have, in fact, shown that they are generally equal in potency, efficacy, and side effects. However, several studies indicate that fluphenazine decanoate may be slightly more long-acting and may produce slightly fewer extrapyramidal side effects. A number of studies have directly compared fluphenazine decanoate to fluphenazine enanthate. Fluphenazine decanoate appears to be a slightly more potent drug. It requires a lower dosage and less frequent administration, that is, more extended intra-individual dose. Donlon and coworkers found that extrapyramidal side effects may emerge with a slightly higher incidence following treatment with enanthate relative to decanoate. The drugs are extremely similar, yet the five comparison studies have shown that the decanoate form is slightly longer acting and produces slightly fewer side effects. Thus, it is probably the preferable formulation for the administration of long-acting depot fluphenazine.

Van Praag and Dols have described an unusual experimental design for the comparison of these drugs. Thirty patients were randomly assigned to one or another of these drug treatments for the control of an acute schizophrenic

episode. Clinicians who were blind to this assignment were permitted to administer supplementary chlorpromazine or antiparkinsonian drug if necessary. One injection for a four-week period was given. The reasoning was that if the influence of the drug diminished during this interval, the patient would then require a greater amount of supplementary chlorpromazine. All patients in the study received placebo throughout so that when chlorpromazine was required on a clinical basis, it replaced the placebo in an identical tablet to maintain the double-blind procedure. The same method was followed if an antiparkinsonian drug was required. Especially during the initial two weeks, it was found that patients receiving enanthate needed more antiparkinsonian drugs. The antipsychotic effect tended to endure longer in the decanoate group, since considerably fewer patients required additional chlorpromazine during the third and fourth week of this trial.

New Antipsychotic Agents

A notably "pure" dopamine antagonistic drug is pimozide. It is this characteristic that makes it a particularly interesting antipsychotic agent. Careful research has documented its antipsychotic properties compared with a placebo among both acute and chronic schizophrenic patients when administered for maintenance treatment. Of additional relevance are data that support the equivalence of maintenance pimozide and standard antipsychotics. Relatively higher doses of the latter are, however, required to

achieve an effect that is comparable to the former. Since the efficacy of pimozide has been substantial, it is likely that its approval for release by the Federal Drug Administration is imminent.

TABLE 5-6 Summary of Studies on the Antipsychotic Efficacy of Loxapine and Molindone in Schizophrenia

INVESTIGATORS	NO. OF PATIENTS	PATIENT GROUP (SCHIZOPHRENICS)	OUTCOME*
Clark et al. (1975)	37	Newly admitted	lox = tri > pla**
Denber (1970)	3	Newly admitted	lox = tri
Moore (1975)	57	Newly admitted	lox > CPZ
Shopsin et al. (1972)	30	Newly admitted	lox < CPZ
Simpson and Cuculic (1976)	43	Newly admitted	lox = tri
Smith (pers. comm.)	12	Newly admitted	lox = tri
Steinbook et al. (1973)	54	Newly admitted	lox = CPZ***
Van Der Velde and Kilte (1975)	25	Newly admitted	lox = tri > pla
Charalampous et al. (974)	54	Subacute	lox = pla < tri
Bishop and Gallant (1970)	24	Chronic	lox = tri
Clark et al. (1972)	50	Chronic	lox = CPZ > pla

Moyano (1975)	48	Chronic	lox = tri
Schiele (1975)	49	Chronic	lox = CPZ
Simpson et al. (1971)	5	Acute	mol = tri
Clark et al. (1970)	43	Chronic	mol = CPZ > pla
Freeman and Frederick (1969)	28	Chronic	mol — tri
Gallant and Bishop (1968)	43	Chronic	mol = tri
Ramsey et al. (1970)	20	Chronic	mol = tri

* Abbreviations: lox, loxapine; mol, molindone; tri, trifluoperazine; thi, thiothixene; CPZ, chlorpromazine; pla, placebo,

**Use of equals sign means any overall difference which might exist could not be detected on basis of number of patients, population, etc.

***lox > CPZ on some, but not all measures.

Two new agents, molindone (which has an indole structure) and loxapine (which belongs to the dibenzoxapine category), have been clearly shown to have antipsychotic effects (see table 5-6). Six controlled studies involving approximately 200 patients found molindone similar in efficacy to the standard antipsychotic drug: it was slightly superior in one study, not different in three, and slightly inferior in two. Clark and associates conducted a placebo-controlled study and found molindone to be superior to placebo. Qualitatively, molindone improved the same range of schizophrenic symptoms as the other antipsychotic agents and had similar prophylactic

effects. Although molindone generally produces the same range of extrapyramidal and autonomic side effects as the phenothiazines, it does not cause weight gain. Also, since it does not inhibit the noradrenaline (norepinephrine) uptake pump mechanism, it probably does not interfere with the hypotensive action of guanethidine.

Clark and associates have provided the best evidence on the efficacy of loxapine. They tested loxapine in carefully executed double-blind studies of hospitalized patients with chronic and acute schizophrenia. In all three studies, loxapine was significantly superior to placebo. Van Der Velde and Kiltie also found loxapine superior to placebo. In another fifteen studies involving about 600 patients, loxapine was found to be indistinguishable from standard antipsychotics. Twelve of those studies showed loxapine to be more effective than thiothixene in younger, but not in older patients, while one group found loxapine less effective than thiothixene and another found loxapine less effective than chlorpromazine. Considered as a group it seems that loxapine is an effective antipsychotic. It has the same range of side effects as the other antipsychotics. Both new antipsychotics are effective drugs and their use is recommended. No ocular, liver, blood, or phototoxicity has been reported.

Antiparkinsonian Medications

Prophylactic antiparkinsonian drugs have become a highly controversial issue. Many psychiatrists advocate such treatment for all patients regardless of the specifics of the diagnosis. Others guard against their indication. One research design has been the discontinuation of antiparkinsonian drugs in a group of chronic schizophrenics. Such studies tend to show that between 20 to 50 percent of the subjects will exhibit parkinsonian side effects following withdrawal of the antiparkinsonian drug. Many of the studies did not include a comparison group. Further, it is noteworthy that when a comparison group was used, (antipsychotic + antiparkinsonian drugs versus antipsychotic + placebo) extrapyramidal side effects were detected among some of the group in spite of the drug. Nevertheless, it is clear that when many patients who have received prophylactic antiparkinsonian drugs for extended periods did not relapse, the drug was terminated. Therefore it is reasonable to recommend that after the administration of antiparkinsonian drugs for more than three months, it should be slowly tapered, with eventual discontinuation. Only patients who display parkinsonian symptoms should continue on antiparkinsonian drug treatment. In sum, however, one cannot conclude that antiparkinsonian drugs have no prophylactic efficacy. No doubt, the majority of patients included in these investigations were placed on prophylactic antiparkinsonian drugs. Their failure to show re-emergence of extrapyramidal side effects when their antiparkinsonian drug was discontinued may be accounted for by the large possibility that they never

would have had parkinsonian side effects in the absence of prophylactic antiparkinsonian drugs. A more appropriate research design for answering such questions would be to arrange for patients to receive either a prophylactic antiparkinsonian drug or a matched placebo. This was in fact, the methodology employed by Hanlon. Twenty-seven of the patients who had not received antiparkinsonian drugs experienced extrapyramidal side effects, whereas when an antiparkinsonian drug was used, these effects were identified among only 10 percent. This was almost a threefold reduction. A similar study was conducted by Chien and associates.

The Antidepressants

Occasionally, there is a statement in the British literature that the tricyclic drugs are not clinically effective. This is obviously not true. There is overwhelming evidence that all the tricyclic drugs are clinically effective. We, hereby, present an analysis of thirty well-controlled studies of imipramine to demonstrate that if data are properly combined (even in a very crude fashion and based on the simplest dichotomized data), the statistical probability is overwhelming. Substantial evidence for efficacy is found in double-blind studies for all the tricyclics, including the new tricyclics.

Investigators usually express drug effectiveness in one of two ways: (1) by noting the percentages of patients who improve with a drug or placebo or

(2) by using a rating scale that demonstrates the mean change in a patient population. Among the forty-four controlled studies comparing imipramine with a placebo, thirty provided data on the percentage of improvement associated with a drug or placebo.

Collectively, the data from these thirty studies yield a total of 1,334 patients treated with imipramine or placebo. Approximately 65 percent of the subjects treated with imipramine showed significant improvement, compared to 30 percent on the placebo. None of the studies in this group demonstrated a greater therapeutic effect from the placebo. The average drug-placebo difference of 35 percent was obtained after subtracting the percentage of improvement with a placebo from the percentage of improvement with imipramine. It is not surprising that since imipramine predicted more favorable improvement than the placebo, there is only an infinitesimal statistical probability that chance alone could lead to these results. The probability of these results, which favor imipramine over a placebo, obtained by chance is 10'. By enlarging the sample size, one can achieve a highly statistically significant result in a drug that is otherwise of only moderate effectiveness. However, there is an urgent need for sensitive and effective treatment methods since approximately 15 to 30 percent of the depressed patients did not respond to the medication. Covi, and coworkers detected a significant therapeutic effect from imipramine, but were unable to show that group therapy was beneficial. Klerman and coworkers conducted an

important controlled study comparing depressed patients who were placed on one of the following treatment modalities—tricyclics, psychotherapy, or combined tricyclics and psychotherapy, as well as a control group. They set up an unusual control group that allowed the patients to request emergency appointments if they felt that they desired assistance. This "demand only" psychotherapy serves as an alternative to "waiting list" controls. The studies demonstrated that tricyclics and psychotherapy, given independently, yield a better therapeutic antidepressant effect than "demand only" psychotherapy. Interestingly, the treatments administered jointly had a significantly better antidepressant effect. This clearly shows that both forms of treatment (chemotherapy together with psychotherapy) do not contradict each other; rather, they tend to complement one another so that the overall therapeutic efficacy is increased.

It is important here to consider what constitutes an adequate "placebo" for psychotherapy, and to remember that patients who were on "waiting list" or "demand only" control were aware that they were not actually receiving psychotherapy. The "demand characteristics" are quite dissimilar from psychotherapy. A highly suitable control experiment would be to compare a given type of standard acceptable "specific" psychotherapy against a "nonspecific, nontherapeutic" type of psychological support, based on an equal number of hours. This control experience will lack the ingredients regarded as specific to psychotherapy. It would also be important to arrange

for approximately the same demand characteristics. A key consideration in this type of investigation is that blind assessment may not be blind in actuality. Some patients may be cognizant of their particular psychological intervention and may inadvertently communicate to the blind assessors the "demand characteristics."

Drug Maintenance in Affective Disorders

A major therapeutic question facing the clinician, once the patient is discharged from the hospital, contingent on a good response to treatment with tricyclic indications, is when to discontinue the antidepressant drugs. Since depression is a recurrent disorder, one often wonders whether continued treatment with tricyclic drugs will actually prevent relapse. In an attempt to answer this unsettling question, Mindham and coworkers completed a collaborative study that included thirty-four psychiatrists in Great Britain. Patients studied had suffered a depressive illness and had responded to treatment with either imipramine or amitriptyline in doses of at least 150 mg a day. One group of these patients was continued on treatment with tricyclic drugs in doses of 75 to 100 mg a day, while the other was placed on a placebo for a period of fifteen months. Following this period, relapse was observed among 22 percent of the tricyclic maintenance group, compared to 50 percent of the group treated with a placebo. The relapse rate appears to be linear across time, given that the appropriate correction is made (see

"Antipsychotics"). Data are not yet available for predicting which patients needed tricyclic drugs to check relapse. Currently, however, there are numerous studies demonstrating that maintenance tricyclics prevent the recurrence of depression among individuals with multiple relapsing episodes. In two of these studies, patients were first treated successfully with electroconvulsive therapy (ECT), in the five other studies, they were first given tricyclics. Placebo or maintenance tricyclics were administered in a double-blind, random-assignment design. Upon pooling the data from these various studies, there remains no real doubt that maintenance tricyclics are able to prevent relapse (see table 5-7). In cases of multiple relapses, maintenance tricyclics should be considered for the prevention of recurrence. Some patients may have experienced only a single previous depressive episode which might well be their last. Maintenance tricyclics are obviously not recommended for such cases. The decision for prophylaxis should be based on clinical indications, such as the severity of depressions, the frequency of depression, risk of suicide, and so forth. It is interesting to note that maintenance lithium is also used to prevent relapses in patients with recurrent unipolar depression. Lithium is clearly the drug of choice in prevention of relapse in bipolar disease (see table 5-8). The relapse of mania is not prevented by tricyclics, which can, on occasion, precipitate a manic attack.

Klerman and coworkers examined the role of psychotherapy and

maintenance treatment. Psychotherapy was not effective in preventing relapse, yet did improve adjustment at the social level. Again, this research describes a qualitatively important role for drugs in the treatment of depressed patients. In sum, both the psychological therapies and drug treatment should be seriously considered.

Plasma Levels

Antidepressant drugs have been shown to assist at least 70 percent of depressed patients. Certainly, some percentage of the patients who have not benefited are suffering from a type of depression that does not respond to this class of drugs. However, others may not respond as a function of clinical and/or pharmacological factors. Plasma levels build up for about two weeks, or until they reach a fairly stable level which is maintained over the course of tricyclic drug administration.

Patient populations yield broad inter-individual differences in plasma levels. This raises the question of whether the lack of response can be attributed to an abnormality in the metabolic rate of the tricyclic drug (see table 5-9, figures 5-6,5-7, and 5-8). Certain individuals might metabolize the drug quickly, fail to build up a sufficient blood level, and, subsequently, show low brain levels. Other patients may have a defective metabolism, so that high plasma brain level may accumulate. Patients may fail to improve clinically

either because they are the recipients of toxic doses, or because the drug may lose efficacy at increased levels. It seems, therefore, that there are two possible explanations for nonresponse. Asberg and coworkers examined associations between plasma nortriptyline concentrations and therapeutic response. It was found that some patients who failed to respond had notably reduced levels of blood nortriptyline, while other such patients had relatively higher levels of nortriptyline.

It is predicted that there will be a lower limit to the therapeutic window with virtually all drugs. In other words, if a sufficiently low dose is given, an insufficient quantity of the drug will be available to the receptor site and so fail to produce a therapeutic response. It was reported that the lower level of the therapeutic window was approximately 50 ng/ml because five patients who had levels below this had failed to respond (the precise location of the "low window" derives from data from these five patients). This same study reported that patients who had plasma levels exceeding 140 ng/ml tended to display an unfavorable clinical response. This did not appear to be a result of CNS toxicity; rather, the drug seemed to lose its therapeutic effectiveness when plasma levels were elevated (see figure 5-6).

In view of the tremendous theoretical interest generated by the paradoxical property of the drug, namely, that it seems to diminish in efficacy at high plasma levels, it was studied closely by several investigators. Kraugh-

Sorenson and Montgomery both confirmed this result, in that they noted poor responses with plasma levels above 175 ng/ml and 200 ng/ml, respectively. Montgomery noted that from among a group of sixteen patients with high plasma levels who had had their clinical doses reduced, twelve improved within approximately a week. Kraugh-Sorensen examined patients whose doses had been adjusted to either above 180 ng/ml or below 150 ng/ml; a disproportionately large number of subjects in the first group showed a poor clinical response. This study progressed to a second phase in which a subgroup of the original sample was selected at random and the levels of the subgroup of the high plasma level group (180 + ng/ml) were lowered to the therapeutic range. Five out of five patients improved. In contrast, six patients who continued to have high plasma levels had a poor response. Whyte and coworkers suggested an inverted U-shaped relationship with a lower limit to the therapeutic window of below 140 ng/ml and upper above 260 ng/ml using a 40 mg dose. Biggs and Ziegler, using a 20 ng/ml dose, found poor responses in patients with plasma levels under 70 ng. This group used a 50 percent lower dose than did Whyte and coworkers, but observed disproportionately lower plasma levels. Biggs' GCMS method would be specific. The two investigators concur in that there may be a lower limit to the therapeutic window, but disagree as to what this limit would be, that is, 70 or 140 ng/ml.

Table 5-7 Placebo versus Tricyclics for Prevention of Relapse of Recurrent

*Depression**

NO. OF PATIENTS WHO RELAPSE OR REMAIN WELL C PLACEBO OR DRUG

RESEARCHERS		PLACEBO	DRUG
Prien et al., 1973	Relapse	24	17
	Well	2	10
Mindham et al., 1975	Relapse	21	11
	Well	21	39
Klerman et al., 1974	Relapse	27	6
	Well	40	33
Coppen et al., 1978	Relapse	5	0
	Well	11	13
Quitkin et al., 1978a	Relapse	6	5
	Well	2	3
Seager and Bird, 1962	Relapse	11	2
	Well	5	10
Kay et al., 1970	Relapse	24	8
	Well	27	26

*P = 2 X 10^{-9} (Fleiss, 1973).

*Table 5-8 Lithium Prevention of Relapse of Unipolar Depression**

RESEARCHERS	NO. OF PATIENTS WHO RELAPSE OR REMAIN WELL	
	PLACEBO	LITHIUM

Baastrup et al. 1970	Relapse	9	0
	Well	8	17
Prien et al., 1973	Relapse	14	13
	Well	2	14
Persson, 1972	Relapse	14	6
	Well	7	15
Coppen et al., 1963	Relapse	12	1
	Well	3	10
Dunner et al., 1976	Relapse	9	8
	Well	5	6

*$p = 3 \times 10^{-8}$

Table 5-9 Plasma Level Studies

INVESTIGATORS	DOSE	PLASMA LEVELS	NUMBER	STATUS	DRUG*	RESULTS
	mg.	*mg./ml.*				
Asber et al., 1971a	75-225	32-164	29	Inpatients	Nor.	Curvilinear poor results below 50 or above 139 ng./ml.
Kraugh-Sørensen et al., 1973	150	48-238	30	Inpatients	Nor.	Poor results above 175 ng./ml.
Kraugh-Sørensen et al., 1976	Adj.	Adj. > 180	24	Inpatients	Nor.	Poor response with plasma level above 180 ng./ml.
Ziegler et al., 1977	Flex.	53-252	19	Outpatients	Nor.	Poor results above 139 ng./ml.
Montgomery et al. 1978	100m	120-290	18	Inpatients	Nor.	Poor results above 200 ng./ml.
Whyte et al.,	40	129-427	28	Inpatients	Prot.	Curvilinear poor

1976						response with low (<14) ng./ml. and poor response above 280 ng./ml.
Biggs et al., 1978	20	22-167	21	Outpatients	Prot.	Poor response in patients with plasma levels under 70 ng./ml.
Khalid et al., 1978	100-150	29-318	15	Outpatients	Dmi	Linear high plasma level = good response
Olivier-Martin et al., 1975	150	108-118 Imip. 130-160 DMI		Inpatients	Imip	Good response above Imip + Dmi level of 200 ng./m. in selected endogenous depression
Reisby et al., 1977	225nm	58-809	66	Inpatients	Imip	Linear good response above 204 ng./ml.
Glassman et al., 1975	3.5 mg./kg.	50-1050	42	Inpatients	Imip	Linear good response above 180 ng./ml.
Muscettola et al., 1978	Flex.	42-432	15	Inpatients	Imip	Nonsignificant trend for patients over 200 ng./ml. to have better response.
Braithwaite et al., 1972	150	40-313	15	Inpatients and Outpatients	Ami.	Good response when level above 90 ng./ml.
Ziegler et al., 1977	Flex. Mean	52-318	22	Outpatients	Ami.	Good response above 75 ng./ml.
Kupfer et al., 1977	20 mg.	Mean 275	15	Inpatients	Ami.	Good response above 200 ng./ml.

*Nor. = nortriptyline; Prot = protriptyline; Dmi. = desipramine; Imip. = imipramine; Ami = amitriptyline.

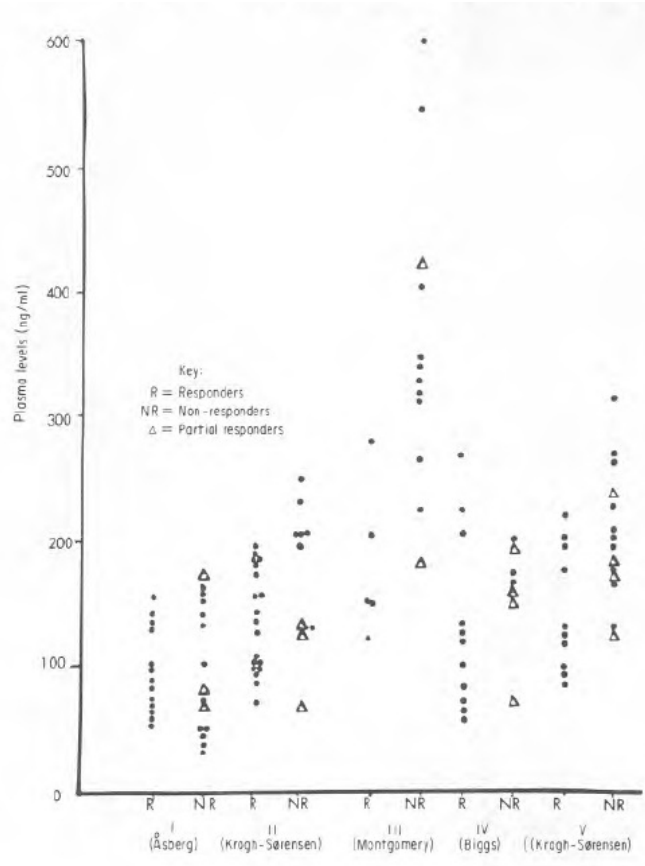

Plasma levels (ng/ml)
600
500
400
300
200
100
0
Key:
R = Responders
NR = Non-responders
△ = Partial responders
R
NR
I
(Åsberg)
II
(Krogh-Sørensen)
III
(Montgomery)
IV
(Biggs)
V
((Krogh-Sørensen)

Figure 5-6.

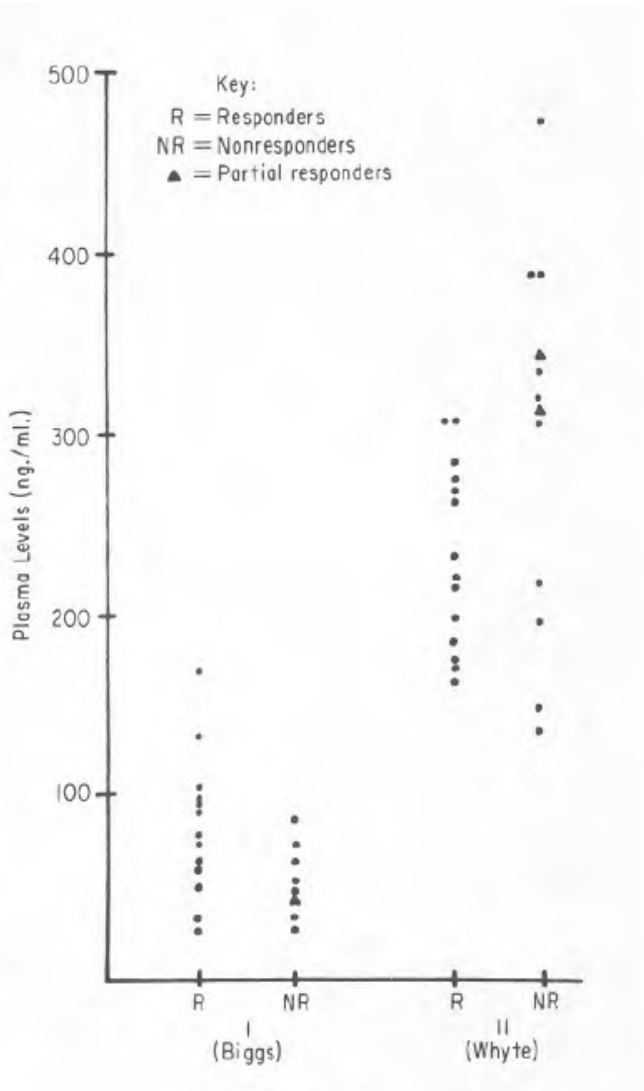

Key:
R = Responders
NR = Nonresponders
▲ = Partial responders
Plasma Levels (ng./ml.)
500
400
300
200
100
R
NR
R
NR
I
(Biggs)
II
(Whyte)

Figure 5-7.

All three studies of amitriptyline find a lower limit to the therapeutic window —poor clinical response when plasma levels are below 90 ng/ml, 200 ng/ml, or 75 ng/ml, respectively, but they differ substantially as to the lower-end location. In the well-controlled studies of Glassman and Reisby, patients were administered a fixed dose of imipramine yielding plasma levels from 50 ng/ml to 1,000 ng/ml (see table 5-10). Both workers plus Olivier-Martin reported poor clinical responses with low plasma levels—under 180 ng/ml or 240 ng/ml, respectively. They did not find an upper limit for the therapeutic window in the sense that they did not find a loss in the efficacy of the drug effect with high plasma levels. They did, of course, find toxicity in some patients with very high plasma levels, yet this defines a different type of upper limit to the therapeutic window. Most reviews place absolute limits on the upper and lower limits of the therapeutic window. If the limit of the therapeutic window is from 100 to 200, then a patient with 99 ng/ml is certainly below, and a patient with 201 is certainly above the window. From inspection of figures 5-6,5-7, and 5-8 it would appear that such an absolute interpretation of the therapeutic window is not supported. This is shown most clearly by protriptyline and amitriptyline. Patients within the therapeutic window in one study would be clearly below the therapeutic window in another study. Different authors measured the tricyclics at different times. For example, Asberg measured tricyclics during the first two weeks; Kraugh-Sorensen at the fourth ,week. This is a particularly difficult

problem with protriptyline due to its very long half-life. A method is needed to predict steady state from a test dose or from the first weeks of treatment because values not drawn on steady state are too low for comparison to the norms. Steady state levels should be appropriate levels for normative purposes and plasma levels should be proportioned to doses. We suggest a given value be used to correct the steady state that is relative to the observed normative values. A relatively low dose can be adjusted upward, or a high dose can be adjusted downward, if this makes clinical sense. The most important data for dose adjustment are side effects and clinical response. Plasma levels in the relative sense can sometimes help in dose adjustment.

image

Figure 5-8.

TABLE 5-10 Plasma Levels versus Clinical Response of Patients Treated with Imipramine

Glassman and Perel, 1974	R*	6		19**
	NR	16		1
Reisbey et al., 1977	R	1	1	10
	NR	17	4	4
Martin et al., 1978	R	0	2	2
	NR	3	1	3
Muscettola et al., 1978	R	2	0	3
	NR	4	4	1

Plasma levels in ng./ml.	0-180	180-240	+ 240

*R = responders; NR = non-responders. ** Author gave plasma levels only as 180 and above.

More work is needed to define the therapeutic window so that the plasma levels can be clinically useful. Not only must the existence of the therapeutic window be firmly established, but it is also necessary for laboratories to agree on its exact location. These figures will help the reader place a given plasma level within perspective. Plasma levels differ widely among individuals due to differences in the rate of metabolism in the liver. Hence, the clinician must adjust the dose for each patient to achieve maximum benefit with minimal side effects. Accurately determined plasma levels may well aid in dose adjustment when the literature provides enough data to establish the therapeutic window. We believe that the best way to get a feel for plasma levels is not through arbitrarily selected numbers defining the upper or lower end to the therapeutic window, but by placing a given plasma level in the context of the data presented graphically.

Several studies indicate that imipramine or amitriptyline, given at a dose range of 240 to 300 mgs, are far more effective than an average dose of approximately 150 mg.

Tricyclic Drug Toxicity

Tricyclic drugs differ in their anticholinergic properties. A patient who has experienced unfavorable anticholinergic side effects, such as urinary retention, constipation, or the like may be better suited to treatment with a tricyclic that possesses few anticholinergic properties. Snyder and Yamamura find that amitriptyline displays the most potent anticholinergic properties, doxepin has intermediate characteristics, and desipramine is the weakest. Several *in vitro* techniques exist for assessing the anticholinergic properties. One can, for example, measure the binding of atropine-like agents to the muscarinic receptor of the brain, intestine, or other tissue. However, the magnitude of the correlation between the *in vitro* preparations and the *in vivo* effects is not clear. Amitriptyline reduces saliva significantly more than does desipramine, yet a precise comparison requires data on dose response for both drugs with respect to saliva flow and therapeutic efficacy. Taking into consideration this and the percentage difference in anticholinergic effects at a given dose, it is reasonable to conclude that desipramine generally has fewer anticholinergic properties than amitriptyline.

Anticholinergic properties should not be confused with cardiac properties. While it is true that atropine-like drugs can cause tachycardia, atropine remains a safe drug with a high LD_{50}. The more dangerous cardiac properties of the tricyclics are their direct myocardial depressant qualities and quinidine-like characteristics, such as conduction defects.

Atropine-like psychosis, or the "central anticholinergic syndrome," characteristically produces florid visual hallucinations (for example, bugs or colors), loss of immediate memory, confusion, disorientation, and so forth. The symptoms may be apparent following the administration of tricyclics. It can occur with a given tricyclic alone or when the anticholinergic properties of multiple anticholinergics summate. They are reversible by the administration of physostigmine which is an agent that increases brain acetylcholine and pharmacologically overcomes the atropine blockade. The usual clinical treatment is discontinuation of the anticholinergics, which allows the syndrome to subside within a day. In selected cases, physostigmine can be introduced to produce this dramatic reversal. Misdiagnosis or the use of too much physostigmine may produce cholinergic toxicity. The more conservative course of treatment is the withdrawal of the anticholinergics.

Since tricyclics may frequently convert a depression into a mania, one should remain alert to this switch among bipolar patients. Although the relevant control studies are lacking, some clinicians use lithium tricyclic combinations for the treatment of bipolar depressive episodes. Tricyclics do not usually exacerbate schizophrenia, although on occasion they may do so. Mild withdrawal reactions have been observed upon the sudden termination of imipramine, following two months of treatment at a dosage of 300 mg daily. The reactions consist of nausea, vomiting, malaise, and headaches. A gradual decrease in dosage is usually preferred to abrupt withdrawal, so these

reactions should not present a serious clinical problem. The sedation produced by the more sedative-type antidepressants may add to the sedation produced by ethyl alcohol. Indeed, empirical studies verify the common sense observation that the sedation caused by the different sedative type of drugs, or by alcohol, can combine to exert a greater effect than either agent acting alone. This need not necessarily apply to all tricyclics, but only to those with significant sedative properties.

Cardiovascular Effects

Tricyclic drugs, administered in accordance with the generally prescribed dosage schedule, may have various side effects. Electrocardiograms have revealed tachycardia, flattened T-waves, prolonged QT intervals, and depressed S-T segments. Most importantly, the tricyclics have quinidine-like properties. Imipramine has been demonstrated to decrease the frequency of premature ventricular contractions as a beneficial effect. Unfortunately, these drugs may prolong conduction, causing a significant problem in patients with a conduction defect. It is imperative that the clinician remain attentive to the evidence of impaired conduction and omit tricyclics from the treatment programs of patients who display conduction defects. These drugs also become arrhythmogenic at elevated plasma levels.

Moir and coworkers have documented cases of cardiovascular upset in patients for whom heart disorders have been previously diagnosed. When co-occurrence with the drug treatment arises by chance, this exacerbates the difficulty associated with distinguishing actual cardiac malfunctioning from an unfavorable event directly caused by introduction of the pharmacological agent. Systematic surveillance of cardiac function, coupled with dosage that is initially lower, is strongly advocated.

Over-dosage of Antidepressants

Over-dosage of an imipramine-type antidepressant results in a clinical picture marked by temporary agitation, delirium, weakness, increased muscle tone, slurred speech, hyperreflexia, and clonus. The patient then progresses to coma with hypotension. The most important problems are disturbances of cardiac rhythm, such as tachycardia, atrial fibrillation, ventricular flutters, and atrioventricular or intraventricular block. The lethal dose of these drugs is from ten to thirty times the daily therapeutic dose level.

Treatment of tricyclic overdoses should include vomiting or gastric aspiration and lavage with activated charcoal to reduce tricyclic absorption. Tricyclic coma is generally of short duration—less than twenty-five hours. Since death due to cardiac arrhythmia is not uncommon, management of cardiac function is critical. If the patient survives this acute period, recovery

without sequelae is probable, and vigorous resuscitative measures (such as cardioversion, continuous electrocardiogram monitoring, and chemotherapy to prevent and manage arrhythmias) should be applied in an intensive care unit. Arrhythmias may be mediated, in part, by the tricyclics, which are direct myocardial depressants and have quinidine-like properties. Detection of conduction defects is particularly important.

Physostigmine has a most dramatic effect in counteracting anticholinergic toxicity or coma produced by the tricyclics. It slows down the atropine-induced tachycardia, thus rousing the patient from atropine coma. Given this unusual action, physostigmine has the risk of overuse. Cholinergic toxicity, such as excess secretions, respiratory depressions, or seizures, can occur when physostigmine is given to a patient who is erroneously diagnosed as having atropine coma. Physostigmine toxicity may also occur if too great a quantity is given to a patient who is in actual atropine-like coma. Generally, the best treatment response to atropine overdose is “benign neglect.” This atropine toxicity disappears as the atropine-like agent is metabolized. Physostigmine should be used selectively and judiciously and should be administered only by those familiar with its toxicity.

Bicarbonate is also helpful in preventing arrhythmias. Propranolol is useful in this treatment. It is recommended that patients be placed under medical supervision for several days since cardiac difficulties may occur a few

days later, following the regaining of consciousness. Even though the average half-life of tricyclics ranges between approximately sixteen and twenty-four hours, there are many patients in whose case the half-life is significantly longer than the average. Hence, the plasma level can be expected to be high even as late as three to five days after ingestion of tricyclics.

The internist is chiefly responsible for the management of serious over-dosage; however, the psychiatrist should be familiar with the gravity of the various difficulties associated with tricyclic overdose (for example seizures and arrhythmias) that are not always recognized. Caution is advised to ensure that the suicidal depressed patient does not gain access to an excessive quantity of antidepressant tablets, since several grams (twenty to forty of the 50 mg tablets) can be fatal.

Over-dosage of MAO Inhibitors

Intoxication produced by MAO inhibitors is generally characterized by agitation that progresses to coma, hyperthermia, increased respiratory rate, tachycardia, dilated pupils, and hyperactive deep tendon reflexes. Involuntary movements, particularly of the face and jaw, may be present. The clinician should be aware of the lag period, which is an asymptomatic period lasting between one and six hours after ingestion of the drugs, prior to the general appearance of the symptoms of drug toxicity. Acidification of the urine

markedly hastens the excretion of tranylcypromine, phenelzine, and amphetamine.

New Antidepressants

Maprotiline was compared to a standard tricyclic preparation (usually amitriptyline or imipramine) by means of the random assignment of 2,078 patients to one of these drugs. Examination of outcomes by number and percentage of individuals, as well as an analysis of the data by means of the method of Fleiss, revealed no difference in efficacy among the groups. Six hundred and sixty patients (73.6 percent) who had received maprotiline did well, while six hundred and forty (72.6 percent) showed moderate improvement, or better. In contrast, 247 patients on maprotiline and 255 patients on one of the two standard tricyclics demonstrated either marginal improvement, no change, or a less favorable result.

Another heavily investigated drug, whose safety and efficacy have been demonstrated by a large number of double-blind studies, is amoxapine. Maprotiline and amoxapine are both norepinephrine uptake inhibitors.

Numerous studies of nomifensine have been conducted in Europe and South America. An impressive number of double-blind studies has compared it to standard antidepressants and/or placebo. It has been demonstrated that nomifensine is effective as an antidepressant and comparable in efficacy to

the standard antidepressants. It is both a safe and non-sedating agent and is associated with a relatively reduced incidence of anticholingergic side effects. It has also been shown to inhibit the uptake of norepinephrine and dopamine. It has been extensively investigated and is, at present, under serious consideration by the Food and Drug Administration for release. Mianserin has been shown to be an effective antidepressant. While not an uptake or MAO inhibitor, it does increase the turnover through a presynaptic mechanism. Other experimental antidepressants, such as the NE uptake inhibitor, viloxazine, and the 5HT uptake inhibitor, are now undergoing clinical investigation. Trazodone is used in Europe and has been thoroughly investigated in a number of well-controlled double-blind trials in the United States. It is unequivocally an effective antidepressant. Another interesting antidepressant initially developed as a minor tranquilizer is triazolam. Early clinical-drug evaluation study shows it to be promising as an antidepressant.

Benzodiazepines As Antidepressants

Since anxiety is often associated with depression, the logical question that comes to mind is: Are benzodiazepines effective antidepressants? In a review of the relevant literature, Schatzberg and Cole failed to find any study that indicated that benzodiazepines were significantly better than antidepressants. However, benzodiazepines were significantly inferior to the antidepressants in ten studies and there were no significant differences in the

other nine studies.

Ives and coworkers divided depressed patients into several groups and treated them with phenelzine plus chlordiazepoxide, phenelzine alone, a placebo alone, and a placebo plus chlordiazepoxide. Chlordiazepoxide did not alleviate depression with the placebo nor with the phenelzine. In separate studies, Kay, Lipman and co-workers, and Covi and coworkers found that diazepam was inferior to imipramine in treating depression. The majority of the studies show that benzodiazepines are virtually ineffective in the treatment of depression. There are some investigations, however, that show that minor tranquilizers may temporarily relieve symptoms of depression. More studies of the exact role of benzodiazepines in depression are needed.

Anxiolytic Tricyclic Combinations

A fixed dose preparation that combines chlordiazepoxide and amitriptyline for the treatment of mixed anxiety depression in outpatients has recently been introduced. The effectiveness of this combination was demonstrated by the results from a double-blind, multicenter collaborative study that compared their combination (trade name Limbitrol), which consists of 10 mg chlordiazepoxide plus 25 mg amitriptyline, to amitriptyline alone, chlordiazepoxide alone, and placebo. There were 279 outpatients in this study. The criteria for primary depression were derived from scores

obtained on the Hamilton Depression Scale (twenty points or higher), the Beck Depression Scale (fourteen points or higher), and the Covi Anxiety Scale (eight points or higher). Chlordiazepoxide and amitriptyline are both sedative drugs that possess antianxiety properties that are beneficial to insomnia and psychic and somatic anxiety. Due to their combined sedative-anxiety properties, it is not surprising that they contribute to the sedative and antianxiety effects. The combination clearly produces greater improvement on items from the Hamilton Depression Rating Scale such as insomnia, agitation, and somatic and psychic anxiety during week one of treatment. Overall scores on the Global Hamilton Depression Scale and the Beck Inventory demonstrated that the combination was superior to either of the individual drugs by the end of the first week. The superiority of all drugs, relative to placebo, is quite clear. At present, a relevant research question is if the degree of increased improvement observed after one week is a function of the extra antianxiety properties of two sedative drugs, or if it reflects the added therapeutic influence on depression. It is interesting to note that the combination resulted in greater improvement on the Depression Inventory on items such as pessimism, dissatisfaction, and guilt. After several weeks, amitriptyline alone was as effective as the combination on many of the measures, and slightly, but not significantly, exceeded effectiveness of the combination on certain measures, such as the depression factor of the Hopkins Symptom Checklist and the Beck Depression Inventory. The

combination was slightly superior to amitriptyline alone by other measures, such as the Hamilton Depression Scale. Unfortunately, the investigators presented a selected finding, rather than a more systematic portrayal of the data. Indeed, it would be desirable to examine a detailed publication of this collaborative study.

Rickels and coworkers conducted a comparable study, which included 243 mild to moderately depressed outpatients suffering from either a reactive neurotic depression or from a mixed anxiety depressive reaction. Owing to the fact that patients were evaluated at the end of two and four weeks, it is impossible to determine if the initial improvement of the combination observed by the Roche collaborative study at one week occurred here as well. This study demonstrated that the drug effects were statistically significant for both the combination and for each of the individual components, in comparison to a placebo. However, it is difficult to interpret this study, due to the failure of the investigators to present statistics on the comparisons between the combination versus each drug separately. It is difficult for the reader to acquire a complete grasp of whether the combination was superior to one or another of the individual drugs.

Hare completed two modest studies that included twenty outpatients with mixed anxiety and depression. He compared the influence of the drug combination against amitriptyline given alone. In the first study, after one

week, the former appeared superior on a number of dimensions. By the third week, similarity as to the degree of improvement from both increased, so that the initial difference had been largely observed. In the second study, the effects of the combination were similar to those from the amitriptyline alone. The statistically significant improvement on some measures still persisted for the combination, however. Haider, examining seriously depressed inpatients, noted that the combination was superior to amitryptyline alone at the end of a three week period.

Clearly, the addition of chlordiazepoxide to a tricyclic does not alter its therapeutic action. Some evidence available from the two studies cited here-indicates that it may be helpful after week one of treatment. However, one study failed to find it to be superior at that time, and another did not investigate efficacy at the close of one week. After three weeks, it is not clear that the combination is superior. Another methodological problem is diagnostic homogeneity. A method is needed to separate out the two populations of patients: the one with pure depression with only secondary anxiety, and the other with pure anxiety accompanied by only secondary depression. Also, note the nonspecific nature of these rating scales: for example, depression scales have anxiety items and vice versa. Furthermore, improvement in anxiety may artificially improve depression due to a sort of halo effect. The evidence of the addition of a minor tranquilizer was summarized here so that the reader can draw his own conclusion. The

addition of an antianxiety agent in the first week would do no harm and possibly have some beneficial effect, but more work is needed before forming definitive conclusions.

Minor Tranquilizers

For many years, physicians have treated anxiety with sedative agents—alcohol, barbiturates, Meprobamate, chlorpromazine, and benzodiazepines. Do the benzodiazepines offer any advantages over the classical barbiturates?

Comparison With Other Drugs

Several studies have compared the sedative properties of benzodiazepines with those of barbiturates, Meprobamate, and a placebo. There is inconclusive evidence that some benzodiazepines may be slightly superior to barbiturates in the treatment for anxiety. Schapira and coworkers found 4.55 mg a day of lorazepam slightly more effective than similar doses of barbiturates. Similarly, in another study 25 mg of diazepam was superior to 463 mg of amobarbital. In general, benzodiazepines have slightly stronger antianxiety effects than barbiturates at equal sedative doses. One can only make a weak case for this. Overall, there are more visible similarities than differences between benzodiazepines and barbiturates. The therapeutic efficiencies of benzodiazepines, Meprobamate, and barbiturates are about equal, although some research indicated that benzodiazepines may be slightly

superior.

A substantial number of studies have firmly established that benzodiazepines are more efficient sedative-type antianxiety agents than placebos. The therapeutic efficacy of prazepam was verified in controlled multi-clinical investigations by its sponsor and several academic researchers. The antianxiety effects of clorazepate have been proved superior to a placebo and comparable to diazepam. Since both benzodiazepines are precursors of the same active metabolite, desmethyldiazepam, they should be equally efficient as tranquilizers. In a thorough investigation of lorazepam, Richards found the drug more effective than a placebo for treating anxiety neurosis, anxiety manifested in gastrointestinal and cardiovascular disorders and as a component of depression. The study reports on combined data from a large number of controlled trials involving 5,960 patients, of whom 3,520 received lorazepam. Davis and Greenblatt offer a recent review of the treatment of anxiety and personality disorders.

Metabolism

The similarity of the benzodiazepine derivatives can be understood by looking at the active intermediates found in their metabolism. Chlordiazepoxide first metabolized to desmethylchlordiazepoxide, which is in turn converted to demoxepam. Demoxepam is then metabolized to

desmethyldiazepam, which is converted to oxazepam. Oxazepam is then conjugated to its glucuronic acid. Probably these four metabolites are all clinically active. The unchanged drug along with the first two metabolites constitutes most of the compounds that are found in the plasma, with their observable levels ranging from approximately 300 ng/ml to 3,000 ng/ml. Desmethyldiazepam and oxazepam are minor metabolites of chlordiazepoxide with a lower plasma level of about 200 ng/ml. Desmethyldiazepam is a major metabolite of diazepam. Direct metabolism of diazepam to desmethyldiazepam is followed by conversion to oxazepam, which, in turn, is metabolized to its inactive conjugate glucuronic acid. Two studies compared the plasma levels of diazepam and desmethyldiazepam. Robin and coworkers found steady state plasma levels after a 5-mg, three-times-a-day dose of diazepam and desmethyldiazepam to be 2,400 ng/ml and 3,500 ng/ml., respectively. Similarly, Tansella and coworkers found plasma levels of diazepam (742 ng/ml) and desmethyldiazepam (762 ng/ml) using a mean dose of 26 mg per day.

Prazepam, a recently introduced benzodiazepine, is essentially a precursor of desmethyldiazepam. It is almost completely metabolized to desmethyldiazepam in a first-pass effect. The possible metabolites, 3-hydroxy prazepam and oxazepam, are not observed in the plasma after administration of prazepam. This suggests that desmethyldiazepam is the active substance responsible for the drug's antianxiety effect.'

Another desmethyldiazepam precursor is clorazepate, which is completely converted to this metabolite by rapid spontaneous dehydration and decarboxylation occurring in the acidic environment of the stomach. One study found that after administering equal molar doses of clorazepate and diazepam, the plasma levels of desmethyldiazepam transformed from clorazepate are essentially equal to the sum of the plasma levels of diazepam and its converted desmethyldiazepam.

Clorazepate, prazepam, and diazepam have similar clinical effects since each drug is metabolized to the same active substance— desmethyldiazepam. Considering that the half-life of desmethyldiazepam ranges from 30 hours to 200 hours, one daily dose is quite sufficient for all three drugs. Both clorazepate and prazepam are precursors of desmethyldiazepam since they are nearly completely converted to it during metabolism. Thus, they are essentially identical from a clinical point of view. The two products do differ in the rate in which conversion to desmethyldiazepam occurs. The pharmacokinetics of clorazepate are rapid; once in the stomach, the drug is immediately converted to desmethyldiazepam and rapidly absorbed. If the stomach is not maintaining its usual low pH level, the rapid conversion rate may not apply. Prazepam, however, results in a slower appearance of desmethyldiazepam due to the first-pass effect in the liver. Its plasma level versus time plot yields a curve similar to the one observed for sustained released preparation. The clinical effects due to the pharmacokinetic

differences are most notable when they involve the first dosage of clorazepate and the subsequent rapid sedative action. Using multiple dose administrations, the differences between prazepam and clorazepate are minimal. There may be differences in the pharmacological properties of diazepam and the two products since 40 percent of the compound present in the plasma is unchanged diazepam.

As mentioned earlier, the half-life of desmethyldiazepam can vary greatly. However, several studies show a steady-state half-life of approximately fifty hours. Unconverted diazepam exhibits a similar long steady-state half-life of about forty to fifty hours. Chlordiazepoxide, the first of the benzodiazepine derivatives, and its two principal active metabolites, diazepam and desmethyldiazepam, have half-lives in the range of twenty to forty hours.

Each of the four benzodiazepine derivatives discussed achieves a steady state in two to three weeks. However, pharmacological effects should persist for a few days following termination of treatment with chlordiazepoxide, diazepam, and desmethyldiazepam because of their long half-lives.

Lorazepam and oxazepam exhibit pharmacokinetic similarities. Both compounds are metabolized at the 3-hydroxy position by conjugation with glucuronic acid. The resultant conjugate, which is excreted in the urine, is

pharmacologically inactive. Compared to other benzodiazepine derivatives, oxazepam and lorazepam have a substantially shorter half-life. Their half-lives range between ten to twenty hours for the majority of patients with oxazepam showing a slightly shorter half-life. Since the B-phase half-life is less than fifteen hours, two- or three-times-a-day dosage schedules are practicable, and steady state levels can be reached within four days after initiating such treatment. However, after suspension of treatment, the pharmacological effects of oxazepam and lorazepam are maintained for a much shorter time than for other benzodiazepines.

Benzodiazepines and Liver Disease

The half-life and volume distribution of some benzodiazepines are markedly greater in patients with liver diseases, such as alcoholic cirrhosis, acute viral hepatitis, and hepatic malignancy. This is caused by the pathway of metabolism through the liver. In the case of diazepam and chlordiazepoxide plasma bindings are reduced, thus increasing the volume of distribution and decreasing clearance (this does not apply in extrahepatic obstructive liver disease). Lorazepam and oxazepam are relatively unaffected by liver disease since they are excreted by a different route. However, in cirrhosis, there is a small increase in the half-life of lorazepam and a significant change in its plasma clearance.

It is well known that the effects of sedatives on the elderly, who are especially sensitive to these agents, suggest that the mechanism of this effect may be increased brain sensitivity to the drug and impaired metabolism resulting in elevated brain drug levels. Specifically, there is a lowered clearance of desmethyldiazepam and chlordiazepoxide in the elderly. The clearances of diazepam, oxazepam, and lorazepam are unaffected by age.

Physical Dependence and Tolerance

Very little research has been directed to documenting the dependence liability of antianxiety drugs. Limited information has suggested that 3,200 mg of Meprobamate for forty days or 300 mg of chlordiazepoxide for a month can cause addiction. There is approximately one case of benzodiazepine dependency per 50 million patient months of therapeutic use. Pevnick and coworkers studied the withdrawal symptoms of dependency on diazepam. These were characterized by tremor, dysphoric mood, muscle twitches and cramps, facial numbness, insomnia, anorexia, weakness, nervousness, weight loss, and increased orthostatic pulse. This collective syndrome usually starts on the sixth day of withdrawal, peaks on the seventh day, and disappears by the ninth.

Anxiety-dysphoric symptoms may occur after discontinuation of long-term benzodiazepine treatment, but it has been extremely difficult, if not

impossible, to determine whether these symptoms were induced by physical dependence or the re-emergence of the previously suppressed anxiety. Further research on this question is necessary, and physicians should watch patients for any signs of addiction, such as obtaining early refills or consulting several doctors simultaneously for medication.

Cross-tolerance exists among sedative drugs. One can be utilized to treat the withdrawal symptoms caused by addiction to another. As of late, diazepam is replacing pentobarbital as the standard detoxification agent because it is a longer-acting drug.

Hydergine

Many well-controlled double-blind scientific studies found that Hydergine is effective in treating mental disorders in the elderly. However, it is unclear whether the alleviation of symptoms such as confusion, anxiety, agitation, and irritability result from Hydergine's vasodilating action. Improvement with Hydergine is noted to be slow in onset (about three months), and further research is essential to determine the mechanism by which the drug accomplishes clinical improvement.

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