American Handbook of Psychiatry

ANTIANXIETY DRUGS

JONATHAN O. COLE
JOHN M. DAVIS

Antianxiety Drugs

Jonathan O. Cole and John M. Davis

e-Book 2015 International Psychotherapy Institute

From *American Handbook of Psychiatry: Volume 5* edited by Silvano Arieti, Daniel X. Freedman, Jarl E. Dyrud

Table of Contents

Antianxiety Drugs

Introduction

Man has been looking for ways to escape or reduce anxiety for centuries. Alcohol was probably the first drug to be used for this purpose. In common with many modern antianxiety drugs, it not only decreases anxiety at some initial dosages but also acts as a disinhibiting agent, allowing its imbibers to behave in ways which they sometimes regret the next morning. Alcohol raises the convulsive threshold initially. On prolonged chronic administration it produces both psychological and physical dependence. Its abrupt withdrawal can precipitate convulsions (rum fits) and delirium (DTs). Moderate single doses can produce muscle relaxation. Large single doses produce sleep, and very large doses (e.g., a quart of whisky) can produce death through depression of the brain's respiratory center (Ritchie, 1970).

All the above actions alcohol shares in principle, and sometimes in practice, with a wide range of sedative, hypnotic, and antianxiety drugs. Alcohol differs chiefly in being easily available, and being subject to a wide range of laws, superstitions, and customs which influence its use. Although as many as 4 percent of

American adult males are said to have a serious drinking problem, fifteen to twenty times as many adult males use the drug without appreciable

trouble. It's impossible to assess the real efficacy of alcohol as an antianxiety agent. It is probably useful in acute episodic or reactive anxiety of short duration (e.g., the aftereffects of a bad day at the office), but alcohol's short duration of action and tendency to release catecholamines and elicit some rebound anxiety, interferes with its use in long-term therapy. Chronic alcoholics, consuming alcohol on research wards, appear more anxious and irritable than drunk and happy (McNamee, 1968).

Nevertheless, alcohol has been found useful in some clinical situations. Not surprisingly, efficacy studies have been conducted in institutional settings where elderly patients do not ordinarily have access to alcoholic beverages. Here, alcohol appears to reduce anxiety and tension, and increase cheerfulness and social interaction when given in small daily doses (Chien, 1971, Chein, 1972). It is possible that in the elderly the vasodilating effect of alcohol may cause slight improvements in organ functioning over and above the drug's benign disinhibiting antianxiety effect at the doses used (one can of beer or one glass of wine). The contribution of social setting and expectations to the clinical drug response to alcohol has not been adequately studied.

Alcohol seemed an excellent drug to consider as an introduction to a discussion of the use of antianxiety drugs in psychiatry since it illustrates the full range of problems encountered in other drugs, plus a few unique ones (e.g., Wernicke's syndrome, cirrhosis of the liver). Some uses, which seem at

first to be characteristic of alcohol, like recreational use, are clearly no longer unique. Actually many other sedatives (ether, nitrous oxide, barbiturates, even chloral hydrate) have been used for kicks at one time or another (Goodman, 1970). A major issue, which will be discussed in more detail below, is the issue of the abuse liability of antianxiety drugs.

Terminology

There are serious problems in the terminology, definition and measurement of anxiety which are mainly beyond the scope of this chapter. For present purposes, a combination of free-floating fear or apprehension, psychic and somatic manifestations of anxiety and of tension spreading over into depression, irritability or hypochondriasis must be considered loosely as the target area of antianxiety drugs. Attempts to cluster anxiety symptoms into coherent subgroups and to separate anxious symptoms from depressive symptoms have produced either no separation, confusion, or relatively unhelpful groupings of semantically related items (Derogatis, 1972). Since many rating scales which include selections from this mixture of symptoms show clear drug-placebo differences in patients identified by psychiatrists as being "anxious," one almost has to assume that a more detailed delineation of anxiety symptoms is not empirically necessary to determine the efficacy of most drugs (Kellner, 1970).

Major exceptions to this general approach to anxiety are: (1) recurrent severe episodic panic attacks; (2) anxiety clearly secondary to a schizophrenic illness; and (3) severe agitation in a major depressive illness. Under these three conditions antianxiety drugs are not useful, although they may sometimes have a mild palliative effect in low doses and can, in very high doses, render such patients temporarily asymptomatic by putting them to sleep.

Other kinds of patients clearly show anxiety symptoms, such as chronic alcoholics after initial detoxification, or patients with reactive acute first-episode anxiety symptoms of short duration (Gallant, 1969; Rickels, 1968). Both groups improve so much on inert placebo plus ordinary supportive therapy that it is difficult to show any need for the use of antianxiety drugs under such conditions.

Drug terminology can be handled with greater clarity. The term "antianxiety agent" is probably preferable as describing a desired clinical action which can often be achieved. The earlier term "minor tranquillizer" is useless in the United States and only slightly more useful in Europe. In the United States, antipsychotic agents like chlorpromazine, and antianxiety agents like meprobamate, were both initially called "tranquillizers" on the correct but vague assumption that they often made patients more peaceful. Unfortunately, the most important use of chlorpromazine and other

phenothiazines is in the treatment of schizophrenic psychopathology, an area in which meprobamate and the antianxiety drugs are essentially ineffective. To call both kinds of drugs "tranquillizers" even if they are segregated into "major" and "minor" tranquillizers implies a nonexistent similarity in the pharmacology and clinical utility of the two groups of drugs. In the United States, the terms "antianxiety drug" and "antipsychotic drug" are becoming more widely used and are much more informative. In Europe the term "neuroleptic" is used instead of "antipsychotic" and the term "tranquillizer" is reserved for drugs which we, in the United States, should call antianxiety agents.

Hollister, in an excellent book on clinical psychopharmacology (1973), neatly handles another dimension of drug classification by dividing agents effective or probably effective in reducing anxiety into two classes:

1. The sedative-hypnotics, into which class alcohol—our prototype anxiety drug—would fall, as well as meprobamate, barbiturates, and benzodiazepines (e.g., diazepam). As noted above, sedative-hypnotics usually and in varying degrees *decrease* muscle tone, *raise* the convulsive threshold, produce motor ataxia at higher dosages, and elicit tolerance and physical dependence.

Table 21-1.Antianxiety and Sedative Agents Used in the United States

DRUG	HYPNOTIC	SEDATIVE DOSE*	ADDICTIVE

	DOSE*		PS.	PH.
Sedative-Hypnotics				
Benzodiazepines				
Chlordiazepoxide		5-25 mg. tid or qid	+	+
Diazepam		2-10 mg. bid or tid	+	+
Oxazepam		10-30 mg. tid or qid	±	+
Clorazepate		7.5 mg. qid	+	+
Flurazepam	15-30 mg.	—	?	?
Others				
Meprobamate	800 mg. hs	400 mg. tid	+	+
Solacen		350-500 mg. tid or qid	–	–
Methaqualone	150-300 mg.	75 mg. tid or qid	+	+
Diphenylhydantoin		200 mg./day	–	?
Barbiturates				
Phenobarbital	100-200 mg.	30-60 mg. tid or qid	±	+
Butabarbital	50-100 mg. hs	15-30 mg. tid or qid	±	+
Pentobarbital	100-200 mg. hs	30 mg. tid or qid	+	+
Amobarbital	100-200 mg. hs	30-50 mg. tid or qid	+	+
Secobarbital	100 mg. hs		+	+
Sedative-Autonomic Agents				
Hydroxyzine		25-100 mg. tid	–	–
Diphenhydramine		50 mg. po tid or qid	–	–

Doxepin	50-150 mg.	–	–

Legend: tid = three times a day; qid = four times a day; hs = bedtime; Ps. = psychological dependence; Ph. = physical dependence.

* Dose and action recommended by drug company and FDA approved.

2. The sedative-autonomic drugs which decrease anxiety. In contrast to the sedative-hypnotics, they *increase* muscle tone, *lower* convulsive threshold, and do not produce physical dependence. Into this class fall sedative antihistamines (e.g., hydroxyzine or diphenhydramine), phenothiazines when used in low doses to relieve anxiety, and sedative tricyclic antidepressants with antianxiety effects (e.g., doxepin).

Table 21-1 presents antianxiety and sedative agents currently in general use in the United States.

To date the only type of possible antianxiety drug under clinical study that does not readily fit into this classification is propranolol, a non-sedative autonomic agent (a beta-adrenergic blocker) which may relieve anxiety symptoms through peripheral blockade rather than through central action on the brain (Granville-Grossman, 1966; Wheatley, 1969).

A question may well be raised at this point. Are barbiturates really the typical hypno-sedatives and are drugs like chlordiazepoxide really very

different? Should the newer sedative antianxiety agents be classified separately from the older sedative hypnotics?

Hypno-sedative vs. Antianxiety Agents?

Despite almost two decades of advertising by drug companies, the authors are unconvinced that the therapeutic and pharmacological main actions of barbiturates and benzodiazepines are so markedly different as to deserve separate classificatory groupings. Both types of drugs decrease anxiety and elicit sedation or drowsiness as a side effect. At median effective dose (ED-50 in pharmacological jargon) for anxiety reduction, a barbiturate should, in theory, produce more drowsiness and ataxia than a drug similar to diazepam, and at doses of the two drugs producing equal sedation, patients on a benzodiazepine should be less anxious. Although the clinical literature is vague in this direction, the trend is weak and the magnitude of the differences in efficacy and sedation between the two classes of drugs is not large enough to warrant separate classifications. Nevertheless, benzodiazepines are generally judged more effective than barbiturates in controlled studies (at dosages used which are often low for the barbiturates). The really important differences between the two drug classes are to be found elsewhere in this paper.

Benzodiazepines have a much longer half-life in the body than

barbiturates like amobarbital, have a slower onset of action when taken orally, and are far, far safer when taken with suicidal intent (Hollister, 1973). There is no recorded successful suicide in which only benzodiazepines were taken (e.g., in doses as high as 2250 mg. of chlordiazepoxide) while ten short-acting barbiturate capsules can sometimes be lethal. The benzodiazepines are probably also less prone to abuse than short-acting barbiturates because of the benzodiazepines' slower onset, and because of the longer duration of action that deprives spree users of a quick intense "high."

Possible Mechanisms of Action

Although antianxiety drugs have usually been identified and selected by drug companies because, in animals they prolong hexa-barbital sleeping time, raise convulsive threshold, and elicit ataxia and reduce motor activity at some dose, these actions are of little psychotherapeutic interest per se. The intriguing action from a psychiatric viewpoint is the ability of the sedative-hypnotics to disinhibit suppressed behavior in an operant test system. Typically, hungry animals, pressing a lever for an occasional food reinforcement, are taught that, when a red light is on, a lever press may sometimes yield a painful shock as well as a food pellet. Animals treated with saline (or phenothiazine, opiate, or amphetamine) stop pressing the lever while the light is on. Animals treated with barbiturates or benzodiazepines risk the shocks by pressing the lever anyway.

Also, even though sedative-hypnotics can reduce psychomotor activity, at lower doses they often increase exploratory behavior and increase responsiveness to environmental stimuli. They do not suppress conditioned avoidance behavior.

Phenothiazines reduce motor activity at all dosages, decrease exploratory and social behavior, and inhibit conditioned avoidance responses (e.g., acting at a learned warning signal so as to avoid a subsequent imminent shock).

Irwin has extrapolated these animal observations to the clinical situation (1968). He proposes that benzodiazepines should be used to treat anxiety when the patient is shy and underactive and more risk-taking behavior is to be encouraged. Phenothiazines should be used to reduce anxiety when the patient is overactive and takes too many risks, where decreased social responsiveness and physical activity are clinically indicated.

Although no specific clinical trial has tested Irwin's hypothesis, there are some clinical data which tend to support his ideas. Lipman et al (1965). in a study comparing chlordiazepoxide (CDP) with placebo in anxious outpatients found that patients on CDP report significantly more "good things" happening to them during the trial than do placebo patients. Many of the "good" events had an aggressive risk-taking component, e.g., "My wife and

I finally had it out and now we understand each other!" DiMascio's observation that benzodiazepines, particularly CDP and diazepam, elicit increased hostility in normal subjects with low pretreatment anxiety levels could also be considered a form of disinhibition (1973). Klein's finding that phenothiazines stabilize and inhibit the behavior of patients with emotionally unstable personality disorders (1973) also supports Irwin's thesis.

It is difficult for us to summarize or interpret the neurophysiological effects of the sedative-hypnotic antianxiety agents in any clinically meaningful manner. On the other hand, a recent paper by Stein et al. has intriguing content with relevance for clinical usage (1973). He reports a direct effect by oxazepam on both norepinephrine and serotonin in the brain. He then demonstrates, by the skillful use of research drugs, that the effect of oxazepam on norepinephrine is short-lived and related to sedation while the effect on serotonin lasts for many hours and is relatable to anxiety reduction.

Assuming this differential action is true of man as well as of the rat, an excellent argument can be made for giving the generally long-lasting benzodiazepines at bedtime (hs) rather than on a three-times-a-day (tid) or four-times-a-day (qid) basis. A single hs dose should improve sleep at night while allowing anxiety reduction uncomplicated by ataxia or drowsiness to occur in the daytime. Given half-lives in the body of over twenty-four hours for both chlordiazepoxide and diazepam, this approach should be clinically

useful. A study providing a clear test of the proposition is badly needed.

A recent study of hs butabarbital in elderly psychiatric patients supports this proposition (Stotsky, 1971), but with a presumably shorter acting drug. In the course of a study of the efficacy of butabarbital as an hypnotic, ward behavior ratings were collected on general principles. It turned out that during the week on 50 mg. butabarbital hs the patients not only slept better than they did on placebo but also showed improved daytime ward behavior.

Enzyme Induction

There is increasing laboratory evidence about the ability of some drugs to cause the body to make more and more of the enzyme by which they are detoxified. This "induced" extra enzyme will often metabolize other unrelated drugs as well.

The classic example is phenobarbital. A few days' administration of phenobarbital not only increases a person's ability to metabolize that drug but also makes the body metabolize the anticoagulant, warfarin, more rapidly. This effect can have serious consequences in cardiac or other patients who have been stabilized on warfarin. Warfarin blood levels can be reduced by adding phenobarbital or, alternately, elevated after withdrawing phenobarbital (Conney., 1967; Hollister, 1973).

Luckily, the benzodiazepines do not induce metabolic enzymes appreciably (Robinson, 1973). Choral hydrate, interestingly, affects warfarin blood levels by a totally different mechanism. A metabolite of choral hydrate, trichloroacetic acid, kicks warfarin molecules off of their binding sites on plasma proteins, causing a sudden rise in plasma warfarin levels and a drop in prothrombin time, with attendant risk of hemorrhage.

Abuse Liability

Everyone agrees that drugs like secobarbital, amobarbital, and pentobarbital are abused on the "street" illicitly. At an approximate level of daily use of six 100-mg. capsules, physical dependence on these drugs begins to appear (Goodman, 1970; Wikler, 1957). Untreated abrupt withdrawal in markedly physically dependent individuals can lead to severe agitation and tremulousness, convulsions, delirium and, rarely, death. In contrast to opiate withdrawal, which can be terminated at any time by an adequate dose of an opiate agonist, barbiturate withdrawal becomes non reversible in its more severe stages.

Probably the vast preponderance of sedative-hypnotic addicts—those both physically and psychologically dependent on these drugs —are "street" users and originally took such drugs for "kicks" or possibly as a replacement for heroin or some other drug of abuse. Occasionally a patient becomes

markedly dependent on either barbiturates, meprobamate or the benzodiazepines through medical channels by being given—or obtaining by ruse—such pills from one or more physicians. Apparently, the recent Quaalude abuse scare arose in that manner (Hollister, 1971; Schwartzburg, 1973).

Clearly, physical dependence can be developed to methaqualone (Schwartzburg, 1973), diazepam, chlordiazepoxide (Hollister, 1961), and meprobamate (Hollister, 1970). It can probably be produced by all the agents listed as sedative-hypnotic agents in Table 21-1 except tybamate (Shelton, 1967), the latter being exempted presumably by its short half-life in the body. A steadily elevated drug blood level is apparently needed to induce physical dependence.

The autonomic sedatives do not appear capable of inducing either physical dependence or drug-seeking behavior induced by psychological craving.

To obtain true physical dependence of the barbiturate type, one needs sedative-hypnotic agents available on the street with a real or believed ability to induce an intense, pleasurable "high" and an action long enough to induce real physical dependence. Pentobarbital meets these criteria as, apparently, does methaqualone. It seems possible that longer acting drugs (e.g.,

chlordiazepoxide, butabarbital, phenobarbital) are less liable to abuse not because they do not induce tolerance or physical dependence but because their "flatter highs" fail to induce much drug-seeking behavior. Currently there is no systematic work in progress to compare older and newer antianxiety agents on these abuse-relevant dimensions in either animals or man.

One last point needs stressing. Nightly ingestion of one or even two sleeping pills will not produce physical dependence. It may well make patients demand such medication vigorously and may induce a little insomnia after the nightly drug is stopped. It may even be therapeutically irrational to continue such medication, since the hypnotic efficacy may drop with successive nightly administrations (Kales, 1969). It is not clear whether the hangover effects seen after single bedtime doses of hypnotics (Kales, 1969; Von Felsinger, 1953) are also seen after regular nightly use. One suspects that some tolerance to these might also develop. Overprescribing or overdependence on nightly hypnotics may be a misuse of such drugs but is probably not a major one.

Overuse of Antianxiety Drugs

The issue of overuse or overprescription of antianxiety drugs in the United States is charged with emotion, with some claiming that the problem is

very serious and probably due to undue pressure from unscrupulous drug companies (Lennard, 1970). These claims seem grossly exaggerated. Fortunately, data are becoming available which are relevant to this problem. A 1973 report (Perry, 1973) on a well-conducted national survey of drug use by individuals shows that about one in five adults in the United States had used a prescription psychotherapeutic drug in the twelve months preceding the year. About two-thirds of the drugs used were antianxiety agents. One in five women had used such drugs at some time in that year vs. less than one in ten men. About one in twenty adults had used antianxiety agents daily for two months or more.

It is worth noting that data from the National Disease and Therapeutic Index, a survey of doctors' drug use, indicate that only half the patients for whom antianxiety agents are prescribed are given a psychiatric-type diagnosis. Since antianxiety drugs are used as muscle relaxants and, one of them, phenobarbital, is used in epilepsy, the above use figures may well be a bit inflated. The authors of the survey (Perry, 1973) also obtained comparable data from several European countries and find that the drug use in the United States is comparable to that in other Western nations.

The above information can be interpreted in many ways. We judge it to be generally reassuring, in that antianxiety drug use is not really very rampant. Others could, of course, argue that too many people are being given

these drugs. The fact that 77 percent of people surveyed who were using psychoactive drugs felt helped "a great deal or quite a bit," is reasonable evidence of consumer satisfaction. Since about 5 percent of the population surveyed had taken over-the-counter tranquilizers in the past year, the generally lower "improved" rate for all such psychoactive drugs (39 percent vs. 77 percent for prescription drugs) is worth noting. This confirms the highly negative controlled study of Compoz, a major over-the-counter tranquilizer, by Rickels and his group (Rickels, 1973).

The issue of overprescribing by the doctor or overconsumption by the patient must remain moot until some agreement develops as to specific criteria for appropriate or rational use. As Rickels et al. (Rickels, 1972) have noted, general-practice patients getting antianxiety drugs are a good deal more symptomatic than patients seen in the same practice with gynecological problems, and only those neurotic patients judged moderately to markedly improved approach, after drug treatment, the subjective distress scores of the gynecologic patients.

Unusual Clinical Actions of Antianxiety Drugs

Before going on to consider the general clinical efficacy of antianxiety drugs, some atypical clinical uses and effects deserve comment.

Sodium amobarbital, IV at 250-500 mg., has some unique properties. It

is the fastest way to quiet a wildly disturbed patient if one has enough staff to make access to a vein possible, and if one avoids stopping respiration by injecting the drug too rapidly (e.g., a few seconds vs. two to four minutes). Injected more gradually the same drug often produces a dramatic change in patients in catatonic stupor (Wheatley, 1969). Such patients become often fully relaxed, and able to talk and move normally for an hour or two before the stupor and rigidity returns. Interviews with otherwise mute or under responsive psychotic patients are sometimes made possible by intravenous barbiturates. Sometimes this device makes it possible to get a history and establish identity when the patient is unable to provide the information in an ordinary interview. It is worth noting that information provided under barbiturate sedation (popularly known as "truth serum") is by no means always true. It can be confounded by the patient either consciously or unconsciously.

There is reasonable evidence from research done in World War II that intravenous barbiturate-induced catharsis can produce immediate and dramatic, enduring relief in patients suffering from an acute traumatic neurosis following severe exposure to stress (Grinker, 1943; Grinker, 1945).

The value of IV barbiturates in facilitating dynamic psychotherapy in more routine neurotic conditions is less clear. Patients often talk more freely about highly charged material which had previously been either suppressed

or repressed. Whether or not this increased verbal fluency leads to clinical improvement is less clear.

Similarly, barbiturate-induced relaxation has been tried along with desensitization and other forms of behavior therapy. Its value in this context is as yet unclear, but tends toward the positive (Lipsedge, 1973; Silverstone, 1970).

As Shagass (Shagass, 1972) and others have reported, the sedation threshold (the amount of intravenous drug required to produce sedation-related changes in the EEG or GSR) discriminates between neurotics and psychotics, with psychotics developing sedation at significantly *lower* dosages of barbiturate.

Hyperkinetic children are made worse by barbiturates. A history of excitement caused by barbiturates is thought to be an indication of a good clinical response to amphetaminelike agents. Similar sedative-induced excitements occur on occasion in senile or younger organically impaired patients. Organic patients often show marked increases in denial and distortion under the influence of barbiturates (Weinstein, 1955).

Two points remain to be made here:

1. Diazepam, available for intravenous use, may be as useful and a bit

safer for any or all of the above purposes. Much of the above work was done before diazepam came into use. In a single study of the effect of IV diazepam on anxiety, 10 mg. were infused over a ten-minute period. A clear reduction in subjective and objective components of anxiety was observed but the peak effect appeared ten to twenty minutes after the injection was stopped, which suggests that diazepam has a less immediate onset of action IV than do the fast-acting barbiturates (Lader, 1966).

2. Intravenous use of barbiturates has one serious side effect besides suppression of respiration. Laryngospasm can occur, particularly if the patients' larynx has a preexisting irritation from infection, intubation, or gastric gavage. Laryngospasm can be fatal.

The Efficacy of Antianxiety Drugs

Two sets of apparent facts plague the study of clinical effectiveness in the antianxiety area. The first is that many standard drugs are often found to be more effective than placebo. This is truest of chlordiazepoxide, diazepam, oxazepam, and tybamate (over 80 percent of reported controlled studies show a drug to be significantly better than placebo: chlordiazepoxide 27 of 28, diazepam 16 of 1S, oxazepam 8 of 9 and tybamate 15 of 16). In the case of meprobamate and the barbiturates, the proportion of positive controlled studies is about 66 percent (barbiturates 13 of 19, meprobamate 18 of 27).

Comparisons between various newer antianxiety drugs, and older drugs like meprobamate or the barbiturates, produce a more mixed picture with no clear superiority emerging overall, though diazepam and tybamate have the best records in a handful of comparative studies.

All this is reasonably clear. A problem arises when one tries to explain the negative studies on any rational basis. Both Rickels (1970) and Wheatley (1973) present evidence that outpatients with symptoms of only a few months' duration and little previous exposure to antianxiety drugs show over 80 percent improvement on placebo, a figure no current drug can surpass. In chronic cases, an active drug can still give high improvement rates but the placebo response drops to about 25 percent. Large-scale well-designed studies often show less clear drug-placebo differences than more informal private practice studies. Although one can view private practice studies with skepticism, if one so desires, Rickels' data suggest that a real difference exists between private practice and clinic settings (Hesbacher, 1970). He finds a considerable diazepam-placebo difference in patients seen in general-practice (GP) settings with phenobarbital somewhat less effective than diazepam. In patients seen in a clinic, he found phenobarbital as good as diazepam, and smaller drug-placebo differences. Generally, Rickels has found GP patients to discriminate a drug from placebo better than either poor clinic patients or private psychiatric patients. Wheatley has had equally impressive success with drug studies in general practice in the United Kingdom (1969).

One outstanding failure among the more elaborate attempts to detect drug-placebo differences was an outpatient collaborative study (McNair, 1965) by the Veterans Administration, which ran for eight weeks. Significant differences were found between chlordiazepoxide and placebo mainly at week 5 of the study (if you want to feel better for Christmas, start the drug at Thanksgiving!). This result can be attributed to the general chronicity or schizophrenic coloring of V.A. outpatients, but it can equally be a victim of the curse which pursues collaborative studies.

The NIMH's psychopharmacology program tried a series of studies to identify major variables which might be affecting the results of controlled clinical trials of antianxiety drugs. The first study compared meprobamate vs. placebo in three outpatient clinics. Half the psychiatric resident therapists were trained to be enthusiastic about the effectiveness of the double-blind medication while the other half expressed a cautious neutrality (therapeutic vs. experimental set). An early analysis (Fisher, 1964) came out beautifully with the therapeutic doctors obtaining a much bigger drug-placebo difference than the neutral ones. When the results were all in, however, all we had was a statistically significant but confusing mess! There was a triple interaction (Uhlenhuth, 1966), and the results differed reliably as a function of drug, set (doctor behavior), and clinic. For example, the biggest drug-placebo difference at Johns Hopkins University occurred with the patients exposed to the experimental set, while at Philadelphia General Hospital the biggest

difference occurred with patients exposed to the therapeutic set. In both clinics the other kind of therapist produced no drug-placebo difference at all!

The NIMH-PRB group, of which one of us was a member, next tried to replicate a study by Kast (1959). He found that if you give atropine to produce dry mouth and tell the patients that dry mouths are a good sign, atropine will potentiate the antianxiety effects of antianxiety drugs, presumably by reinforcing suggestibility. Again in three clinics we compared chlordiazepoxide vs. placebo. Half of both drug groups received atropine in their capsules and of the resulting four groups, half of each were told to expect a dry mouth and to expect real improvement if they got a dry mouth. What happened was exactly the opposite of our prediction (Lipman, 1971). The group on Librium or placebo plus atropine with positive instructions got dry mouths and did remarkably poorly, while the group told to expect a dry mouth who got no atropine (and no dry mouth) improved very nicely. The study showed (1) chlordiazepoxide is more effective than placebo, and (2) anxious outpatients dislike dry mouths.

The third study compared, in the same three clinics, chlordiazepoxide, meprobamate, and placebo. Two kinds of practicing psychiatrists were recruited to treat study patients: (1) psychiatrists known to favor drug therapy; and (2) those known to be unenthusiastic about drug therapy. It was hoped the graduate psychiatrists with firm therapeutic opinions would

influence patient response more than coached residents had. This study mainly showed that actively interacting psychiatrists (independent of drug attitude) elicited more improvement than more reserved therapists (Rickels, 1971). Chlordiazepoxide was again shown to be superior to placebo but meprobamate, for unknown reasons, was less effective than in the three earlier clinical studies.

More promising recent approaches to this problem include McNair's work with an "acquiescence" measure (1968) and Goldstein's work with symptomatic normal volunteers (Goldstein, 1973).

Predictors of Clinical Response

Uhlenhuth, Rickels, and Lipman separately and together have done most of the work attempting to predict the outcome of patients under treatment with antianxiety drugs. After studying several representative publications (Downing, 1973; May, 1969; Uhlenhuth, 1972) one finds oneself with a bad case of intellectual dyspepsia. The studies are carefully and sensibly done and employ promising and approved statistical approaches but the results offer little practical advice to the working clinician. Can it be true that chlordiazepoxide is better than hydroxyzine if the doctor likes the patient (May, 1969), while the opposite is true if the doctor's initial reaction to the patient was less favorable? Should a clinician act on this clue? A number of

predictors do not discriminate between patients receiving antianxiety drugs and those receiving placebo.

Agoraphobia and Related Conditions

Klein has defined a clear drug-responsive syndrome consisting of primary severe panic attacks, usually associated with secondary phobias about going out or being left alone. This condition—or at least the panic attacks— responds well to imipramine and does not respond to antianxiety or antipsychotic drugs (Klein, 1964; Quitkin, 1972). The secondary phobias can then be handled by psychotherapy or behavior therapy and may be blunted by antianxiety agents.

It is unclear whether Klein's patients are within the group that Sargant (1967) and coworkers would classify as atypical depressions and treat with monoamine oxidase inhibitors (MAOIs) or MAOIs plus tricyclic antidepressants (Pollitt, 1971). More recent studies have reported both iproniazid and phenelzine to be superior to placebo in the treatment of phobic conditions and of atypical depressions (Lipsedge, 1973; Robinson, 1973).

Since many of the patients treated successfully in the above studies do not suffer from typical neurotic or psychotic depressions, it seems as easy to assume that these drugs have special antianxiety properties in phobic or

related patients as to assume that phobic states mask hidden depressions.

Mixed Anxiety-Depressions

Klerman and Cole in their review in 1965 observed that controlled studies comparing tricyclic antidepressants with placebo showed a striking drug-placebo difference in outpatients, a very modest drug-placebo difference in acutely depressed inpatients and a large difference in chronic depressions or in depressions manifesting endogenous retarded psychotic features. Since the outpatients cannot have had primarily endogenous psychotic depressions, one is forced to suspect that tricyclics may be useful in anxiety states or mixed anxiety-depression states of neurotic or reactive varieties.

This introduction makes more believable recent studies showing the tricyclic, doxepin, to be quite effective—even better than chlordiazepoxide on occasion—in outpatients being treated by psychiatrists for anxiety and/or depression (Goldberg, 1972; Goldberg, 1974; Goldstein, 1973). In fact, the outpatient use of doxepin is much better documented than is this tricyclic drug's efficacy in major inpatient depressions.

Why is doxepin a good outpatient drug in anxiety states mixed with depression? It may be, as Fink (forthcoming) suggests, that the drug has central-nervous-system effects in man which resemble both imipramine and diazepam. It may also be that anxiety and depression are almost inseparable

in dysphoric psychiatric outpatients (Conney, 1967), and that any tricyclic drug would be as effective as doxepin. A collaborative controlled study testing the latter proposition is currently in progress.

However, these data plus the data on drugs in phobic states, raise serious questions as to the simple-minded acceptance of such face-valid drug classes as "antianxiety agents" or "antidepressant drugs."

Phenothiazines in Anxiety

Klein makes a good case for phenothiazines having a useful stabilizing effect in emotionally unstable personality disorders (1973), a case which is weakened by the tendency for such patients to dislike the drug and to stop taking it as soon as they leave the hospital.

Under the Irwin hypothesis (1968) one can propose that phenothiazines should be used in low doses in patients who tend to act out or abuse sedative drugs. Most antipsychotics in low dose will probably be shown to be better than placebo in the treatment of anxiety although most were marketed at a time when such evidence was not required by the FDA.

The major deterrent to their use is the remote but present possibility that the phenothiazines might elicit a chronic dyskinesia (FDA Task Force, 1973) in vulnerable patients. Since such patients cannot be identified in

advance (though age and organic brain defect increase the odds) the energetic and prolonged use of these drugs as antianxiety agents cannot be strongly endorsed.

In abuse-prone patients, tybamate with its inability to produce physical dependence (Hall, 1972; Rickels, 1968) or one of the non-phenothiazine "sedative-autonomic" drugs, such as hydroxyzine, diphenhydramine or doxepin, could be used instead of a barbiturate or a benzodiazepine.

Side Effects

The major side effects of hypnosedative antianxiety agents in general clinical use at recommended dosages are oversedation or ataxia. Patients should be warned about driving cars when sleepy and about mixing such drugs with more than very modest amounts of alcohol. Fortunately, such severe toxic or allergic effects as agranulocytosis or acute yellow atrophy of the liver do not seem to be caused by these drugs. As a caution against relaxation on the part of the physician, it should be noted that thalidomide was a good hypnosedative.

It should also be noted that occasional patients on diazepam and perhaps on other disinhibiting drugs, can develop suicidal ideas and severe emotional upsets (Rickels, 1968). This side effect has been noticed in a controlled clinical trial (Gundlach, 1966) and is confirmed by DiMascio's

literature review (1973), but its real frequency in clinical practice is probably low. It is mentioned here to alert clinicians to the possibility of such effects occurring.

Conclusions

Antianxiety drugs are reasonably effective in the treatment of outpatient anxiety. Benzodiazepines are probably more effective than earlier sedative-hypnotics and are clearly safer when taken with suicidal intent. They also appear to lack enzyme-inducing action and may have lower abuse liability than do the barbiturates or other nonbarbiturate hypno-sedatives (except tybamate). Tricyclic antidepressants have a place in the treatment of phobic-panic states and in mixed anxious-depressed outpatients.

Bibliography

Berger, F. "The Relation between the Pharmacological Properties of Meprobamate and the Clinical Usefulness of the Drug," in D. H. Efron, ed., *Psychopharmacology. A Review of Progress,* pp. 139-152. Washington: U.S. Govt. Print. Off., 1960.

Bond, A. J. and M. H. Lader. "Residual Effects of Hypnotics," *Psychopharmacologia,* 25 (1972), 117-125.

Brill, N. Q., R. R. Koegler, L. J. Epstein et al. "Controlled Study of Psychiatric Outpatient Treatment," *Arch. Gen. Psychiatry,* 10 (1964), 581-595.

Chien, C. P. "Psychiatric Treatment for Geriatric Patients: 'Pub' or Drug?" *Am. J. Psychiatry,* 127 (1971), 1070-1075.

Chein, C. P., B. A. Stotsky, and J. O. Cole. "Psychiatric Treatment for Nursing Home Patients: Drug, Alcohol and Milieu," *Am. J. Psychiatry,* 130 (1972), 5-12.

Conney, A. H. "Pharmacological Implications of Microsomal Enzyme Induction," *Pharmacol. Rev.,* 19 (1967), 317-366.

Derogatis, L. R., R. S. Lipman, L. Covi et al. "Factorial Invariance of Symptom Dimensions in Anxious and Depressive Neuroses," *Arch. Gen. Psychiatry,* 27 (1972), 659-665.

DiMascio, A. "The Effects of Benzodiazepine on Aggression: Reduced or Increased?" *Psychopharmacologia,* 30 (1973), 95-102.

Downing, R. W., K. Rickels, and H. Dreesmann. "Orthogonal Factors vs. Interdependent Variables as Predictors of Drug Response in Anxious Outpatients," *Psychopharmacologia,* 32 (1973), 93-112.

FDA Task Force, American College of Neuropsychopharmacology. "Neurological Syndromes Associated with Antipsychotic Drug Use," *Arch. Gen. Psychiatry,* 28 (1973), 463-472.

Fink, M. "EEG Applications in Psychopharmacology" in M. Gordon, ed., *Psychopharmacological Agents,* Vol. 3. New York: Academic, forthcoming.

Fisher, S., J. O. Cole, K. Rickels et al. "Drug-set Interaction: the Effect of Expectations in Drug Response in Outpatients," in P. B. Bradley, F. Fluegel, and P. Hoch, eds., *Neuropsychopharmacology,* Vol. 3, pp. 149-156. Amsterdam: Elsevier, 1964.

Gallant, D. D., M. P. Bishop, R. Guerrero-Figuero et al. "Doxepin versus Diazepam. A Controlled Evaluation in 100 Chronic Alcoholic Patients," *J. Clin. Pharmacol.,* 9 (1969), 57-63.

Goldberg, H. L. and R. J. Finnerty. "The Use of Doxepin in the Treatment of Symptoms of Anxiety Neurosis and Accompanying Depression: A Collaborative Controlled Study," *Am. J. Psychiatry,* 1 (1972), 129-133.

----. "Doxepin in a Single Bedtime Dose in Psychoneurotic Outpatients," *Arch. Gen. Psychiatry,* 31 (1974), 513-520.

Goldstein, B. J., B. Brauzer, R. M. Steinbook et al. "Psychotropic Drug Treatment of Mixed Anxiety and Depression in Non-Psychiatric Office Patients," *South. Med. J.,* 66 (1973), 892-897.

Goodman, L. S. and A. Gilman, eds. *The Pharmacological Basis of Therapeutics,* Chaps. 7, 9, 10. New York: Macmillan, 1970.

Granville-Grossman, K. L. and P. Turner. "The Effect of Propranolol on Anxiety," *Lancet,* 1 (1966), 788-789.

Grinker, R. R. and J. P. Spiegel. *War Neuroses in North Africa.* New York: Josiah Macy, Jr., Foundation, 1943.

----. *War Neuroses.* New York: McGraw-Hill, 1945.

Gundlach, R., D. M. Engelhardt, L. Hankoff et al. "A Double-Blind Outpatient Study of Diazepam (Valium®) and Placebo," *Psychopharmacologia,* 9 (1966), 81-88.

Hall, R. and J. Joffe. "Aberrant Response to Diazepam: a New Syndrome," *Am. J. Psychiatry,* 129 (1972), 738-740.

Hesbacher, P. T., K. Rickels, J. Hutchinson et al. "Setting, Patient and Doctor Effects on Drug Response in Neurotic Patients. II. Differential Improvement," *Psychopharmacologia,* 18 (1970), 209-226.

Hollister, L. E. "Anxiety, Depression and Psychotropic Drugs," *Drugs*, 1 (1971), 189-227.

----. *Clinical Use of Psychotherapeutic Drugs.* Springfield, Ill.: Charles C. Thomas, 1973.

Hollister, L. E. and F. S. Glazener. "Withdrawal Reaction from Meprobamate Alone and Combined with Promazine: A Controlled Study," *Psychopharmacologia,* 1 (1970), 336-341.

Hollister, L. E., F. P. Motzenbecker, and R. O. Dec.an. "Withdrawal Reactions from Chlordiazepoxide (Librium®)," *Psychopharmacologia,* 2 (1961), 63-68.

Irwin, S. "A Rational Framework for the Development, Evaluation and Use of Psychoactive Drugs,"

Am. J. Psychiatry (Suppl. Drug Ther.), 124 (1968), 1-19.

Kaim, S. C., C. J. Klett, and B. Rothfeld. "Treatment of the Acute Alcohol Withdrawal State: A Comparison of Four Drugs," *Am. J. Psychiatry,* 125 (1969), 1640-1646.

Kales, A., E. J. Malmstrom, M. B. Scharf et al. "Psychophysiological and Biochemical Changes following Use and Withdrawal of Hypnotics," in A. Kales, ed., *Sleep, Physiology and Pathology,* pp. 331-343. Philadelphia: Lippincott, 1969.

Kast, E. C. and J. Loesch. "A Contribution to the Methodology of Clinical Appraisal of Drug Action," *Psychosom. Med.,* 21 (1959), 228-234.

Kellner, R. "Drugs, Diagnosis, and Outcome of Drug Trials with Neurotic Patients," *J. Nerv. Ment. Dis.,* 51 (1970), 85-96.

Klein, D. F. "Delineation of Two Drug-Responsive Anxiety Syndromes," *Psychopharmacologia,* 5 (1964), 397-408.

Klein, D. F., G. Honigfeld, and S. Feldman. "Prediction of Drug Effect in Personality Disorders," *J. Nerv. Ment. Dis.,* 156 (1973). 183-192.

Klerman, G. L. and J. O. Cole. "Clinical Pharmacology of Imipramine and Related Antidepressant Compounds," *Pharmacol. Rev.,* 17 (1965), 101-141.

Lader, M. H. and L. Wing. *Physiological Measures, Sedative Drugs, and Morbid Anxiety,* Maudsley Monogr. no. 14, p. 1. London: Oxford University Press, 1966.

Lennard, H. L., L. J. Epstein, A. Bernstein et al. "Hazards Implicit in Prescribing Psychoactive Drugs," *Science,* 169 (1970), 438-445.

Lipman, R. S., L. Covi, L. R. Derogatis et al. "Medication, Anxiety Reduction, and Patient Report of Significant Life Situation Events," *Dis. Nerv. Syst.,* 32 (1971), 240-242.

Lipman, R. S., H. M. M. Hammer, J. F. Bernardes et al. "Patient Report of Significant Life Situation Events," *Dis. Nerv. Syst.,* 26 (1965), 586-590.

Lipman, R. S., L. C. Park, and K. Rickels. "Paradoxical Influence of a Therapeutic Side-Effect Interpretation," *Arch. Gen. Psychiatry,* 15 (1966), 462-474.

Lipsedge, M. S., J. Hajioff, P. Huggins, L. Napier et al. "Management of Severe Agoraphobia: a Comparison of Iproniazid and Systematic Desensitization," *Psychopharmacologia,* 32 (1973), 67-80.

Lorr, M., D. M. McNair, and C. J. Weinstein. "Early Effects of Chlordiazepoxide (Librium) Used with Psychotherapy," *J. Psychiatr. Res.,* 1 (1963), 257-270.

Lorr, M., D. M. McNair, F. J. Weinstein et al. "Meprobamate and Chlorpromazine in Psychotherapy," *Arch. Gen. Psychiatry,* 4 (1961), 389-396.

McNair, D. M., A. P. Goldstein, M. Lorr et al. "Some Effects of Chlordiazepoxide and Meprobamate with Psychiatric Outpatients," *Psychopharmacologia,* 7 (1965), 256-265.

McNair, D. M., R. J. Kahn, L. F. Droppleman et al. "Patient Acquiescence and Drug Effects," in K. Rickels, ed., *Non-specific Factors in Drug Therapy*, pp. 59-72. Springfield, Ill.: Charles C. Thomas, 1968.

McNamee, H. B., N. K. Mello, and J. Mendelson. "Experimental Analysis of Drinking Patterns of Alcoholics: Concurrent Psychiatric Observations," *Am. J. Psychiatry,* 124 (1968), 1063-1069.

May, P. R. A. and J. R. Wittenborn, eds., *Psychotropic Drug Response: Advances in Prediction.* Springfield, Ill.: Charles C. Thomas, 1969.

Perry, H. J., M. B. Balter, G. D. Mellinger et al. "National Patterns of Psychotherapeutic Drug Use," *Arch. Gen. Psychiatry,* 28 (1973). 769-783.

Pollitt, J. and J. Young. "Anxiety State or Masked Depression? A Study Based on the Action of Monoamine Oxidase Inhibitors," *Br. J. Psychiatry,* 119 (1971), 143-149.

Quitkin, F. M., A. Rifkin, J. Kaplan et al. "Phobic Anxiety Syndrome Complicated by Drug Dependence and Addiction, *Arch. Gen. Psychiatry,* 27 (1972), 159-161.

Rickels, K., T. W. Clark, J. H. Ewing et al. "Evaluation of Tranquilizing Drugs in Medical Outpatients. Meprobamate, Prochlorperazine and Amobarbital Sodium and Placebo," *JAMA,* 171 (1959), 1649-1656.

Rickels, K., I. Csanalosi, R. W. Downing et al. "Prognostic Indicators of a 4-Week Clinical Improvement with Chlordiazepoxide and Hydroxyzine in Anxious Neurotic Outpatients," *Int. Pharmacopsychiatry,* 6 (1971), 249-253.

Rickels, K. and P. T. Hesbacher. "Over-the-Counter Daytime Sedatives, a Controlled Study," *JAMA,* 223 (1973), 29-33.

Rickels, K., P. Hesbacher, W. Vandervort et al. "Tybamate: A Perplexing Drug," *Am. J. Psychiatry,* 125 (1968), 320-324.

Rickels, K., P. T. Hesbacher, C. T. Weise et al. "Pills and Improvement, a Study of Placebo Response in Psychoneurotic Outpatients," *Psychopharmacologia,* 16 (1970), 318-326.

Rickels, K., R. S. Lipman, C. Garcia et al. "Evaluating Clinical Improvement in Anxious Outpatients: a Comparison of the Normal and Treated Neurotic Patients," *Am. J. Psychiatry,* 128 (1972), 1007-1009.

Rickels, K., R. S. Lipman, L. C. Park et al. "Drug, Doctor Warmth and Clinic Setting in the Symptomatic Response to Minor Tranquillizers," *Psychopharmacologia,* 20 (1971), 128-152.

Rickels, K., R. Lipman, and E. Raab. "Previous Medication, Duration of Illness and Placebo Response," *J. Nerv. Ment. Dis.,* 142 (1966), 548-554.

Rickels, K., I. Raab, R. Desilverio et al. "Drug Treatment in Depression. Antidepressant or Tranquilizer," *JAMA,* 201 (1967), 675-680.

Rickels, K. and L. Snow. "Meprobamate and Phenobarbital in Neurotic Psychiatric Patients and Medical Clinical Outpatients," *Psychopharmacologia,* 5 (1964), 339-346.

Rickels, K., C. H. Ward, and L Schut. "Different Population, Different Drug Responses; a Comparative Study of Two Antidepressants, Each Used in Two Different Patient

Groups," *Am. J. Med. Sci.,* 247 (1964)-328-337.

Ritchie, J. M. "The Aliphatic Alcohols," in L. S. Goodman and A. Gilman, eds., *The Pharmacological Basis of Therapeutics.* New York: Macmillan, 1970.

Robinson, D. S. and E. L. Amidon. "Interaction of Benzodiazepines with Warfarin in Man," in S. Garattini, E. Mussini, and L. O. Randall, eds., *The Benzodiazepines,* pp. 641-644. New York: Raven Press, 1973-

Robinson, D. S., A. Nies, C. L. Ravaris et al. "The Monoamine Oxidase Inhibitor, Phenelzine, in the Treatment of Depressive-Anxiety States," *Arch. Gen. Psychiatry,* 29 (1973), 407-413.

Sargant, W. "The Treatment of Depressive States," *Int. J. Neurol.,* 6 (1967), 53-71.

Schwartzburg, M., J. Lieb, and A. H. Schwartz. "Methaqualone Withdrawal," *Arch. Gen. Psychiatry,* 29 (1973), 46-47.

Shagass, C. *Evoked Brain Potentials in Psychiatry.* New York, Plenum, (1972).

Shelton, J. and L. E. Hollister. "Simulated Abuse of Tybamate in Man: Failure to Demonstrate Withdrawal Reactions," *JAMA,* 199 (1967), 338-340.

Silverstone, T. "The Use of Drugs in Behavior Therapy," *Behav. Ther.,* 1 (1970), 485-497.

Stein, L. S., C. D. Wise, and B. D. Berger. "Antianxiety Action of Benzodiazepines: Decrease in Activity of Serotonin Neurons in the Punishment System," in S. Garattini, E. Mussini, and L. O. Randall, eds., *The Benzodiazepines,* pp. 299-308. New York: Raven Press, 1973.

Stephens, J. H. and J. W. Shaffer. "A Controlled Study of the Effects of Diphenyl-hydantoin on Anxiety, Irritability and Anger in Neurotic Outpatients," *Psychopharmacologia,* 17 (1970), 169-181.

Stotsky, B. A., J. O. Cole, Y. T. Tang et al. "Sodium Butabarbital (Butisol Sodium) as an Hypnotic Agent for Aged Psychiatric Patients with Sleep Disorders," *J. Am. Geriatr. Soc.,* 19 (1971), 860-870.

Tyrer, P., J. Candy, and D. Kelly. "Preliminary Communication: Phenelzine in Phobic Anxiety: A Controlled Trial," *Psychol. Med.,* 3 (1973), 120-124.

Uhlenhuth, E. H., L. Covi, K. Rickels et al. "Predicting the Relief of Anxiety with Meprobamate, an Attempt at Replication," *Arch. Gen. Psychiatry,* 26 (1972), 85-91.

Uhlenhuth, E. H., K. Rickles, S. Fisher et al. "Drug, Doctors' Verbal Attitude and Clinic Setting in the Symptomatic Response to Pharmacotherapy," *Psychopharmacologia,* 9 (1966), 392-418.

Von Felsinger, J. M., L. Lasagna, and K. Beecher. "The Persistence of Mental Impairment following a Hypnotic Dose of a Barbiturate," *J. Pharmacol. Exp. Ther.,* 109 (1953), 284-291.

Weinstein, E. A. and R. L. Kahn. *Denial of Illness. Symbolic and Physiological Aspects.* Springfield, Ill.: Charles C. Thomas, 1955.

Wheatley, D. "Comparative Effects of Propranolol and Chlordiazepoxide in Anxiety States," 115 (1969), 1411-1412.

----. *Psychopharmacology in Family Practice.* London: Heinemann Medical Books, 1973.

Wikler, A. *The Relation of Psychiatry to Pharmacology.* Baltimore: Williams & Wilkins, 1957.