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BENZODIAZEPINES: A Review of Research Results, 1980

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Alcohol, Drug Abuse, and Mental Health Administration

Benzodiazepines:
A Review of Research Results, 1980

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A RAUS Review Report

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Preface

The Research Analysis and Utilization System (RAUS) is designed to serve four functions:

- Collection and systematic classification of findings of all intramural and extramural research supported by the National Institute on Drug Abuse (NIDA);
- Evaluation by scientific peers of the latest research findings;
- Regular dissemination of findings to researchers in the field and to administrators, planners, instructors, and other interested persons:
- Provision of a feedback mechanism to NIDA staff and planners so that administration and monitoring of the NIDA research program reflect the very latest knowledge gleaned from research in the field.

Since there is a limit to the number of research findings that can be intensively reviewed annually, four subject areas are chosen each year and subjected to a thorough review. The reviewers, distinguished scientists in the selected field, are provided with copies of all pertinent literature and reports from NIDA-funded research. They are invited to add to this any information derived from their own research and that of colleagues not funded by NIDA. Each reviewer writes a state-of-the-art paper in his or her particular subject area. These papers make up a RAUS Review Report in the NIDA Research Monograph series.

Additionally, an evaluative meeting is held for presentation of the papers and exchange of ideas among the scientists and with NIDA staff. This meeting has sometimes been referred to as the "therefore" meeting: Here is our position: *therefore,* where are we going next, and where should further research lead? Should we alter our path? Step up NIDA support because new needs have arisen or new developments hold special promise? Discussions at the meeting and the specific recommendations of the experts in the field provide a basis upon which NIDA evolves its plans for future research.

In Fiscal Year 1980 the abuse liability of the benzodiazepines was chosen as an area for RAUS review. The subject was ripe for review because much conflicting information was circulating among scientists and clinicians about the abuse liability of the highly popular "tranquilizers"; because of pronounced public interest, as reflected by the Congress and the press; and because of a perceived need by NIDA for objective evaluation of research on the benzodiazepines.

The reviewers were invited to discuss:

- The basic biochemistry and neuroanatomy underlying the question of the abuse potential of benzodiazepines, including the existence and sites of receptors involved;
- Studies on self-administration in animals and humans;
- Carryover effectiveness, rebound insomnia, and performance effects;
- Clinical use patterns and their relationship to misuse and abuse;
- Dependence on benzodiazepines.

The results of these reviews are presented in this monograph. The review meeting was chaired by Dr. William Martin, of the University of Kentucky, former Director of the Addiction Research Center, in Lexington, Kentucky. Dr. Edward Truitt, of Northeast Ohio College of Medicine, summarized the reviews and discussions. Dr. Stephen Szara, Chief, Biomedical Branch, NIDA Division of Research, served as moderator and directed the scientific discussion.

Jacqueline P. Ludford, M.S.
Coordinator
Research Analysis and Utilization System

Contents

Introduction

Stephen I. Szara, M.D., D.Sc.

The benzodiazepines represent a class of drugs that are widely prescribed and used as so-called "minor tranquilizers." At the latest count, in 1979 alone, 62.3 million prescriptions for minor tranquilizers were filled (National Prescription Audit 1979). Because of the sheer volume of traffic in these drugs, if there is a potential for misuse and abuse, it is inevitable that a potential also exists for creation of a public health problem.

When widespread clinical use of benzodiazepines began some 20 years ago, they were considered to have a relatively large margin of safety and they were prescribed quite liberally. Very soon, however, some adverse reactions started to appear, and by the mid-70's concerns about the potential problems of abuse of the newly developed congeners of benzodiazepines prompted the National Institute on Drug Abuse (NIDA) to convene a technical review to discuss the need for new methodologies to assess the abuse potential of these drugs. That meeting took place in 1976 at the Addiction Research Center in Lexington, Kentucky, under the chairmanship of Dr. William Martin (NIDA 1976).

Since then two major developments have occurred that are specifically related to NIDA's interest in benzodiazepines. The first was the discovery of specific binding sites for benzodiazepines in the brain in 1977 by Squires and Braestrup (1977) and by Mohler and Okada (1977) and the emergence of a plausible hypothesis to explain how benzodiazepines may interact with normal brain function. Biochemical research on benzodiazepine receptors in brain and their relation with neurotransmitter mechanisms has developed rapidly tom become one of the most active areas of psychopharmacology. If dependence develops, as some clinicians feel it does under certain circumstances, the obvious question arises Whether or not the receptors are in some way involved in this phenomenon.

The second major development is social and political. I am referring to the 1979 hearing by the Senate Subcommi ttee on Health and Scientific Research that became known as the "Valium hearing," focused on the "growing and very serious public health problem"

of which the American people may not be aware. Senator Edward M. Kennedy, subcommittee chairman, pointed out: "If you require a daily dose of Valium to get through each day, you are hooked and you should seek help."

The hearings resulted in a predictable aftereffect: a flood of testimonials in the media about adverse reactions and dependence, and congressional inquiries to various agencies. These appear to have created a climate which may lead to a reassessment of present scheduling policies towards this class of drugs. For this reason, as well as from a purely scientific perspective, NIDA has become involved, especially since NIDA plays a role as one of the Federal agencies Supplying scientific data on abuse potential and dependence liability.

When we look at NIDA's program, as most of the contributors to this monograph were asked to do, we find that our research has been limited to a relatively few projects, and most of these have struggled to solve the methodological problems in obtaining reliable, reproducible data on dependence liabilities of benzodiazepines. Furthermore, we are faced with the fact that the pharmacological laboratories are producing new and different kinds of benzodiazepines faster than our researchers are able to catch up in determining their abuse potentials, based on experimental animal data.

These considerations, among others, have led us to convene this meeting so that NIDA can have the benefit of "cross-fertilization" of basic scientists on the one hand and clinical scientists on the other. By taking a look at the receptor research and pharmacokinetic data as well as at the clinical experience with the various benzodiazepines, we may come up with some new suggestions on how to improve our knowledge base so that we will be ready to supply reliable information for the process of public health decisionmaking.

In the course of this discussion, we hope that new ideas for research will be generated as each of us becomes aware of new data, new observations, and new experience in fields other than that of our own focus. We also hope that these discussions may lead to a better understanding of actions of these drugs and ultimately contribute to better and safer use of benzodiazepines.

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Benzodizepines: Biochemistry to Function

John F. Tallman, Ph.D.

PROPERTIES OF DIFFERENT BINDING SITES

Peripheral Versus Central

The high affinity and stereospecific binding sites for benzodiazepines in brain seem to represent the places where benzodiazepines exert their pharmacological effects. This conclusion is based upon the high degree of correlation between the ability of an extensive series of benzodiazepines to displace binding of [^{3}H]diazepam from the high-affinity sites in brain and their activity in a number of behavioral tests including conflict, muscle relaxant, and anticonvulsant tests (Braestrup and Squires 1978). One of the most potent benzodiazepines is clonazepam, 5-(o-chloropenyl)-1, 3--dihydro-7-nitro-2H-1,4-benzodiazepine-2-one; clonazepam is also a potent displacer of [^{3}H]diazepam binding to brain specific sites (Braestrup et al. 1977; Braestrup and Squires 1977; Möhler and Okada 1977a,b). At the other end of the spectrum of potency is R05-4864, 7-chloro-1,3-dihydro-l-methyl-5-(pchlorophenyl)-2H-l,4-benzodiazepine-2-one, which does not have central behavioral effects and is inactive in displacing [^{3}H]diazepam from the high-affinity sites in brain (Braestrup et al. 1977). The lack of potency of RO5-4864 is particularly striking because it is quite similar to diazepam, differing from diazepam only by possessing a p-chloro substituent.

Initial investigations of the binding of [^{3}H]diazepam indicated that specific high-affinity binding of [^{3}H]diazepam could be obtained not only to brain but also to several peripheral tissues including kidney (Braestrup et al. 1977). The sites on the kidney cells, although possessing a high affinity for [^{3}H]diazepam, showed a different pharmacological spectrum from the brain site. R05-4864 is a rather potent displacer of [^{3}H]diazepam binding; in contrast, clonazepam is much weaker. Thus, although peripheral tissues possess high-affinity sites for diazepam, they seem to be different from the central sites.

In addition to the kidney, the "peripheral sites" seem to be on cultured cells of various types, including those of presumptive neuronal origin (Guidotti et al. 1979; Strittmatter et al. 1979; Syapin and Skolnick 1979). Both rat astrocytana (Syapin and Skolnick 1979) and neuroblastoma (Guidotti et al. 1979; Strittmatter et al. 1979;

Chang et al., in press) cells possess a large number of these peripheral sites-they do not possess the clonazepam displaceable binding. The nature and biological significance of this peripheral binding site is obscure; it is interesting to note that this site may activate phospholipid methylation either directly or indirectly (Strittmatter et al. 1979). The existence of such peripheral binding sites for Valium is not only of academic interest. Much of the literature about drug levels following single doses and chronic administration of Valium would indicate that these receptors should be occupied following single doses and chronic administration of Valium would indicate that these receptors should be occupied following clinical use of Valium (Peskar and Spector 1973). Thus, a number of investigations into the nature and function of the peripheral site are in order, if only because some side effects of Valium may be mediated through this site.

One of the early issues that investigators examined was the cellular localization of the central type of receptor. Although initial reports indicated a neuronal localization (Braestrup and Squires 1977); Mohler and Okada 1977a,b), subsequent reports (Chang et al. 1979; Henn and Henke 1978) supported a glial localization. These reports used kainic acid lesioning or tissue culture; in the case of the kainic acid lesioning experiments, it became clear that a sufficient degeneration period was necessary before neuronal membrane fractions containing sites from lesioned animals could be degraded. If such a period is observed, degeneration studies support a neuronal localization for the binding sites (Chang et al., in press).

Recently, a nuclear benzodiazepine binding site was described in brain (Bosmann et al. 1980). This site has lower affinity for the benzodiazepine [^{3}H]flunitrazepam than the cell membrane binding site; however, clonazepam is far more potent in displacing binding than R05-4864 (unpublished) indicating that the nuclear site has properties similar to the membrane binding site.

Multiple Central Receptors

In addition to the distinction between peripheral and central receptors, some investigators have also examined the possibility that multiple central sites may exist based on thermostability studies (Squires et al. 1979). These earlier studies did not consider the newly described nuclear sites. Additionally, several triazolopyridazines displace binding of [^{3}H]diazepam with properties indicating that they are displacing binding from a heterogeneous set of sites (Hill coefficient ~0.5) (Squires et al. 1979). Such methods indicate that multiple sites may exist in brain but are not conclusive. It is not known whether these multiple sites would be genetically distinct or vary in their association with other membrane proteins such as a GABA recognition unit (see article by M. Kuhar and associates, this volume). By this criterion of heat denaturation, two such sites are said to exist in cerebral cortex and one site in cerebellum (Lippa et al., in press). Additionally, a recent paper

indicates microheterogeneity of benzodiazepine receptors as measured in different brain regions on sodium dodecyl sulfate gels (Sieghart and Karobath 1980).

MODULATION OF CENTRAL BENZODIAZEPINE BINDING SITES

Understanding the mechanism of action of Valium at central sites demands an understanding of the modulation of the central receptor complex of proteins. It now is clear that both the affinity of the Valium receptor and the number of receptors is under pharmacological control, and it is important to relate this biochemical control to a behavioral function.

Affinity Changes

The early (primarily electrophysiological) literature is strongly in favor of an interaction between the benzodiazepines and GABA (Tallman et al. 1980; Gallager 1978). Initial binding studies did not indicate the presence of such an interaction (Braestrup et al. 1977; Mohler and Okada 1977a); subsequently, we (Gallager et al. 1978; Tallman et al. 1978, 1979) and others (Tallman et al. 1980) have obtained definitive evidence that the central benzodiazepine binding site can interact with a GABA recognition site. When GABA, muscimol, and other GABAergic agonists occupy this site, the affinity of the benzodiazepine binding site for [^{3}H]diazepam is enhanced. This enhancement is seen in all preparations that contain clonazepam displaceable benzodiazepine binding.

The magnitude of GABA-enhancement depends on the ability to remove the large amounts of endogenous GABA present in brain membrane preparations and on the region of the brain chosen for study (Karobath and Sperk 1979). It is not yet clear whether the regional distribution reflects altered proportions of GABA receptors and benzodiazepine sites or different amounts of residual GABA. Regionally altered proportions of high-affinity GABA binding proteins and benzodiazepine sites are indicated by autoradiographic studies (Young and Kuhar 1980). The contribution of nuclear binding sites to these regional distributions has not been studied, and it is not clear if multiple benzodiazepine sites may be defined upon their interaction or lack of interaction with GABA.

Most GABA agonists enhance the affinity of central benzodiazepine sites. Two compounds, isoguvacine and THIP (4,5,6,7-tetrahydroisoxazolo[5,4-c]pyridine-3-ol), behave in an anomalous fashion. Isoguvacine is a partial agonist for GABA by the criterion of enhancement of [^{3}H]diazepam binding and will decrease muscimol activation of binding to the isoguvacine level (Braestrup et al. 1979b; Krogsgaard-Larsen and Johnston 1978); THIP, on the other hand, does not enhance binding of [^{3}H]diazepam, reverses muscimol activation of benzodiazepine binding (like bicuculline), and yet appears to be an agonist (Braestrup et al. 1979b). Neither isoguvacine nor THIP protects the benzodiazepine site from heat denaturation, a property both GABA and muscimol possess (Squires et al. in press). Among other explanations, it seems

possible that THIP in particular may possess agonistic properties at a GABA receptor that is not coupled with a benzodiazepine site and may indicate that several different GABA receptors exist in brain (Krogsgaard-Larsen et al. 1980). The difficulties in detecting and separating multiple GABA receptors have been discussed in great detail recently (DeFeudis 1978; Nistri and Constanti 1979).

Lesion experiments also support the close interaction of GABA sites and benzodiazepine sites. Following kainic acid lesion of the striato-nigral GABAergic pathway, an apparent increase in the number of GABA receptors in the substantia nigra was noted without changes in the affinity for the ligand (Waddington and Cross 1978). Concurrent with this short-term denervation supersensitivity in nigral GABA receptors, no change in the number of benzodiazepine sites was noted under these experimental conditions. The affinity response of the benzodiazepine sites to occupancy of the GABA receptor shows a shift to the left in the GABA dose-response curve (indicating a GABAergic supersensitivity) (Biggio et al. 1979). Thus the lesion studies support the interdependence of GABA and the benzodiazepines.

The affinity of central sites for [^{3}H]diazepam is also enhanced by a pyrazolo(3,4-6)pyridine called SQ65,396 (Beer et al. 1979; Williams and Risley 1979). Although initially thought to be via a GABAergic mechanism (Williams and Risley 1979), SQ65,396 now has been said to be a direct allosteric modifier of binding based upon studies with soluble binding sites (A. Lippa, personal communication). This compound may be a prototype for an interesting series of anxiolytic agents; it does not seem to be an effective anticonvulsant (Beer et al. 1979).

Another agent that affects benzodiazepine binding by affinity change is pentylenetetrazole (and its analogues). They seem to block GABA enhancement of benzodiaxepine binding but not basal levels. This blockage seems to be correlated to their convulsant properties (Paul et al., in press).

In addition to the pharmacological agents, certain anions such as chloride, iodide, nitrite, and thiocyanate have been shown to enhance the affinity of central binding sites for [^{3}H}diazepam (Costa et al. 1979a,b). This effect is separate from the GABA enhancement and is additive to it. The possibility that SQ65,396 interacts at this site has not been examined. Recently, the action of SQ65,396 has been shown to be reversible by picrotoxin, an agent which acts at the chloride ionophore (Supavilai and Karobath 1979).

Binding Site Number Changes

One of the early reports on alterations in central binding sites indicated a rapid and transient increase in the number of binding sites following either electrically or chemically induced seizures (Paul and Skolnick 1978). What is remarkable about this finding is the rapid increase and rapid decrease in the binding sites; most central nervous system receptors show alteration over a period of

days rather than minutes. The magnitude of this effect is approximately 15 percent; but it is interesting to note that only 20 to 30 percent of the benzodiazepine sites must be occupied to fully protect against seizures (Lippa et al. 1979). Thus, increases of this magnitude (or affinity changes) probably possess physiological significance.

The anticonvulsant agent diphenylhydantoin can also rapidly elicit a 20 to 30 percent increase in the number of benzodiazepine binding sites following pretreatment in vivo (Gallager et al. 1980). This increase is dose-dependent and is elicited in the range of diphenylhydantoin's anticonvulsant properties. The exposure of new sites for [^{3}H]diazepam is transient, and within a few hours the binding returns to control levels. In addition to the increase in the number of sites, the diphenylhydantoin treatment enhances the electrophysiological properties of the benzodiazepines but does not alter the response to GABA. Accordingly, it is still possible to obtain GABA enhancement of benzodiazepine binding in membranes prepared from diphenylhydantoin-treated animals. It is not known yet what chronic diphenylhydantoin will do to adult animals; however, pretreatment of pregnant rats has been shown to decrease the number of central binding sites in offspring during early postnatal life (Gallager and Mallorga 1980). 'Ibis decrease is transient and can be correlated to increased susceptibility to seizures. Diphenylhydantoin does not increase binding of [^{3}H]diazepam in vitro.

Another compound, EMD 28422 (N^6-[2-(4-chlorophenyl)-bicyclo-2.2.2. octyl-(3)]-adenosine), which is a purine derivative, also elicits an increase in the number of benzodiazepine binding sites without a change in affinity. This effect was noted both in vivo (Speth et al. 1979) and in vitro (P. Skolnick, in preparation), and has been correlated to anticonvulsant properties of this molecule (Skolnick et al., in press). In the presence or absence of GABA or chloride, the magnitude of the effect was the same (about 20 to 30 percent new sites). In spite of the lack of effects of GABA upon the unmasking, the GABA antagonist, bicuculline, is capable of blocking the effects of EMD 28422, indicating a possible permissive role for the GABA receptor in the rapid modulation of the benzodiazepine binding site.

EFFECT OF CHRONIC DRUG TREATMENTS ON BENZODIAZEPINE RECEPTORS

The clinical and basic literature is not clear concerning the chronic effects of the benzodiazepines. One recently published study seriously underplays the potential hazards of the benzodiazepines (Marks 1978), particularly when contrasted to a recent critical report of the Institute of Medicine (National Academy of Sciences 1979). Clearly, this is an area that needs much more clinical investigation and laboratory studies.

At the receptor level, chronic (several weeks, not months) administration of high doses of benzodiazepines leads to a modest decrease in the apparent number of binding sites in brain (Rosenberg and Chin 1979; Chin and Rosenberg 1978; Braestrup et al. 1979a). However, another study did not find this decrease (Möhler et al. 1978). The cleanest study to date (J.N. Crawley et al., in preparation) indicates

that the potency of the benzodiazepine administered may affect the result. Clonazepam binding and chlordiazepoxide binding were compared, and the investigators found that clonazepam gave a much larger decrease than chlordiazepoxide; clonazepam is much more potent.

Behaviorally, depending on the animal test used, there are small or no effects on anti-pentylenetetrazole activity of the benzodiazepines (Lippa et al. 1978), but tolerance seems to develop to the effects of benzodiazepines on strychnine- or bicuculline-induced seizures (Lippa et al. 1978). Overt tolerance does not develop to the anticonflict effects of the benzodiazepines (J.N. Crawley, personal communication). A factor in all of this may be the low fractional occupancy necessary to elicit the full biological effects of the benzodiazepines (Lippa et al. 1979). Thus, a certain amount of redundancy may exist in the benzodiazepine system.

CONCLUSIONS

I have attempted to update the current picture about the functioning of the benzodiazepines in vivo. Much important work remains to be done to correlate the biochemical with the behavioral effects of the benzodiazepines and to relate them to the clinical situation.

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The Benzodiazepine Receptor: Anatomical Aspects

Michael J. Kuhar, Ph.D.

INTRODUCTION

A site in brain tissue that has the properties of a relevant and pharmacologically active benzodiazepine (BZ) receptor has been identified by binding techniques (Squires and Braestrup 1977; Mohler and Okada 1977; Tallman et al. 1980). Thus it is possible to study molecular and anatanical mechanisms of BZ drugs more extensively than before. This report will focus on the anatomical localization of BZ receptors and their significance.

Biochemical studies have shown that the BZ receptors are unevenly distributed in brain regions (Squires and Braestrup 1977; Mohler and Okada 1977, 1978; Braestrup et al. 1977; Speth et al. 1978). Phylogenetic studies suggest that the BZ receptors appear relatively late in evolution (Nielsen et al. 1978). Overall, these results strongly suggest that the receptor is not some simple, universal constituent of neuronal membranes, but rather a unique entity specially involved in certain brain regions (and therefore certain physiological functions) and possibly associated with a unique, endogenously-occurring "active" compound such as a neurohormone (Marangos et al. 1979; Tallman et al. 1980). Hence, anatanical studies of the BZ receptor are necessary for a full understanding of the action of BZ drugs. The usefulness of anatomical studies of receptors for providing insights to mechanisms of drug actions has been demonstrated in the cases of, for example, the opiate receptor (Atweh and Kuhar 1977), and the alpha-adrenergic receptor (Young and Kuhar 1980b).

NEURONAL VERSUS NON-NEURONAL LOCALIZATION

An obvious first issue is whether the BZ receptor is localized to neurons in the brain or to various non-neuronal elements or to both. While some initial studies suggested a non-neuronal localization, recent data indicate a neuronal localization. Injection of kainic acid, a toxin specific for intrinsic neurons (Coyle et al. 1978), results in a loss of BZ receptor at a time when degeneration is thought to be complete (Sperk and Schlogl 1979). Electron microscopic autoradiographic studies show that the BZ receptors are associated with synapses (Mohler et al. 1980). In the caudate nucleus and putamen from brains of patients with Huntington's disease characterized

by a neuronal cell loss in these regions, there was a significant reduction of BZ receptors (Mohler and Okada 1978). In the cerebella of mutant mice having a loss of neurons there was a reduction of BZ receptors (Lippa et al. 1978; Skolnick et al. 1979; Speth and Yamamura 1979). All of these findings, as well as the observed close interaction between GABA receptors, potential chloride channels, and BZ receptors (Tallman et al. 1980), are strongly supportive of a neuronal localization of the receptor. However, it seem difficult to rule out the possibility that some receptors in the brain may be non-neuronal (Henn and Henke 1978). There are BZ binding sites in the kidney, liver, lung, and some tissue culture cell lines, but they do not have pharmcological properties associated with anxiolytics (Tallman et al. 1980) and their significance is not understood.

REGIONAL LOCALIZATION IN BRAIN--INSIGHTS TO DRUG ACTION

Biochemical studies in several species showed that cerebral and cerebellar cortical and limbic areas had relatively high levels of BZ receptors (Squires and Braestrup 1977; Mohler and Okada 1977; Braestrup et al. 1977; Speth et al. 1978). Other areas tended to have lower, sometimes much lower, levels. The high levels in cortical areas may be unique among receptor distributions. The receptors in limbic areas may be important for the anxiolytic actions of the drugs.

Light microscopic autoradiographic studies of receptors are useful because they provide great sensitivity in measurement and a high degree of anatomical resolution (Kuhar 1978; Young and Kuhar 1979a). Accordingly, the distribution of BZ receptors was examined in the brains of humans and animals by microscopic methods. In agreement with the biochemical studies, there were striking regional variations in receptor densities that, in some cases, were species-dependent. The light microscopic studies involved labeling receptors in vitro in mounted tissue sections and generating autoradiograms by the apposition of emulsion-coated coverslips (Young and Kuhar 1979a,b).

In rat brain, receptor density was high in the cerebral cortex, the molecular layer of the cerebellum, parts of the limbic system, olfactory bulb, hypothalamus, substantiae gelatinosae of the spinal trigeminal nucleus, and spinal cord. White matter areas showed negligible levels of receptor. In human tissues, there was also a striking absence of BZ receptor in white matter. In the human cerebellum, there was a high density of receptors in association with both the granule cell layer and the molecular layer. In the cerebral cortical areas, there were variations in the autoradiographic grain densities. For example, in the calcarine cortex, BZ receptors were highest in layers III, IVa, and IVc. In mice, the distribution was quite similar to that found in the rat. An interesting species difference was found in the cerebellum where there was a high density of BZ receptors in the molecular layer of mice and rats, but compared with the human tissues, there was a markedly reduced level of BZ receptors in the granule cell layer (Young and Kuhar 1979b, 1980a). The receptor distributions in the rat have been presented schematically on stereotaxic drawings (Young and Kuhar 1980a).

In agreement with biochemical reports (Began et al. 1980; Howells et al. 1979), autoradiographic studies showed high densities of BZ receptors in the rat retina (Young and Kuhar 1979b). They were found highly localized to the inner plexiform and ganglion cell layers while a few receptors were also present in the inner nuclear layer.

Following the administration of BZ drugs, a variety of physiological effects are observed (Greenblatt and Shader 1974; Haefely et al. 1980). It is interesting, but admittedly speculative, to relate brain regions containing high densities of BZ receptors with physiological functions known to be altered by BZ administration. One must be cautious in assuming connections between brain regions laden with high densities of receptors and clinical drug effects, because it is possible that brain regions with rather low levels of receptor may also be critical for clinical effects. Also, species differences are likely to be significant as well. However, it seems that some relationships between brain areas with high receptor levels and certain drug effects are striking. For example, anxiety is a complex function possibly involved with the limbic system that has been implicated as an anatomical area related to emotion and its physiologic, behavioral, and endocrinological sequelae. The circuitry is complex and involves a number of brain areas including the hippocampus, amygdala, hypothalamus, frontal cortex, and other associated areas (Papez 1937). It has been speculated that the antianxiety action of BZ drugs is due to suppression of the limbic system. Spontaneous and evoked activity of the hippocampus, amygdala, and related structures are profoundly depressed by BZ administration (see Young and Kuhar 1980a and Haefely et al. 1980 for references). The amygdala may be especially important for certain actions of BZ drugs because behavioral studies involving direct injection into the amygdala have revealed potent effects. Direct injection of diazepam into the anterior amygdaloid nucleus showed anticonvulsant effects in that it resulted in an elevated pentylenetetrazol (PTZ) threshold for appearance of spike activity in the EEG; and also elevated the threshold of limbic system after discharges. Thus, it seems that the anterior amygdaloid nucleus could be particularly important for the anticonvulsant effects of diazepam (which is an antianxiety model) as the dorsal hippocampus did not show such effects (Nagy and Decsi 1979). In another similar study using a "conflict situation" model for anxiety it was found that the direct intra-amygdala application of diazepam produced an antianxiety effect (Nagy et al. 1979). In the receptor distribution studies, high densities of BZ receptors were found in much of the limbic system, including parts of the amygdaloid complex, hippocampal formation, pyriform cortex, medial septal nuclei, and hypothalamus. The anatomical results suggest more specifically the parts of the limbic system important for BZ anxiolytic effects. For example, only certain amygdaloid nuclei (centralis, medialis, and lateralis) contain high levels of receptors.

Benzodiazepines are also used extensively as anticonvulsants. They have been shown to prevent the spread of seizures from the cortex, thalamus, and limbic structures (Haefely et al. 1980). The high level of BZ receptors in the cortex and limbic structures suggests that the drug action at receptors in these areas could directly

prevent the spread of seizures. It is also interesting to hypothesize a relationship between receptors in the reticular formation with the muscle relaxant action of the drugs, receptors in the lateral hypothalamus with the appetite stimulation effects, and receptors in the cerebellum with the ataxia and incoordination observed with high intake of the drugs.

Thus, one can make a number of interesting associations between anatomical distributions of BZ receptor and physiological effects of the drugs. However, it is recognized that these associations are only new hypotheses and their validity will rest on future experiments. Nevertheless, these studies seem to provide some suggestions and directions for future experiments. There are also many other areas of the brain having high levels of BZ receptors, and no one is aware of the significance of these areas (for example, the receptors in the retina and superior colliculus).

MULTIPLE BZ RECEPTORS

While early studies indicated the presence of only a single homogenous class of BZ receptor sites, more recent evidence has suggested the existence of at least two pharmacologically, biochemically, and functionally distinct receptor sites. Experiments demonstrating multiple BZ receptors have involved heat inactivation experiments as well as pharmacological studies with a novel series of triazolopyriazines (TPZ) (Squires et al. 1979; Williams et al. 1980; Lippa et al. 1979a, 1980). Hofstee's analysis of the ability of several TPZ drugs to displace BZ receptor binding from rat brain cortical synaptosomal membrane fragments yielded curvilinear plots that could be resolved into two components. The data suggested at least two populations of BZ receptors, one with a high affinity site for TPZ and another with low affinity for TPZ. These sites varied in their relative proportions in the various brain regions (Lippa et al. 1980). Since pharmacological and behavioral studies of TPZ drugs have demonstrated activity in tests believed predictive of anxiolytic activity without much of the accompanying sedation and ataxia produced by benzodiazepines (Lippa et al. 1979a, b), and since the TPZ-sensitive BZ receptors appear to have a unique regional distribution, it might be supposed that an understanding of those regions containing high densities of BZ receptors with a high affinity for TPZ would provide some clue about brain regions critical for anxiolytic activity as opposed to side effects of the benzodiazepines. Biochemical experiments suggested that the cerebellum contained mostly "type 1" receptors (the subclass of BZ receptors for which TPZ's have a high affinity) while the hippocampus and cortex contain both type 1 and "type 2" (the subclass of BZ receptors having a low affinity for TPZ drugs) receptors (Lippa et al. 1980). Light microscopic autoradiographic studies of the distribution of the two types of receptors have confirmed and extended the biochemical experiments (Young et al. 1981). Areas with high densities of BZ receptors with a high affinity for TPZ drugs include the cerebellum, globus pallidus, and parts of the cerebral cortex. Areas having BZ receptors with a low affinity for the drugs include the superficial layer of the superior colliculus, the caudate-putamen, and parts of the dentate gyrus.

Since type 1 receptors may be more related to the antianxiety action of benzodiazepines, it was of interest to note whether type 1 receptors were found in parts of the limbic system including the hippocampus, amygdala, and frontal cortex. It is interesting that these areas were not the most enriched in type 1 receptors overall, but substantial amounts of type 1 receptors were observed in some parts of these areas. In the hippocampal formation, for example, receptors in the dentate gyrus were resistant to TPZ drugs while binding in the hippocampus proper was affected by them. The frontal cortex appearedtohave a mixture of both type l and type 2 receptors, although type 1 receptors appeared to predominate in lamina IV. Thus, if the TPZ-related receptors are in fact related to the antianxiety action of the drugs, then only certain anatomical pathways within these brain regions may be involved in the complex symptomatology known as anxiety. However, as stated earlier, additional experiments on the mechanism of anxiety and effects of TPZ will be necessary before these ideas can be accepted. These notions must be considered with additional caution since there are important regional and species differences as described above and extrapolation of data from rat brain to human tissues may not be valid. Also, while TPZ drugs show "antianxiety" action in animal model studies, they have not yet been shown to have such action in humans. Nevertheless, the clear demonstration that there are two types of BZ receptors with very different regional distributions in rat brain will help to explain the physiological differences between benzodiazepines and TPZ drugs and point out target sites in the brain for additional studies of the two apparently different receptors. Whether the two receptors are biochemically and structurally different or whether the differences are due to environmental or allosteric effects cannot be determined from these data. However, receptor purification techniques have suggested the presence of multiple molecular weight forms of the BZ receptors (Sieghart et al. 1980).

ELECTRON MICROSCOPIC LOCALIZATION OF RECEPTOR

A serious limitation of the biochemical as well as the light microscopic studies of receptor distributions is the lack of ultrastructural resolution. Because the resolution of the light microscope is limited, it is not possible to associate the receptors with specific membranes in brain regions, but only to associate receptors with brain regions in a fairly generalized fashion. Accordingly, ultrastructural studies at the electron microscopic level are very important and, presumably, this area will receive a great deal of attention in the future. A recent electron microscopic autoradiographic study of BZ receptors provided evidence that the receptors are associated with synaptic contacts (Mohler et al. 1980). The study utilized flunitrazepam in a radiolabeled form, which not only binds to the BZ receptor but also can be used as a photoaffinity label to produce a covalent labeling of the receptor. The cellular and subcellular localization of BZ receptors was analyzed in autoradiographs of photolabeled brain slices. It was found that 55 percent and 74 percent of the grains in cerebral and cerebellar cortex slices respectively were associated with synaptic contacts (because of the method of analysis, the regions of synaptic contacts include nerve endings

and adjacent postsynaptic and glial structures). This large fraction of grains is much higher than would occur on the basis of random chance and it is clear that the BZ receptor is associated in some way with synaptic contacts. It is possible that BZ receptors are associated with other structures as well. One cannot absolutely rule out an association of some BZ receptors with glial structures in synaptic areas or even distinguish between presynaptic and postsynaptical localizations because of the limited resolution of electron microscopic autoradiography. The investigators felt that their observed distributions were at least compatible with the association of benzodiazepine receptors with GABAergic transmission (Mohler et al. 1980).

In a study combining the electron microscopic autoradiographic localization of BZ receptors and the immunocytochemical localization of glutamic acid decarboxylase, it was found that a large fraction of BZ receptors were associated with GABAergic terminals (Mohler and Richards, personal communication). However, BZ receptors were apparently more widespread than the terminals containing the enzyme. Thus, it was suggested that all BZ receptors are not associated with GABA receptors. Light microscopic data could be interpreted to be in agreement (Young and Kuhar 198Ob; Palacios et al. 1980). However, the precise relationship between BZ receptors and GABAergic transmission is not yet totally understood, although it is well known that BZ drugs have a profound effect on GABAergic transmission (Haefely et al. 1980, Costa et al. 1975).

Because of the limited resolution of autoradiography, even at the electron microscopic level, additional techniques will be necessary to more precisely localize benzodiazepine receptors in tissues. Perhaps electron microscopic immunocytochemical studies will be useful for this, and they are feasible if antibodies to the receptor can be produced.

FUTURE DIRECTIONS – THE BENZODIAZEPINE (BZ) RECEPTOR

Since anatomical studies are so important for understanding several aspects of BZ drug action, work in this and related areas will continue to be fruitful. Specific topics that could be explored further are fairly obvious and include the following:

1. More detailed light microscopic mapping of receptor locations in animal models (rat and monkey) and also in human tissues. Receptor distribution in brain is very basic information and should be studied. Techniques for accomplishing this are adequate and available.

2. Identification of endogenous ligand(s). In other words, why is the BZ receptor in the brain and what is its normal significance in the absence of BZ drug?

3. Electron microscopic localization of BZ receptors. The location of the receptor needs to be studied by high resolution methods. Perhaps the most promising is an immunocytochemical approach. Thus, isolation and purification of, and production of antibodies against BZ receptors is an important goal.

4. Functional anatanical studies. In other words, which brain areas are most critical for therapeutic effects? Perhaps behavioral studies combined with direct micro-injections of drug into discrete brain areas is the best approach.

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Benzodiazepine Self-Administration in Animals and Humans: A Comprehensive Literature Review

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One approach to studying drug abuse has been the development of experimental paradigms for controlled investigations of drug self-administration in laboratory animals and humans. Such experimental models can provide various types of information relevant to drug abuse, including comparative information about the relative efficacy with which different drugs maintain drug self-administration. The validity of this approach is supported by the good correspondence between those drugs that are self-administered by laboratory animals and those self-administered and abused by man (Griffiths and Balster 1979; Griffiths et al. 1980a). The purpose of this paper is to review the current status of the scientific literature on benzodiazepine self-administration. The first two sections review the animal and human data, respectively. The final section summarizes major findings and outlines directions for future research on benzodiazepine self-administration.

ANIMAL STUDIES

Experimental studies with nonhuman primates and rats have examined self-administration of a variety of benzodiazepines via the intravenous, intragastric, and oral routes. As a whole, these studies show that a number of the benzodiazepines can sustain responding at rates higher than vehicle but that the efficacy of the benzodiazepines in maintaining self-administration behavior is generally less than for other sedative-hypnotic drugs (e.g., barbiturates, ethanol) with which they have been compared.

Nonhuman Primates

Studies of benzodiazepine self-administration in nonhuman primates have employed the intravenous (I.V.) and intragastric (I.G.) routes, and the majority have been conducted with rhesus monkeys. The animals are prepared with indwelling catheters that are connected to infusion pumps. An injection typically depends on the animal's pressing a lever, which activates the pump to deliver a drug dose. Rates of self-injection of drug can be compared with rates of self-injection of the vehicle to determine whether drug reinforcement is demonstrated.

Yanagita and Takahashi (1973) investigated self-administration of three benzodiazepines (chlordiazepoxide, 1 mg/kg I.V., 10 mg/kg I.G.; diazepam, 0.4 mg/kg I.V.; oxazolam, 10 mg/kg I.G.). Groups of rhesus monkeys first had saline available for up to 2 weeks and then drug available for at least 4 weeks. Drug injections depended on a single lever press response and were continuously available 24 hours per day. Though complete data are not presented, it appears that diazepam maintained more self-administration than the other two drugs. Three of four drug-naive monkeys initiated lever pressing and maintained rates above those maintained by saline (20 to 25 injections per 24 hours resulting in a mean daily dose of 8 to 10 mg/kg). Mean daily intake of chlordiazepoxide was 10 to 20 mg/kg I.V. and 100 mg/kg I.G. (i.e., regardless of route of self-administration, the monkeys pressed the lever approximately 10 times in 24 hours). Unfortunately no saline control data were presented. Although I.G. self-administration of chlordiazepoxide continued longer than 8 weeks, daily intake via the I.V. route declined after 4 weeks (to two to four injections per day). No data were reported on levels of oxazolam intake, except that two of four monkeys initiated responding but did not show "high intake." The report concluded that diazepam was "moderately reinforcing," and that chlordiazepoxide and oxazolam were 'mildly reinforcing."

Using the same procedures, Yanagita and his colleagues also investigated I.G. self-administration of two other benzodiazepines: Sch 12041 (7-chloro-1, 3-dihydro-5 phenyl-l-(2,2,2-trifluoroethyl)-2 H-1,4-benzodiazepine-2-one) (Yanagita et al. 1975) and ID-540 (l-methyl-5(o-fluorophenyl)-7-chloro-1,3-dihydro-2 H-1, 4-benzodiazepine-2-one) (Yanagita and Kiyohara 1976). None of the four monkeys self-administered Sch 12041 at a dose of 20 mg/kg above the levels maintained by water. When the dose was decreased to 5 mg/kg, three of the four monkeys increased rates of self-administration to levels greater than those maintained by the higher dose. Whether the levels were reliably higher than maintained in the water control condition is not clear due to variability in the water data. The authors concluded that the reinforcing effect of Sch 12041 was "positive but weak." The report on ID-540 is available in English in abstract form only. One of four self-administration-experienced monkeys was said to have self-administered the drug (taking about 10 injections per day at doses of 0.25 and 1 mg/kg).

Using procedures similar to those described above, Altshuler and Phillips (1978) found that rhesus monkeys with I.G. catheters did not self-administer diazepam but did self-administer chlordiazepoxide. Unfortunately, no information on dose, length of exposure, drug history, or vehicle controls permits assessment of this experiment.

Two studies of I.V. diazepam self-administration initially maintained responding of rhesus monkeys at a high rate with codeine reinforcement (0.05 mg/kg) and substituted doses of diazepam or saline. Hoffmeister (1977) showed that the number of injections of diazepam (0.005 to 0.05 mg/kg) was less than for codeine but higher than for saline at all but the highest dose, with the 0.05 mg/kg dose maintaining the highest rate of self-injection. Increasing the number of responses required

per injection of that dose produced a monotonic decrease in number of injections. In contrast Hackett and Hall (1977) failed to find response rates above those maintained by saline when diazepam doses (0.05 to 0.04 mg/kg) were substituted for codeine. The reason for the difference in results is unclear, and lack of complete procedural description (i.e., specification of response requirement and session duration) in the Hoffmeister report makes further methodological comparisons impossible.

Johanson and Balster (1978) summarized several unpublished studies that evaluated the I.V. self-administration of two benzodiazepines in rhesus monkeys using drug substitution procedures. In these studies doses of a test compound were substituted for a dose of drug (e.g., cocaine or codeine) already maintaining self-administration. Self-administration was rated as positive if the test drug maintained a greater number of injections than vehicle for at least one dose in more than half of the monkeys studied. According to these criteria, self-administration results were positive with flurazepam and equivocal with chlordiazepoxide (positive results were obtained in one laboratory while negative results were obtained in another).

Griffiths et al. (1981) extended the study of I.V. benzodiazepine self-administration to a different procedure and primate species. Baboons were trained to respond to a lever which produced cocaine injections (0.32 mg/kg) for the 160th response. A 3-hour time-out (a period during which drug was not available) followed each injection, permitting a maximum of eight injections per day. A range of doses (e.g., 0.01 to 17.8 mg/kg) of each of a number of benzodiazepines and the vehicles alone were substituted for 12 to 15 days with a return to the cocaine reinforcement condition preceding each substitution. The highest rate of self-injection was obtained with midazolam, an ultra-short-acting benzodiazepine. Doses ranging between 1.0 and 10.0 mg/kg were self-administered above saline levels in all five baboons tested and, in several animals, were self-administered at levels comparable to that of cocaine control. The other benzodiazepines (diazepam, clonazepam, clorazepate, flurazepam, and medazepam) all sustained some self-administration--average injections per day maintained by drug exceeded levels maintained by the vehicle for at least two baboons at one or more doses.

One study employed a procedure designed to induce self-administration of chlordiazepoxide by manipulation of environmental conditions and exposure to the drug. Findley et al. (1972) trained two rhesus monkeys to press a lever under a complex choice procedure in which I.V. injections of either drug or saline occurred after meeting a shock-avoidance response requirement. Initial selection of the drug option over the saline option was promoted by pairing a lower shock-avoidance response requirement with the drug option. Initial exposure to the drug was further assured by presenting the shock-avoidance/drug-choice trials automatically every 3 (or 4) hours, but the monkeys could produce them more frequently by pressing a separate lever. Drug dose was varied between approximately 0.5 to 2.0 mg/kg chlordiazepoxide. Evidence of drug reinforcement included increasing frequency of trial initiation by the monkeys and the more frequent choice of

the drug option over the saline option. The influence of the initial pairing of the drug option with the lower shock-avoidance requirement seemed not to persist, since, when the same drug dose later was made available in both options, choice of each became 50 percent.

A number of the studies cited above compared responding maintained by benzodiazepines with responding maintained by other drugs under the same procedures and, in some cases, in the same animals. In these studies the percentage of animals self-administering the drug, the rate of drug self-administration, or drug choice performance are taken as indicators of the relative reinforcing efficacy of the drug. These studies showed that benzodiazepines as a class are more efficacious than some drugs, including chlorpranazine (Altshuler and Phillips 1978; Griffiths et al. 1981; Hoffmeister 1977; and Yanagita and Takahashi 1973), imipramine, haloperidol, or perphenazine (Hoffmeister 1977). The studies also showed, however, that benzodiazepines were clearly less efficacious than a range of other drugs, including pentobarbital (Altshuler and Phillips 1978; Griffiths et al. 1981; Hoffmeister 1977; Yanagita and Takahashi 1973), alcohol (Hoffmeister 1977; Yanagita and Takahashi 1973), amobarbital (Griffiths et al. 1981), secobarbital (Findley et al. 1972; Griffiths et al. 1981), and cocaine (Altshuler and Phillips 1978; Griffiths et al. 1981; Hoffmeister 1977). On the whole, these data suggest that benzodiazepines can be considered to be moderately reinforcing.

Rats

The majority of benzodiazepine self-administration studies with rats have employed the oral route, while only three studies have examined intravenous or intragastric drug delivery. Davis et al. (1978) reported in abstract form that both I.G. and I.V. self-administration of chlordiazepoxide (0.1 to 1.0 mg/kg) occurred at rates higher than those maintained by saline. The authors noted that higher numbers of injections were obtained with the I.V. route. Götestam (1973) investigated I.G. self-administration of medazepam (2.5 to 10.0 mg/kg) in groups of rats, each having saline or a different drug dose available 24 hours a day. Over 6 days of drug availability, the mean number of injections per day increased, with the greatest increase at the 10.0 mg/kg dose and the least for the saline group. A final study by Walton and Deutsch (1978) investigating I.G. and oral self-administration provided no evidence for the reinforcing effects of diazepam (0.25 to 1.0 mg/ml). It is possible that these negative results reflect procedural limitations of the study. The rats were deprived of fluid for 23 hours at the time of each daily session and each dose was in effect for only two sessions. In addition, the drug vehicle was a 3 percent ethanol solution, a concentration that was consumed in another study at greater volumes than water by drug-naive rats of the same species as those used by Walton and Deutsch (Veale and Myers 1969).

The remainder of the studies with rats to be discussed involved oral drug self-administration (i.e., the drug was added to drinking water), and all but one involved self-administration of chlordiazepoxide. Because of problems inducing rats to consume oral drug solutions

(e.g., Wolf et al. 1978), several studies have employed conditions of forced chlordiazepoxide intake by making the drug solution (0.2 or 0.5 mg/ml chlordiazepoxide) the only fluid available (Harris et al. 1968; Kamano and Arp 1965; Stolerman et al. 1971). Drug preference was then tested by presenting the rats with a choice of water and the drug solution in the home cage. In all three studies a history of forced chlordiazepoxide intake was not sufficient to induce a higher proportion of total fluid to be taken as drug solution on choice days. In fact, other data suggest that forced consumption of a nonpreferred drug solution may actually decrease the probability of that solution's being preferred in a choice test (cf. Veale and Myers 1969).

A number of other experimental manipulations have been investigated as means of inducing higher oral benzodiazepine intake. It is well established that rats that receive food pellets intermittently in a daily session will exhibit excessive levels of water intake immediately post-pellet (cf. Sanger and Blackman 1978). This paradigm (schedule-induced polydipsia) has been used to generate consumption of chlordiazepoxide solutions (Jacquet and Stokes 1975; Sanger 1977). Sanger (1977) provided some evidence for the reinforcing effects of chlordiazepoxide. The group of rats that had 0.1 mg/ml chlordiazepoxide available drank a slightly higher volume than the group having only water available, and volume consumed decreased when water was substituted for drug. Rats having 0.4 mg/ml chlordiazepoxide available consumed less than that of the water group, and volume increased when water was substituted for the drug solution. Jacquet and Stokes (1975) also reported schedule-induced drinking of chlordiazepoxide solutions, but the limited information (given in an abstract) does not provide evidence for the reinforcing properties of the drug.

Some studies have manipulated remote environmental contingencies thought to produce stress in an effort to determine whether this would result in increased intake of chlordiazepoxide. Rats were provided chlordiazepoxide solutions in the home cage and were submitted to supposedly aversive conditions in daily sessions in separate chambers. Exposure to shock-avoidance trials, inescapable shock conditions (Kamano and Arp 1965) and operant extinction (i.e., lever presses ceased to produce food reinforcement; Harris et al. 1968) failed to increase drug consumption in the home cage.

Another experimental manipulation employed by Harris et al. (1968) apparently was more successful in modulating chlordiazepoxide intake. Following 25 days of daily sessions in which food pellets depended on licking a tube containing chlordiazepoxide (0.5 mg/ml), rats drank more drug solution during a choice condition in the home cage than prior to training and more than another group of rats following a 25-day period in which drug solution was the only fluid available. This result is particularly interesting since, under the latter condition, total drug intake was two to three times greater. Food deprivation was not a confounding factor, since all rats in this experiment were maintained at 85 percent of ad libitum weight throughout all conditions.

Although the question of whether a history of self-administration of other drugs will increase the subsequent likelihood of benzodiazepine self-administration has not been investigated systematically, one study provides some data suggestive of this possibility. Amit et al. (1973) found that rats that showed high daily alcohol intake for an extended period of time later drank a greater proportion of total daily fluid as a diazepam solution (0.06 mg/ml) in a choice condition with water than either drug-naive rats or rats that had consumed less alcohol per day.

Few of the rat studies reviewed above have attempted to directly compare the self-administration of benzodiazepines with other drugs (Davis et al. 1978; Götestam 1973; Harris et al. 1968; Stolerman et al. 1971). The lack of adequate dose manipulations, in particular, makes any conclusion about relative drug reinforcing efficacy hazardous. The study by Davis et al. (1978) provides some suggestive evidence that chlordiazepoxide may be a less efficacious reinforcer than d-amphetamine: rats that had failed to self-administer I.V. chlordiazepoxide (0.25 mg/kg) subsequently acquired self-administration behavior when d-amphetamine (0.25 mg/kg) was substituted.

Overall, studies of benzodiazepine self-administration in rats provide only limited evidence for drug reinforcement. Several studies have demonstrated benzodiazepine intake over vehicle control levels intravenously (Davis et al. 1978), intragastrically (Davis et al. 1978; Götestam 1973), and orally (Amit et al. 1973; Sanger 1977). The remaining studies reviewed either failed to demonstrate drug reinforcement or did not experimentally address the question of drug reinforcement per se. The limited research with rats to date comparing benzodiazepines to other drug classes provides no basis for drawing meaningful conclusions about the reinforcing efficacy of the benzodiazepines relative to other drugs.

HUMAN STUDIES

A variety of different experimental approaches in treatment and laboratory settings has provided information about the reinforcing properties of benzodiazepines in various subject populations, including normal student volunteers, patients with insomnia, alcoholics, psychiatric patients, and volunteers with histories of sedative drug abuse. As a whole, these studies demonstrate that benzodiazepines maintain self-administration; however, their efficacy as reinforcers appears to depend on the subject population studied and the conditions of drug availability.

Rothstein et al. (1976) investigated self-administration of medication in a group of alcoholic patients who were treated in an outpatient clinic setting. The study involved 108 patients who were followed for at least 1 year while receiving free prescriptions for various tranquilizers (95 percent chlordiazepoxide; 4 percent diazepam; 1 percent phenothiazine). Patients were instructed to use the medication as needed for relief of anxiety, but urged to take as little as possible. Daily self-administration doses of

the most commonly used drug, chlordiazepoxide, ranged between 10 to 200 mg. Eighty-six percent of the total patient group reported not taking their prescribed drug every day, while 50 percent went without the drug for more than 30 days during the study period. In the group of patients studied, overall drug intake apparently remained relatively stable (17 percent of patients increased intake; 14 percent decreased intake, and 7 percent stopped using the drug during the study period). Clinical evidence of abuse or misuse (e.g., exceeding prescribed dose range or using the drug as an alcohol substitute) was seen in 5 percent of the patients. The authors concluded that benzodiazepine use in alcoholics appears quite safe.

Kryspin-Exner and Demel (1975) described a series of three studies involving benzodiazepine self-administration by alcoholic and drug-abuse patients in a treatment context. In the first, alcoholics in a supervised outpatient setting were given prescriptions for benzodiazepines for a period of at least 4 weeks (mean observation time was 1 year). Characteristics of dependence, including a tendency toward increased doses and corresponding psycho-organic deficit symptoms were shown by 3.6 percent of the 111 patients given chlordiazepoxide and 2.3 percent of the 302 patients given diazepam. Of the 11 patients, 7 had histories of abusing sedatives or analgesics in addition to alcohol. In a second study, the double-blind self-administration of diazepem (5 mg/tablet) or placebo was studied in a group of hospitalized male alcoholics who did not have histories of abusing drugs other than alcohol. All patients had abstained from alcohol for approximately 7 days prior to the study. They were told that medication was important for treatment of their withdrawal symptoms and that they could take up to 10 tablets a day. patients were assigned to either placebo (N=23) or diazepam (N=24) and the study was conducted for a 32-day period. Under these conditions, relatively low levels of self-administration occurred (average of 1.7 tablets per patient per day) with no significant difference between diazepam and placebo. In a final study, 20 patients with histories of abuse of hypnotic drugs were placed on a canbination of four tranquilizers (oxazepam, lorazepam, diazepam and nitrazepam) at almost unrestricted doses. The authors noted that within a few weeks 8 of the 20 patients became dependent on the tranquilizers that were originally prescribed for therapeutic purposes. These studies emphasize the potential importance of a patient's history in determining levels of benzodiazepine self-administration. Patients with histories of abusing sedatives or analgesics may be more likely to misuse benzodiazepines than patients with histories of abusing only alcohol.

Winstead et al. (1974) encouraged all patients admitted to a 16-bed general psychiatric ward to request diazepam (10 mg) when necessary (prn), every 4 hours. patients were told to seek medication from staff if they felt unusually tense, anxious, or worried. Over the 6-month study period 83 patients participated. patients differed greatly in their tendency to request medication--27 percent sought none, and requests were made on an average of only once every 3 days. The characteristics correlated with drug taking were anxiety, being female, being white, and having an elevated psychasthenia

scale on the MMPI. Although within-subject analysis indicated that drug taking decreased over the duration of the hospital stay, drug taking for the entire ward increased over the 6-month study period. The authors suggest that this increase may be attributable to au increasingly favorable staff attitude toward minor tranquilizer use that developed over the study. The authors concluded that when diazepam was made freely available, psychiatric patients of all diagnoses sought it for the appropriate indication of anxiety, and most used it conservatively.

Jick et al. (1966) and Fabre at al. (1976) used a procedure for assessing drug preference while evaluating the efficacy of various benzodiazepine hypnotics in outpatients with insomnia. The two drugs being compared were identically packaged and labeled as either Drug A or Drug B. One drug was administered on a double-blind basis in random order on the first night, with the comparison drug given on the second night. Patients subsequently were asked to express their preference for Drug A or Drug B, or, alternatively, indicate that they had no preference. Fourteen to thirty-five patients participated in each preference comparison. Using such procedures Jick et al. (1966) showed that the benzodiazepine hypnotic flurazepam (7-chloro-1 [2-diethylaminoethyl]5-[2-fluorophenyl]-1,3-dihydro-2H-l, 4 benzodiazepine-2-one dihydrochloride) was preferred to placebo in two separate experiments. In a third experiment, no difference in preference was obtained when 15 mg flurazepam was compared with l00 mg secobarbital. Using similar procedures, Fabre et al. (1976) reported that the benzodiazepine triazolam (0.5 mg) was clearly preferred to placebo. In subsequent paired comparisons, 0.5 mg triazolam also was found to be preferred to 500 mg chloral hydrate and 30 mg flurazepam. Overall, these studies show that the reinforcing effects (as indicated by a verbal preference measure) of hypnotic benzodiazepines can be demonstrated under conditions that may favor the self-administration of sedative drugs (i.e., at night in people complaining of insomnia).

Johanson and Uhlenhuth (1978) used a paired preference procedure, somewhat similar to that described above, to assess choice between diazepam and placebo and diazepam and d-amphetamine. Normal student volunteers participated in sessions involving drug administration in the morning. Each experiment consisted of nine sessions, three per week. During the initial four sampling sessions, the subjects were given an opportunity to experience the effects of the two drugs that were dispensed blind in different colored capsules. During the five subsequent choice sessions subjects were instructed to choose between the two colors, and their choice determined which they received. Eight to 11 subjects participated in each paired comparison. The results indicated that there was no preference between placebo and 2 mg diazepam, but placebo was preferred to both 5 and 10 mg diazepam. d-Amphetamine (5 mg) was preferred to diazepam (2 mg). Overall, the study provides no evidence for the reinforcing properties of diazepam in normal volunteers.

A series of studies conducted at Baltimore City Hospitals examined diazepam and pentobarbital self-administration in male volunteer subjects with histories of sedative drug abuse (Bigelow et al. 1976; Griffiths et al. 1976, 1979). Subjects lived on a residential research ward and were required to ride a stationary exercise bicycle in order to obtain a maximum of 20 ingestions of drug during daily sessions. When dose of drug was varied under blind (Griffiths et al. 1979) or nonblind (Griffiths et al. 1976) conditions, the number of ingestions taken increased as dose increased with both pentobarbital (30 to 90 mg/ingestion) and diazepam (2 to 20 mg/ingestion). Furthermore, increases in the response requirement to obtain drug (Bigelow et al. 1976), or increases in the minimum time period imposed between the availability of successive drug ingestions (Griffiths et al. 1976) produced decreases in the number of ingestions consumed for both pentobarbital and diazepam. These results show that diazepam and pentobarbital are similar to the extent that they both maintain self-administration and that they are similarly responsive to manipulation of dose, response requirement, and minimum interingestion interval.

Several of the studies conducted at Baltimore City Hospitals provided some information about the reinforcing efficacy of diazepam relative to other drugs having sedative properties. Griffiths et al. (1979) directly compared the self-administration of pentobarbital (30 or 90 mg/ingestion), diazepam (10 or 20 mg/ingestion), chlorpromazine (25 or 50 mg/ingestion) or placebo under double-blind conditions. In this study a drug was made available for 5 to 15 consecutive days and the order of exposure to different drugs was mixed. A maximum of 10 ingestions was available during a 7.5 hour session each day. On the first day of drug availability ingestions were available upon request of the subject, provided that 15 minutes had elapsed since the last dose was dispensed. After the first day subjects were required to obtain each ingestion of drug by riding a stationary exercise bicycle for 15 minutes. Although all three drugs produced subjective effects and observable signs of sedative intoxication, the drugs were associated with different amounts of self-administration. With the exception of one idiosyncratic subject, chlorpromazine was similar to placebo in that it did not maintain self-administration. Both diazepam and pentobarbital maintained self-administration with the higher dose of each associated with higher average levels of self-administration than the lower dose. The high dose of pentobarbital was associated with higher levels and more regular self-administration than was the high dose of diazepam. A subsequent set of experiments (Griffiths et al. 1980b) provided more information about the relative reinforcing efficacy of diazepam in comparison to pentobarbital by using a choice procedure in which subjects were given repeated opportunities to choose between two available drug alternatives. In this study drug-free days alternated with drug administration days. Following experimenter-scheduled exposures to the test drugs under double-blind conditions, subjects were given repeated opportunities to choose between two available drug alternatives. In Experiment 1, pentobarbital (200 to 900 mg) produced dose-related increases in subject- and observer-rated drug

effects, and subjects generally chose higher pentobarbital doses over lower doses. In Experiment 2, diazepam (50 to 400 mg) produced only modest elevations in drug effect ratings and subjects did not consistently choose higher doses over lower doses. In Experiment 3, 400 mg pentobarbital and 200 mg diazepam produced subject and observer drug effect ratings of similar magnitude while placebo produced negligible effects. All subjects chose pentobarbital over placebo and diazepam over placebo on all occasions; all subjects chose pentobarbital over diazepam on the majority of choice trials. Overall, these studies conducted in subjects with histories of sedative drug abuse suggest that the reinforcing efficacy of diazepam is greater than that of chlorpromazine, but less than that of pentobarbital.

CONCLUSIONS AND FUTURE DIRECTIONS

In spite of methodological limitations described below, the literature on animal and human studies reviewed in the preceding sections provides remarkably similar assessments of the overall efficacy of the benzodiazepines in maintaining self-administration behavior. The experimental reports indicate that benzodiazpines can serve as reinforcers in both animals and humans, although the precise conditions for demonstrating these reinforcing effects are not clear. To the extent that the benzodiazepines maintain self-administration, they are more efficacious than drugs such as chlorpromazine, which have not been shown to maintain self-administration in animals or humans. However, both animal and human data show that benzodiazepines are less efficacious in maintaining self-administration behavior than classic drugs of abuse such as pentobarbital. The inescapable conclusion is that benzodiazepines, as a class, appear to be modest reinforcers. This conclusion is compatible with the fact that, although there are a number of reports describing human abuse of the benzodiazepines, the abuse liability of these compounds is generally considered to be relatively low (Marks 1978).

Drawing more specific conclusions about the self-administration of benzodiazepines at this time must be tempered by the recognition that the present data base is at a very preliminary stage of development. Many of the animal and human reports reviewed should be viewed as pilot studies, since they lack experimental thoroughness or methodological rigor. For instance, many of the animal benzodiazepine self-administration studies investigated only one dose level (e.g., Amit et al. 1973; Harris et al. 1968; Kamano and Arp 1965; Stolerman et al. 1971; Yanagita and Takahashi 1973) and others have not provided adequate descriptions of methods and/or results (e.g., Davis et al. 1978; Jacquet and Stokes 1975; Hoffmeister 1977; Altshuler and Phillips 1978). In the human research, lack of appropriate controls in some of the reviewed studies would suggest that these reports should most properly be viewed as clinical descriptions rather than experimental evaluations. For instance, the results of several reports purporting to show that benzodiazepine self-administration is quite modest in a treatment context would have been greatly strengthened by appropriate double-blind placebo or inactive medication controls (Kryspin-Exner and Demel 1975, Experiment 1; Rothstein et al. 1976; Winstead et al.

1974). Clearly, given the preliminary nature of these studies, future research investments could be profitably placed in further rigorous studies of animal and human benzodiazepine self-administration.

Both animal and human research suggest that the likelihood of self-administering benzodiazepines may depend on the history of the subject population examined. In the single relevant animal study to date, Amit et al. (1973) presented evidence suggesting that oral diazepam intake in rats was greater in animals with histories of self-administering other drugs than in drug-naive rats. In human research, the nonblind studies conducted in a therapeutic context (Kryspin-Exner and Demel 1975) suggest that patients with histories of abusing sedatives or analgesics may be at substantially greater risk for developing abusive patterns of benzodiazepine self-administration than patients without such histories. Among the studies conducted with double-blind placebo controls, several studies with alcoholics or normals (Johanson and Uhlenhuth 1978; Kryspin-Exner and Deme1 1975, Experiment 2) failed to show any reinforcing properties of diazepam, in contrast to other double-blind studies with sedative abuser subjects that clearly demonstrated reinforcing effects with diazepam (Griffiths et al. 1979, 1980b). Future research with both animals and humans should provide more basic experimental and epidemiological information on drug history and other population differences as potential determinants of benzodiazepine self-administration. In addition, possible pharmacological and physiological mechanisms that may underlie these differences should be explored.

The results of several of the animal and human studies underscore the potential importance of environmental conditions as a determinant of the reinforcing efficacy of benzodiazepines. In a study of oral chlordiazepoxide self-administration in rats, Harris et al. (1968) found that pairing drinking with obtaining food reinforcement was sufficient to induce a higher drug intake in a choice situation. The contribution of other contextual variables to benzodiazepine self-administration was suggested but not demonstrated experimentally by the results of other animal studies (e.g., Findley et al. 1972; Sanger 1977). In human research, the only studies to suggest that benzodiazepines were reinforcers in nonabuser subjects were those of Jick et al. (1966) and Fabre et al. (1976) whose research showed preference for hypnotic benzodiazepines over placebo under conditions in which the drug was dispensed at night to subjects complaining of insomnia. It seems likely that these subjects would not have preferred the drug if it had been dispensed in the morning, as was the procedure in the preference study by Johanson and Uhlenhuth (1978). Such findings emphasize that the reinforcing efficacy of a drug should not be considered apart from the context of drug availability. It seems quite possible that such contextual modulation is particularly important to the establishment of abusive patterns of drug use with drugs showing only modest reinforcing efficacy in the laboratory, such as nicotine, caffeine, or benzodiazepines. Future animal and human research should explore more fully the environmental and situational conditions (for example, experimentally-induced stress) that may modulate the reinforcing efficacy of benzodiazepines.

Only one of the reviewed studies attempted a systematic comparison of compounds within the benzodiazepine class (Griffiths et al. 1981). That study compared the intravenous self-administration of six benzodiazepines in baboons, and showed that the ultra-short-acting benzodiazepine, midazolam, was more efficacious in maintaining self-administration than compounds with longer durations of action. Future research in animals and humans should provide more canparative data about the reinforcing efficacy of different benzodiazepines. In these studies particular attention should be given to differences in rates of absorption (cf. Bliding 1974) and duration of action (cf. Griffiths et al. 1981) as properties that may covary with reinforcing efficacy.

The animal research reviewed on oral or intragastric self-administration of benzodiazepines has been quite limited in scope. Interpretation of results of oral benzodiaxepine self-administration studies in rats is particularly problematic, especially since levels of drug intake rarely exceeded those of the water controls (Amit et al. 1973; Sanger 1977), and assessment of more than one drug concentration was rare. Since the oral route is the most common route by which benzodiazepines are abused in man, and because solubility problems may compromise some of the results of the intravenous route in animals, future research investments should be made into the development of good animal models of oral and intragastric benzodiazepine self-administration. Such models should be used to provide comparative information about drug reinforcing efficacy both within and between relevant pharmacological classes.

Finally, it should be noted that it has been beyond the purview of this review to examine the data concerning the consequences of benzodiazepine self-administration. Clearly, a balanced view of the abuse liability of the benzodiazepines must consider the consequences of use as well as the reinforcing efficacy of these compounds. Notable adverse effects of benzodiazepine self-administration include memory deficits (e.g., Clarke et al. 1970; Ghoneim et al., in press), and sensory/motor impairment (e.g., McNair 1973; Wittenborn 1979), along with possible subtle adverse changes in mood and behavior (e.g., Griffiths et al. 1980b; Hendler at el. 1980). Future animal and human research should determine the magnitude and prevalence of such effects through a range of therapeutic and abused dose levels.

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Benzodiazepine Dependence Studies in Rodents

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GENERAL ISSUES

Drug dependency has several dimensions related to drug needs. Drug abusers may have hereditary, congenital, or induced need for certain drugs. These needs maybe related to personality disorders. Alcoholics, narcotic abusers, and polydrug users have abnormal psychometric profiles and prevailing affective disorders as a group. Several types of drugs of abuse, including narcotic analgesics, amphetamines, and barbiturates, have been shown to produce subject states of well-being that are polarly opposite to hypophoria and depression. These feelings of well-being improve self-image. Martin et al. (1973) found that feelings of hypophoria were part of the protracted abstinence syndrome. Thus chronic drug ingestion may induce a drug need. Finally, the abstinence syndrome has been thought to create both a physiologic and a psychologic need. Drug dependence thus has several dimensions.

Animal research on dependence on barbiturates, sedative-hypnotic drugs, and antianxiety drugs has focused to a large extent on physiologic dependence as manifested by withdrawal convulsion and deliriun and, to a lesser degree, on their reinforcing properties. Lesser attention has been paid to those aspects of abstinence symptoms and their associated physiologic mechanisms responsible for discomforting symptoms which may give rise to and perpetuate drug-seeking behavior once the important connection between the drug-related relief of the abstinence discanfort and drug ingestion has been established. In trying to establish methodologies for identifying these various properties of abused drugs, each of these aspects of dependence must be considered.

Theantianxietyproperty of the benzodiazepines has been assessed using inhibition of operant behavior. The literature on the effect of benzodiazepines on conditioned avoidance responsing has been recently reviewed by Haefly (1978). The extent to which this important therapeutic action of the benzodiazepines contributes to their dependence-producing effect is not known. As will be discussed subsequently, the ability of oxazepam to decrease conditioned inhibition of bar-pressing behavior persists with chronic administration.

A very limited amount of work has been done in assessing the physical dependence-producing properties of the benzodiazepines, and none to determine if chronic intoxication produces a drug need during or following the abstinence syndrome in the rat. Further, a detailed description of the benzodiazepine abstinence syndrome in the rat has not been made.

EFFECTS OF CHRONIC ADMINISTRATION OF BENZODIAZEPINES

Randall et al. (1961) administered large doses (10, 100, and 1,000 mg/kg) of diazepam in food to rats for a B-week period and reported a large reduction in food consumption, loss of weight, and a debilitated (unthrifty) appearance. There were no abnormal laboratory observations. Margules and Stein (1968) studied the effect of the chronic daily administration of oxazepam (20 mg/kg) on lever pressing for food and its inhibition by foot shock punishment in the rat. Oxazepam depressed bar pressing and decreased foot shock inhibition of bar pressing. Tolerance developed to oxazepam's inhibition of bar pressing but not to its ability to disinhibit the effect of punishment.

Sansone (1979) found that when chlordiazepoxide (5 and 10 mg/kg) was administered for 5 days to rats, the increase in motor activity seen with these doses was enhanced, while some tolerance to the motor depressant actions of 20 and 30 mg/kg was seen.

SELF-ADMINISTRATION

Götestam (1973) found that rats would self-administer medazepam and morphine by the intragastric route. Rats would not spontaneously consume (drink) chlordiazepoxide or neprobamate-containing solution when offered in a free choice situation or in a free choice situation after forced consumption. Bats would consume these drugs when they had to drink them to obtain food (Harris et al. 1968). Bats participating in a shock avoidance or an unavoidable shock experiment did not consume more chlordiazepoxide solution than they did under a nonstressful condition (Kamano and Arp 1965). Diazepam decreased alcohol consumption in naive rats but not in rats previously dependent on alcohol (Ferko et al. 1979). Stolerman et al. (1971) found that forced ingestion of chlordiazepoxide in drinking water of rats for 20 days resulted in a progressive increase in the amount consumed (26.3 to 34.0 mg/kg). Chronic ingestion of chlordiazepoxide in drinking water did not affect the quantity of chlordiazepoxide ingested when it was offered in a choice situation in which the rat had the opportunity of ingesting either water or a chlordiazepoxide solution. Prior chronic ingestion of chlordiazepoxide did not affect the consumption of a morphine solution in either a choice situation or when the rats were given access to the morphine solution as their only source of drinking water.

PHYSICAL DEPENDENCE

The dependence-producing properties of the benzodiazepines have received little attention until recently. Fraser and Jasinski (1977), in their review, report on experimental methods for measuring physical

dependence on minor tranquilizers only in the dog (meprobamate) and monkey (meprobamate, diazepam, and chlordiazepoxide). Hollister et al. (1961, 1963) reported on experimentally induced physical dependence with chlordiazepoxide and diazepam in man. Following withdrawal of chlordiazepoxide from 12 subjects who had received 300 to 600 mg/day, the following symptoms and signs of withdrawal were observed: depression (6 subjects), seizures (2), twitching (l), insomnia (2), loss of appetite (4), agitation (3), and a worsening of their psychosis. Some of these signs appeared by the second day and persisted through the ninth day of withdrawal (Hollister et al. 1961). One seizure and other withdrawal signs were seen in 6 of 13 patients in which the dose of diazepam was increased to 120 mg/day.

Yanaura et al. (1975) allowed rats to ingest diazepam mixed with food. The rats were offered a choice of food containing 0.05 and 0.1 percent diazepam or 0.1 and 0.2 percent. The low-dose group consumed 60 to 90 mg/kg/day of diazepem, while the high-dose group consumed 110 to 115 mg/kg/day of diazepam. These dose levels did not impair growth or decrease food intake. When the rats were abruptly withdrawn after 7 days of treatment, they lost some weight and food intake was curtailed. Phenobarbital in food prevented the decrease in food intake and loss of weight. Diazepam also suppressed the decrease in food intake and weight loss in abstinent phenobarbital-treated rats.

EXPERIMENTAL STUDIES OF SEDATIVE-HYPNOTICS AND ANTIANXIETY DRUGS IN THE GASTRIC FISTULA RAT

We are conducting studies in the gastric fistula rat to identify pharmacologic parameters that are associated with the dependence-producing capacity of drugs used as sedatives and for the treatment of sleep disorders, which could lead to the development of safe, effective agents of low abuse potential.

We have selected the gastric fistula preparation because it allows ready acute and chronic dosing of rats with water-insoluble drugs. Drug-containing capsules can be placed directly into the stomach. Using this preparation it has been possible to conduct crossover studies with sedative-hypnotic drugs and to obtain valid potency estimates on two measures: behavioral depression (using a Behavioral Rating Scale, BRS) and depression of respiratory rate. In our first study, pentobarbital, secobarbital, methaqualone, diazepam, and chloral hydrate were compared using four- to eight-point assays. Valid potency estimates were obtained between pentobarbital, secobarbital, and methaqualone for both behavioral depression and depression of respiratory rate. Secobarbital and pentobarbital were found to be equi-potent while methaqualone was l/4 to l/5 as potent as pentobarbital. Valid assays were not obtained between pentobarbital on the one hand and diazepam or chloral hydrate on the other. The diazepam BRS dose response line had a shallower slope than the pentobarbital dose response line, and a ceiling was encountered at the 40 mg/kg dose level. Eighty mg/kg of diazepam did not produce a greater depression than did 40 mg/kg. Diazepam did not depress the respiratory rate in doses up to 80 mg/kg. The chloral hydrate BRS dose response line had a steeper slope than that of pentobarbital; however, it did not depress respiration.

In another series of studies, we have investigated the interaction between alcohol and pentobarbital, chloral hydrate, or diazepam. In these studies it was found that diazepam modestly enhanced alcohol depression (BRS) to a degree greater than could be attributed to additivity, whereas alcohol and pentobarbital were additive. Alcohol and chloral hydrate were less than additive.

PENTOBARBITAL DEPENDENCE IN THE RAT

Since the pioneering work of Seevers in the dog and Isbell (1950) in man, demonstrating that seizures and delirium tremens were important signs of abstinence in barbiturate-dependent dogs and man, much work has been directed to the study of these phenomena. However, in the classic paradigm of drug seeking behavior, it can be questioned whether these two phenanena are related to a drug need or are early and important factors in drug seeking behavior of sedative-hypnotics and antianxiety drugs.

We are studying physical dependence on pentobarbital and diazepam in the rat with the end of measuring seizure incidence and type, signs that could be indicative of murine delirium as well as other signs of abstinence, and to determine their time course. At the present time our data, which are preliminary, have been most thoroughly analyzed for dependence on pentobarbital in the rat. Rats that have been prepared with a gastric fistula have been made dependent on pentobarbital by administering pentobarbital-containing capsules into the stomach through the fistula. The stabilization dose levels have ranged from 227 mg/kg/day (ca 20 mg qid) to 500 mg/kg/day (ca 40 mg qid) at approximately equal intervals. Rats have been maintained at these dose levels for 4 months. These doses make most of the animals ataxic and cause loss of righting reflex 40 to 50 percent of the time. Rats maintained their body weight. In some animals it is necessary to curtail food intake to maintain body weight at approximately 300 gm.

Signs of abstinence have been studied from 8 to 48 hours following withdrawal. The signs of abstinence that have been noted during this period are (1) an early hyperphagia, followed by a decrease in food intake which becomes apparent 12 to 16 hours after the onset of abstinence, and (2) a decrease in body weight, which also becomes manifest at 12 to 16 hours after abstinence and is maximal from 24 to 32 hours after withdrawal. Pupillary diameter and body temperature are not markedly changed during withdrawal. Convulsions have appeared in some animals (4/8) 13 to 15 hours after withdrawal. Other signs of abstinence identified include head and body tremors, wet dog shakes, twitches and jerks, prolonged tremors, poker tail, stiff-legged walking, and teeth chattering. Most of these signs of abstinence appear or are apparent within 8 hours after withdrawal and gradually diminish thereafter. Some signs are still present some 40 hours after withdrawal. We are in the process of attempting to determine the relative contribution of these various signs of abstinence to the withdrawal syndrome. It appears that the withdrawal syndrome of pentobarbital is a complex one. Parts of it have a rapid onset, which may be correlated with the onset of drug-seeking

behavior. The loss of weight and appetite are later phenomena, appearing approximately 1 day following the above-described signs of abstinence.

Rats have been made dependent on 80 to 100 mg/kg/day of diazepam administered 4 times daily intragastrically for over 35 days. Preliminary data on abstinence signs present from the 8th through the 40th hour indicates that the rats exhibited a progression of changes. From the 8th to the 20th hour of abstinence, the rats exhibited increased activity and wet dog shakes. In addition these rats exhibited a poker tail and lost weight, signs which were present by the 8th hour and persisted through the 40th hour. An increase in head and body tremor as well as body twitches or spasms, jerks, and hostility was seen by the 20th hour of abstinence and persisted through the 40th hour. From the 25th through the 40th hours of abstinence, violent and explosive awakening and turning movements were seen. These movements were rapid and propelled the rats to the top or side of the observation cage. Between these episodes the rats would sleep or exhibit fixed posture and staring. One rat showed rapid turning and biting movements and vocalized while turning.

CONCLUSIONS

There is only a small amount of information concerning benzodiazepine dependence in the rat. Although benzodiazepines will decrease conditioned avoidance responding, adverse circumstances do not seem to give rise to increased ingestion. Other problems related to dependence that can be dealt with experimentally are (1) the relative agonistic actions of the different benzodiazepines; (2) the characterization of their dependence-producing ability, including whether they produce protracted abstinence or not; (3) identification of signs of abstinence that are predictors of drug seeking behavior; and (4) the relative threat of the abstinence syndrome to health.

The rat certainly is an economic species in which these assessments can be made. The rat has been extensively used in operant studies. It now appears that rats dependent on pentobarbital and diazepam have an abstinence syndrome rich in signs. The gastric fistula rat allows the ready enteric administration of the water-insoluble benzodiazepines. The viability of this preparation is such that a variety of crossover and dependence studies can be conducted, which should allow the efficient generation of quantitative data of relatively low variability.

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Benzodiazepines: Clinical Use Patterns

Karl Rickels, M.D.

INDICATIONS FOR BENZODIAZEPINE USE

Research conducted over many years has shown that nonpsychotic anxious patients respond best to anxiolytics if they suffer primarily from emotional and somatic symptoms of anxiety, and less from depression and interpersonal problems (Rickels 1978).

Benzodiazepines are usually not very effective in clear-cut depressions, in anxiety associated with schizophrenia, in agitation associated with chronic brain syndrome, and in phobic and obsessive-compulsive disorders. Indications for benzodiazepines, using DSM III Diagnostic Criteria (American Psychiatric Association 1980), are generalized anxiety disorder, atypical anxiety disorder, anticipatory anxiety, panic disorder, posttraumatic anxiety, adjustment disorder with anxious mood, several somatization disorders, formerly described as psychophysiological reactions, and, finally, many nonpsychotic anxiety reactions not clearly diagnosable according to the DSM III, such as anxiety in patients who have been told of the need for a coronary bypass operation, anxiety in cancer patients, or anxiety present with or triggered by many physical illnesses.

Many social phobias, in fact, while possibly improving more with behavioral therapy or with imipramine than with the benzodiazepines, do respond, to some extent at least, to treatment with benzodiazepines.

Anxiety is perceived as a subjective feeling of heightened tension and diffused uneasiness, defined as the conscious and reportable experience of intense dread and foreboding, conceptualized as internally derived and unrelated to external threat. It is not merely fear because it lacks a specific object. It is a painful dread of situations that covertly symbolize unconscious conflict and impulses.

The many symptoms of anxiety are attributable to the fact that anxiety, more than any other type of emotional disorder, can induce widespread physiologic changes. Anxiety is perceived as a threat arising primarily from within, triggering somatic and visceral responses through the autonomic nervous system and the hypothalamic-pituitary-endocrine system (Lader 1974). Frequently some remembrance of a past threat, triggered by some unrecognized present situation, signals a feeling tone and somatic responses of the past fearful state.

Anxiety can be partly bound by such mechanisms as phobias, obsessions, and conversions, or it can be diverted into the soma, leading to somatization. In fact, pure anxiety states are relatively-rare because such syndromes as depression, hysteria, hypochondriasis, somatization, phobias, and obsessional thinking are often concomitantly present.

Anxiety can be operationally defined in term of scores on various patient- or physician-completed checklists and rating scales.

While the use of anxiolytics in the above-mentioned nonpsychotic anxiety states is well established, the relatively high use pattern, both in and out of the hospital, of benzodiazepines, particularly diazepam, in nonanxious patients suffering from physical disorders, particularly cardiovascular, raises the question of whether or not the use of anxiolytics in such medical disorders is appropriate. Despite several small short-term studies (Dunbar et al. 1971; Benson 197l; Hackett and Cassem 1972), no good scientific data are presently available to support or refute the prophylactic use of anxiolytic agents for the prevention of a second heart infarct or for the prolongation of expected lifespan.

One could theorize that since anxiety and stress may lead to increased triglyceride and cholesterol levels, and also to a facilitation of platelet clotting, anxiolytics given prophylactically may indeed increase the lifespan of such cardiac patients. In fact, it may be worthwhile to consider a national multicenter study to test such a hypothesis, particularly in light of recent reports indicating that aspirin may exert no beneficial effects in such patients (Horwitz 1980).

APPROPRIATE EMPLOYMENT OF ANXIOLYTIC TREATMENT

It must be emphasized that antianxiety agents work symptomatically, not etiologically. They do not, for example, directly affect the psychodynamic and environmental factors responsible for emotional problems; they do not, at least in a direct sense, affect the basic personality attributes of the patient. By relieving the symptoms of anxiety and tension, however, these drugs may render a patient less miserable and better able to cope with intrapsychic and extrapsychic stress. Antianxiety agents may also facilitate problem-solving and the deconditioning and reconditioning of emotional responses.

For the achievement of good therapeutic results, antianxiety agents must be prescribed appropriately. The physician who uses these agents for the achievement of unobtainable goals rather than for symptomatic relief, or as a vehicle of rejection rather than within the context of a supportive relationship, will see only a few beneficial effects. In other words, drugs must be prescribed for the right reasons. Equally important for achieving good results is that the physician be knowledgeable about the antianxiety agents he uses. Even if prescribed for the right reasons, the wrong agent, or the right agent given in the wrong treatment regimen, will not prove helpful to the patient (Rickels 1978).

Drug treatment should be employed only when warranted by the patient's degree of disability or discomfort, and should be primarily symptom-oriented. Duration of treatment should be influenced by duration of symptoms. Thus, many acutely anxious patients may require treatment for only a few days or weeks, as their complaints are often short-lived and of a situational nature. Within these acutely anxious patients, the main function of drug treatment is generally to render the patient less miserable until the anxiety attack runs its course. Short-term treatment, however, may well prove inadequate for more chronically ill anxious patients. In fact, it seems likely that many chronically anxious patients are currently being treated inadequately and for too short a period of time.

It is the opinion of the author that many anxious patients simply need a more protracted course of pharmacologic treatment than is generally provided. For some, even a form of maintenance treatment similar to that of diabetics receiving insulin or hypertensive patients receiving antihypertensive medication may be necessary. In fact, this type of maintenance treatment with antianxiety agents is frequently being provided by the primary care physician, even though no research data seem to be available to support or refute such a treatment strategy.

Finally, some chronically anxious patients need a small crutch or support in order to cope with life, and an occasional pill is much less expensive and time-consuming for the patient than seeing a psychiatrist for many years. If such a patient's functioning capacity decreases, more rigorous psychiatric treatment should be seriously considered.

NONSPECIFIC FACTORS PREDICTING IMPROVEMENT WITH ANXIOLYTICS

Clinical experience indicates that drug response in anxiety appears to be influenced by many factors above and beyond those associated with the pharmacology of the medication the patient receives: improvement often occurs spontaneously; any effort at treatment, no matter how small, may produce at least some placebo response; and any doctor-patient contact may result in some change in clinical status (Uhlenhuth et al. 1969).

The isolation of the most important nonspecific factors that influence drug treatment response in neurotic anxiety, and the evaluation of the nature and extent of their impact, represent a complex and challenging research undertaking. For the past 15 years the Psychopharmacology Research Group at the Department of Psychiatry of the University of Pennsylvania has devoted considerable effort to this particular research area.

From this research, a certain pattern of relationships between nonspecific factors and response to treatment with anxiolytics has emerged. Table 1 summarizes some of these relationships; it gives only those nonspecific factors that have been replicated rather consistently in research conducted by this research group or in research conducted by others (Rickels 1978). Of particular interest is that such predictors as more realistic aspirations toward mental

health, high ego strength, low hostility, and better social advantage are also good predictors for psychotherapy outcome.

Table 1

Predictors of Improvement with Anxiolytics

Physician Attributes	Social Advantage
Warmth	More education
Liking patient	Higher occupational level
Feeling comfortable with patient	Higher socioeconomic class
Positive attitude toward drugs	More marital stability
Believing patient has good prognosis	Treatment Orientation
Patient Personality Characteristics	Realizes problems are emotional rather than somatic
More verbal intelligence	Expects drug treatment
More canpliance	
More realistic treatment goals	Prior Treatment Characteristics
High ego strength	
Low verbal hostility	Treated with fewer prior psychiatric drugs
Low acquiescence	Better response to prior psychiatric drugs
Neurotic Psychopathology	
More severe somatization	
Less severe obsession-compulsion	
Less severe interpersonal sensitivity	
More severe anxiety	
Less severe depression	

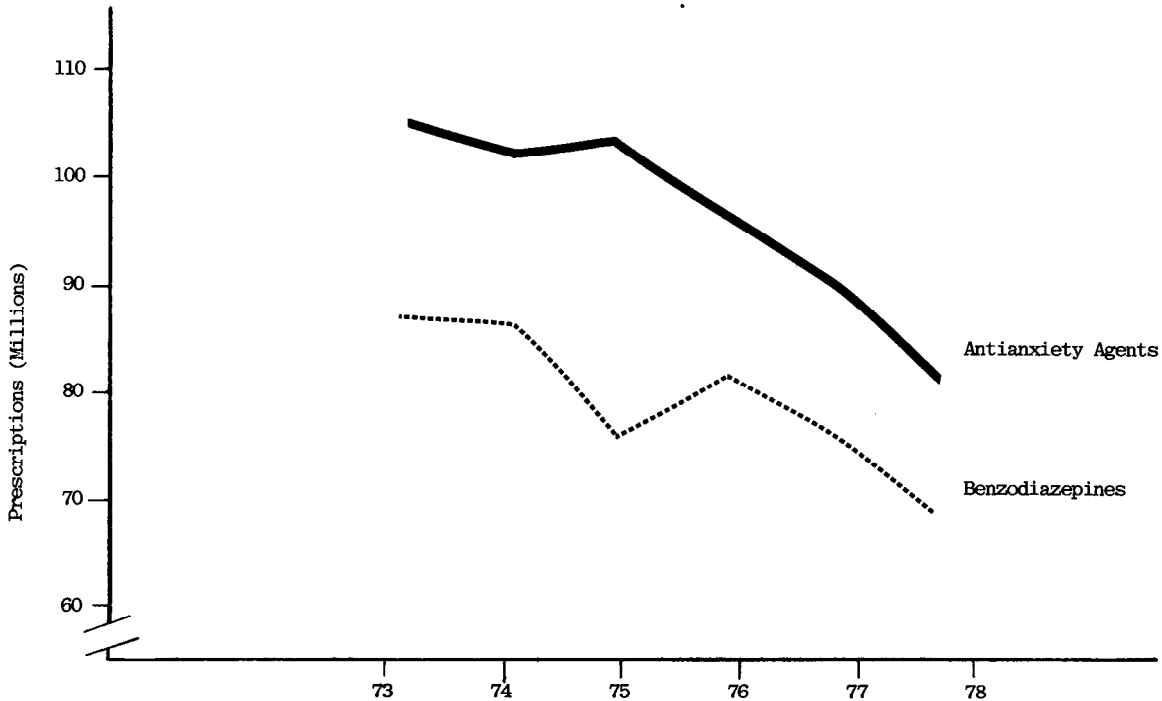
from: Rickels, K. Use of antianxiety agents in anxious outpatients. Psychopharmacology, 58:1-17. ©1978, Springer-Verlag.

BENZODIAZEPINE USE PATTERNS

The benzodiazepines are some of the most widely used drugs in medicine. Data based on prescription audits (Balter 1975; Blackwell 1975; National Prescription Audit 1979; DHEW 1980) indicate that psychotropic drug use peaked in 1973 and has declined slightly during the past few years, probably as a result of the negative publicity the benzodiazepines received (figure 1). Data based on a variety of surveys in the United States and Europe provide convincing evidence that psychotropic drugs, including the benzodiazepines, are used rather conservatively (Parry et al. 1973; Balter 1973; Mellinger et al. 1978; Uhlenhuth et al. 1978; Hesbacher et al. 1976; Bergman et al. 1979; Idanpään-Heikkalä 1977). A more detailed description of these and other surveys has been given elsewhere (Rickels, in press).

Figure 1

Antianxiety Drug Prescriptions Filled in U.S. Drug Stores
1973 - 1978



From: Rickels, K. Benzodiazepines: Use and misuse. In: Klein, D. F., and Rabkin, J., eds. Anxiety: New Research and Changing Concepts. pp. 1-26. ©1981, Raven Press, New York.

Survey data certainly support an interpretation of conservative use of psychotropic drugs including the anxiolytics. Many more individuals suffer from significant degrees of psychic distress than take psychotherapeutic drugs.

We may therefore conclude that (1) psychotropic drugs are conservatively used and possibly even underused at times; (2) patient attitudes express doubts concerning the morality of drug use and are associated with traditional stoic values; (3) little support is provided for a "self-indulgent consumer" interpretation of drug use (Balter 1973); and (4) the majority of physicians are conservative and rather astute in their psychotropic drug-prescribing habits.

It should be stated that it is also true that a minority of physicians do over- and underprescribe psychotherapeutic drugs, and that some physicians may prescribe drugs irrationally, for unobtainable goals (Rickels 1978). It is also true that patients, particularly alcoholics and addiction-prone individuals, may at times overuse benzodiazepines (Hollister 1977a; Kielholz 1973).

No clear-cut scientific evidence exists either supporting or refuting the use of benzodiazepines in patients suffering from medical disorders such as cardiovascular or gastrointestinal illnesses without concomitant anxiety, i.e., for prophylactic use in these illnesses, and therefore such use cannot at present be regarded as either appropriate or inappropriate.

TOXICITY AND DRUG ABUSE

The benzodiazepines are remarkably safe substances. Their major side effect is sedation; if initially present, it tends either to disappear or, at least, to subside in intensity with time and/or as a result of dosage adjustment. An interesting phenomenon of the anxiolytics is that tolerance develops swiftly for their sedative but not for their antianxiety effects. Because of the possible occurrence of early sedative (frequently dose-related) side effects, physicians should start patients on a low dosage and increase the dosage fairly quickly. We need to warn patients to exercise caution when driving or using heavy machinery should they feel drowsy.

As with any type of sedative drug, the addition of other sedating substances such as antihistamines, many of which are available over the counter, and particularly alcohol, may lead to increased sedation. While the combination of alcohol in small quantities, i.e., one or two drinks, with a normal dose of a benzodiazepine (e.g., 20 to 30 mg/d of diazepam) does not produce much of a problem, the overuse of either or both may produce serious consequences.

In view of the wide use of the benzodiazepines, particularly diazepam, it is not surprising that they are frequently overused, either accidentally or intentionally. Many such cases are seen in hospital emergency rooms (Hollister 1977a; Peterson and Chambers 1975). But serious intoxication and death caused solely by benzodiazepine overdose are most unusual. Personally, I am not aware of any death that

has been clearly demonstrated to be caused solely by benzodiazepine intake. Multiple drugs are involved in most instances in which death occurs from benzodiazepine overdose. A similar opinion has been expressed by many experts in the field (Greenblatt and Shader 1974). Benzodiazepine overuse is nearly always complicated by alcohol abuse and/or other drug intake.

One of the most extensive reviews of the use, overuse, and misuse of the benzodiazepines in the United Kingdom has been reported recently by Marks (1978). He estimated that in 1976, of the total British population, 75 percent or more used alcohol, 50 percent used tobacco, but only 12 percent used psychotropics, excluding the barbiturates. Thus, such abuse substances as alcohol and tobacco that have had rather serious medical consequences were used much more frequently than were the psychotropic drugs. This finding closely agrees with that of the national survey in the United States reported by Parry and his colleagues (1973).

Marks also reviewed death rates per 100,000 adults; he estimated that alcohol led to 27 deaths, tobacco to 250, and psychotropic drugs, excluding barbiturates, to only 3. Such data reflect a remarkably safe record for the psychotropic drugs, and particularly for the benzodiazepines, inasmuch as Marks' statistics included not only anxiolytics but also antidepressants and neuroleptics. Marks concluded that it was impossible to kill oneself with benzodiazepines alone, but that a combination of benzodiazepines with other sedatives, particularly alcohol, may well be deadly. A more extensive discussion of toxicity and abuse of benzodiazepines can be found elsewhere (Rickels, in press).

Thus, we can conclude that the benzodiazepines are extremely safe drugs and that intentional or accidental overuse of benzodiazepines alone will rarely have severe consequences, a finding which contrasts markedly with the findings for other centrally acting agents. In hospital emergency rooms, the frequent mention of benzodiazepines as drugs ingested either accidentally or used in suicide attempts is not only an indication of their general availability but, in the opinion of many, a blessing. If benzodiazepines were not available, the individuals overusing them would be taking barbiturates or other central nervous system drugs, drugs that have much more serious consequences when overused. The combination of benzodiazepines with other sedatives, including antihistamines and/or alcohol, should be avoided because such combinations, particularly when abused, may lead to serious medical consequences including death.

PHYSIOLOGICAL DEPENDENCE

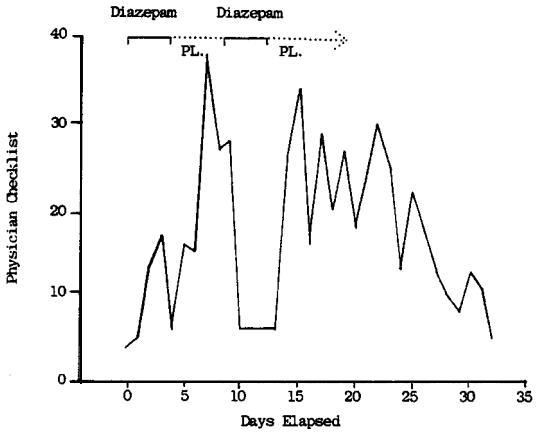
Considering their widespread use, physiological dependence upon the benzodiazepines, frequently hard to differentiate from a return of anxiety symptomatology after withdrawal, has been reported remarkably rarely. Most reports are anecdotal and often involve patients taking medication in much higher than the recommnended dosages and for long periods of time.

One of the earliest studies assessing the addictive potential of benzodiazepines was conducted by Hollister et al. (1961). This study demonstrated clearly that some patients, who received chlordiazepoxide (100 to 600 mg/d) for several months and were then abruptly withdrawn from the medication, suffered clear-cut withdrawal symptoms, which included convulsions in three instances. About 10 years later, Covi et al. (1973) compared sudden discontinuation effects in two groups of anxious patients; one group was treated with an anxiolytic for 10 weeks and the other group was treated for 20 weeks. The authors observed more evidence of distress after withdrawal in those patients treated for 20 weeks than in those treated for 10 weeks. No seizures or muscular fasciculations were observed.

A number of individual case reports have appeared in the literature describing withdrawal reactions occurring after the abrupt withdrawal of benzodiazepines, particularly diazepam, the most widely prescribed anxiolytic (Winokur et al. 1980). All these case reports were uncontrolled and are frequently anecdotal. Hollister (1977b) noted in his reply to Preskorn and Denner's (1977) report of three psychotic episodes occurring after withdrawal from diazepam, that for each of these three cases there existed another equally plausible explanation.

Winokur and his associates reported what is probably the first well-controlled, double-blind case study of withdrawal reactions in a patient who had been on therapeutic dosages (15 to 20 mg/d) of diazepam for 6 years. (See figure 2.) Withdrawal reaction occurred 1 to 2 days after switching from diazepam to a placebo. The symptoms were completely reversed by reinstitution of diazepam treatment and then slowly decreased over time during placebo treatment in the supportive environment of a clinical research center. Although neither psychotic episodes nor convulsions occurred, the patient was disturbed by the withdrawal symptoms. They included extreme anxiety and irritability, tremulousness, perspiration, nausea, constipation,

Figure 2. Diazepam Withdrawal



From: Winokur et al. Withdrawal reaction from long-term, low-dosage administration of diazepam. Arch. General Psychiatry, 37:101-105. ©1980, American Medical Association.

difficulty in urination, headaches, insomnia, and intermittent hypersensitivy to auditory and olfactory stimuli.

Very few other systematic data regarding the possible incidence of withdrawal reactions with benzodiazepine treatment or the possible facilitating events that may provoke these reactions are presently available. Yet, most clinicians agree that the higher the patient's daily dosage and the longer the patient has been continuously on medication, the greater the possibility for the development of at least a mild withdrawal reaction. But even after many years of benzodiazepine therapy, patients treated with therapeutic doses do not seem to develop seizures upon cessation of treatment.

NIMH/UNIVERSITY OF PENNSYLVANIA DIAZEPAM MAINTENANCE STUDY

Because of the lack of data regarding the value of long-term treatment with benzodiazepines and about the possible incidence of both return of symptoms and withdrawal reactions that may occur after abrupt discontinuation of medication, a large-scale NIMH-supported study was initiated several years ago by our group at the University of Pennsylvania (USPHS Grant MH-08957-16). The study involves chronically anxious patients who are being treated with daily dosages of 20 to 40 mg diazepam for up to 6 months.

Preliminary Results

Preliminary results indicate that:

- Patients who dropped out while on diazepam did so primarily because of improvement; no tolerance to diazepam's anxiolytic effect.

- Patients experienced maximal improvement during the initial 4 to 6 weeks of treatment; no additional improvement occurred over the entire maintenance phase (figure 3). Thus, the study showed that maintenance of chronic anxious patients was necessary to continue the level of improvement.

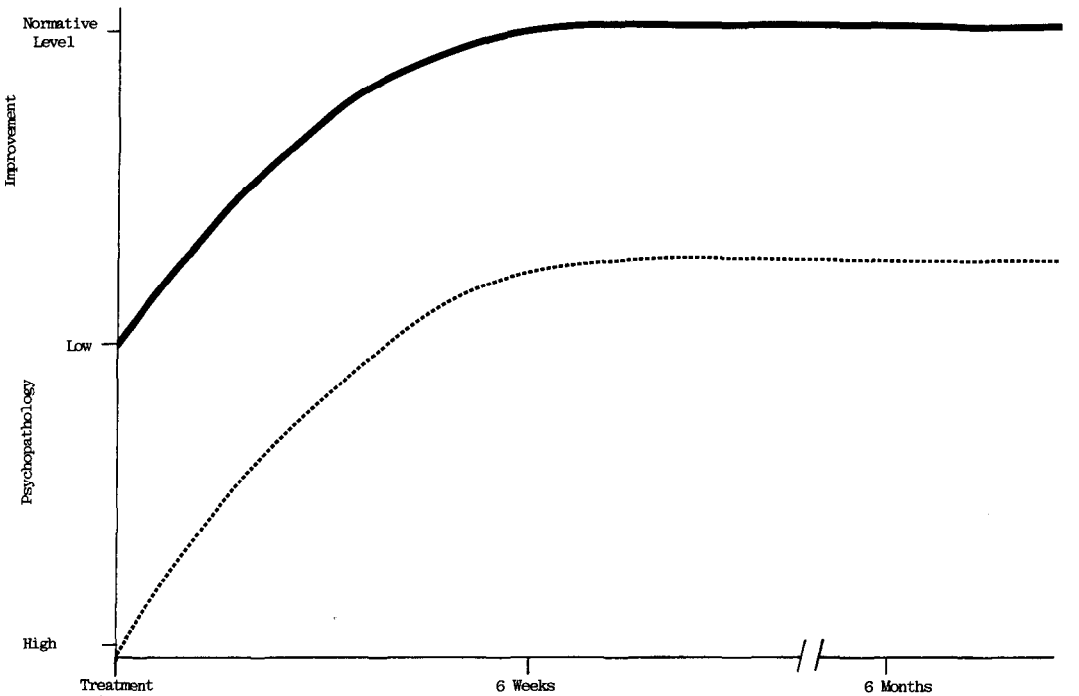
- A most important finding for clinicians was that early response (during the first week of treatment) was a very strong predictor of B-week improvement (figure 4). Patients who improved during the first week of treatment continued to show excellent improvement subsequently, whereas those showing no improvement during the first week had a very poor chance of improving later.

- About 40 percent of all patients showed a clear-cut pattern of return of symptoms when switched to a placebo; the symptoms usually returned slowly over a 2- to 4-week period. But 60 percent of all patients stayed well when changed to a placebo, thus indicating no need for long-term diazepam treatment.

- Of 100 patients who were switched abruptly from diazepam treatment to placebo, only 11 reported some type of withdrawal reaction. Of these 11, 6 experienced transient reactions that lasted only a few days at the most. On followup, patients made such statements as: "For a few days I felt like I did when I stopped

Figure 3

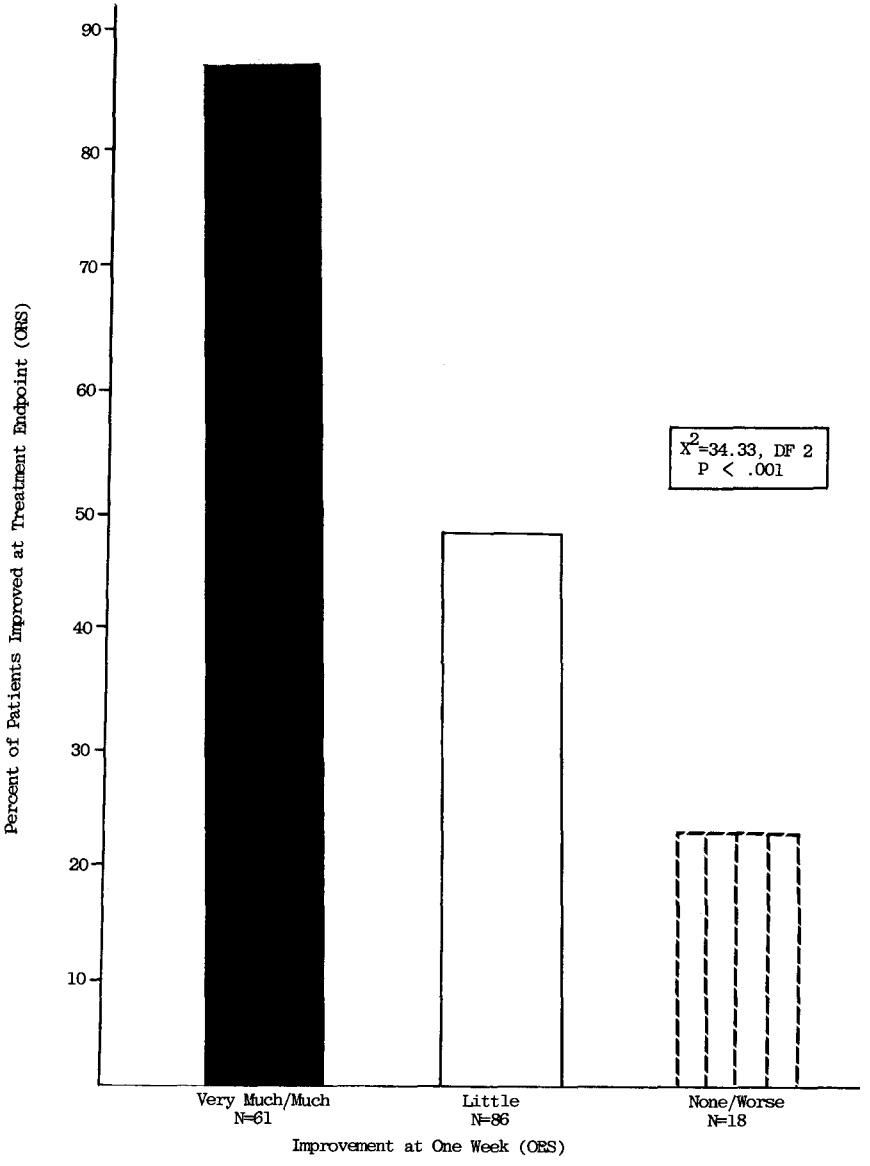
Improvement as a Function of Initial Psychopathology and Duration of Treatment



From: Rickels, K. Benzodiazepines: Use and misuse. In: Klein, D. F., and Rabkin, J., eds. Anxiety: New Research and Changing Concepts. pp. 1-26. ©1981, Raven Press, New York.

Figure 4

Percent of Patients Very Much or Much Improved
at Treatment Endpoint
as a Function of One Week Improvement



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smoking." "For a few days I slept restlessly and dreamt a lot." "For a few days I felt a little tense." None of these patients had any increased symptmatology or any signs of withdrawal reactions when seen by their physician after 1 or 2 weeks on placebo and none of them needed further treatment.

Five patients suffered from clear-cut withdrawal reactions that included gastrointestinal symptoms, lethargy, tremulousness, weakness, insomnia, and anxiety. These reactions began within 2 days, peaked at about 5 to 7 days, and then abated during the next 7 to 10 days without any further treatment. Figure 5 gives a schematic presentation of the difference in time between a return of symptom and the occurrence of physiological withdrawal reactions. Two of the five patients with clear-cut withdrawal reactions had been on chlorazepate for 8 months and on oxazepam for 5 years, respectively, prior to participating in the study. Three patients reported no prior psychotropic drug use but admitted to king fairly heavy social drinkers. Since there is cross-tolerance between alcohol and diazepam, these three withdrawal reactions occurring after 4 months of diazepam treatment in patients with no prior psychotropic drug use may be related to their alcohol intake. No patient experienced seizures, psychotic reactions, or muscle fasciculations.

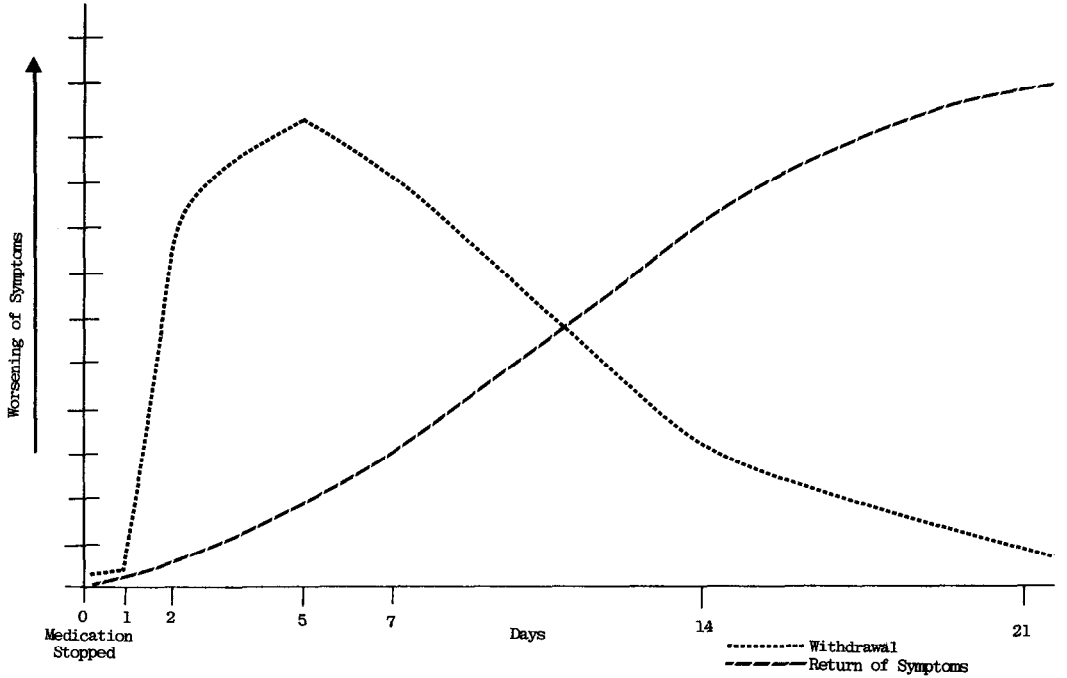
This study thus lends support to the clinical impression that abrupt withdrawal of anxiolytic medication should not be instituted in patients who have been regularly treated for 4 months or longer without discussing with the patient the possibility of a withdrawal reaction or a temporary return of symptoms and the several ways of dealing with such phenomena. It should be emphasized that withdrawal symptoms after abrupt termination of medication have also been reported with other psychotropic drugs including the tricyclic antidepressants (Kramer et al. 1961). More recently, withdrawal reactions have been reported for such nonpsychotropic medications as beta-adrenergic blockers and other antihypertensive agents (Garbus et al. 1979).

The recent findings (Tallman et al. 1980) that specific benzodiazepine receptors exist in certain parts of the brain may help to explain why some patients who have been treated for long periods of time with benzodiazepines and then have medication abruptly discontinued may have temporary withdrawal reactions. The implication of the receptor theory is that human beings must have a built-in calming and anticonvulsive chemical substance, i.e., an endogenous ligand, which has not yet been discovered. We can speculate that such endogenously produced ligands are suppressed during benzodiazepine treatment. Consequently, abrupt discontinuation of long-term treatment may not allow for an immediate availability of enough endogenous ligands to replace the benzodiazepines at the receptor sites.

The pharmacokinetic properties of most benzodiazepines (i.e., a long half-life, active metabolites, accumulation in the blood and tissues, and anticonvulsant properties) may help to explain why benzodiazepines are only rarely associated with serious withdrawal phenomena and have

Figure 5

Schematic Time Course Graph:
Return of Symptoms vs Withdrawal Reactions
After Abrupt Diazepam Withdrawal



From: Rickels, K. Benzodiazepines: Use and misuse. In: Klein, D. F., and Rabkin, J., eds. Anxiety: New Research and Changing Concepts. pp. 1-26. ©1981, Raven Press, New York.

a low dependency-producing potential. Additional reasons for the rare observation of clear-cut physiological withdrawal reactions may be the short-term use of these drugs by most patients; their frequent use on an as-needed basis (Rickels 1978; Winestead et al. 1974); and the almost universal practice, recommended by physicians and practiced by patients, of discontinuing benzodiazepine use gradually.

AREAS OF FURTHER EXPLORATION

- The addiction potential of different benzodiazepines, assessed by incidence, type, and intensity of acute withdrawal reactions produced by abrupt cessation of medication, should be studied as a function of drug dosage and treatment duration. Patient characteristics including personality attributes, prior drug use, history of alcoholism, and predisposition toward or history of substance dependence also should be studied in this context.

- Attempts should be made to identify appropriate and inappropriate indications for long-term benzodiazepine treatment.

- The phenomena of drug withdrawal and the most appropriate means of coping with such phenomena also need further investigation. Gradual medication withdrawal will most likely be the least painful for the patient; but it is probably also true that abrupt withdrawal is not dangerous, even if possibly rather uncomfortable for most patients.

- Sociological studies are needed to investigate long-term benzodiazepine uses in order to provide information regarding how these drugs are being actively utilized (Tessler et al. 1978). Other studies may want to identify patients in family practice who are emotionally distressed, and then record their drug-taking behavior. Such surveys would enable the investigator to determine which types of anxious patients are treated with benzodiazepines and which are not; which patients are treated for short and which for long periods of time; and which factors other than level of anxiety may determine drug-prescribing behavior as well as actual drug taking.

- Further studies should address the effects of benzodiazepines on memory, cognition, and performance, to mention only a few of the many psychological parameters to be studied. Patients suffering from varying degrees of anxiety and treated for varying lengths of time with drug or placebo should be included. Nonanxious individuals may serve as controls.

- The role of benzodiazepines in physical illness should be assessed in greater detail.

- Use of benzodiazepines in the elderly is of particular importance, and pharmacokinetics should play an important role in these investigations.

- Patients who have been on therapeutic dosages of benzodiazepines for various periods of time (e.g., 3 months, 6 months, 1 year, 3 years) could be obtained from family practice networks such as our own. Attempts to withdraw medication should be made under controlled conditions. Subgroups of patients, treated for varying lengths of time, should be withdrawn at different rates: one subgroup withdrawn slowly with gradually reduced dosages, e.g., one-fourth dosage reduction every 2 weeks; another subgroup withdrawn abruptly, receiving placebo in the same dosages as the patients on medication. If these latter patients should develop disturbing or severe withdrawal reactions with which they cannot cope, they could be placed again on benzodiazepines and withdrawn gradually. Those patients who cannot be withdrawn on an outpatient basis should be placed in a clinical research center (Winokur et al. 1980) in an academic setting and be withdrawn under closely supervised conditions. An attempt should be made to clearly define withdrawal reactions, which frequently occur early after termination of drug treatment, and further differentiate them from the slow return of symptoms that may well occur in many chronic anxious patients.

- Some of the most important nondrug factors that may influence the occurrence of a withdrawal reaction of patients on a given benzodiazepine should also be investigated. These factors should include prior history of drug taking, both over-the-counter and prescription medications, to assess accurately the prior use, if any, of cross-tolerant substances including alcohol.

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Benzodiazepine Hypnotics: Carryover Effectiveness, Rebound Insomnia, and Performance Effects

Anthony Kales, M.D.

Since insomnia is frequently a long-term or chronic condition, sleeping pills are often prescribed for lengthy intervals. One study has shown that over 40 percent of all prescriptions for sleeping pills extend for periods longer than 3 months (Kales et al. 1975). Yet most clinical trials of hypnotic drugs have evaluated the effects of only 1 to 3 nights of drug administration. In addition, they have not provided comprehensive profiles of degree and duration of effectiveness and with drawal effects.

Sleep laboratory studies, because of their precise and objective measurements, are being used more frequently to evaluate hypnotic drugs. These studies have enabled researchers to establish comprehensive profiles of benzodiazepine drugs and to provide clinicians with detailed information regarding drug efficacy, duration of effectiveness, and effects on sleep architecture. For example, in contrast to traditional clinical studies, in which effectiveness has usually been evaluated for only one to several nights, the designs of certain sleep laboratory studies have enabled investigators to evaluate the continued effectiveness of hypnotic drugs. In addition, the use of consecutive-night designs in the evaluation of baseline, drug administration, and withdrawal conditions has allowed for the detection of such withdrawal effects as carryover effectiveness and rebound insomnia (Guidelines 1977). Finally, the demonstration of pharmacokinetic differences among short-, intermediate-, and long-acting benzodiazepine drugs has provided direction for the investigation of possible effects on daytime performance.

CARRYOVER EFFECTIVENESS

To date, only two benzodiazepine hypnotics (flurazepam and quazepam, the latter an investigational hypnotic) have been shown to provide carryover of effectiveness during the first few nights following drug withdrawal. When the short- and intermediate-ten efficacies of nine different hypnotic drugs were compared in the sleep laboratory, a considerable loss of effectiveness was observed for each of the drugs except flurazepam (Kales et al. 1977). Furthermore, a summary of six separate studies of flurazepam in our laboratory showed that while flurazepam improved sleep on the first night of administration, it did not reach peak effectiveness until the second and third consecutive drug nights (Kales et al. 1976a). In addition, values for total wake time continued to be significantly lower than baseline for the first 2

nights following withdrawal. These findings of a carryover of effectiveness over the first few nights of drug administration and during the first few nights following withdrawal were corroborated by another sleep laboratory study that assessed the long-term (4 weeks) effectiveness of flurazepam (Dement et al. 1978).

Quazepam, in an intermediate-term (2-week) sleep laboratory study, was found to be effective with continued use, to become increasingly effective over the first several nights of use, and to have a carryover of effectiveness after withdrawal (kales et al. 1980). As with flurazepam, peak effectiveness was reached on the second and third drug nights, and sleep was significantly improved over baseline on the first night following withdrawal.

Since flurazepam and quazepam have the same long-acting metabolite (N desalkyl flurazepam) (Kaplan et al. 1973), the carryover effectiveness has been considered to reflect the gradual buildup and elimination of this metabolite. However, other drugs with long-acting metabolites, such as diazepam, have not been shown to demonstrate carryover effectiveness. Thus, carryover effectiveness may be related to high blood levels of active metabolites, but also to the specific hypnotic efficacy of the compound.

Carryover effectiveness can provide a number of clinical advantages as well as disadvantages. An advantage of carryover effectiveness, for example, is the potential for including drug-holiday periods in the course of therapy. In addition, the continuation of improved sleep (compared to baseline) for the first and, possibly, second nights of withdrawal facilitates withdrawal from the drug (Kales et al. l976a). Carryover effectiveness can be disadvantageous, however, because of its potential to cause decrements in daytime performance. The area of benzcdiazepine-induced decrements in performance is discussed later in this paper.

REBOUND INSOMNIA

A number of short- and intermediate-acting benzodiazepine drugs have been shown to cause rebound insomnia--a worsening of sleep difficulty beyond baseline levels-following their withdrawal (Kales et al. 1978, 1979). This phenomenon is unique to benzodiazepines because it occurs after administration of only single doses of drugs taken for short-term periods, and it is not accompanied by a REM rebound. Furthermore, its occurrence may be independent of the degree of effectiveness at the time of withdrawal. The question of whether rebound insomnia occurs at all with long acting benzodiazepines needs to be evaluated in studies that include extended withdrawal periods.

To date, rebound insomnia has been shown to follow the abrupt withdrawal of fosazepam (Allen and Oswald 1976), triazolam (Roth et al. 1976; Vogel et al. 1975, 1976), temazepam (Bixler et al. 1978; Mitler et al. 1975), lorazepam (Globus et al. 1974), lormetazepam (Oswald et al. 1979), nitrazepam (Adam et al. 1976), and flunitrazepam (Bixler et al. 1977). It has not been reported to follow withdrawal of

flurazepam or diazepam. These two groups of benzodiazepine drugs differ primarily in the duration of the half-lives of the parent compounds and their metabolic products (Mitzler et al. 1977). The half-lives of fosazepam (4 hours), triazolam (4.5 hours), temazepam (4 to 10 hours), lormetazepam (9.9 hours), and lorazepam (9 to 22 hours) are short, and the half-lives of nitrazepam and flunitrazepam (about 24 hours) are intermediate, when compared with those of diazepam (20 to 50 hours) and flurazepam (47 to 100 hours) (Allen and Oswald 1976; Mitzler et al. 1977; Breimer 1977; Shader and Greenblatt 1977; Wendt 1976; Humpel et al., in press).

The relationship between the half-lives of these benzodiazepines and the occurrence of rebound insomnia following their withdrawal can be interpreted in light of the presence of specific benzodiazepine receptors in human brain tissue (Mohler and Okada 1977). 'Ibis discovery suggests that substances that normally occupy these receptors may exist in the brain, and that the production of these endogenous substances may be regulated by concentrations of the ligand and feedback mechanism. Production of endogenous, benzodiazepine-receptor ligands would decrease if active, exogenous benzodiazepine drugs or metabolites were introduced. We have proposed that abrupt withdrawal of benzodiazepine drugs with relatively short half-lives could therefore result in rebound insomnia because of a lag in the production and replacement of endogenous, benzodiazepine-receptor ligands (kales et al. 1978, 1979). If Benzodiazepines with long-acting metabolites were withdrawn, however, effects on the benzodiazepine receptors would be less abrupt because the endogenous ligands would be partially restored before the active metabolites of the exogenously administered drugs were completely eliminated.

Although rebound insomnia has not been reported to follow the withdrawal of flurazepam and diazepam after relatively short periods of use, this syndrome could appear after periods of withdrawal longer than those evaluated in these studies (kales et al. 1978, 1979). The lack of rebound insomnia with flurazepam and diazepam suggests that this syndrome may occur less frequently following withdrawal of long-acting benzodiazepines as compared with short-acting and intermediate-acting benzodiazepines when these drugs have been used in low doses for relatively short periods (kales et al. 1978, 1979).

It is likely that an analogue of rebound insomnia occurs when certain short-acting or intermediate-acting benzodiazepine tranquilizers are taken during the day (kales et al. 1979). As these drugs' durations of action are exceeded, anxiety may rise above baseline levels, causing a condition that we call rebound anxiety (kales et al. 1979). This hypothesis is supported by results of one study in which the withdrawal of fosazepam was associated with a significant increase above baseline in ratings of anxiety (Allen and Oswald 1976). The paucity of reports of rebound anxiety following withdrawal of short-term use of benzodiazepines, or of rebound anxiety during benzodiazepine administration, may be explained by the similarity between any withdrawal symptoms and the original clinical complaints. Neither the patient nor physician may attribute the symptoms to drug withdrawal. In fact, the patients

themselves may see these symptoms as justifying their need for continuing the drug therapy.

PERFORMANCE DECREMENTS

The effects of benzodiazepine hypnotics on daytime performance have recently received considerable attention (Institute of Medicine 1979). One study has shown that repeated use of flurazepam in insomniac subjects may have a cumulative effect on motor behavior; reaction time increased with flurazepam administration (Church and Johnson 1979). Similar effects were noted in another investigation (Salkind and Silverstone 1975). Still another group reported performance decrements in noninsomniac volunteers following flurazepam administration (Saario and Linnoila 1976), although they did not find that flurazepam produced similar effects in insanniac patients (Linnoila et al. 1980). Instead, they found that insomniac patients tended to perform at a lower level and with greater individual variability than noninsomniac subjects. Finally, flurazepam was shown to cause an impairment in vigilance that persisted throughout 3 weeks of drug administration (Oswald et al. 1979). In a study of over 2,000 patients, the side effects associated with flurazepam administration were found to be related to dosage and patient age (Greenblatt et al. 1977). Adverse reactions consisted primarily of unwanted residual drowsiness and usually occurred within the first 3 days of administration. In all cases, patients recovered spontaneously or after the dose was reduced or discontinued (Greenblatt et al. 1977). These data strongly suggest that patients taking long-acting benzodiazepines should be clearly cautioned about the potential for impaired daytime performance.

There have been few studies on the effects of short-acting benzodiazepines on daytime performance. One study evaluated the effects of triazolam on daytime mood and performance by assessing subjects at 3.5 hours, 10 hours, and 22.5 hours after drug administration (Roth et al. 1977). The data demonstrated a dose-related decrement in performance at the 3.5 hour time point, but there were no significant performance decrements at subsequent time points (Roth et al. 1977). Lorazepam has also been shown to cause dose-related decreases in motor coordination (Bell et al. 1973), but no studies have reported the duration of these effects. Further studies are needed to characterize the effects of short-acting benzodiazepine hypnotic drugs on daytime performance.

MEMORY IMPAIRMENT

Certain benzodiazepines are known to cause anterograde amnesia (Greenblatt and Shader 1974). This effect has been reported most often with lorazepam, but also has been found with other benzodiazepines such as bromazepam, diazepam, and flunitrazepam. Though anterograde amnesia may be beneficial when these drugs are used as premedicants in surgery, endoscopy, or cardioversion, it may pose serious problems when they are used for their hypnotic effects. From the standpoint of safety, then, it would be preferable that a benzodiazepine not induce amnesia when taken orally as a tranquilizer or hypnotic (Greenblatt and Shader 1974).

The frequency of reports of anterograde amnesia varies among the different benzodiazepines and appears to be related to dose and route of administration (Greenblatt and Shader 1974). For example, while anterograde amnesia often results from intraveneous administration of diazepam, it is much less frequent with intramuscular administration of the drug and appears to be rare with oral administration.

The actual incidence and characteristics of anterograde amnesia produced by oral administration of benzodiazepine drugs have not been well-established. Most current information is limited to anecdotal reports rather than objective, controlled studies. In one controlled study of flunitrazepam, 2 mg, and secobarbital, 100 mg, anterograde amnesia followed oral administration of flunitrazepam (Bixler et al. 1979). Amnesia has also been reported to follow oral administration of 5 mg of lorazepam (Elliot et al. 1975). Similarly, anterograde amnesia has been reported in patients taking triazolam, 0.5 mg (Kales et al. 1976b). It should be kept in mind that amnesia and memory impairment are likely to be under-reported because of the nature of the symptoms.

Since hypnotics are often taken l/2 to 1 hour before bedtime, there also may be a decrement in memory retrieval of information acquired before sleep onset. Further studies are needed to evaluate the various benzodiazepines' potentials for inducing anterograde impairment of memory following oral administration. The persistence of anterograde amnesia with continued use of a given drug also needs to be assessed.

FUTURE RESEARCH DIRECTIONS

A number of the proposed research objectives have already been discussed in the text of the paper. In this section, however, specific aspects of these objectives are raised.

Carryover Effectiveness

Studies are needed to evaluate the relationship of carryover effectiveness and benzodiazepine pharmacokinetics more comprehensively. Is the carryover of effectiveness observed with quazepam and flurazepam a function of their pharmacokinetics? Does this occur with other long-acting benzodiazepines, such as diazepam, chlordiazepoxide, or chlorazepate? Since the blood !evels of N desalkyl flurazepam are sufficient to cause improved sleep induction and maintenance for 2 days following drug withdrawal, why do the side effects and symptoms of daytime drowsiness usually diminish by the end of 3 days of consecutive use?

Rebound Insomnia

Does rebound insomnia occur following withdrawal of all benzodiazepines, regardless of their length of action? Does the occurrence of rebound insomnia have any predictive value for the potential of particular benzodiazepines to produce drug dependency? How long does

rebound insomnia last, and is there a relation between the duration of drug administration and the duration of subsequent withdrawal phenomena? Is rebound insomnia indicative of a general rebound syndrome that would include rebound anxiety? Can gradual drug withdrawal decrease the severity of rebound insomnia? What are the benzodiazepine receptor correlates that might underly the development of rebound insomnia?

Performance and Memory

To what extent do all benzodiazepine hypnotics impair daytime performance? Are the potential performance decrements reported with long-acting benzodiazepine hypnotics greater than those seen in benzodiazepines taken as daytime anxiolytics? How long do performance levels remain decreased? Since performance has been reported to improve following withdrawal of short-acting benzodiazepines, is this indicative of a hyperactive withdrawal state, and what is its clinical significance?

What is the relative incidence of memory impairment caused by long-acting as opposed to short-acting benzodiazepines taken in oral-dose form? Is the incidence of amnesia caused by benzodiazepine hypnotics higher in elderly patients compared with young adults? Does tolerance develop quickly to the effects of drugs on memory? What receptor-mediated events could account for these effects?

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Dependence on Benzodiazepines

Leo E. Hollister, M.D.

The benzodiazepines and related compounds are a rapidly expanding group of drugs. For some years, diazepam has been the most widely prescribed drug in most of the developed countries of the world, with its close relative, chlordiazepoxide, also retaining a high degree of use. Success has brought canpetition, first with oxazepam and clorazepate dipotassium; more recently with lorazepam, prazepam, and others. It is difficult to determine how much these drugs are used as hypnotics, even though they are not specifically promoted as such. Flurazepam is the only benzodiazepine promoted solely as a hypnotic, but it may soon have competition from a chemically close relative, triazolam. One benzodiazepine, clonazepam, is promoted as an anticonvulsant. Many other benzodiazepines are in clinical use in countries other than the United States.

Most benzodiazepines share a common pharmacological spectrum: sedative, hypnotic, muscle relaxant, and anticonvulsant actions. Their major differences are based on their pharmacokinetics. The larger group (chlordiazepoxide, diazepam, clorazepate dipotassiun, and prazepam) is composed of drugs that produce long-lived metabolites, most notably nordiazepam. The smaller group (oxazepam and lorazepam) is composed of drugs that produce no metabolites and thus can be rapidly inactivated. Whether or not differences in plasma disappearance rates are important for determining clinical indications for these drugs, or for their potential for creating dependence, is still uncertain.

CURRENT USE PATTERNS OF BENZODIAZEPINES

Prescriptions for antianxiety drugs in the United States during 1976 were distributed as follows: benzodiazepines accounted for 78 percent, long-acting barbiturates for 12 percent, and meprobamate for 10 percent (National Prescription Audit 1976). The total number of prescriptions for antianxiety drugs had remained virtually constant during the preceding 5 years.

Prescriptions for hypnotics in the United States during 1976 were distributed as follows: flurazepam accounted for 51 percent, short-acting barbiturates for 22 percent, and the remaining 27 percent were accounted for by the so-called "nonbarbiturate" hypnotics (National Prescription Audit 1976). Total prescriptions for hypnotics declined by about 31 percent during the preceding 5 years.

Quite possibly the overall decline may represent some use of anti-anxiety drugs as hypnotics, an interchangeable clinical application.

The best epidemiologic study of the use of antianxiety drugs is now several years old. As the number of prescriptions for these drugs has probably declined during the intervening period, the findings of this study probably still reflect current patterns. In 1971, households chosen by usual sampling techniques in the United States, as well as in nine European countries, were asked about their use of antianxiety drugs (Balter et al. 1974). The two major questions were whether any adult member (over age 18 years) had used such a drug in the preceding 12 months and if so, whether the use had been for as long as 1 month. The highest overall use of antianxiety drugs was in Belgium, where 16.8 percent of adults queried had used such a drug on at least one occasion in the preceding year; only 9.7 percent answered positively to this question in Spain. Other data from the United States indicated a figure of 15 percent. One month or more of chronic use of these agents followed a similar pattern with a maximum of 8.6 percent and a minimum of 3.4 percent of adults using these drugs in this manner. In the United States such use was reported by 6 percent of those surveyed. Those persons who had used them were quite positive in their opinions about the benefits derived; 77 percent claiming substantial benefit."

What emerged from these data was the remarkable fact that medical use of sedative-hypnotics is not out of hand, but seems to have stabilized at a reasonable level. Further, despite vast cultural, political, and economic differences between developed countries, use of these agents is remarkably comparable within a rather narrow rank. This use pattern suggests that a relatively small proportion of the population perceives a need for these drugs and benefits from their use. Further analysis of the data from this survey indicates that physicians prescribe these drugs in a medical model, the rate of prescription increasing proportionally to the degree of "life stress" or "psychic distress" reported by the patients (Mellinger et al. 1978). Actually, the number of persons with high levels of stress was considerably greater than the number who take drugs, indicating that many persons are able to cope with stress without the use of drugs at all.

TOLERANCE TO AND DEPENDENCE ON BENZODIAZEPINES

Tolerance

All sedative drugs, regardless of class, may produce some degree of tolerance and dependence. These phenomena are observed with most drugs only when they are used chronically and usually when doses are large. Drugs differ in the degree to which tolerance develops over time, the degree to which dependence may occur as a function of multiples of the usual therapeutic dose, and the degree to which tolerance develops in various pharmacological actions.

Tolerance implies that increasing amounts of drug are required to maintain equal pharmacological effects. Tolerance is almost a requisite for development of physical dependence. Several types of tolerance are recognized. Metabolic tolerance signifies an increased ability of the body to dispose of the drug during continuing exposure to it. Phenobarbital and meprobmate induce drug-metabolizing enzymes that increase their own metabolic as well as that of many other drugs, so that tolerance quickly develops. The benzodiazepines also stimulate drug-metabolizing enzymes, but less so than the other two types of drugs. Pharmacodynamic tolerance indicates a change in the sensitivity or numbers of receptors or cellular membrane macromolecules, upon which the drug acts. It may also include alterations in intracellular responses such as the rate of synthesis or release of neurohormones. Finally, psychic or behavioral tolerance may develop; persons using these drugs are able to compensate for certain deficits in function while maintaining other desired effects. The concept of "immune" tolerance, due to formation of antibodies to a drug, is controversial and is not pertinent to the drugs under consideration. In the case of benzodiazepines, tolerance seem most rapidly developed to the sedative actions of the drugs and much less likely to other pharmacological actions.

Dependence

Psychic dependence is related somewhat to tolerance and is a requisite for physical dependence, yet it is separate from either. It signifies some reward to users in terms of euphoria, greater confidence, or less depression, so that they are impelled to continue its use without interruption. Not all drugs to which psychic dependence develops are associated with tolerance or physical dependence. Cocaine, for instance, produces strong psychic dependence, but in man shows little evidence of tolerance or physical dependence. Benzodiazepines undoubtedly produce psychic dependence.

Physical dependence refers to a time-related syndrome that develops when a subject who has been overusing a drug suddenly stops taking it or sharply reduces its dose. Physical dependence on sedative-hypnotic drugs resembles that from alcohol, so that withdrawal reactions are called "alcohol-barbiturate" types. They consist of alterations of consciousness (delirium), neuromuscular irritability (tremors and seizures), and vegetative disturbances (vaniting, sweating, tachycardia). The syndrome of deliriun tremens is well known from alcohol but can be mimicked by withdrawal of sedative-hypnotics (Mellinger et al. 1978).

Animal Studies

Several studies have indicated that, under the proper experimental conditions, the benzodiazepines may produce tolerance in animals. The development of tolerance to chlordiazepoxide in the rat was demonstrated using the conditioned avoidance-escape response (Matsuki and Iwamoto 1966). Increased rates of tissue disappearance and excretion of ^{14}C-labeled chlordiazepoxide were also found in rats made tolerant to chlordiazepoxide, suggesting a degree of metabolic

tolerance (Hoogland et al. 1966). The development of tolerance to chlordiazepoxide in rats and mice was also shown by a variety of pharmacologic tests (Goldberg et al. 1967). Acute tolerance to diazepam was shown using the linguomandibular reflex in the cat (Barnett and Fiore 1971). Similar tolerance was observed in the cat using the anterior tibia1 flexor reflex or the EEG; amplitude as the test response. Rats developed tolerance toward the depressant action of oxazepam after three to four doses, while the disinhibitory action on punished behavior did not show tolerance (Margules and Stein 1968). Similar observations were reported following lorazepam administration (Stein and Berger 1971). Short-term treatment of rats with flurazepam reduced the spontaneous activity and unmasked the disinhibitory effect (Cannizzaro et al. 1972).

Psychic dependence may be construed as reflecting the reinforcing properties of the drug, that is, the extent to which subjects maintain self-administration. Studies with rhesus monkeys showed that pentobarbital was more effective than diazepam in maintaining self-administration, while chlorpranazine did not maintain self-administration (Yanagita and Takahashi 1973). Similar relationships have been found in self-administration studies in man, using polydrug abusers as subjects (Griffiths et al., submitted).

Evidence for physical dependence has been less clear. Rats reduced their liquid intake when forced to drink water containing chlordiazepoxide, and later, when given a free choice, the animals returned to pure water with no evidence of either addiction or tolerance (Harris et al. 1968). However, when rats were conditioned to drink an aqueous solution of chlordiazepoxide in order to obtain food pellets, after 25 days of conditioning the animals preferred the chlordiazepoxide solution rather than pure water. When a 0.5 mg/ml aqueous solution of chlordiazepoxide was made freely available to rats, none developed dependence upon the drug (Stolerman et al. 1971).

Monkeys with an indwelling intravenous catheter were forced to choose between the self-infusion of chlordiazepoxide solution or saline. The animals exposed to a 24-hour continuous experimental procedure preferred chlordiazepoxide over saline. However, the animals addicted to chlordiazepoxide preferred intravenous secobarbital when offered a choice of the two drugs (Findley et al. 1972). In another series of experiments, daily intravenous administration of chlordiazepoxide, diazepam, or oxazolam to monkeys produced physical dependence. However, during this experiment, the animals were not heavily depressed and did not exhibit marked withdrawal signs (Yanagita and Takahashi 1973).

The evidence available indicates that both tolerance and physical dependence can be developed with the benzodiazepines in animals under the proper experimental conditions, but it is more difficult to accomplish with the benzodiazepines than with the barbiturates.

Human Studies

Benzodiazepines may have been taken by more persons than any other prescribed drug. This extensive medical use has provided innumerable opportunities for misuse by every conceivable type of stable and unstable person. Consequently, it would be expected that instances of misuse and abuse should be recorded. The question is whether the number of such instances is excessive relative to the degree of use.

Production of physical dependence on benzodiazepines was first done experimentally in 1961, not long after chlordiazepoxide was marketed. Ten of eleven patients treated for several weeks or months with daily doses of 300 to 600 mg, 8 to 20 times the usual therapeutic dose, experienced new symptoms and signs after being abruptly switched to placebos without their knowledge. Depression, agitation, insomnia, loss of appetite, and nausea appeared between 2 and 8 days after withdrawal. Two patients had seizures, one at 7 days after withdrawal, the other after 8 days. A third patient, not in the experimental study, had a seizure 12 days after discontinuation of treatment with a daily dose of 300 mg. The difference between the withdrawal syndrome from chlordiazepoxide as compared with that from short-acting barbiturates, or drugs such as meprobamate, is that it was both milder and more attenuated than the acute explosive withdrawal reaction seen with the short-acting drugs (Hollister et al. 1961).

Another study employed large doses of diazepam for the treatment of schizophrenic patients. Clinical signs of withdrawal reaction were seen in 6 of 13 patients abruptly switched to placebos after daily doses of 120 mg, or about 8 times the usual therapeutic dose. One patient had a major seizure on the eighth day of withdrawal (Hollister et al. 1963). In other cases, the diazepam withdrawal reaction was mild and attenuated.

Clinical Reports of Dependence

Since these early experimental studies in man, a number of clinical reports of spontaneous dependence on benzodiazepines has appeared. As might be expected from their use pattern, the majority of these were concerned with chlordiazepoxide or diazepam. The reports in the literature through most of 1978 have been reviewed (Marks 1978). Slightly more than 402 individual patients have been reported to be dependent on benzodiazepines. The majority of these patients were dependent in the context of concurrent abuse of alcohol and other drugs. Only 56 cases of physical dependence were specifically noted, the vast majority of patients being assumed to have only psychic dependence. Based on the results of this extensive survey of the literature, the author, previously biased towards finding a significant abuse problem, came to the following conclusions:

- Physical dependence upon a benzodiazepine can be produced in man if given in excessive doses over a prolonged period, particularly to patients with unstable personalities.

- The dependence risk factor is low and certainly less than that of the other commonly used sedatives and anxiolytics.

- The risk factor and the dangers to society are of such a low order that no extension of controls is necessary.

- In the interest of good medical care and to minimize the risks of dependence, patients should be thoughtfully selected for benzodiazepine administration, and drug therapy should be discontinued as soon as it is therapeutically practical to do so.

The frequency of dependence was found to be somewhat higher in another study. Over a 2-year period in the Stockholm area, 55 persons, the majority women, were found to be dependent on sedative-hypnotic drugs. Twenty-two were dependent only on benzodiazepines. Most patients were highly nervous, had been under previous psychiatric treatment, and had much accompanying somatic illness. Overuse had gone on for several years prior to their hospital admission, after which 40 percent showed some signs of physical dependence (Allgulander 1978). Swedish women, as judged by the epidemiologic study mentioned earlier, have the highest rate of use of antianxiety drugs, with 21.5 percent of women surveyed using them.

PHARMACOKINETIC CONSIDERATION IN WITHDRAWAL REACTIONS

One is faced with a paradox that despite the unprecedented use of the benzodiazepines over a long period of time, reports in the medical literature are relatively few and the picture of dependence is rather mild. It should be remembered that the withdrawal syndrome from drugs such as chlordiazepoxide and diazepam is quantitatively different than from shorter-acting drugs, such as secobarbital sodium. Withdrawal symptoms and signs often are not evident until the third day following cessation of the drug and at that time they resemble the symptom initially being treated: nervousness, irritability, and insomnia. It is quite likely many patients construe these symptoms as a recrudescence of those for which they originally took the drug. Either by resting taking the drug they had taken before, or taking another sedative, or taking alcohol, they are able to abort the incipient withdrawal reaction. Others may endure the complete withdrawal reaction without realizing what is wrong. The peak symptoms from withdrawal of these long-lived drugs occurs at about the fifth day after cessation of the drug and almost all symptoms and signs disappear by the eighth or ninth day. Thus, the milder and attenuated withdrawal syndrome from these drugs may be missed, something unlikely to occur with the abrupt and severe withdrawal reaction from short-acting drugs such as meprobarmate or secobarbital sodiun.

The general rule, then, is that drugs with a plasma disappearance rate of between 6 and 24 hours are most likely to show severe withdrawal reactions, while those with effective disappearance rates (of parent drug as well as active metabolites) of 36 hours or more are likely to have a mild but longer withdrawal syndrome. Drugs with a very slow disappearance rate, such as phenobarbital, may protect against the development of a withdrawal syndrome, which is dependent

upon the rate of decline of plasma and tissue concentrations of drug. Few sedative-hypnotics to reach the market have plasma disappearance rates below 6 hours. Tybamate is such a drug, with a plasma half-life of 3 hours or less. It is impossible to give this drug in an ordinary divided dose schedule in such a way as to maintain continually high levels of the drug (Shelton and Hollister 1967). Accordingly, physical dependence on this drug is virtually unknown. These relationships between plasma half-life and the intensity of the withdrawal syndrome from various drugs are shown schematically in figure 1.

Dependence on Therapeutic Doses of Benzodiazepines

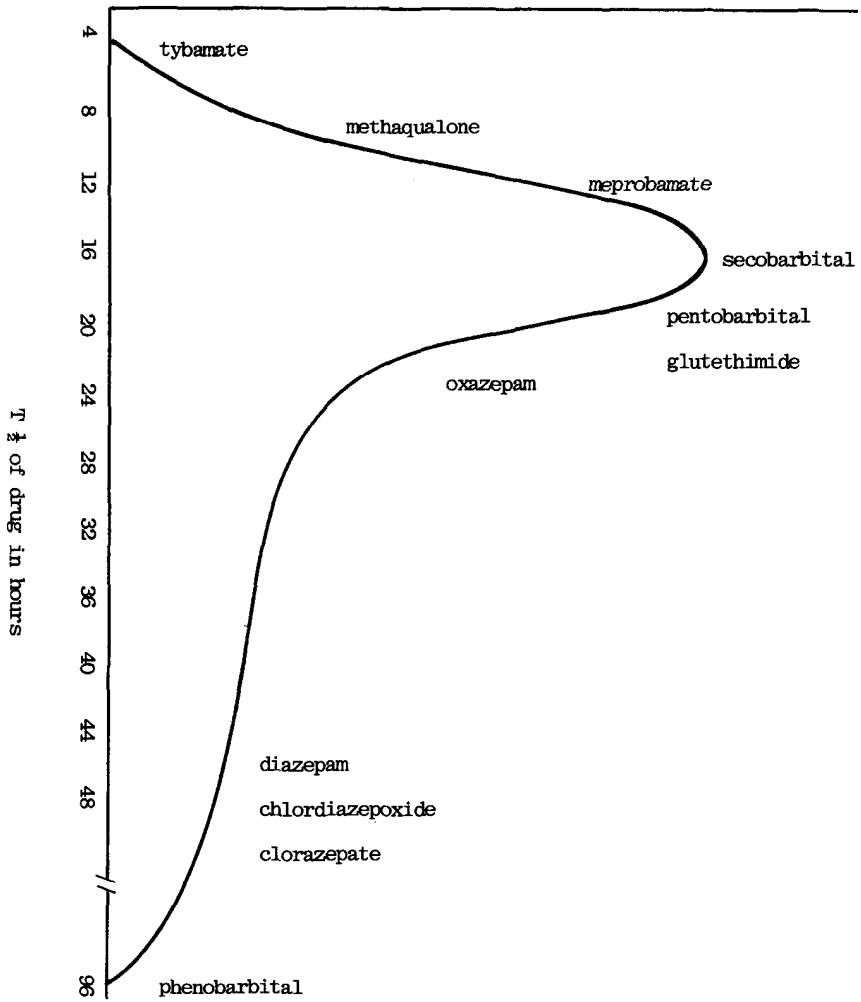
Normally one associates withdrawal reactions to sedatives or other drugs with excessive doses over substantial time periods. It may very well be that the interaction is between dose and time so that as the latter becomes longer the dose becomes less. Discontinuation of chlordiazepoxide 45 mg/day in patients who had been treated with this dose for several months produced minor withdrawal symptoms that seemed clearly to be distinguishable from mere return of anxiety. Subsequently, a number of other cases of withdrawal from therapeutic doses of diazepam have been reported, most of which are included in the review of such reports mentioned above (Marks 1978). A patient who had been treated with 30 to 45 mg/day of diazepam for 20 months, which was suddenly stopped, showed a clearcut withdrawal reaction. Precipitous weight loss and orthostatic tachycardia accompanied the typical dysphoria of withdrawal, which occurred between the fifth and ninth days after discontinuation of the drug (Pevnick et al. 1978). In other cases, the withdrawal reaction under these circumstances has been markedly protracted, though mild. An even more extreme example of a protracted withdrawal reaction followed withdrawal of phenobarbital after 30 years of chronic use. Almost 7 months of treatment were required to stabilize the patient (Epstein 1980).

The concept of dependence from sedative drugs given at therapeutic doses is still relatively new. The mechanism of action is not clear. One might speculate that in the case of drugs that act on receptors, such as the benzodiazepines, prolonged use may cause subsensitivity of receptors. When the drug is withdrawn, the response to any endogenous ligand might be reduced. Further, the possibility exists that patients who require these drugs on a continuing basis could be deficient in such endogenous ligands. Thus, such patients might not be protected against sudden withdrawal of the drug as well as others. Of course, all of this speculation has no substantial evidence as yet to support it.

PRESENT CLINICAL IMPLICATIONS OF BENZODIAZEPINE DEPENDENCE

Whatever the extent of dependence on these drugs, and whatever the relationship to dose and time of treatment, there seem to be little doubt that benzodiazepine dependence should be avoidable in the majority of instances. Some relatively simple rules about the use

Figure 1
Intensity of withdrawal reaction



Postulated relationship between severity of withdrawal reaction and plasma disappearance rate of sedative drug.

of these drugs would help to avoid many of the potential problem. Among these are the following:

- One must use these drugs only when symptoms of anxiety create either considerable discomfort or disability. If the patient can cope without drugs or with nondrug treatments, that is fine. While benzodiazepines are of proven value in actual muscle spasm, they need not be used for all acute strains with spasm. Heat and aspirin may be as effective, if not actually better.

- One must constantly assess whether the drug is efficacious. A beneficial effect will usually be evident within a week or so, if it is going to be obtained at all. Failure of an anxious patient to respond should alert one to other diagnostic possibilities. One cannot justify the continued use of any drug if no benefit is obtained.

- One should contract with the patient in advance for brief periods of treatment. Disabling anxiety is often episodic, which is why clinical experiments to prove these drugs against placebo axe sometimes disappointing. One should tailor treatment to the course of the illness, which generally allows for brief episodes of treatment.

- One should expect that drugs of this type will be abused by persons with a prior history of drug or alcohol abuse. The majority of instances of abuse of these drugs are in precisely such patients. Other classes of antianxiety agents, such as sedative antihistamines, may be more suitable for drug-abusing patients, as these drugs are noxious when large doses are taken.

- When these drugs have been used for long periods of time, even though doses may have been in the usual therapeutic range, discontinuation of drug should be gradual.

SUMMARY

Dependence is probably less frequent with current use of benzodiazepines than was the case when barbiturates were the primary sedative-hypnotic drugs. Dependence still occurs, both in the context of other types of drug abuse as well as solely in medical treatment. The withdrawal syndrome produced by most of these drugs is mild and attenuated, seldom leading to any serious consequences. The preponderance of reports of physical dependence on benzodiazepines involve diazepam or chlordiazepoxide, a proportion that reflects their rate of use. The short-acting derivatives, lorazepam and oxazepam, also produce a similar withdrawal reaction. It is unlikely that any other members of the class would be less likely to produce dependence. Benzodiazepine dependence is a largely avoidable problem.

FUTURE RESEARCH DIRECTIONS

All the questions that need to be asked will not be proposed, nor will those proposed be highly original. If they have merit, it is that they may be answered without too much difficulty or expense.

1. A simple animal model of physical dependence is badly needed. Although the dog, and to a lesser extent, the cat, have been useful, these animals require a great deal of maintenance and have long lives. A model in some small animal would be most helpful. Already some investigators believe that they can show a replicable syndrome of physical withdrawal in rats. Such a model might be highly useful for answering two pertinent questions:

   a. What factors determine "low-dose" dependence? What is the minimum period required for exposure to such doses to produce physical dependence? Does the degree of dependence increase in a linear fashion with increased time of exposure? What proportion of animals develops such a syndrome? In answering these questions, it is essential that animals be exposed to the drug on a continuing basis that is not labor intensive. Gavage feeding is not especially useful and has risks when used over the long periods required. Addition of drug in small amounts to feed might be the most expeditious way to provide sustained drug exposure. NIDA might wish to contract with feed producers to see if various benzodiazepines can be incorporated into feed so that it is still acceptable to the animals and so the dose per day is appropriate. To assure that doses used in animals are appropriate to the nature of the problem in man, plasma concentrations of drug should be monitored to assure that they are comparable to those expected from similar low-dose exposure in man. Ratings of the withdrawal syndrome should be done blindly.

   b. Do the kinetics of the various drugs influence the development of physical dependence? Clinical evidence suggests that withdrawal reactions following over-use of these drugs may be more rapid in onset and more severe following short-acting drugs than after long-acting drugs, where reactions are slower in onset, milder in degree, but longer in duration. Such relationships could be most expeditiously studied in an animal model. The range of 1,4- or 1,5-benzodiazepine plasma half-lives is such that one could explore withdrawal reactions from drugs with half-lives as short as 2 to 3 hours to those with half-lives greater than 100 hours. It is possible that ultra-short or ultra-long acting drugs might be less likely to produce signs of physical dependence.

2. Does the fact that benzodiazepines react with specific "receptors" in the brain make them different from other types of sedatives in their predilection for producing physical dependence? Studies in animals should determine the changes in the number, the affinity, and the responses of benzodiazepine receptors following various types of exposure to benzodiazepines. Is sub-sensitivity during treatment a factor?

3. What is the reinforcing value of low doses of drugs? Most prior studies have used relatively high doses and compared one class, such as sedatives, against another, such as phenothiazines. To show that the latter drugs are aversive is like shooting fish in a barrel. What we need to know is whether reinforcement differs between various types of sedatives or within certain classes, and whether this phenomenon can be demonstrated at so-called "therapeutic doses." Is it possible that different absorption kinetics of benzodiazepines alter reinforcement?

4. How often does low-dose physical dependence occur clinically and what characteristics of patients might predict such reactions? Rather, should one organize systematic studies that would, under blind conditions, abruptly withdraw patients from benzodiazepines and observe the effects produced? Apparently enough patients are interested in caning off benzodiazepines to make such studies possible and ethical. The problem is that those who feel the need to discontinue the drug may not be a representative sample. But there are ways to manage that.

5. How many patients abuse benzodiazepines? Although patients vary considerably in the plasma concentrations of drug that they achieve following any given daily dose, we now have enough experience to be able to set a reasonable limit on what one might expect from a given dose. Periodic monitoring of plasma concentrations of drug during treatment would provide possibly the most objective way to determine which patients may be abusing the drugs by taking more than prescribed. Permission to draw blood samples (perhaps without the reason being given) should be made a condition of treatment to assure that not only the good patients will comply with the study. This use of plasma concentrations might be their most practical application.

6. Can physicians be educated to use benzodiazepines better without being so frightened of their use that patients will be deprived of the well-established benefits? Several approaches to education of physicians should be set up and compared, using some predetermined operational criteria for success.

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Benzodiazepines: Executive Summary and Discussion

NOTE: Dr. Leo Hollister's paper was not presented orally, but copies were distributed to the participants at the meeting. Drs. Richard Shader and David Greenblatt, who spoke on the metabolism and pharmacokinetics of benzodiazepines but did not submit a paper for this monograph, participated in the discussions. Their comments are incorporated in the appropriate summaries of discussions and new research directions.

Benzodiazepines: Executive Summary and Discussion

Edward B. Truitt, Jr., Ph.D.

EXECUTIVE SUMMARY

Benzodiazepines: Biochemistry to Function
. . . John F. Tallman

Dr. Tallman began with the important question of whether the binding of benzodiazepines to receptors in the brain to produce such diverse effects as anticonvulsant, muscle relaxant, anxiolytic, and sedative-hypnotic actions represents a continuum of actions at different levels or an action on discrete areas or receptors in the brain. Neurophysiologists have shown benzodiazepines to produce enhancement of the action of the inhibitory neurotransnitter GABA on cerebral neurons, an effect blocked by the stimulant picrotoxin. Not all GABA receptors interact with diazepam and not all actions of diazepam are necessarily mediated through GABA receptors. Much evidence points to the presence of multiple receptors for diazepam in the brain with different characteristics as well as differences from the peripheral receptors for diazepam, which may be associated with diazepam side effects. There are many important areas of research into chronically produced changes in the number and sensitivity of benzodiazepine receptors. Complete (100%) occupancy may not be necessary to produce antiseizure effects, and prolonged protection may occur without full occupancy.

Tallman speculated on the nature of endogenous ligands that might occupy the benzodiazepine receptors normally, including such candidates as the purine compounds hypoxanthine and inosine, a beta-carboline derivative of tryptophane identified by Braestrup, nicotinamide, and an endogenous peptide.

DISCUSSION

Discussion of Dr. Tallman's presentation centered on the possibility that diphenylhydantoin enhancement of benzodiazepine receptor sensitivity may relate to occupancy by endogenous ligands of the purine type, particularly an action of methylxanthines such as caffeine or theophylline. Other drugs that are known to interact with GABA include alcohol and barbiturates. The latter may act on benzodiazepine receptors that are blocked by picrotoxin, but there are wnvulsant barbiturates that confound this idea. The most important aspect of benzodiazepine receptors may be the small but important changes produced by chronic diazepam administration.

EXECUTIVE SUMMARY

The Benzodiazepine Receptor: Anatomical Aspects
. . . Michael J. Kuhar

A site in brain tissue that has the properties of a relevant and pharmacologically active benzodiazepine receptor has been identified by binding techniques. Thus it is possible to study molecular and anatomical mechanisms of benzodiazepine drugs more extensively than before. This report focuses on the anatanical localization of benzodiazepine receptors and their significance.

Biochemical studies have shown that the benzodiazepine receptors are unevenly distributed in brain regions. Phylogenetic studies suggest that the benzodiazepine receptors appear relatively late in evolution. Overall, these results strongly suggest that the receptor is not some simple, universal constituent of neuronal membranes, but rather a unique entity specially involved in certain brain regions (and therefore certain physiological functions) and possibly associated with a unique, endogenously occurring "active" compound such as a neurohormone. Hence, anatanical studies of the benzodiazepine receptor are necessary for a full understanding of the action of benzodiazepine drugs. The usefulness of anatomical studies of receptors for providing insights to mechanism of drug actions has been demonstrated in the cases of, for example, the opiate receptor and the alpha-adrenergic receptor.

DISCUSSION

Discussion of Dr. Kuhar's presentation focused on localization, as did his talk. Central receptors are of more interest than the peripheral ones. Fluorescent antibody reactions would localize receptors better than autoradiographic techniques with the light microscope. Spinal cord receptors have been identified but the muscle relaxant action is probably supraspinal. Dr. Kuhar was asked about localization in areas of the cortex other than the occiput. Patterns are similar in the supraspinal and sensory cortex areas in the rat, but human studies have not been done. Dr. Kuhar concluded the discussion by emphasizing the differences in mechanism of action between benzodiazepines and the sedative hypnotic drugs such as barbiturates and alcohol. Whereas sedatives and hypnotics act directly on both inhibitory and excitatory neurons, the benzodiazepine drugs act indirectly through potentiating the actions of an endogenous inhibitory substance, GABA.

EXECUTIVE SUMMARY

Benzodiazepine Self-Administration in Animals and Humans:
A Comprehensive Literature Review
. . . Roland R. Griffiths and Nancy A. Ator

One approach to studying drug abuse has been the development of experimental paradigms for controlled investigations of drug self-administration in laboratory animals and humans. Such experimental models can provide various types of information relevant to drug abuse, including comparative information about the relative efficacy with which different drugs maintain drug self-administration. The validity of this approach is supported by the good correspondence between those drugs that are self-administered by laboratory animals and those self-administered and abused by man. This paper reviews the current status of the scientific literature on benzodiazepine self-administration. The first two sections review the animal and human data, respectively. The final section summarizes major findings and outlines directions for future research on benzodiazepine self-administration.

DISCUSSION

In a brief discussion of his paper, Dr. Griffiths pointed out the need to discuss the consequences, such as memory effects, of self-administered doses of benzodiazepines. Considerable variation in sensitivity to diazepam and pentobarbital exists among drug abusers and sedative-hypnotic users regarding the occurrence of ataxia and euphoria. The setting in which the drugs are tested is important. Shorter acting benzodiazepines such as midazolan are more readily self-administered in baboons, although this property may depend upon rapid absorption as well as fast metabolism. Some animals will show self-administration only during periods of stress.

EXECUTIVE SUMMARY

Benzodiazepine Dependence Studies in Rodents
. . . William R. Martin and L.F. McNicholas

There is only a mall amount of information concerning benzodiazepine dependence in the rat. Although benzodiazepines will decrease conditioned avoidance responding, adverse circumstances do not seem to give rise to increased ingestion. Other problems related to dependence that can be dealt with experimentally are (1) the relative agonistic actions of the different benzodiazepines; (2) the characterization of their dependence-producing ability, including whether they produce protracted abstinence or not; (3) identification of signs of abstinence that are predictors of drug seeking behavior; and (4) the relative threat of the abstinence syndrome to health.

The rat certainly is an economical species in which these assessments can be made. The rat has been extensively used in operant studies. It now appears that rats dependent on pentobarbital and diazepam have an abstinence syndrome rich in signs. The gastric fistula rat allows the ready enteric administration of the water-insoluble benzodiazepines. The viability of this preparation is such that a variety of crossover and dependence studies can be conducted, which should allow the efficient generation of quantitative data of relatively low variability.

DISCUSSION

In the discussion of Dr. Martin's paper, it was noted that his observed pattern of withdrawal symptoms following diazepam dependence in the rat resembled that for serotonin receptor hypersensitivity. It was suggested and he agreed that the study of withdrawal patterns should recognize that these symptoms follow a discernible pattern. This occurs for the study of receptors also and may be related to cycles in the production of an endogenous ligand acting on the receptor.

EXECUTIVE SUMMARY

Benzodiazepines: Clinical Use Patterns
. . . Karl Rickels

Tracing the patterns of benzodiazepine use in a clinical setting, Dr. Rickels noted a flattening or slight decline in the use of these drugs in the United States from 1973 to 1978. The proper use of anti-anxiety drugs in various psychotic and nonpsychotic states is well described in the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association (DSM-III). However, the widespread use of anxiolytic drugs both in and out of the hospital in nonanxious patients suffering from physical and particularly cardiovascular disorders raises the question of whether these drugs have any appropriate treatment or prophylactic benefit such as the prevention of reinfarct or effects on stress-induced contributory factors such as increased triglycerides, cholesterol, or platelet aggregation.

Rickels described the appropriate use of benzodiazepines and criticized the widespread physician misprescribing practices of overuse as well as underuse. Many nonspecific factors involving the physician's and the patient's personalities affect the optimum use of mild tranquilizers. Benzodiazepines are remarkably safe drugs when used alone and most adverse reactions involve alcohol or multiple drugs.

Physiological dependence at recommended therapeutic doses is rare and it is difficult to distinguish withdrawal symptoms from return of the original symptoms. In a largestudy of 100 chronically anxious patients continued on 20 to 40 mg diazepam for up to 6 months, Rickels proved that improvement is inversely related to symptom intensity and that most patients plateau in about 4 to 6 weeks. An early good response during the first week is the best indicator of long-term improvement. Only 11 of the 100 patients suffered withdrawal reactions upon abrupt termination of the drug, and 6 of these were mild and lasted only a few days. Three of the remaining five reactions may have been partly related to alcohol use. This report lends support to the clinical impression that anxiolytic medication should not be stopped abruptly after prolonged treatment.

DISCUSSION

The discussion pointed out the need to know which endogenous ligands acting on the benzodiazepine receptor may be depressed by long-term therapy. Also, the usefulness of propranolol and other peripherally acting symptomatic therapy should be studied for use in withdrawal reactions. Indicators of the induction of increased drug metabolism such as the ratio of drug to metabolite and a high rate of decline in blood levels have not been studied well but may be predictive of withdrawal reactions. The inverse relationship between half-life and severity of withdrawal is a testable hypothesis with currently available drugs. Differences betweenmen and women in withdrawal reactions are not evident, but women have a menstrual cycle variation in their response to benzodiazepines.

EXECUTIVE SUMMARY

Benzodiazepine Hypnotics: Carryover Effectiveness, Rebound Insomnia, and Performance Effects

. . . Anthony Kales

Sleep laboratory studies offer greater precision and objectivity than other methods frequently used to evaluate hypnotic drugs. Since insomnia is frequently a long-term or chronic condition, sleep studies can examine the effectiveness of benzodiazepine drugs over longer periods and measure withdrawal and carryover effects as well.

Carryover effectiveness has been shown for only two benzodiazepine drugs, flurazepam and quazepam (the latter drug is a new investigational hypnotic). Since both drugs have the same long-acting metabolite (N desalkyl flurazepam), the carryover effectiveness has been considered to reflect the gradual buildup and elimination of this metabolite. However, other drugs with long-acting metabolites have not shown carryover effects, so the hypnotic efficacy of the metabolite must be important. The advantages and disadvantages of carryover effectiveness were compared.

Rebound insomnia, a worsening of sleep beyond the original baseline condition, occurs with some benzodiazepine drugs with short or moderate duration of action, but has not yet been found with long-acting compounds. Kales proposes that rebound insomnia occurs because of a lag in the regeneration of an endogenous ligand that normally occupies the receptor and is suppressed by benzodiazepine drugs.

Decrements in daytime performance and memory impairment are two important side effects of benzodiazepine drug administration. Drowsiness and impaired performance the following day are related to dose, age, and long duration of benzodiazepine action. Anterograde amnesia has been reported anecdotally but has not been well studied.

DISCUSSION

In the discussion of this paper, Dr. Martin B. Scharf explained the reasons for disagreement with Dr. Hartse and her colleagues, in Science magazine, over the existence of rebound insomnia--foliowing use of some benzodiazepines, and stated the belief that it is related to short-acting benzodiazepines. Subjective evaluation of sleep quality is as important or more important than objective EEG; data, and subjectively the subjects with rebound insomnia feel they sleep badly, in agreement with objective data. Rebound insomnia after benzodiazepine use differs basically from barbiturate rebound insomnia in that there is no rapid eye movement (REM) increase. Benzodiazepines apparently do not increase the density of eye movements during REM rebound as do the barbiturates and glutethimide.

EXECUTIVE SUMMARY

Dependence on Benzodiazepines
. . . Leo E. Hollister

Dr. Hollister reviewed current use patterns of benzodiazepine drugs and pointed out how the use of sedative-hypnotic drugs has plateaued recently at a reasonable level. Tolerance occurs with benzodiazepine drugs most rapidly to the sedative actions of the drugs and probably much less to other pharmacological actions. Both metabolic and pharmacodynamic tolerance occurs with benzodiazepine drugs. Dependence of both the psychic and physical types can be demonstrated for benzodiazepine drugs in animals, but is more difficult to accomplish than with the barbiturates.

After an extensive review of the literature on human dependence, Hollister came to the following conclusions:

1. Physical dependence upon benzodiazepine drugs can be produced in man if the drugs are given in excessive doses over a prolonged period, particularly to patients with unstable personalities.

2. The dependence risk factor is low and certainly less than for other commonly used sedatives and hypnotics.

3. The risk factor and the dangers to society are of such a low order that no extension of controls is necessary.

4. For better medical care and minimal risk of dependence, patients should be thoughtfully selected for benzodiazepine therapy and the drug should be discontinued as soon as it is therapeutically practical to do so.

Hollister noted a remarkable inverse correlation between drug half-life in the plasma and severity of withdrawal reactions. Prolonged administration also pranotes severe withdrawal effects. His concluding principles for benzodiazepine use are:

1. Use only for anxiety producing considerable discomfort or disability.

2. Continuously assess efficacy and discontinue if ineffective.

3. Contract with the patient for brief periods of treatment because anxiety is usually episodic.

4. Expect benzodiazepine abuse from patients with a history of drug or alcohol abuse and use other classes of drugs for sedation such as antihistamine drugs for these patients.

5. When these drugs have been used for long periods of time, discontinuation of drug should be gradual.

GENERAL DISCUSSION

Dr. Szara acknowledged in the discussion that the DAWN data on street abuse of drugs have been criticized and have been only partially validated. There is a need for better data on abuse of benzodiazepines, since some persons do not consider their use of these drugs as abuse, depending on how the question is phrased.

General discussion followed about how better understanding of benzodiazepine receptors could lead to better clinical use of benzodiazepine drugs and less abuse. Development of a partial agonist was suggested as a possible means of preventing abuse.

Caffeine was named as a general antagonist for benzodiazepines and it was suggested that excess caffeine consumption may be related to attempts by the user to curb benzodiazepine carryover effects. Combined abuse of benzodiazepine-type drugs with methadone was described. Diazepam is useful in neonatal opiate withdrawal, although clonidine is more effective.

The relationship between benzodiazepines and opiates should be examined further because naloxone antagonizes some diazepam depressant actions. Meprobamate may interact weakly with benzodiazepine receptors. Other interactions might be identified among the group of drugs termed interneuronal blocking agents. Benzodiazepine drugs are the choice for treating phencyclidine (PCP) overdose.

Further interest was expressed in the ratio of desmethyl diazepam to diazepam as an index of the induction of benzodiazepine metabolism and its possible relationship to the severity of withdrawal. Many variables characterize the degree of response to benzodiazepine drugs as well as rate of metabolism including blood levels, patient personality, physician-patient relations, plasma binding, lipid compartments, prior drug history, etc.

Long-term changes in the benzodiazepine receptor should be studied, but these studies are difficult because residual drug must be removed from the receptors before assay. Many other nonspecific factors such as heating, seizures, diphenylhydantoin, and other treatments can change receptor binding.

The discussion concluded with this summary by Dr. Martin:

1. Benzodiazepine drugs include many very useful drugs that do have the potential for abuse, but the abuse is of a modest nature since these drugs are less abusable than previously used tranquilizers and hypnotics such as barbiturates.

2. The true size of the public health problem owing to abuse of these drugs is still not established, but there is cause for concern.

3. Proper use of these drugs for their indications and better understanding of their phamacokinetics are needed by physicians.

4. Many physicians are using benzodiazepine drugs incorrectly, sometimes overprescribing and sometimes underprescribing them as a result of adverse publicity, even when a clear-cut indication for their use exists.

5. Better understanding is needed of their basic mode of action and complexities of use in order to develop improved drugs with better selectivity.

RAUS Summary of New Directions for Research

Jacqueline P. Ludford, M.S., and Stephen I. Szara, M.D., D.Sc.

Future benzodiazepine research should, first and foremost, be methodologically strong and rigorous. Future investigations need to be based on sound experimental and epidemiological data, and there is much work to be done in developing such data for benzodiazepines. Much of the research already performed has been methodologically flawed and is open to some question.

Some areas of special interest for NIDA might include:

A. Receptor Studies

1. Detailed light microscopic mapping of receptor locations in animals and also in human tissues. Such information is basic to further studies; techniques are now available to accomplish this goal.

2. Identification of endogenous ligands. The implication of benzodiazepine receptors in the brain is that endogenous benzodiazepine-like substances must exist in the body and may contribute to modulation of behavior.

3. Location of receptors as studied by high resolution methods. The most promising method appears to be the immunocytochemical approach; thus isolation, purification, and production of benzodiazepine antibodies is an important goal.

4. Psychopharmacological experiments to explore which areas of the brain are responsible for which effects. Of special interest should be to relate benzodiazepine receptor occupancy to the reinforcing effects of the drug.

B. Abuse Liability Studies

1. Systematic comparative behavioral. study examining different compounds within the benzodiazepine class. Study of

dose-response relationship, and comparative effects of long-acting vs. short-acting benzodiazepines.

2. Self-administration studies, both animal and human, which take into account the environment and characteristics of the population being studied. Future research should include information about drug history, including over-the-counter, prescription, and illicit drugs, and environmental factors including drug availability and stress as well as the contribution of contextual variables such as food, nicotine, and caffeine. Patient characteristics, especially age, sex, and obesity, should be considered.

3. Investigations of the role of various drug combinations in altering the reinforcing properties of benzodiazepines. Commonly used drugs, such as alcohol, caffeine, aspirin, antihistamines, etc., should be explored in this context.

4. Study of the personality traits, settings, and physician attitude interactions which may be related to benzodiazepine abuse.

C. Clinical Studies

1. More detailed exploration of the abstinence syndrome. Can there be a protracted abstinence syndrome with benzodiazepines? What are the physical signs of dependence? What is the nature and prevalence of low-dose dependence clinically, both in psychiatric and general medical practice patients, and what characteristics might predict such reactions? What is the minimum period of exposure to produce physical dependence at a given daily dosage? Does the degree of dependence increase in linear fashion with increased time of exposure? To what extent is it a clinical problem?

2. Investigations of the pharmacokinetics of differing kinds of benzodiazepines, particularly in the elderly and in those with physical impairments. Do the kinetics of the various drugs influence the development of physical dependence? What is the significance of the ratio of diazepam to desoxydiazepam, for example, and how is this related to withdrawal symptoms?

3. In studying the rebound phenomena following withdrawal of benzodiazepines, is it predictive of dependency? Is it associated with rebound anxiety? What are the determinants? How long does it last?

4. Is there cross-tolerance and/or interaction between benzodiazepines and opiates? There are striking overlaps in receptor areas, and benzodiazepines are sometimes used with methadone by patients to get a "boost." What are the

implications for drug abuse treatment and for the common practice of prescribing benzodiazepine with opioids for pain?

5. Food strongly affects absorption. Since the user loses the peak effect if he takes a "tranquilizer" shortly after a big meal he may, for example, increase the dose at bedtime and wake up with continued drug effect ("hangover") the next day. This is an interesting clinical observation that needs to be explored by further research.

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14 MARIHUANA RESEARCH FINDINGS: 1976. Robert C. Petersen, Ph.D., ed. Technical papers on which the 6th Marihuana and Health report to Congress was based.
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