Adverse Behavioral Effects of Benzodiazepines

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The benzodiazepines are one of the most commonly prescribed classes of drugs in clinical medicine. Their general safety and efficacy have been well documented, but a group of adverse behavioral effects associated with their use has been less well acknowledged. These adverse effects include the risk of dependency, increases in hostile-aggressive feelings and behavior, and suicidal depression.

Physiologic dependence on benzodiazepines has been documented not only in patients taking very high doses over protracted periods of time or who have "high addictive potential," but also in healthy adults taking therapeutic doses for 20 or more weeks. Increases in hostility-aggression, originally considered a paradoxical drug effect, have been repeatedly demonstrated to be associated with diazepam and chlordiazepoxide. There is even some evidence that this ought to be considered a true drug effect rather than a paradoxical effect occurring in a substantial proportion of the people taking these drugs. Depression, with or without suicidal ideation, is another potentially hazardous effect of benzodiazepines. A specific syndrome of ego-alien suicidal ideation has been identified and reported.

The risks of dependency, hostility, and depression are markedly attenuated by the physician's awareness and acknowledgement of these adverse effects. Thus far, the literature on the potentially hazardous effects has not seemed to have substantially influenced clinical practice, but as benzodiazepine use continues to proliferate, the need for careful monitoring of effects also increases.

The benzodiazepines are one of the most commonly prescribed classes of medications in clinical medicine. Diazepam (Valium) is the most commonly prescribed drug, while its close analog, chlordiazepoxide (Librium) ranks third. Other commonly prescribed benzodiazepines include oxazepam (Serax), flurazepam (Dalmane), and chlorazepate (Tranxene), while newer benzodiazepines are being marketed continually. Their popularity can be attributed to a combination of well-proven efficacy, high safety index, and relatively few side effects. The only commonly reported side effect is central nervous system depression, manifested primarily by drowsiness, fatigue, and somnolence.

While there has been increasing concern with their over-prescription and indiscriminate use,[1] there has been little clinical concern about potential adverse effects. However, an expanding body of literature is emerging on a wide variety of relatively overlooked but often serious adverse behavioral effects, ie, organic brain syndromes,[2] sleep disturbances,[3-5] abuse and misuse,[6] potential depression especially in the elderly,[7] dependency,[8] paradoxical hostility and rage,[9-20] and suicidal ideation.[21-23] This paper explores the adverse behavioral effects of benzodiazepines, particularly dependency, paradoxical hostility, and suicidal ideation as they impinge upon three commonly held myths of benzodiazepine safety: nondependence, constant tranquilization, and low suicidal potential.

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Myth 1: Benzodiazepines are not associated with tolerance or withdrawal symptoms.

That benzodiazepines have an extremely low potential for tolerance or withdrawal symptoms has become almost axiomatic. This assertion is based primarily on clinical experience and anecdotal reports in that few well-controlled, systematic studies have been completed. However, the longer these drugs are on the market, the more reports appear concerning abuse, habituation, and addiction. Some reports suggest particular groups that may be especially vulnerable to benzodiazepine dependence. For example, Ayd suggests that "there are infinitesimally few abusers of chlordiazepoxide and Valium . . . and these abusers are unstable inadequate personalities with prior histories of abuse of alcohol and/or drug."[24] Woody,[6] Finer,[25] and Krypsin-Exner[26] have presented data supporting the particular vulnerability of this patient group; however, additional reports suggest that dependency may well be a problem for a broad range of patients who are not necessarily unstable, or alcohol or drug abusers.

Sudden withdrawal of large doses of benzodiazepines has been shown to produce severe symptomatology in a variety of patient types. Hollister et al[27] administered 300 to 600 mg of chlordiazepoxide per day to hospitalized psychiatric patients for up to six months. Of the 11 patients who were abruptly withdrawn, ten experienced significant symptoms including two with frank seizures. Relkin reported on a 20-year-old man with basal ganglion disease who died three days after diazepam was discontinued.[28] Preskorn reports on three people who developed acute psychoses after large doses (60 to 250 mg) of diazepam taken over several months (6 to 24) were suddenly withdrawn.[29] Two of Preskorn's patients were diagnosed as drug abusers while one was diagnosed as having "cardiac neurosis with secondary depression."

Discontinuation of moderate to low doses can produce less severe withdrawal symptoms. Covi et al[30] demonstrated a minor abstinence syndrome of the barbiturate type following abrupt withdrawal of therapeutic

doses of chlordiazepoxide when taken for longer than 16 weeks. Their study population consisted of outpatient psychiatric patients, not drug or alcohol abusers, who had no signs of severe behavioral disorders. Hanna,[31] Bant,[32] and Haskell[33] have described minor abstinence symptoms associated with withdrawal of other benzodiazepines, such as oxazepam and diazepam. Maletzky and Klotter studied a group of 50 patients referred from a variety of outpatient clinics on the basis of current use of diazepam.[8] While most of their patients had been taking relatively low doses over long periods of time, about 20 percent had been increasing their doses without asking their physicians, and only four percent were able to discontinue diazepam voluntarily. Sixty percent of the patients viewed themselves as at least slightly dependent on diazepam. Neither sex, age, source of referral, psychiatric history, nor the presence of current psychiatric problems had the slightest relationship to drug use or abuse potential.

Thus, it is a myth that physicians need not worry about the problems of dependency when prescribing benzodiazepines. The risk may be particularly great in drug abusers or alcoholics, but it is by no means confined to these populations. Discontinuation of high doses can produce severe withdrawal symptoms, including seizures and psychoses; discontinuation of therapeutic doses taken over protracted periods can produce minor abstinence symptoms. In addition, the benzodiazepines can produce psychological habituation more frequently than is generally recognized. Patients like their benzodiazepines and are loath to give them up. The following case history illustrates benzodiazepine dependence.

Case Illustration and Discussion

The patient is a 34-year-old married woman referred by a neurologist for evaluation of anxiety symptoms. Her anxiety has lasted about ten years, precipitated by the death of her mother, who had been institutionalized for Huntington chorea. The patient's initial symptom was bilateral upper extremity tremor, one of the few symptoms she knows is associated with Huntington chorea. There is no history of alcoholism, drug abuse, severe personality disorders, or other significant psychiatric disturbances.

Following the onset of her anxiety, she was treated with diazepam, 5 mg three times a day as needed. During the past ten years she had taken diazepam regularly. Over the past year, she has found it necessary to take increasing doses for symptomatic control. Over the past several months, she has been taking 40 to 60 mg per day with a modicum of relief. The patient notes at least two previously unsuccessful attempts to discontinue diazepam involving the exacerbation of all anxiety symptoms and the appearance of muscle cramps, nausea, and diaphoresis, symptoms not generally associated with her anxiety. She notes that her first daily activity is to take approximately 5 to 15 mg of diazepam.

In this case, as in many others, it is difficult to demarcate the boundaries between the recurrence of anxiety, physiologic dependence, and psychological habituation; it is quite possible that all were operative. Her physician had set the stage for her continued tranquilization for problem solving. She came to expect all subsequent physicians to continue prescribing diazepam. Unfortunately, her expectations were all too readily met.

This case exemplifies the need for clinical guidelines regarding benzodiazepine use. First, treatment alternatives other than benzodiazepines should always be considered. Whereas the temporary use of benzodiazepines may be a valuable adjunct to the treatment of acute anxiety states, their value in chronically anxious patients is less obvious.[20] If the physician chooses to prescribe benzodiazepines for an acute situation, he or she should communicate the expectation that the patient will eventually be able to handle life stresses and anxiety without relying on chemical tranquilization. Offering patients a professional relationship which allows them to voice concerns, examine conflicts, initiate positive action, and grow through problem solution is often more appropriate and beneficial than merely prescribing tranquilizing medications. To the patient demanding benzodiazepines, the physician must learn to say no. The physician must be firm yet understanding in helping the patient see that the problem requires something other than chronic medication.

Kaufman has demonstrated relatively simple methods that can greatly reduce the number of tranquilizers prescribed.[34] His program includes educating patients and physicians on the negative aspects of drug abuse, the possibility that drugs may lose therapeutic efficacy over time, and the hazards to daily living and diminished alertness due to drugs. This approach may require the physician to participate more actively in helping the patient with problems in living. If the physician does not have time to deal with the patient's emotional problems or is not able to help the patient through brief discussion, then referral to a psychiatrist, psychologist, social worker, or public health nurse is indicated.

If patients have been taking therapeutic doses for more than four months, they should be warned of minor abstinence symptoms which will subside in time. Occasionally, the physician may want to withdraw the patients gradually for purposes of patient comfort and compliance. For patients who have taken large doses of benzodiazepines for several months, particularly if other central nervous system depressants are involved, hospitalization with gradual withdrawal should be strongly considered. And, finally, patients with either a past or present history of drug abuse should be given benzodiazepines only with great caution.

Myth 2: Benzodiazepines predictably and consistently produce tranquilization.

Benzodiazepines are frequently prescribed to lessen anxiety, fear, and irritability. However, there are reports that these drugs sometimes produce "paradoxical" effects, increasing the very symptoms they are expected to alleviate. In minimally anxious subjects, for example, benzodiazepines have been shown to actually increase anxiety.[16] Rage attacks, often quite intense, have been reportedly induced by chlordiazepoxide,[20] diazepam,[12] and chloraxepate,[13] but possibly not by oxazepam.[10,16] Such a drug reaction may result from an interaction of drug, personality, and environment.[14] Some have argued that this reaction syndrome is not really a paradoxical effect but rather a predictable response occurring in certain patients

whose past histories of poor impulse control interact with the drug's pharmacologic, hostility-increasing properties.

More common than frank rage attacks is an increase in hostile-aggressive feelings induced by benzodiazepines. Gardos et al found that chlordiazepoxide simultaneously decreased anxiety but increased hostility as measured by paper and pencil tests.[16] However, they did not observe any evidence of behavioral hostility. Saltzman et al confirmed the findings of the previous study but also demonstrated that chlordiazepoxide can induce interpersonal behavior hostility in situations of frustration.[18] They suggest that this increase in hostility may be a regular rather than a "paradoxical" effect of chlordiazepoxide, but that overt hostility becomes apparent only in settings of interpersonal frustration. Shader and DiMascio have reviewed the reasons why this increase in hostility seems so clinically unrecognized.[15] The following case is one of a small series that illustrates the interaction of drug effect, personality, and environment in producing a "paradoxical" rage reaction.

Case Illustration and Discussion

The patient is a 22-year-old black male referred for psychiatric evaluation by his attorney after being apprehended for "going berserk and trying to kill his first sergeant." The patient comes from a socioculturally deprived background and spent most of his formative years fending for himself in the streets. After completing high school, he decided to leave the streets, join the army, and "make something of myself." During the first 2½ years of military service, he had an exemplary record, got along well with peers and authorities, avoided any drugs or alcohol, and was generally considered an outstanding soldier.

Four weeks before the first psychiatric evaluation, the patient fell off a truck while on maneuvers. That evening he went to the Emergency Room because of continued low back pain. X-rays and examinations were negative. He was put on 24 hours rest, aspirin, heat therapy, and diazepam, 5 mg every six hours as needed. Two days later he went to the dispensary because of continued pain. Diazepam was increased to 30 mg a day, and an appointment was made for the orthopedic clinic the following week. By his next appointment, he complained of feeling "funny inside," a feeling which he was unable to further define. He was told that this was "nerves" and diazepam was increased to 40 mg a day. Three days later he returned to the orthopedic clinic complaining of feeling jumpy and irritable. He was sleeping poorly and was argumentative with friends and feeling defiant of authorities. He was told to stay on diazepam and return for follow-up visits at the dispensary in one month.

Two days after this visit he was getting dressed for a party when his first sergeant confronted him about his recent lackadaisical, negativistic attitude. He suddenly "went into a rage," grabbed a knife, and attacked his first sergeant. That night he was apprehended, incarcerated, and diazepam was discontinued. The following day, results from his physical examination, neurologic evaluation, and laboratory studies were all within normal limits. The next two to three days he continued to feel "funny and in a fog," a feeling which gradually cleared. During six months of follow-up there was no recurrence of hostile or overly aggressive behavior.

The preceding case illustrates the potential risk of benzodiazepine-induced hostility-rage. Management recommendations emerge from the recognition of this possibility. First, in patients with a prior history of acting-out behavior or in whom impulse control is tenuous, benzodiazepines should be used with great caution. Minimal doses for minimal durations are in order. Complaints of increased irritability or behavioral changes indicating increasing anger are indications for dosage reduction rather than increase. If a benzodiazepine must be given, oxazepam should be the first choice since it has not been associated with hostile or aggressive behavior. Secondly, chlordiazepoxide or diazepam may be the benzodiazepine of choice for treating the anxious patient who is also severely inhibited; here, the drug may help release therapeutically beneficial, self-assertive behavior. Further research to help elucidate and clarify the clinical ramifications of this benzodiazepine-induced aggression is clearly indicated.

Myth 3: Benzodiazepines are not associated with significant risk of suicide.

That benzodiazepines have a relatively high safety index has lulled many physicians into a false sense of complacency regarding the risk of suicide. Few "successful" overdoses are reported, despite the great number of people abusing these drugs and the large number of suicidal gestures or attempts. This "safety" at least partially explains why physicians are so generous in prescribing benzodiazepines, even to patients who may be mildly depressed. However, this generosity needs to be reexamined. Most drug overdoses presenting to Emergency Rooms involve benzodiazepines.[35] Although the benzodiazepines may not be intrinsically lethal, combinations with other central nervous system depressants can be lethal. Whether other forms of suicide, such as gunshot wounds or automobile accidents, are significantly associated with benzodiazepines has not been adequately tested. But clinical experience raises this possibility.

A number of reports have emphasized the risk of suicidal ideation induced by benzodiazepines. Gundlach found suicidal thoughts and impulses associated with therapeutic doses of diazepam but not placebo.[21] Ryan reported on seven patients who developed suicidal thoughts and tendencies after starting therapeutic doses of diazepam.[22] Five of these patients improved within a few days after discontinuing diazepam, whereas in two of the cases suicide actually took place. In another study, Hall reported on a syndrome of "ego alien" suicidal ideation induced by large doses of diazepam in patients with organic disorders.[23] In Hall's series all of the patients showed a cluster of symptoms consisting of tremulousness, apprehension, and insomnia, followed soon after by depression related to "ego alien" suicidal ideation. The syndrome was abrupt and severe. All of the patients had been previously emotionally stable and all were significantly improved within seven days after diazepam was discontinued.

Thus, benzodiazepines are given freely to a large group of patients, some of whom may already be at high risk for suicide and others who become at high risk after taking the

benzodiazepines. The following case recounts a patient who developed suicidal ideation associated with therapeutic doses of diazepam.

Case Illustration and Discussion

The patient is a 63-year-old widowed woman referred for psychiatric evaluation because of "bizarre behavior." Four years previously she was treated with a radical mastectomy and radiation for a breast carcinoma. Two weeks before consultation there was a change in behavior along with signs and symptoms of an organic brain syndrome. One week before consultation she was hospitalized for a work-up for cognitive and behavioral changes. No evidence of central nervous system metastases was found.

Because of agitation, crying spells, and insomnia, she was started on diazepam, 2 mg three times a day, which was increased to 5 mg three times a day by the fourth hospital day. The patient's behavior became more subdued, but she began complaining of feeling "blue." On the sixth hospital day, psychiatric consultation was obtained. The patient was found to be moderately depressed and perplexed about her feelings of "wanting to end it all." She had spent the evening before conjuring up thoughts of ways she might kill herself but felt that she would not actually go through with it.

The psychiatric consultant recommended diazepam be discontinued. Within two days of diazepam discontinuation, the patient felt more anxious, but no longer suicidal. She was seen in the outpatient psychiatry department for further evaluation and treatment of her anxiety. Three months of follow-up revealed no further evidence of depression, suicidal ideation, or behavioral aberrations. Mild memory and cognitive deficits continued, but the etiology remained unclear. She was scheduled to be followed by the departments of surgery and oncology to further assess the progression and etiology of her cognitive impairment.

The patient had clearly been upset before receiving benzodiazepines, but there was no suicidal ideation until after she was receiving 15 mg of diazepam each day; suicidal thoughts vanished within two days of discontinuation. This case illustrates that suicidal ideation is potentially induced by benzodiazepines. Thus far, this phenomenon has been reported only with diazepam. The risk appears much greater in the elderly, in patients with central nervous system impairment, and in patients taking large doses of diazepam. In these patient groups, therefore, extra care must be taken to use the smallest doses of benzodiazepines for the briefest periods of time. All increases in depression, irritability, apprehension or insomnia should alert the physician to discontinue administration of benzodiazepines and re-evaluate the patient.[23] Benzodiazepines should be prescribed with great caution, if at all, for patients on other central nervous system depressants, especially alcohol.

Conclusion

This paper has examined three myths of benzodiazepine safety: non-dependence, consistent tranquilization, and low suicidal potential. Each of these myths at least partially accounts for the widespread use and abuse of benzodiazepines. But there is an expanding body of literature challenging these myths and suggesting alternative treatment strategies. In every case, the literature suggests that the physician not substitute chemical tranquilization for comprehensive patient care. We agree with Katz's recommendation that "every time a physician reaches for his prescription pad he should ask himself if he is prescribing a sedative or tranquilizer because he has a room full of patients waiting and is in a hurry to get on to his next patient whose illness he considers more serious, or whether he has carefully considered all the evidence, has found that sympathy, understanding, suggestions, and reassurance are not sufficient, and has decided to prescribe a sedative or tranquilizer for positive reasons rather than as an easy way out."[36]

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