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Can Buspirone Induce Rebound, Dependence or Abuse?

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Buspirone is a newer anxiolytic which differs chemically and pharmacologically from the benzodiazepines. The question as to whether buspirone can induce rebound, dependence, or abuse can be examined through a variety of clinical and control studies, as well as animal studies, together with meticulous follow-up of adverse reports. It is concluded that, on present evidence, the short-term use of buspirone is unlikely to be followed by rebound or long-term use through dependence; nor is abuse likely to be a problem.

Anxiety disorder affects about 5% of the adult population (Weissman, 1985). A variety of treatments have been devised to treat the condition, ranging from counselling, relaxation, psychotherapy, and cognitive therapy, to pharmacotherapy. The last has seen several classes of compounds wax and then wane in popularity. For example, the barbiturates were widely used until the 1950s or 1960s. They were partly replaced by meprobamate, and then largely ousted by the benzodiazepines. Among the reasons for the eventual unpopularity of the barbiturates was the increasing realisation of a major potential for dependence and abuse. More recently, it has become apparent that the benzodiazepines, which were originally believed to have a low potential for dependence and abuse, are likely to lead to dependence on long-term use, even if the dosage is maintained within therapeutic levels (Woods *et al*, 1987). Dosage escalation is uncommon with the benzodiazepines, but abuse is an increasing problem.

By far the commonest problem with the benzodiazepines is a withdrawal syndrome after discontinuing long-term use (Petursson & Lader, 1984). However, even after short-term use, rebound anxiety can occur, with the consequent danger of resumption of the medication and eventual long-term use (Chouinard *et al*, 1983; Power *et al*, 1985). The fact that benzodiazepines can readily substitute for barbiturates and for alcohol provides evidence that the dependence phenomena are typical of the sedative/hypnotic class.

Dissatisfaction with the barbiturates led to the ready acceptance of the benzodiazepines into clinical use, but in turn these drugs have been heavily criticised and limitations proposed on their use (Royal College of Psychiatrists, 1988). This growing unpopularity has led to a search for the development of alternative remedies. Among older compounds, antihistamines such as hydroxyzine, and β-adrenoceptor antagonists like propranolol, have been undergoing reappraisal (Lader, 1988), while new compounds have also been developed. Some, like the cyclopyrrolones and the imidazopyridines, are closely related pharmacologically to the benzodiazepines; others, mostly affecting serotonin pathways, are dissimilar. In the latter category, compounds have been developed which act on 5-HT_1, 5-HT_2, and 5-HT_3 receptor mechanisms.

As is inevitable and commendable, the same questions that have been raised about the dependence potential of the benzodiazepines are being asked about these new compounds. Cynics believe that any substance that lessens anxiety has a propensity to induce dependence and/or abuse. The enthusiasts aver that, at last, we can assuage anxiety without appreciable risks of this type. However, both formal and experimental data and clinical experience on these questions are limited. Only one compound has so far been marketed – the azapirone derivative buspirone. It has already been prescribed for over two million people, mostly in the USA, and has been closely monitored. This experience, together with animal pharmacology and about 12 controlled studies in both normal subjects and patients, provides the basis for some interim conclusions.

This review discusses issues relating to dependence and abuse, and examines the evidence with respect to buspirone. It would be important to raise the alarm early if the data seem disquieting; on the other hand, it is equally important to allay such anxieties if problems of dependence and abuse seem absent or minimal. We should neither condemn nor extol a potentially valuable therapeutic agent without an adequate basis of information.

Definitions

The definitions of abuse and dependence, let alone of addiction, are fraught with controversy. Nevertheless, it is essential to define these terms, lest confusion persist in the minds of non-specialists (Perry, 1985). The following terms have been suggested by DuPont (1986) in a guide for the physician:

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"**Abuse** – Self-administration of any drug in a culturally disapproved manner that causes adverse consequences.
Addiction – A behavioral pattern of drug abuse, characterized by overwhelming involvement with the use of a drug (compulsive use), the securing of its supply, and a high tendency to relapse after discontinuation.
Dependence – The physiologic state of neuroadaption produced by repeated administration of a drug, necessitating continued administration to prevent the appearance of the withdrawal or abstinence syndrome.
Reinforcement – The tendency of a pleasure-producing drug to lead to repeated self-administration.
Tolerance – Tolerance has developed when, after repeated administration, a given dose of a drug produces a decreased effect or, conversely, when increasingly larger doses must be administered to obtain the effects observed with the original use.
Cross-tolerance and cross-dependence – The ability of one drug to suppress the manifestations of physical dependence produced by another drug and to maintain the physically dependent state.
Withdrawal – The psychologic and physical reactions to abrupt cessation of a dependence-producing drug.
Relapse – The reoccurrence, upon discontinuation of an effective medical treatment, of the original condition from which the patient suffered.
Rebound – The exaggerated expression of the original condition sometimes experienced by patients immediately after cessation of an effective treatment."

Prediction of dependence and liability to abuse

Although the final arbiter of the practical problems of abuse and dependence must remain clinical observation and trial, pre-clinical studies can provide both strong predictors and supporting evidence of the degree or absence of such potential. Biochemical, physiological, and behavioural techniques can all contribute to building a useful corpus of knowledge.

A range of data can be accrued, from behavioural studies (Nelson, 1986) to the anecdotal case report. The tests performed can be divided fairly clearly into, firstly, those relating to the potential for rebound and dependence and, secondly, those relevant to the liability for abuse.

In animals, the potential for dependence of an anxiolytic would be confirmed by:

(a) physical withdrawal syndrome, spontaneous or induced
(b) suppression of withdrawal to known dependence-inducing drugs
(c) negative reinforcement during withdrawal
(d) ability to produce tolerance
(e) cross-tolerance to known dependence-inducing drugs.

In normal subjects, potential for dependence is assessed by:

(a) short-term studies of rebound
(b) cross-tolerance to known rebound-inducing drugs.

In patients, potential for dependence is assessed by:

(a) short-term studies of rebound
(b) suppression of rebound to known rebound-inducing drugs
(c) long-term studies of withdrawal
(d) suppression of withdrawal to known withdrawal-inducing drugs
(e) case reports
(f) post-marketing surveillance
(g) epidemiological surveys
  (i) prescriptions
  (ii) usage
(h) evaluation of special groups (e.g. the elderly).

In assessing potential for abuse of an anxiolytic, the animal studies examine:

(a) reinforcement of drug-seeking behaviour
  (i) self-administration
  (ii) place preference
(b) drug discrimination
(c) ability to produce tolerance.

In normal subjects and casual misusers, potential for abuse is assessed by:

(a) preference studies
(b) reinforcement
(c) subjective assessment.

In patients, the assessment comprises:

(a) case reports
(b) post-marketing surveillance
(c) casualty reports (e.g. DAWN)
(d) polydrug abusers' 'street-lore'.

No one test or even battery of tests is totally predictive, but together with clinical experience, a useful overall picture can emerge.

Studies in animals

Buspirone is chemically distinct from the benzodiazepines, but much more important is the probability that it acts on a totally different mechanism. It binds neither to benzodiazepine nor to GABA receptors, but instead to 5-HT_{1A} and to some dopamine receptors (Taylor *et al*, 1984). (The last property is probably irrelevant, as the congener, gepirone, has little if any dopamine-binding affinity, but is still anxiolytic.) In physiological terms, it is a partial agonist at 5-HT_{1A}

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receptors, and this has the effect of decreasing the firing rate in 5-HT neurones.

In a self-administration study (Balster & Woolverton, 1982) four adult male rhesus monkeys were trained to press levers for cocaine injections. On average, the monkeys would self-administer 50 injections per day of cocaine (30 μg/kg). However, buspirone was not self-administered, and neither were chlordiazepoxide or clorazepate.

The discriminative stimulus properties of buspirone were the focus of a study by Hendry *et al* (1983). Using a lever-pressing task, two groups of rats were trained to discriminate either intraperitoneal buspirone from the vehicle of injection or intraperitoneal oxazepam from the vehicle. Discrimination was readily established in the oxazepam group, but only with difficulty in the group receiving buspirone. Generalisation occurred in the oxazepam group to pentobarbitone, but not in the buspirone group As a corollary, rats trained to press levers for pentobarbitone generalised to oxazepam, but not to buspirone.

Chronic administration in rats of barbiturates or benzodiazepines produces a state of physical dependence, as manifested by a loss of body weight when the drug is withdrawn. Riblet *et al* (1982) gave rats either diazepam or buspirone at a dose of 200 mg/kg per day (by mouth) for 22 days. On discontinuation, weight loss was seen in the diazepam-treated animals, whereas those stopping buspirone showed a slight gain in weight.

Mice can also be made dependent by mixing their food with phenobarbitone. On drug withdrawal, handling will typically induce convulsions. Diazepam at a dose of 5 mg/kg suppressed these convulsions, suggesting cross-dependence, whereas buspirone (50 mg/kg) had no such effect (Riblet *et al*, 1982).

Animal tests, therefore, suggest that buspirone is distinct from the benzodiazepines with respect to potential for abuse and dependence, as evidenced by studies of drug discrimination and withdrawal.

Studies in normal volunteers

Whereas anxiolytic doses of benzodiazepines are pleasant and may even induce euphoria, buspirone in clinical doses usually has no mood-elevating effects, or may even produce some dysphoria (Bond & Lader, 1981).

A direct assessment of such effects was carried out in 24 recreational users of sedative drugs (Cole *et al*, 1982); all participants had used barbiturates, benzodiazepines, or methaqualone in doses at least six times the usual prescribed levels. Each subject was administered buspirone (10 mg and 40 mg), diazepam (10 mg and 20 mg), methaqualone (300 mg), and placebo in random order, in six 4-hour sessions each week. Subjective effects were assessed using the Addiction Research Center Inventory Scales for euphoria, sedation, dysphoria, and liability to abuse. Compared with placebo, methaqualone was associated with high scores on scales for euphoria, physical sedation, and liability to abuse. A 20 mg dose of diazepam also elicited euphoria, sedation, and abuse potential, whereas the 10 mg dose had little effect. By contrast, 40 mg of buspirone produced neither euphoria nor sedation, but rather unpleasantness/dysphoria, while 10 mg was indistinguishable from placebo. The subjects rated only methaqualone and diazepam as worth using again. The mean estimated 'street' values for the various drugs were: methaqualone $3.50; 20 mg diazepam $1.94; 10 mg diazepam $0.68; 40 mg buspirone $0.56; 10 mg buspirone $0.24; and placebo $0.23.

These data accord with the reinforcement studies in animals, and suggest that buspirone is unlikely to be abused by recreational drug users. The higher dose of buspirone appeared mainly unpleasant in its subjective effects, when given in a single dose. Both doses were less euphoriant and stimulant than methaqualone, a drug of known abuse potential, or 20 mg of diazepam.

A similar study has been reported from Toronto. The effects of buspirone (10 and 20 mg), quinalbarbitone (100 mg), lorazepam (2 mg), and placebo were evaluated in 15 male intermittent drug users (Schneiderman *et al*, 1989). Lorazepam had the most pronounced psychomotor effects, whereas 20 mg buspirone significantly impaired memory. Lorazepam was the most well liked drug, and 20 mg buspirone the least liked, although its effects were no different from those of placebo. The authors interpret their results as indicating that buspirone is not likely to be abused by experienced users of substances depressing the central nervous system (CNS).

Studies in patients

Several studies have evaluated the rebound and withdrawal effects of buspirone in comparison with a benzodiazepine; these have varied in the length of treatment before the drugs were withdrawn. A comparison of buspirone, diazepam, and placebo involved 48 out-patients with a diagnosis of generalised anxiety disorder (GAD) according to DSM-III criteria (Fontaine *et al*, 1987). After a week of washout, patients were treated with one of the medications for four weeks, and then abruptly switched to placebo for three weeks. The dosage regimes were flexible: days 1–4, one tablet of 10 mg

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of diazepam or buspirone; days 5–7, two tablets; days 8–11, three tablets and 12–28, four tablets, all under double-blind conditions.

Patients treated with diazepam had a significantly greater reduction in ratings on the Hamilton Rating Scale for Anxiety (HRSA) than did those taking buspirone or placebo. Indeed, it is hard to discern any real efficacy for buspirone over the four weeks. Withdrawal of medication resulted in a larger increase in anxiety symptoms in the diazepam-treated group than in the groups receiving buspirone or placebo. Thus, two weeks following withdrawal, the diazepam group were significantly more anxious than the buspirone or placebo groups, although they had not quite relapsed back to their pre-treatment level. The buspirone group was divided into responders and non-responders. Relapse was seen in the responders, but no increase in psychopathology ratings occurred in the non-responders.

Rebound to levels 10% or more above baseline ratings were seen in four patients treated with diazepam (28%), in one with buspirone (7%), and one with placebo (10%). Rebound anxiety led to resumption of medication in three of the diazepam group, but neither of the other two subjects. Mild withdrawal symptoms such as nausea, insomnia, agitation, sweating, and tremors were noted more frequently during diazepam withdrawal than following that of buspirone or placebo.

A so-far unpublished major efficacy study is on file with the Bristol-Myers Company (Japanese Study, 1989); unfortunately, very modest doses were used in it. Of 93 patients on buspirone, only 18 received 20 mg or above; while of 83 patients on diazepam, only 15 were given 8 mg or more. Not surprisingly, drug efficacy was found only in the higher-dose subgroups. After withdrawal in these subgroups, the mean score on the HRSA among those responding to buspirone continued to fall, whereas that among those responding to diazepam rose by nearly 25%.

In a preliminary report, Petracca *et al* (1990) presented data on 20 patients with GAD treated with buspirone and 20 treated with lorazepam, over a treatment course of eight weeks. By this time, five patients on buspirone and two on lorazepam had dropped out. At pre-treatment after a two-week washout, the buspirone group scored significantly higher on measures of depression, anger/hostility, somatisation, and interpersonal sensitivity. Three HRSA items were also higher in the buspirone than the lorazepam group – depressed mood, psychic anxiety factor, and total score. Therapeutic effects were marked with both treatments, but were prompt with lorazepam.

At eight weeks, both drugs were abruptly withdrawn. The buspirone-associated improvement continued for the next two weeks of assessment. In the lorazepam group, many evaluative measures were much higher than in the treatment phase, with a trend for some to reach baseline levels. In particular, depression ratings were more severe at week 9 than at baseline. Rebound tended to lessen by week 10.

A study in Finland, presented in abstract (Moring *et al*, 1989), assessed 87 patients with GAD, two weeks after they discontinued a six-week double-blind trial with buspirone or diazepam, both given initially 5 mg three times a day. The mean initial HRSA score in the buspirone group was 22.8, dropping to 7.5 at six weeks and 8.1 at eight weeks. The score in the diazepam group dropped from 22.1 to 8.9, but then rose to 11.9 at eight weeks, suggesting some rebound.

Murphy *et al* (1989) administered either buspirone or diazepam over 6 or 12 weeks to 51 out-patients who met DSM–III criteria for GAD. At the end of the period of treatment, they were switched abruptly to placebo and continued until week 14. The Comprehensive Psychopathological Rating Scale (CPRS) and an anxiety subscale derived from it were administered every two weeks. Additional questions were asked to elicit more unusual withdrawal symptoms, such as perceptual distortion (Petursson & Lader, 1984).

Of the 51 patients entered in the study, 11 dropped out – the three on diazepam did so in the first two weeks; of the eight buspirone drop-outs, half occurred during the first four weeks. Reasons for drop-out included headaches, nausea and lack of efficacy (diazepam) and depersonalisation, nausea, and chest pain (buspirone). The dosage range in the 40 patients finishing the study was 1.5–2.3 capsules daily (7.5–11.5 mg of diazepam or buspirone), and was similar in both groups.

Both drugs showed an appreciable anxiolytic effect, although this was more rapid with diazepam. The authors remark that on withdrawal, "the most striking finding was the significant increase in symptoms after stopping diazepam after both six and twelve weeks". Neither group on buspirone showed any such increase in symptom ratings after withdrawal. The difference in rebound between the drugs was significant in the groups undergoing early withdrawal (weeks 6–8), but not in those undergoing late withdrawal (weeks 12–14).

More detailed symptom analysis showed that three out of the ten buspirone early-withdrawal group had a subsequent increase in symptoms, which the authors interpret as suggesting that buspirone should not be regarded as entirely free from potential for

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dependence. It might be that this was a recrudescence of symptoms due to insufficient length of treatment, but it is impossible to distinguish between these two possibilities. However, additional new symptoms reported during weeks 13 and 14 included perceptual hypersensitivity, muscle pain and twitching, vomiting and diarrhoea, headache, and throbbing sensations. New symptoms emerged in 6 out of the 20 patients on diazepam (early and late discontinuers combined), but in only one of the 20 patients on buspirone. Despite these symptoms, all these patients successfully completed the drug-free period.

The longest study was that carried out by Rickels *et al* (1988), comparing six months of continuous treatment with either a long-acting benzodiazepine (clorazepate), or buspirone. This extensive study has several implications.

A total of 150 patients entered the study – 134 with GAD and 16 with panic disorder. After one week of single-blind placebo administration, patients were assigned randomly to either buspirone or clorazepate, given in flexible dosage for four weeks. Those responding favourably continued in the maintenance phase, which extended to week 24. During the withdrawal phase (weeks 24–28), patients were shifted abruptly to placebo at either week 24 or week 25, in a random double-blind fashion. Patients were evaluated weekly during the acute and withdrawal phases, and monthly during the maintenance phase on a range of self-rated and doctor-rated measures of anxiety, mood, and possible withdrawal symptoms.

Of the 150 patients who entered the acute phase, 20 in the clorazepate group dropped out (26%), compared with 33 (45%) in the buspirone group ($P < 0.05$). Patients with panic disorder tended not to respond to buspirone, and in all patients, buspirone was slow to show efficacy. In patients at the end of the acute phase, the mean dosages of clorazepate and buspirone were 31 mg and 27 mg respectively. Drop-out was also significantly higher among patients on buspirone (19/41) than among those on clorazepate (13/56) during the maintenance phase. Patients with a previous history of benzodiazepine use had a higher attrition rate in both groups.

Thus, 43 patients given clorazepate but only 22 given buspirone entered the withdrawal phase. On a range of measures, increases in psychopathology were seen among those on clorazepate but not among those on buspirone. A level of at least five new symptoms was set as the criterion for a probable withdrawal syndrome. By this criterion, 27 of the 40 (67%) clorazepate patients, but only 2 of the 22 (9%) buspirone patients suffered withdrawal. The study design allowed resort to reserve medication: 16 (40%) of the patients on clorazepate did so, compared with none of those on buspirone and the discontinuers. Of the patients who successfully completed the withdrawal phase, about a quarter in each group suffered a gradual return of anxiety. Six-month follow-up data showed that twice the proportion of clorazepate-treated as buspirone-treated patients had resumed anxiolytic medication (Rickels *et al*, 1989).

Another aspect of this topic is possible cross-dependence between buspirone and the benzodiazepines. One way to evaluate this is to take patients who are physically dependent on a benzodiazepine, as evidenced by withdrawal symptoms on attempted discontinuation, and to substitute buspirone. If cross-tolerance occurs, the buspirone should suppress the benzodiazepine withdrawal syndrome and postpone it until the buspirone itself is withdrawn. If no cross-tolerance occurs, then buspirone should not affect the withdrawal at all, except perhaps to lessen anxiety symptoms in a non-specific way. Studies of this type have consistently shown that buspirone does not suppress or relieve benzodiazepine withdrawal symptoms (Schweizer & Rickels, 1986; Lader & Olajide, 1987; Ashton *et al*, 1990).

Possible liability to abuse has been evaluated in 19 subjects who had been admitted to hospital for the treatment of alcohol dependence (Griffith *et al*, 1986). Buspirone (10, 20, and 40 mg) was compared with diazepam (10 and 20 mg) and with placebo, given in a single dose, with double-blind procedures. The Addiction Research Center Inventory and some other scales were administered. Diazepam showed activity with respect to scales indicative of euphoria, whereas buspirone was either much less active or actually induced dysphoria at the highest dose. Both diazepam and buspirone had some sedative properties, but buspirone was generally less well liked by the subjects than diazepam. The authors concluded that "buspirone has only limited, if any, abuse liability".

Reports of adverse events

The manufacturers of buspirone (Bristol-Myers Squibb) have kindly provided the reviewer with all the reports of adverse drug experiences with buspirone from the time of first marketing in each country to February 1989. The company states that in the USA alone more than two million patients have been exposed to the drug.

Under the heading of "Drug dependence", there are four reports – two from Germany and two from the US. In each case, known drugs of abuse were being taken concomitantly, and it is impossible to ascribe any specific problems of abuse to the buspirone.

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Eight cases are filed under "Withdrawal". In two of these, the attending doctor was unconvinced that buspirone was producing withdrawal problems. In a further four cases, data were fragmentary and inconclusive. In the remaining two cases, the patients experienced mild symptoms such as irritability, feeling uncomfortable, blurred vision, headache, and shakiness when attempting to stop medication or if a dose was missed.

Conclusions

The benzodiazepines have largely replaced the barbiturates, partly because of their lower propensity to induce dependence and to be abused. However, after 30 years of use, the benzodiazepines have themselves been subject to adverse comment regarding their long-term use and dependence and withdrawal problems. Abuse has been less of a concern, but has been sufficient to result in the inclusion of benzodiazepines under the United Nations' (1977) *Convention on Psychotropic Substances 1971*. Now, newer anxiolytics have been developed and are being regarded critically, lest history repeat itself yet again.

It is useful in reviewing the data on buspirone to distinguish between normal-dose use, with rebound and withdrawal as dangers, and high-dose abuse, which is outside the medical context. Buspirone has been evaluated in a series of studies, ranging from those in mice to ones in anxious patients. Almost without exception, the pattern of results is predictive of neither withdrawal nor abuse. Furthermore, the animal data suggest a profile differing in crucial respects from that of the benzodiazepines. Normal human data are of limited value, but nonetheless the contrast between buspirone and the sedative hypnotics is striking. In the ultimate test, in patients, short-term use is not followed by rebound, nor is any withdrawal reaction discernible after usage for up to six months. Case reports suggestive of withdrawal or abuse are sporadic and unconvincing.

These data, together with the undoubtedly different pharmacology of buspirone, suggest that anxiolytic properties are not inevitably accompanied by a potential for abuse and dependence. Experience with other classes of psychotropic drugs, such as the tricyclic antidepressants, has emphasised to clinicians that useful therapeutic effects can be obtained without the risk of abuse or dependence. Indeed, the problem is often to improve compliance, not to obviate misuse.

Psychotropic drugs have complex effects on the brain. For this reason, predictability of effects from animals and normal subjects to patients and from formal clinical trials to the realities of medical practice are neither easy nor fail-safe. It is necessary, therefore, to maintain monitoring of the practical usage of buspirone and to evaluate carefully any phenomena suggestive of rebound, dependence, or abuse, however unlikely such clinical reports appear on first examination.

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