

## EDITORIAL

# The biological basis of benzodiazepine dependence<sup>1</sup>

Benzodiazepines are the most widely prescribed psychotropic drugs and while the specific neural pathways mediating their several therapeutic effects remain largely unknown, at least their initial site of action has been identified. For the last decade we have known that the central nervous system contains high affinity, stereospecific binding-sites for the benzodiazepines. These sites are found on a supramolecular complex with  $\gamma$ -aminobutyric acid (GABA) receptors and with a chloride ionophore (channel across the cell membrane), which also has binding-sites for drugs such as the barbiturates (Olsen, 1982).

Recently there has been a growing appreciation that benzodiazepines induce dependence and that tolerance can occur to their behavioural effects. Although initially these phenomena were linked with long-term use, more recent evidence suggests that similar changes can be observed after short-term or even a single administration.

This review covers both the clinical evidence and relevant experimental studies and attempts to explore the possible underlying mechanism(s). Although the precise mechanism is still unknown, we conclude that both rebound and withdrawal symptoms are reflections of a common dependence mechanism and also that tolerance is simply another manifestation of this same mechanism. We further conclude that the same underlying mechanism mediates the rebound phenomena and tolerance seen after short-term or acute benzodiazepine administration.

## DEPENDENCE

Dependence is a hypothetical construct for the state induced by the compensatory change that occurs, for example, in the central nervous system as a result of drug administration. The nature of the compensatory change induced by the benzodiazepines remains unknown, but evidence for physical dependence comes from rebound and withdrawal symptoms. To date rebound and withdrawal have been separated in the literature because the former follows acute or short-term, and the latter chronic, drug treatment. We shall follow the literature and describe each separately, but we shall then argue that the two phenomena cannot be distinguished and therefore that each reflects the same common mechanism of dependence, albeit to a different degree.

## REBOUND SYNDROME

Rebound can be defined as the increase in severity of the original symptoms, beyond pre-treatment levels, after short or long-term drug administration. Rebound effects have been described after sleep-laboratory studies involving 1–2 weeks of benzodiazepine administration (Kales *et al.* 1983 *a*), as well as after longer-term administration (Adam *et al.* 1976; Oswald *et al.* 1982). Rebound insomnia after the use of benzodiazepines as hypnotics is now well-documented (for review, see Lader & Lawson, 1987). It is more severe than the original insomnia, and is characterized by a delayed onset of sleep and by frequent awakenings. The elimination half-life of the benzodiazepine is important in determining the timing and the severity of rebound. Short-acting drugs (e.g. triazolam with a half-life about 2.6 hours) produce severe rebound for the next night or two; medium acting compounds (e.g. temazepam, with a half-life around 8.4 hours) produce less severe rebound 2–3 nights later; and long-acting drugs (e.g. flurazepam, with a half-life or active metabolites of over

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100 hours) produce only minor and sporadic rebound (Kales *et al.* 1983*a*). This phenomenon is dose-related: after 6 consecutive nights of triazolam, normal volunteers showed rebound insomnia after 0.5 mg, but not after 0.25 mg (Roehrs *et al.* 1986). A possible variant of rebound insomnia is early-morning insomnia, an increase in wakefulness during the final hours of drug nights. This has been reported following one or two weeks administration of short-acting benzodiazepine hypnotics (Kales *et al.* 1983*b*). Increased anxiety later in the day has also been found (Morgan & Oswald, 1982).

Rebound symptoms have also been described following the use for less than six weeks of benzodiazepines to treat anxiety. Pecknold *et al.* (1982) found rebound anxiety after 3 weeks of treatment with oxazepam (45 mg/day) or halazepam (120 mg/day). In a placebo-controlled study in general practice, mild rebound anxiety was reported following abrupt termination of treatment after 6 weeks of 15 mg/day of diazepam (Power *et al.* 1985). The importance of the rate of termination of drug treatment is illustrated by a study in which abrupt termination was compared with a gradual reduction over 3 weeks and with placebo administration throughout (Fontaine *et al.* 1984). After 4 weeks of bromazepam (18 mg/day) or diazepam (15 mg/day) the abruptly-withdrawn patients had ratings on the Hamilton Anxiety scale significantly above their placebo scores, whereas those undergoing gradual drug termination returned to placebo levels. Marked rebound anxiety was more common for the patients stopping bromazepam (5/8) than diazepam (2/8), again illustrating that it is harder to detect rebound effects with benzodiazepines with long half-lives.

## WITHDRAWAL SYNDROMES

No attempt has been made to define these syndromes with respect to the duration of treatment, but clinically 2 syndromes have been distinguished on the basis of the dosage involved (Laux & Puryear, 1984; Smith & Wesson, 1983). However, we suggest that both reflect the same underlying mechanism and they are characterized by symptoms in the direction opposite to the effects of the drug. High-dose (normally 2–5 times the normal anti-anxiety dose) withdrawal has been best characterized by Hollister and his colleagues (1961, 1963), but the literature is peppered with single case reports (Marks, 1978; Palmer, 1978). Initially, withdrawal after therapeutic dosage was indicated only by sporadic case reports (e.g. Khan *et al.* 1980), but it has now been confirmed in both laboratory and clinical studies (Hallstrom & Lader, 1981; Tyrer *et al.* 1981; Petursson & Lader, 1981*a*). Even with therapeutic doses there is some evidence that a withdrawal syndrome is found more frequently the longer the treatment, e.g. 6 compared with 22 weeks (Rickels *et al.* 1983, 1984).

Withdrawal symptoms, summarized by Ladewig (1984), fall roughly into three categories: (1) psychological symptoms of anxiety such as apprehension, irritability, insomnia and dysphoria; (2) bodily symptoms of anxiety, particularly tremor, palpitations, vertigo, sweating and severe muscle spasms; (3) perceptual disturbances such as hypersensitivity to light, sound and touch; pains; depersonalization; feeling of motion; metallic taste. It is difficult to distinguish this syndrome from that described as rebound, except perhaps for category 3 symptoms.

The first two categories may resemble the original anxiety, but as with rebound the symptoms are more severe (Ladewig, 1984). Most commonly these symptoms subside in 5–15 days, which is not consistent with a re-emergence of the original anxiety (Owen & Tyrer, 1983). That they are part of a withdrawal response is also indicated by their presence in patients who have been taking benzodiazepines in therapeutic doses for 6 months or more for a non-psychiatric reason, e.g. chronic muscle-spasm following a sports injury (Lader, personal observation).

Gradual withdrawal may be followed by a milder, yet specific syndrome which is the same whether the dosage was high or low (Hallstrom & Lader, 1981). However, even with gradual withdrawal from low doses, prolonged and bizarre responses have been described (Ashton, 1984). Ashton emphasizes how physically ill the patients felt and also describes agoraphobic, panic and depressive symptoms. In some cases a full-blown depressive syndrome occurs (Olajide & Lader, 1985).

In keeping with the evidence that gradual discontinuation of drug treatment gives a less marked

withdrawal response than abrupt termination, it has been claimed that short-acting benzodiazepines produce the most marked withdrawal reactions and that those with elimination half-lives (of parent compound and active metabolites) greater than 36 hours produce milder, but more prolonged withdrawal (Hollister, 1983; Marks, 1983). Nonetheless, the withdrawal response to drugs in the latter category, e.g. clorazepate and clobazam, is still measurable (Winokur & Rickels, 1984; Petursson & Lader, 1981*b*). Support for Hollister's suggestion comes from the findings that diazepam (with its long-acting metabolite desmethyldiazepam) produces a less severe withdrawal syndrome than the short-acting benzodiazepine, lorazepam (Tyrer *et al.* 1981). A study with high-dose users also suggests that an important factor is the rate of disappearance of drug from the brain. The severity of withdrawal was related to the disappearance of diazepam, and desmethyldiazepam both modified and prolonged the withdrawal syndrome (Rhodes *et al.* 1984). Following abrupt termination of treatment, Tyrer *et al.* (1981) compared the rate of decrease of plasma diazepam and desmethyldiazepam in patients with and without a withdrawal syndrome. While there was no difference for diazepam, more pronounced withdrawal symptoms were accompanied by a more rapid reduction in desmethyldiazepam. When withdrawal took place gradually over 4 weeks no such relationship was found, but the rate of decrease of drug concentrations was slower (Tyrer *et al.* 1983).

In conclusion, the duration of action of a particular benzodiazepine might influence both the time at which withdrawal occurs and its severity. The latter is also influenced by the dose and the duration of treatment, but there is no clinical evidence that the withdrawal response is different in nature following different doses. We therefore conclude that there is no evidence for separating either rebound or withdrawal phenomena after low or high doses and therefore propose that they are all manifestations of the same underlying dependence mechanism.

## DEPENDENCE: ANIMAL STUDIES

Benzodiazepine dependence in animals has been assessed from the withdrawal responses that occur when drug treatment is abruptly terminated or after a benzodiazepine antagonist has been given to precipitate withdrawal.

All but one of the studies on spontaneous benzodiazepine withdrawal in animals have used doses that fall well above the equivalent of the human therapeutic range, and might therefore be criticized for simply demonstrating toxic reactions. However, if we are correct in our hypothesis that the same mechanism of dependence is triggered by high and by low doses then these studies are relevant. After 24 days of administration of diazepam at 100–1000 times the anxiolytic dose in rats, they were hyperactive and had a lowered threshold for audiogenic seizures (Kiiänmaa & Boguslawsky, 1981). There was hyperactivity, increased autonomic responses and enhanced polysynaptic activity in spinal neurones in rats withdrawn after 5 weeks of chlordiazepoxide in doses 100–200 times the anxiolytic dose (Ryan & Boisse, 1984). Using doses of diazepam and lorazepam about 100 times the anxiolytic dose, hyperactivity, seizures, explosive awakenings, wet dog shakes, hostility and decreased food and water intake have been found in rats (Martin *et al.* 1982); and tremor, rigidity and decreased food intake have been reported in dogs (McNicholas *et al.* 1983). Using doses around 10 times the anxiolytic dose, hyperactivity and increased anxiety have been found in rats withdrawing from diazepam or chlordiazepoxide (McMillan & Leander, 1978; Emmett-Oglesby *et al.* 1983*a*). While these studies provide a description of the withdrawal syndrome in animals and suggest that the syndrome may not be qualitatively different following high or low doses, they provide no information as to the underlying mechanism.

One possibility is that withdrawal is due to a change in endogenous ligands that act at the benzodiazepine receptor. The benzodiazepine receptor is unusual in that as well as the benzodiazepines that act there to lower anxiety levels and seizure thresholds, it can also mediate the action of the so-called 'inverse agonists' which have behavioural effects in the opposite direction, i.e. they increase anxiety and promote seizures. While no endogenous ligand has yet been identified with certainty, there is evidence that both a benzodiazepine-like and an inverse agonist-like ligand might

exist; it is thought that the behavioural effects observed after the administration of the benzodiazepine receptor antagonist Ro15-1788 reflect antagonism of these two types of ligand (for review, see File & Pellow, 1986). Several studies suggest that withdrawal is not due to an increased action of an endogenous inverse agonist ligand. Following 7 days of administration of flurazepam (40 mg/kg) mice had a lowered seizure threshold 24 hours later, and this threshold was not modified by administration of the benzodiazepine receptor antagonist Ro15-1788 (Little *et al.* 1984). Both mice and rats showed a withdrawal response several hours after lorazepam, indicated by a reduction in seizure threshold, hyperactivity and changes in exploratory head-dipping; none of these behaviours was modified by the administration of Ro 15-1788 (Lister & File, 1986; Lister & Nutt, 1986; Wilks & File, unpublished). These studies suggest that an increase in an endogenous inverse-agonist-like ligand is not responsible for withdrawal responses and, furthermore, they demonstrate that it is possible to see a withdrawal response after a single dose of lorazepam. However, nothing hereto excludes the possibility that the behavioural changes seen in withdrawal are due to the suppression of a normally acting benzodiazepine, or agonist-like, ligand.

The studies using precipitated withdrawal have also in general used very high doses of benzodiazepines. In the most extreme study rats were given over 200 times the anxiolytic dose of diazepam for 6 months. When withdrawal was precipitated with the benzodiazepine antagonist, Ro15-1788, there was increased motor activity, poker tail, wet dog shakes, head and body tremor, occasional clonus and digging (McNicholas & Martin, 1982). Since precipitated withdrawal involves the most rapid decrease of drug bound to receptors it is surprising that it was *less* intense than was spontaneous withdrawal. Using about 10–100 times the anxiolytic dose, mice and rats withdrawn from diazepam were hyperactive and mice had more seizures, particularly after the higher doses (Cumin *et al.* 1982). In contrast to the mild withdrawal seen in rats, withdrawal is more easily detected in cats, a species which is very sensitive to benzodiazepines. After 35 days of about 10 times the anxiolytic dose of flurazepam, cats showed precipitated withdrawal responses of increased muscle tone, tremor, piloerection, pupil dilatation and excess salivation (Rosenberg & Chiu, 1982). Changes were similar after 16 days of 10 times the anxiolytic dose of lorazepam (Cumin *et al.* 1982). Marked changes occurred in monkeys treated for 15 days with 10 times the anxiolytic dose of diazepam (Cumin *et al.* 1982). In baboons, precipitated withdrawal can be detected even after doses of diazepam as low as 0.25 mg/kg for 7 days, comprising abnormal body postures, nose rubbing, retching and limb tremor. Head and body tremor and convulsions were seen only after 35 days of treatment at higher doses (Lukas & Griffiths, 1984). In this study precipitated withdrawal *was* more rapid, severe and of shorter duration than spontaneous withdrawal, in keeping with the rapid offset of receptor occupancy by diazepam. A gradual decline in the severity of withdrawal responses was seen after repeated applications of Ro15-1788 to baboons given diazepam or triazolam for one month (Lamb & Griffiths, 1985). This is unlikely to be due to a developing tolerance to the antagonist properties of Ro15-1788, since these are maintained over 5 days of treatment (File *et al.* 1986). In rats, enhanced anxiety has been found after treatment for 5–6 days with about 100 times the anxiolytic dose of diazepam (Emmett-Oglesby *et al.* 1983*b*), or after 5 days of treatment with 4 times the anxiolytic dose of chlordiazepoxide (File & Pellow, 1985*b*).

Thus at least two studies, one in rats and one in baboons, suggest that precipitated withdrawal can be detected in animals following relatively short-term treatment with doses of benzodiazepines within the therapeutic dose range. This again supports the idea that a common mechanism of dependence is involved.

## COMMENT

At this point we should like to evaluate our proposal that rebound and withdrawal differ only quantitatively from each other and that the duration of drug treatment is not a relevant factor in determining the nature of the withdrawal syndrome. The main difficulty for this hypothesis is that the withdrawal syndrome comprises some features that are not seen in rebound and are not in the opposite direction to known benzodiazepine action. The perceptual hypersensitivity perhaps falls

in this category. However, little is known of the direct effects of benzodiazepines on perceptual functioning, and a depressant action cannot be excluded. Another dramatic feature of withdrawal, albeit infrequent, is a psychotic state, typically paranoid in flavour. Benzodiazepines have little antipsychotic action and therefore this response would not be predicted. However, the rarity of the response suggests it could be a feature of individual predisposed patients rather than a characteristic of benzodiazepine withdrawal.

## TOLERANCE

Tolerance has been defined by Jaffe (1980): 'Following repeated administration, a given dose of a drug produces a decreased effect, or, conversely, increasingly larger doses must be administered to obtain the effects observed with the original dose'. Although different mechanisms might underlie the waning of a response to a constant dose and the maintenance of a response by increasing the dose, there is no evidence to support this and we shall therefore assume that these simply represent two ways of demonstrating tolerance. We shall also show that tolerance can be demonstrated following a single dose of a benzodiazepine. Thus, as with dependence, the duration of treatment is not crucial to the demonstration of tolerance and may affect only the extent of the effect. However, it will be seen that tolerance to the various effects of benzodiazepines proceeds at different rates. The most important question that we shall address is whether benzodiazepine tolerance is simply another manifestation of drug dependence, or whether the two are independent phenomena, coinciding by chance.

The benzodiazepines are undoubtedly effective anxiolytics in the short-term, but the review from the UK Committee on Review of Medicines (CRM) (1980) concurred with the conclusion of a study carried out by the White House Office of Drug Policy (1979) that benzodiazepines have not been shown to be effective over long periods. The CRM further noted that 'there was little convincing evidence that benzodiazepines were efficacious in the treatment of anxiety after four months' continuous treatment'. A major study since then seems to contradict this view (Rickels *et al.* 1983, 1984, 1985). Chronically anxious outpatients were treated for 6 to 22 weeks with diazepam (15–40 mg/day) and the efficacy of diazepam was maintained over this period. If tolerance to the anxiolytic action of diazepam had not developed within this period, then this study provides major evidence against our hypothesis that tolerance is a manifestation of dependence. As was seen in the previous section, withdrawal responses from diazepam can certainly be seen after this period of treatment. However, since anxiety levels rarely remain constant, it is possible that clinical improvement and not drug action was responsible for the decrease in anxiety seen after several weeks of treatment.

In patients who had been taking normal doses of benzodiazepines for 6 months or more, tolerance was assessed by giving test doses of diazepam (Petursson & Lader, 1984). The responses of patients were compared with the effects of the test dose of diazepam in normal subjects. In the patients, the expected increase in plasma growth hormone concentrations to diazepam was almost totally suppressed, indicating marked tolerance. Subjective feelings of sedation to the diazepam were reduced, indicating partial tolerance; and there was no tolerance in the EEG fast-wave response. In patients taking high doses of benzodiazepines for at least one year there was marked tolerance to the psychomotor effects of a test dose of lorazepam; little tolerance was shown in patients taking low doses for one to eleven months (Aranko *et al.* 1985*b*). In long-term benzodiazepine users, the anxiolytic effect, reduction of critical flicker fusion threshold and the short-term memory impairments induced by benzodiazepines were found to persist, whereas there was no longer any psychomotor impairment or sedation (Lucki *et al.* 1986). This suggests that tolerance had developed to the latter effects, but not to the former.

The experiments with patients did not permit evaluation of the onset of tolerance, but at least in normal volunteers tolerance to some of the effects of benzodiazepines seems to develop very rapidly. Tolerance developed after 3 doses to the impairments of driving performance seen in some tests the morning after night-time administration of nitrazepam (Laurell & Tornros, 1986). File &

Lister (1983) found tolerance to some of the effects of lorazepam 2.5 mg after 2–3 doses, even when the intervals between drug administrations were 7 days; the biggest changes were seen from the first to the second dose. Again, the rate of development of tolerance seemed to be task-specific. After three doses it had developed to the decrease in finger-tapping and to self-ratings of dizziness, but not to the drug-induced impairments in learning nonsense-syllable paired associates, in self-ratings of sedation or in changes in heart rate. Ghoneim *et al.* (1981) found that verbal recall was still impaired after 3 weeks of daily diazepam administration to normal volunteers. Similarly, after 3 weeks of diazepam administration to normal volunteers Brosan *et al.* (1986) found no tolerance to the psychomotor or cognitive impairments.

Mattila's group has carried out a series of volunteer studies on tolerance to benzodiazepines; in all cases the subjects were given a battery of tests after a challenge dose of lorazepam (3 mg/kg) or diazepam (15 mg). After 7 days of lorazepam (1 mg twice a day) or diazepam (5 mg twice a day) no definite tolerance was found on subjective effects, but several psychomotor and cognitive effects showed tolerance to lorazepam and cross-tolerance between the two drugs (Aranko *et al.* 1983). Following 7 days of diazepam (5 mg) thrice daily tolerance developed, whereas none could be detected following alprazolam (0.25 mg) thrice daily (Aranko *et al.* 1985*a*). Because a previous study had eliminated the role of diazepam's metabolites in the development of tolerance to diazepam (Aranko *et al.* 1984), the difference between diazepam and alprazolam was probably because the two doses were not equivalent, that for alprazolam being lower. It is not clear why tolerance is found to diazepam in some studies but not in others, although the sensitivity of the tests is likely to be crucial. As is the case for tolerance, cross-tolerance between benzodiazepines is also task-dependent (Aranko, 1985). One of the crucial factors may be whether the subjects are able to learn a compensatory response to the drug and the extent to which this could affect performance in the task. Thus one would expect little tolerance to be manifested in critical flicker fusion (e.g. Lucki *et al.* 1986). In agreement with this suggestion, when nitrazepam (10 mg) or temazepam (20 mg) were given at night for 10 nights, no tolerance could be detected when volunteers were challenged with a test dose of lorazepam (Aranko *et al.* 1985*a*).

Very rapid development of tolerance can be seen after benzodiazepine overdose. In this case the behavioural effects of benzodiazepines rapidly wane despite persisting high plasma concentrations (Greenblatt *et al.* 1978). This, together with the study by Petursson & Lader (1984), suggests that it is possible to demonstrate tolerance after both acute and chronic treatment even when there is still drug acting at the benzodiazepine receptor. This then raises the question of whether withdrawal responses can be elicited when there is still drug acting at the receptor. One animal experiment on withdrawal after acute lorazepam suggests that it is. In the experiment by Lister & Nutt (1986), withdrawal was demonstrated 6 hours after a single dose of lorazepam and the withdrawal response was not modified by Ro15-1788. However, at this same time there was still lorazepam acting at the receptor since a residual anticonvulsant action could be detected and *this effect was reversed* by the receptor antagonist, Ro15-1788. Most important of all to our consideration of the relative time courses of tolerance and withdrawal, it was possible to see both responses at the *same* time after benzodiazepine treatment (see the following section).

## TOLERANCE: ANIMAL STUDIES

Tolerance has been demonstrated to the anticonvulsant action of lorazepam 6 hours after a single dose (1 mg/kg) in mice (Lister & Nutt, 1986). After chronic treatment, tolerance is seen to most of the behavioural effects of benzodiazepines in animals (for review, see File, 1985). As was found for patients and for human volunteers, tolerance develops at very different rates for the various behavioural actions. It develops very rapidly to the sedative and anticonvulsant effects (from 3–5 days), but takes 10–15 days to develop to the anxiolytic effects, as measured in animal tests, and may not develop at all to the locomotor stimulant effects of low doses (at least > 20 days). There is no cross-tolerance between the sedative and stimulant effects of the benzodiazepines in mice (File & Pellow, 1985*a*) and in rats, as tolerance develops to the sedative effects, EEG signs of stimulation

emerge and persist (Mele *et al.* 1984). Thus both human and animal studies suggest that there are different time-courses of tolerance to different behavioural effects and that some might not show tolerance. If we wish to pursue our unitary hypothesis of dependence we would then have to suggest that the time-course of withdrawal would be different for different behaviours; and that the behavioural effects of benzodiazepines to which tolerance could not be demonstrated would in turn not be mirrored in a withdrawal response. There is no evidence to date on the latter part of the prediction, but different withdrawal responses certainly have different time-courses following lorazepam treatment (Wilks & File, 1985; and unpublished). Although different behaviours show different time courses of tolerance, the half-life of the benzodiazepine, the spacing of doses and the dose itself have no effect on the rate at which tolerance develops (File, 1985).

Whilst the mechanism of tolerance remains unknown, we can at least exclude certain possibilities. There is no evidence for any pharmacokinetic contribution to the tolerance seen to low and moderate doses (for review see File, 1985). Similarly, there is no evidence that a few days of treatment with these doses induces any change in benzodiazepine binding (see File, 1985), and acute tolerance is not accompanied by any change in *in vivo* receptor occupancy (Wilks *et al.* 1987). It is unlikely that tolerance involves an increase in an endogenous ligand, since the effects of the receptor antagonist Ro15-1788 is unchanged after chronic treatment in rats (File, 1982*a*) or baboons (Lamb & Griffiths, 1985). Thus, neither tolerance nor withdrawal seems to be mediated by the action of endogenous ligands. However, the latter study suggests that the time-course of tolerance and withdrawal may differ, for the withdrawal responses waned over the course of several days, whereas tolerance persisted.

## CONCLUSION

At this point we should review our hypothesis that both tolerance and withdrawal are manifestations of the same dependence mechanism. We have established that both phenomena can be observed after low and high doses. Indeed, the development of tolerance to the sedative effects is independent of the treatment dose, so long as the dose has a sedative action (File, 1982*b*; Lister *et al.* 1983). It is also possible to observe both phenomena after long- or short-term treatment and after a single administration. We therefore feel that the definition of tolerance should be extended to include acute tolerance, i.e. a reduced response following a single administration of a benzodiazepine. It also seems possible to exclude any increased production of endogenous ligands in tolerance or withdrawal. The time-courses of both phenomena differ for different behaviours, which may reflect recruitment of different neurotransmitter pathways. However, there are some studies that indicate a different time-course for withdrawal and tolerance when the *same* behaviour is measured (e.g. the clinical studies on anxiety). We could accommodate this if tolerance were a less sensitive indication of dependence, or developed more slowly, than withdrawal. In general the human evidence would support this contention. However, the animal evidence is quite to the contrary and there is no obvious reason for such a species difference, although in our favour the animal literature reveals marked species differences in the frequency and intensity of withdrawal responses.

A unitary hypothesis of this sort represents an initial attempt to combine under one heading many, but not all, of the clinical phenomena of withdrawal and tolerance. We do not try to account for high-dose recreational use of benzodiazepines under this heading. This is a different clinical phenomenon and the crucial factors may be related to pharmacokinetic considerations such as speed of onset of action and acute psychotropic, particularly euphoriant, effects (Busto & Sellers, 1986).

We have confined our review to benzodiazepines, but other CNS drugs producing dependence (e.g. morphine) could be susceptible to similar analysis.

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