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Protracted Withdrawal Syndromes From Benzodiazepines

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Abstract—*The benzodiazepine withdrawal syndrome is a complex phenomenon which presents serious difficulties in definition and measurement. It is particularly difficult to set out precise limits on its duration. Many withdrawal symptoms are a result of pharmacodynamic tolerance to benzodiazepines, some mechanisms for which are discussed. Such tolerance develops unevenly in different brain systems and may be slow to reverse. Withdrawal symptoms occurring in the first week after cessation of drug use tend to merge with more persistent symptoms that may last for many months. These prolonged symptoms do not necessarily constitute "true" pharmacological withdrawal symptoms, but are nevertheless related to long-term benzodiazepine use. Such symptoms can include anxiety, which may be part of the learning deficit induced by the drugs, and a variety of sensory and motor neurological symptoms. The protracted nature of some of these symptoms raises the possibility that benzodiazepines can give rise not only to slowly reversible functional changes in the central nervous system but may also occasionally cause structural neuronal damage.*

Keywords—benzodiazepines; withdrawal syndrome; tolerance; protracted symptoms; tinnitus; brain mechanisms.

DRUG WITHDRAWAL SYNDROMES, in general, tend to consist of mirror images of the drugs' initial effects. Thus, abrupt withdrawal from chronic usage of beta adrenoceptor antagonists such as propranolol may give rise to tachycardia and palpitations; abrupt withdrawal from antihypertensive doses of clonidine may be followed by hypertension, anxiety, and other signs of increased sympathetic activity. Benzodiazepines are no exception: On sudden cessation after chronic use, anticonvulsant effects may be replaced by epileptic seizures, muscle relaxation by increased muscle tension, hypnotic effects by insomnia or nightmares, and anxiolytic effects by increased anxiety. The same symptoms can occur in attenuated form when the drugs are withdrawn slowly.

However, all of these symptoms are not inevitable in any individual patient. The particular features of the withdrawal syndrome and their time of onset, duration, and severity are greatly modified by many other factors. Such factors include pharmacokinetic variables, dosage and duration of drug use, rate of withdrawal, the presence or absence of the original disorder (such as anxiety for which the drug was prescribed, personality characteristics, physical make-up and susceptibility, and the use of concomitant treatments. These variables alone make it difficult to characterize specific features of the withdrawal syndrome.

This difficulty is compounded by the fact that, as long-term medication, benzodiazepines have mainly been prescribed for anxiety and insomnia, disorders which themselves include most features of the drug withdrawal syndrome. When such patients undergo reduction of benzodiazepine dosage, especially slow reduction, how can one specify which emergent symptoms are "true," drug-related withdrawal symptoms, which are "pseudowithdrawal" symptoms (Tyrer, Owen, & Dawling, 1983), which represent a return of the original anxiety state, and which are the natural reactions of an anxious personality undergoing the stress of withdrawal? In circumstances such as these, the benzodiazepine withdrawal syndrome becomes largely a matter of definition.

Nevertheless, the existence of a benzodiazepine withdrawal reaction, from both high and low (therapeutic) doses of benzodiazepines, is no longer in dispute, and many attempts have been made to define and measure it and to estimate its incidence and duration.

Definitions and Measurements

Symptoms occurring during benzodiazepine withdrawal have been described by many authors (Ashton, 1984, 1987; Busto, Sellers, Naranjo, Capp ell, Sanchez, & Sykora, 1986; Hallstrom & Lader, 1981; Murphy, Owen & Tyrer, 1983, 1984; Petursson & Lader, 1981a, 1981b; Smith & Wesson, 1983; Tyrer et al., 1983; Tyrer, Rutherford, & Higgatt, 1981; Winokur, Rickels, Greenblatt, Snyder, & Schatz, 1980; among others). Commonly described symptoms are shown in Figure 1. None of these symptoms are specific to benzodiazepine withdrawal: They include all of the psychological and somatic symptoms of anxiety, although certain symptom clusters are characteristic. Owen and Tyrer (1983) and Petursson and Lader (1981a & b) emphasized the appearance of new symptoms, not experienced before withdrawal and uncommon in anxiety states. These new symptoms include hypersensitivity to sensory stimuli (sound, light, touch, taste, and smell) and perceptual distortions (e.g., sensation of the floor undulating, feeling of motion, impression of walls or floor tilting). There also appears to be a higher incidence than usually seen in anxiety of depersonalization, derealization, paresthesias, and extreme dysphoria, an amalgam of anxiety, depression, nausea, malaise, and depersonalization (Petursson & Lader, 1981a, 1981b). Visual hallucinations, distortion of body image, psychotic reactions, formication, muscle fasciculation and twitching (occasionally resembling myoclonus), and considerable loss of weight are also described during benzodiazepine withdrawal and are unusual in anxiety states.

Smith and Wesson (1983) and Ashton (1984) drew attention to the characteristic fluctuation of symptoms, which may wax and wane without obvious psychological provocation. Smith and Wesson (1983) suggest that this wavelike symptomatology is a unique marker for distinguishing [illegible] withdrawal syndrome from symptom re-emergence. However, since symptoms may fluctuate in the course of the day or over periods of days or weeks, accurate recording is difficult.

Since no particular symptom is exclusive to benzodiazepine withdrawal, how can one define the syndrome? Tyrer et al. (1981) [illegible] various methods in placebo-controlled studies:

1. The appearance of [illegible] new symptoms during the withdrawal period. [illegible] one study included paroxysmal disturbances, sensory hypersensitivity, and [illegible] (1981), and in another study [illegible] toms, depression [illegible] and abnormal sensations [illegible] of two new symptoms [illegible] essary to qualify [illegible]
2. An increase in [illegible] Inventory of Clinical Psychiatric [illegible]

of baseline levels, followed by a return to lower values. Symptom resolution is clearly an important feature in differentiating between symptoms due to withdrawal and symptom re-emergence, emergence, or overinterpretation. As Smith and Wesson (1983, p. 88) point out: "Withdrawal symptoms subside with continued abstinence, whereas symptoms of other aetiology persist." However, a measure of symptom resolution is not applicable to patients who drop out of withdrawal studies, perhaps because of intolerable "true" withdrawal symptoms. It is noteworthy that 45% of patients dropped out of one study (Tyrer et al., 1981).

3. A combination of methods (1) and (2) so that a withdrawal reaction is defined as the appearance of new symptoms that resolved before the end of the study (20 and 14 weeks after the end of withdrawal [Tyrer et al., 1983]). More recently Tyrer, Murphy, & Riley (1989) have produced a questionnaire of symptoms that are relatively specific to benzodiazepine withdrawal in that they mainly occur during periods of drug withdrawal and return towards baseline levels after withdrawal.
4. Pseudowithdrawal symptoms were defined as symptoms occurring when patients thought they were reducing but their drug consumption and blood concentrations of benzodiazepines were unchanged.

Such definitions, derived from double-blind, placebo-controlled studies, have been extremely helpful in the recognition of benzodiazepine dependence, especially low-dose dependence. However, they are of necessity arbitrary and can only be approximate, since the appearance or severity of any particular symptom or symptom cluster may actually represent a variable combination of true withdrawal, pseudowithdrawal, and re-emergence of anxiety, and the same patients liable to pseudowithdrawal reactions are also likely to be most vulnerable to true withdrawal effects.

Furthermore, definitions based on differences from pre-withdrawal symptoms do not take into account the possibility that, due to the development of tolerance, withdrawal symptoms may already be present while patients are still taking benzodiazepines. Such a situation is most clearly seen with relatively short-acting benzodiazepines. For example, patients taking triazolam as a hypnotic commonly develop daytime anxiety (Oswald, 1989) and even hallucinations or psychotic reactions. These are almost certainly withdrawal effects since they are immediately relieved by taking the drug and eventually disappear after the drug is stopped (Ashton, 1987). Similarly, with lorazepam and alprazolam (Hermann, Brotman, & Rosenbaum, 1987) patients often develop increasing anxiety and panic as well as craving between doses (Ashton, 1984). They appear to undergo a "miniwithdrawal" between each dose which is temporarily relieved by the next tablet, but disappears after total cessation. An analogous condition is seen with alcohol: alcoholics commonly

WITHDRAWAL SYMPTOMS

Rating: 0=none; 1=mild; 2=moderate; 3=severe;

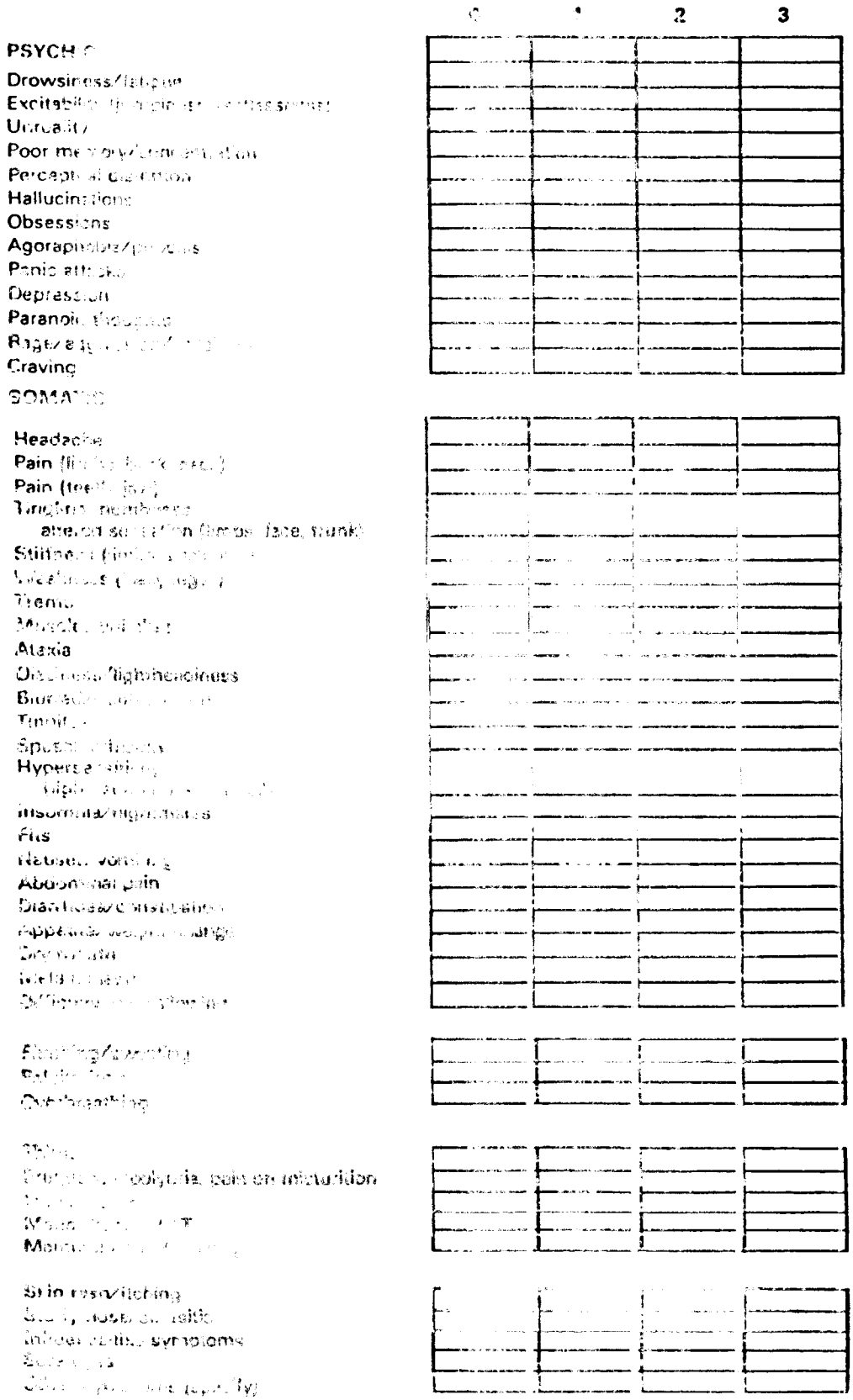

FIGURE 1. Withdrawal Symptom Rating Scale.

complain of tremor and insomnia, symptoms which are temporarily relieved by alcohol but which only disappear after a period of abstinence. Even with long-acting benzodiazepines such as diazepam, there is usually a history of long-term users of steadily increasing anxiety, with the development over the years of new symptoms such as agoraphobia, often with perceptual distortions and depersonalization, despite continued usage of these supposedly anxiolytic drugs. These symptoms may often be temporarily alleviated by a modest increase in dosage or the addition of another benzodiazepine, but even this may change during further chronic use and only disappear after the benzodiazepines are withdrawn (Ashton, 1984, 1987). Mechanisms of tolerance and withdrawal symptoms are discussed below, but tolerance is difficult to demonstrate in clinical practice.

Because of these many unmeasurable factors, it is doubtful whether the phenomenon of a "true" benzodiazepine withdrawal syndrome can ever be clearly demarcated.

Incidence

The overall incidence of the benzodiazepine withdrawal syndrome is difficult to assess with cigarette smokers (Ashton, 1987). First, there may be a large, uncounted population of long-term benzodiazepine users who, for a variety of reasons, never coming to medical attention. Tyrer (1990) notes that it is surprising how many patients in ordinary practice have no difficulties whatsoever in reducing their benzodiazepines, and the incidence of a benzodiazepine withdrawal syndrome in these patients appears to be around 30% (Tyrer et al., 1983; Tyrer, 1988; Tyrer, Murphy, & Riley, 1990). On the other hand, in self-referred patients referred for specialist treatment, the incidence is much higher (Ashton, 1987; Lader & Olajide, 1989; Lader and Lader, 1991a). It is also worth noting that withdrawal syndromes in the form of rebound insomnia (Kales, Scharf, & Kales, 1978) or more generalized symptoms can be experimental subjects after single doses of commonly prescribed benzodiazepines (Hallstrom & Lader, 1981). In addition, a withdrawal syndrome has been described in patients taking "therapeutic" doses of benzodiazepines (Rementeria & Ahern, 1984).

Not surprisingly, the incidence of benzodiazepine withdrawal syndromes depends not only on patient selection but also on the method of measurement. In the study of Busto et al. (1986), in which definitions of withdrawal symptoms were carefully used singly, the incidence of severe withdrawal reactions was around 44% (3) (see above) in patients who had symptoms were difficult to assess

drawal reactions. This incidence of course only applies to those consenting to take part in the study and managing to finish it. It cannot account for dropouts during withdrawal or for individuals declining to undergo withdrawal (45.5% of eligible patients in the study of Tyrer et al., 1981). Thus the incidence of benzodiazepine withdrawal, like its diagnosis, becomes largely a matter of definition.

Duration

The identification of the benzodiazepine withdrawal syndrome is difficult enough; its duration is even more difficult to delineate. Most estimates suggest a duration of approximately 5–28 days, with a peak in severity around 2 weeks post withdrawal, after which most symptoms return to prewithdrawal levels (Busto et al., 1986; Murphy et al., 1984; Owen & Tyrer, 1983; Rickels & Lader, 1981a, 1981b; Tyrer et al., 1981, 1983).

To a large extent the apparent duration depends upon how long the patients are followed up, and several authors have drawn attention to the prolonged nature of post-withdrawal symptoms in some cases. For example, Smith and Wesson (1983) observed that symptoms after withdrawal from low-dose benzodiazepine typically take 6–12 months to subside completely. Prolonged symptoms included anxiety, insomnia, paresthesia, altered sensation, muscle spasms, and psychosis. Ashton (1984, 1987) reported a similar protracted time-course. Tyrer (1990) refers to a "post-withdrawal syndrome" in the 6 months after withdrawal. Hallstrom and Lader (1981) found the Hamilton Anxiety Score still raised above baseline levels 30 days after withdrawal from low-dose benzodiazepines, but it had returned to baseline levels by follow-up several months later when successfully withdrawn patients "had resumed their normal lives" (Hallstrom & Lader, 1981, p. 237). Hajdu and Lader (1984) suggested that depression may be an integral part of the benzodiazepine withdrawal syndrome and may last several months after withdrawal in susceptible individuals; this phenomenon was also observed by Ashton (1987). Busto, Ferrazzini, and Naranjo (1988) described two cases in whom severe tinnitus first appeared during benzodiazepine withdrawal and persisted for 6 and 12 months after discontinuation before finally diminishing or disappearing. In one of these cases the tinnitus was initially alleviated by diazepam in a double-blind placebo-controlled trial conducted over 1 week, 6 months after withdrawal, after a further 6 months of treatment the tinnitus had become tolerable.

In a prospective study of 58 patients who were withdrawn from benzodiazepines over a 6-week period and followed for a further 6 weeks, Tyrer et al. (1989), using visual-analog scales, found a wide variation in the time at which individual symptoms peaked. Mean scores for some symptoms (depression, dizziness, par-

esthesia, feelings [illegible] mean scores for [illegible] faintness, tetch[illegible] were maxima[illegible] Although indi[illegible] ported, and 50% [illegible] ings suggest that [illegible] 5–28 days usual[illegible] withdrawal syndrome.

Ashton, Rawlins [illegible] scale shown in Figure [illegible] of patients undergoing [illegible] blind placebo con[illegible] place over 4 [illegible] 8 weeks after the [illegible] received placebo [illegible] during, and [illegible] the time-course [illegible] 12 patients in the [illegible] completed withdrawal [illegible] after the end of [illegible] ache, dizziness, [illegible] motor symptoms [illegible] scores; other [illegible] had disappeared. [illegible] duration of symptoms [illegible] is often a matter [illegible] ent symptoms [illegible]

Ashton et al. 1990) studies, which differed also in size of sample [illegible] selection, and rate of withdrawal. The [illegible] persistent symptoms are "true" withdrawal symptoms is unknown.

A further problem in assessing the duration of the withdrawal syndrome is the interpretation of the baseline (prewithdrawal) symptoms and anxiety scores. Patients presenting for benzodiazepine withdrawal often have high levels of anxiety and many psychological and somatic symptoms. Figures 2 and 3 show Hospital Anxiety Depression (anxiety) (Zigmond & Snaith 1983) and symptom rating scores for 12 patients on benzodiazepines compared with the scores of 18 healthy university students approaching their exams. Both groups took placebo tablets and were followed for 20 weeks. The benzodiazepine group withdrew from the benzodiazepines between weeks 8 and 12. It is clear that the patients had considerably higher scores than the normal subjects on both scales, even at the beginning of the study while they were still taking benzodiazepines.

Certainly in these patients the benzodiazepines were not effectively controlling anxiety and, as argued above, it is possible that at least some of the presenting symptoms were due to "withdrawal" symptoms experienced in the past, as a result of the development of drug tolerance. Such symptoms would be expected to disappear after withdrawal, but they

TABLE

[illegible] **re, during and after [illegible] drawal** [illegible] in Figure 1)

Symptom	[illegible]	[illegible]	[illegible] after start of withdrawal	Score 8 weeks after end of withdrawal
Declining Symptoms (postwithdrawal [illegible] or less than [illegible]				
insomnia/[illegible]	[illegible]	[illegible]	[illegible]	8
nausea/[illegible]	[illegible]	[illegible]	(5)	4
perceptual [illegible]	[illegible]	[illegible]	(3–6)	0
excitability/[illegible]	[illegible]	[illegible]	(6)	14
sensory [illegible]	[illegible]	[illegible]	(5)	6
poor memory/[illegible]	[illegible]	[illegible]	(5)	6
Persisting Symptoms (postwithdrawal [illegible] greater than [illegible]				
anxiety[b]	[illegible]	[illegible]	(5)	11.75
depression	[illegible]	[illegible]	(4–5)	9
tinnitus	[illegible]	[illegible]	(4–5)	9
headache	[illegible]	[illegible]	(2)	13
dizziness	[illegible]	[illegible]	(5)	8
paraesthesiae[c]	[illegible]	[illegible]	(5)	12
motor symptoms[d]	[illegible]	[illegible]	(5)	35

[a]Sensory hyp[illegible]
[b]Anxiety: Hosp[illegible]
[c]Paraesthesiae: [illegible] face, h[illegible]
[d]Motor symptoms: [illegible] muscle [illegible]

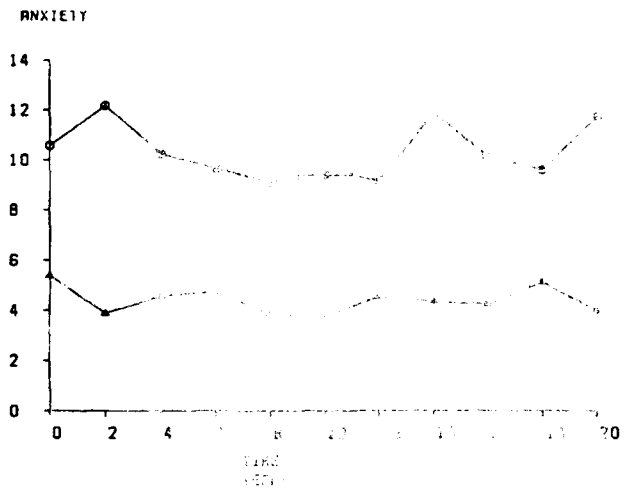

FIGURE 2. Hospital Anxiety Depression (HAD) Scale scores for anxiety over 20 weeks in healthy student and [illegible] patients taking diazepam [illegible] students took placebo tablets [illegible] diazepam during weeks 8–12. One patient dropped out after 12 weeks for domestic reasons. Circles represent placebo group; [illegible]

could be slow to resolve. There was no evidence of resolution before withdrawal, but rather a steady increase after withdrawal. Unfortunately, no further assessment appears to have been carried out, and unstructured clinical contact with most of these patients suggested that anxiety symptoms have declined over time. This slow improvement [illegible] the observations quoted

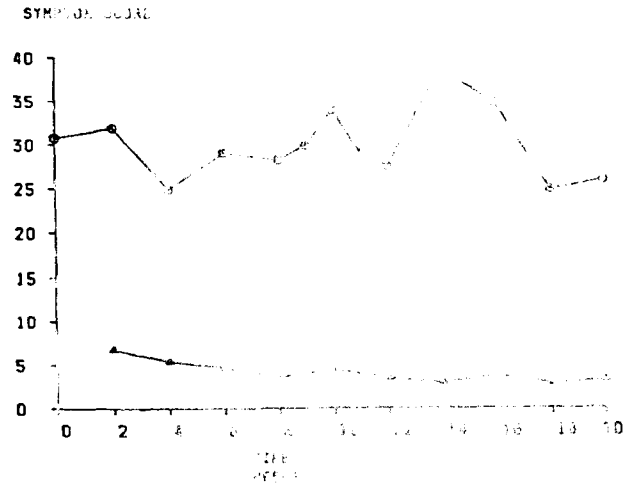

FIGURE 3. With [illegible] healthy students and [illegible] 4.6 daily). Patients and procedure as in FIGURE 2. Symptom rating scale shown in FIGURE 1. Circles represent placebo group; [illegible]

above (Ashton, 1984, 1987; Busto et al., 1988; Hallstrom & Lader, 1981; Olajide & Lader, 1984; Smith & Wesson, 1983) that symptoms improve gradually for [illegible] month after withdrawal, and some patients are able to resume normal lives after years of incapacity before withdrawal.

Which of these long-lasting symptoms can one ascribe to "true" drug withdrawal effects? Is it possible to pinpoint a time at which the benzodiazepine withdrawal syndrome ends and to say with certainty that any residual symptoms must be due to other factors? One problem is similar to that of designating which effects of a bout of influenza or infectious mononucleosis can be attributed to the specific virus. Do such effects include only those of the viral toxemia? Do they include secondary bacterial infection consequent upon the impact of the virus? Do they include the period of postviral lethargy and depression which, like benzodiazepine withdrawal symptoms, tend to recur in wave-like fashion for several months? Conceptually, the benzodiazepine withdrawal syndrome appears to slip through the fingers and one is led back to the question of definition. Probably a clear definition of the condition is impossible because drug-induced perturbations of central neurotransmission merge imperceptibly into the background of individual, genetically determined, and learned patterns of brain activity.

[illegible] Withdrawal

[illegible] problems of definition discussed above are [illegible] to describe protracted benzodiazepine withdrawal syndromes. Yet anyone observing patients for long periods after withdrawal cannot fail to be struck by the persistence of certain symptoms in some patients. These may not be "true" withdrawal symptoms; nevertheless they appear to be related to benzodiazepine use and often present a clinical problem. Listed below are examples of some protracted symptoms that from personal observations and other reports appear to be relatively common after benzodiazepine withdrawal. Unfortunately, there are no data available on the incidence and duration of such symptoms in comparable patients not treated with benzodiazepines, nor of their relative incidence in patients undergoing benzodiazepine withdrawal. Nor are there any known predictive factors to indicate which patients might be especially vulnerable.

[illegible] above, anxiety may persist for many months after benzodiazepine withdrawal, yet [illegible] show pre-withdrawal levels after 1–2 years [illegible]. One reason for the slow resolution [illegible] benzodiazepines inhibit the learning [illegible] strategies. Such effects have been [illegible] in animals and man (Gray, 1987). Con-

sequently there is a long protracted withdrawal when patients have developed coping to cope with stressful events (Murphy, 1988; Murphy & Tyrer, 1988; Owen & Tyrer, 1989). Recovery may require many months of learning new strategies of stress control to replace the coping with stress by means of exogenous drugs.

Hence persisting withdrawal does not necessarily indicate the emergence of an anxiety state existing before benzodiazepine treatment; it may reflect the unlearning of a type of learning deficiency induced by long-term benzodiazepine use. People who take benzodiazepines tend to have high ratings for trait anxiety (Ashton and Golding, 1989; Golding & Gorman, 1985; Golding, Harper, & Brent-Smith, 1985), which may indicate particular vulnerability to [illegible] even without formal psychiatric disorder. Anxiety symptoms, including agoraphobia and panic, may gradually recede after withdrawal (Ashton, 1987), although they may be exacerbated by behavioral treatments.

Depression. Depression may be caused or aggravated by chronic benzodiazepine [illegible] 1981), yet it also [illegible] drawal syndrome [illegible] severe enough to justify [illegible] der (Ashton, 1987) and is persistent in some patients. Olajide and Lader (1984) suggest that [illegible] for postwithdrawal depression [illegible] depletion, but there is no [illegible] Clinically, the depressive [illegible] illness in general [illegible] drugs. It is not [illegible] symptoms are [illegible] ous history of [illegible] sequent years after withdrawal.

Tinnitus. Tinnitus is a common [illegible] azepine withdrawal [illegible] characteristic [illegible] uli. It usually [illegible] qualifies as [illegible] describe two cases [illegible] 12 months after [illegible] tient who was [illegible] pines because [illegible] Further cases [illegible] served and described here.

Case 1. Female [illegible] 8 years. [illegible] 1986. [illegible] tempts at withdrawal [illegible] and is still [illegible] maining mainly [illegible] x-ray, CAT scan [illegible] slight bilateral [illegible] [illegible] depression; all other withdrawal symptoms [illegible] quickly. Taking no medication.

Case 2. Female, aged 47. Duration of benzodiazepine usage: [illegible]. Withdrawn slowly from diazepam 15 mg daily in [illegible]. Bilateral tinnitus first noticed during previous attempts at withdrawal, becoming severe after final withdrawal, and [illegible] present, severe, and continuous 1 year later. ENT investigations [illegible] bilateral high-tone deafness; wears [illegible] and [illegible] depression; no other withdrawal [illegible].

Case 3. Female, aged 52. Duration of benzodiazepine usage: [illegible] months from diazepam 20 mg daily over 4 weeks [illegible]. Developed acute psychotic reaction, which resolved [illegible] week. First noticed left-sided tinnitus 1 month after withdrawal. Three months later restarted diazepam 20 mg daily because of unremitting tinnitus, but experienced only [illegible] improvement on second withdrawal over one year 1988–[illegible] tinnitus severe throughout withdrawal and still [illegible] high tones, becoming intermittent. ENT examination [illegible] except for slight bilateral (symmetrical) high-tone [illegible] 30 mg daily, started after [illegible] benzodiazepine recently added with no ef-[illegible].

Case 4. Female, aged 38. Duration of benzodiazepine usage: [illegible]. First noticed tinnitus, mainly right-sided, on withdrawal from [illegible] diazepam 30 mg daily in 1985. Tinnitus continued over [illegible] level by a course of diazepam. [illegible] Drugs: no psychotropics; inhalers [illegible].

[illegible] is fairly common in the general population [illegible] application to benzodiazepine use may [illegible] raise the suspicion that [illegible] occasionally cause permanent or [illegible] damage. Such damage [illegible] CAT scans; one study (Lader & Petursson, 1984) suggested a mild degree of [illegible] in some benzodiazepine users, but [illegible] in a later study (Perera, [illegible] 1987). Two of the above patients [illegible] bilateral headaches.

[illegible] in the form of tingling, "pins [illegible] numbness of the extremities or circumoral [illegible] a fairly common symptom of benzodiazepine withdrawal. This symptom also occurs in [illegible] and possibly results from hyperventilation. [illegible] increased sensitivity of the respiratory [illegible] to hypoxia (Martin, Corris, Stone, [illegible]). It is possible that the respiratory [illegible] hypersensitive during withdrawal [illegible]. Resolution of [illegible] a few weeks of withdrawal; however, patients complain of [illegible] sensation affecting the fingers [illegible] may be protracted for months [illegible]. These symptoms suggest a peripheral sensory [illegible] may be demonstrable sensory [illegible] on sensation. Two patients summarized

below typify several [illegible] observed at a benzodiaze[illegible]

Case 1. Female, [illegible] 15 years. Severe [illegible] in 1984 during [illegible] mg daily. [illegible] 1 year 1987–8. [illegible] gradually decreas[illegible] peared. No [illegible] cation; prom[illegible]

Case 2. Female, [illegible] 12 years. First [illegible] in 1981 during [illegible] Pain persisted [illegible] drawal in 198[illegible] relieved by chlor[illegible] rological exami[illegible] late and B_{12} [illegible] normal.

Formication, [illegible] withdrawal, and [illegible] of a feeling [illegible] or pits in the [illegible] tions are rep[illegible] running over the [illegible] feeling of [illegible] may be prefer[illegible] the burning [illegible] bly be psychotic, [illegible] benzodiazepine [illegible]

Motor Symptoms. [illegible] reflexia, tremor, [illegible] common feature[illegible] usually resolve [illegible] jerking persists for [illegible] and the [illegible] or exaggerated [illegible] limb muscle[illegible] can occur. [illegible] of the whole b[illegible] cur 20 or more [illegible] may also be pr[illegible] result from [illegible] since they are [illegible] may be exam[illegible] spond to cutaneo[illegible] trolled by local [illegible] mentally induce[illegible] as these raise the [illegible] capable of caus[illegible] toneurons or gan[illegible]

Gastrointestinal symptoms are extremely [illegible] use and in [illegible] users have be[illegible] and foun[illegible] [illegible] Gastrointestinal symptoms may be aggravated by [illegible] stimulation (Lum, 1987) and may [illegible] of [illegible] benzodiazepine withdrawal in patients who have had "irritable bowel syndrome" for years. Nevertheless, there remains a [illegible] who complain of food intolerance and gastrointestinal distension which first appear during withdrawal and is protracted for many [illegible]. Tests for specific food allergies almost always [illegible] and the condition is unresponsive to [illegible] Patients often turn to alternative or "innate" medicine, undergo various forms of diet and become convinced that they have intestinal [illegible] or damage to the immune system. None of these claims have scientific support, although Lum (1987) reports that hyperventilation provokes histamine release and that the incidence of food intolerance and [illegible] allergy is [illegible] high in chronic hyperventilation. The [illegible] of benzodiazepine withdrawal [illegible] and on corticosteroid and [illegible] (both known to be affected by stress) [illegible] further attention.

Pharmacological basis of benzodiazepine withdrawal symptoms

The [illegible] of benzodiazepines is enhancement [illegible] gamma-aminobutyric acid (GABA) activity [illegible] GABA receptors in the brain. The [illegible] interaction with specific benzodiazepine-binding sites on the GABA-receptor complex (Möhler & Okada, 1977; Squires & Braestrup, [illegible] the receptors for [illegible] GABA neurons consist of small [illegible] which exert a powerful [illegible] of other neurons [illegible] cortical domain (Bloom, 1985). [illegible] are widely distributed throughout the brain, including the reticular formation, [illegible] systems, striatum, cerebral and cerebellar cortex (Iversen & Kelly, 1975). GABA is a universal inhibitor of neuronal activity and also inhibits the release of excitatory neurotransmitters (Benton & Rick, 1[illegible]). The [illegible] of benzodiazepines include not only [illegible] activity at many brain [illegible] receptors for acetylcholine, noradrenaline, [illegible] and serotonin (Haefely, Pieri, [illegible]). The clinical effects of benzodiazepines [illegible] a combination of these [illegible] specific sites. For example, [illegible] may be due to decreased [illegible] activity in septo-hippocampal [illegible] whereas benzodiazepine [illegible] related to a particular [illegible] may

[illegible] gradually engenders a [illegible] responses which tend to restore [illegible] presence of the drug. With

chronic benzodi[illegible]es occur in GA[illegible]e-creased sens[illegible]b-ably as a result [illegible]d decreased cerebr[illegible]. In addition, the [illegible]s-tems controlled by [illegible]t-atory neuro[illegible]r the sensitivity [illegible]e complex of primar[illegible]y results in ben[illegible]

This pharmac[illegible]i-evenly to differ[illegible]i-ple, tolerance a[illegible]d anticonvulsant ma[illegible]& Cook, 197[illegible]o vary between ind[illegible]n intrinsic [illegible], which are [illegible]-tics and susce[illegible]r complete ab[illegible]-rium in all [illegible]n for the high [illegible]-pine users [illegible]y to hypnotic [illegible]t chronic tole[illegible]-eral weeks [illegible]n last for mo[illegible]e central neuro[illegible]ol (Cicero, 1979).

The develop[illegible]e sets the scen[illegible]n of the [illegible]-crued to co[illegible]d of uncopposed [illegible]-ters and their [illegible]-ically [illegible]d syndrome [illegible]-pectre of thos[illegible]-tribution, [illegible]d on the part [illegible]o-tive m[illegible]e changes [illegible]-drawal. Some [illegible]d and withdra[illegible]e for both (i.e. [illegible]e reversed by [illegible]-stores the st[illegible]

As the [illegible]-drawal s[illegible]e that of tole[illegible]-ceed every [illegible]-genes and [illegible]g benzodiaze[illegible]l, (1980) and [illegible]t this unrelie[illegible]n induced by be[illegible], and it is [illegible]e

[illegible]s reactive tachi[illegible]. Different symptoms may reflect [illegible]e of the balance between different neuro-[illegible] systems as suggested by Ashton (1984) and [illegible]y to explain large interindividual differences de-[illegible]g on personal characteristics and susceptibili-[illegible]. As discussed above, it is difficult to set a definite [illegible] of the reversal of tolerance and, therefore, [illegible] withdrawal syndrome. In general, tol-[illegible] reversal takes a matter of weeks, but in some [illegible] may take for a year or more (Cicero, 1979). [illegible] or slow reversal of tolerance may account for [illegible] protracted withdrawal symptoms.

[illegible]owever, some of the changes induced by benzodiazepines [illegible] are permanent or only very slowly reversible. [illegible] that benzodiazepines apparently inhibit learning, es-[illegible] of mechanisms for coping with stress (Gray, [illegible]), dependence after many years of use may expose [illegible] long deficits, especially in the ability to cope with [illegible]. This may present as protracted anxiety, and may [illegible] to the development of severe depression. Anxiety [illegible] may then endure until new learning has [illegible] the maladaptive changes, which prob-[illegible] a reduction of endogenous GABA [illegible]

[illegible] the question of whether ben-[illegible] cause permanent neurological dam-[illegible] Benzodiazepines are lipid soluble, [illegible] accumulate in the brain and impair cere-[illegible] and limbic system function. [illegible] over many years could cause [illegible] such as cortical shrinkage, which [illegible]. Such changes have [illegible] studies in young al-[illegible] Kohler, Haubek, & Jenson, [illegible], Danish Medical Journal, 1981) although [illegible] in long-term benzodiazepine users [illegible] Lader, 1983; Parwatikar, Powell, & Jenner, [illegible] may not be sensitive [illegible] standardized [illegible] sensitive enough to detect [illegible] cognitive impairment that may per-[illegible] in long-term users. In re-[illegible] protracted benzodiazepine [illegible] tinnitus and other [illegible] symptoms) could re-[illegible] damage. These [illegible] relieved by restarting [illegible]

[illegible] features of benzodi-[illegible] benzodiazepine story re-[illegible]

[illegible]

[illegible] withdrawal. An unfinished [illegible] 125–140.

[illegible] withdrawal. Outcome in 50 pa-[illegible] 82, 655–671.

[illegible] on benzodiazepine drugs:

[illegible] *nal*, [illegible]

Ashton, H., [illegible] dictors [illegible] Kingdom [illegible]

Ashton, H. [illegible] placebo [illegible] in chronic [illegible] 157, 232–253.

Ashton, H., & [illegible]

Benton, [illegible] GABA [illegible] *Psychopharm*[illegible]

Bloom, F.E., [illegible] vous system [illegible] Molland [illegible] 236–259. [illegible]

Busto, U., [illegible] after [illegible]

Busto, U., [illegible] C.M., & [illegible] therapeutic [illegible] *Medicine* [illegible]

Cicero, T.J. [illegible] Behavioural [illegible]

Costa, E. (1981). [illegible] Holland.

Cowen, P.J. [illegible] drawal from [illegible]

Gilman, A.J. [illegible] (1988). Effects [illegible] control [illegible] *cology*, [illegible]

Golding, J.F. [illegible] medical students [illegible] *and Health* [illegible]

Golding, J.F. [illegible] drinking [illegible]

Gray, J.A. (19[illegible]). [illegible]

Gray, J.A. (1982). [illegible] ality. In [illegible] *Cognitive* [illegible] versity Press.

Haefely, W., [illegible] pharmacology [illegible] atives. In [illegible] *perimental* [illegible] Springer-Verlag.

Hallstrom, C. [illegible] non [illegible]

Hermann, [illegible] bound anxiety [illegible] acute [illegible] (Suppl. [illegible])

Kales, A. [illegible] A new [illegible]

Lader, M. (19[illegible]). [illegible] diazepine [illegible] *national* [illegible] University [illegible]

[illegible] (19[illegible]). [illegible] comparison of buspirone and [illegible] withdrawal symptoms. *Journal of* [illegible], 1, 11–15.

[illegible] (19[illegible]). Benzodiazepine derivatives—[illegible] *Biological Psychiatry*, 16, 1195–1212.

[illegible] R.J. (1984). Computed axial brain tomography [illegible] benzodiazepine users. *Psychological Medicine*, [illegible]

[illegible] E., Haubek, A., & Jenson, E. (1979). [illegible] and liver damage in young males. [illegible]

[illegible] syndromes in medicine and psychiatry. *Journal of the Royal Society of Medicine*, 80, [illegible]

[illegible] (1977). Benzodiazepine receptors: Demonstration [illegible] nervous system. *Science*, 198, 849–[illegible]

[illegible] S.M., [illegible] & Tyrer, P.J. (1984). Withdrawal symptoms [illegible] with diazepam. *Lancet*, 2, 1389.

[illegible] M., & Tyrer, P. (1988). The essence of benzodiazepine [illegible] (Ed.), *The psychopharmacology of addiction*. [illegible] Oxford University Press.

[illegible] Benzodiazepine dependence in the clinic: Reason [illegible] *Pharmacological Sciences*, 7, 457–460.

[illegible] (1986). Depression following withdrawal [illegible] A report of four cases. *Psy*[illegible]

[illegible] (1985). [illegible] syndrome 10 years on. *Lancet*, 1, [illegible]

[illegible] (1983). Benzodiazepine dependence: A review [illegible] *Drugs*, 25, 385–398.

[illegible] (1987). Computerised [illegible] following long-term use of benzodi[illegible] *Medicine*, 17, 775–777.

[illegible] (1981). Withdrawal from long-term [illegible] *British Medical Journal*, 283, 634–635.

[illegible] (1985). Benzodiazepine dependence. *British Journal of Addiction*, 76, [illegible]–145.

Rementeria, J.L., & Bhatt, K. (1977). Withdrawal symptoms in neonates from intrauterine exposure to diazepam. *Journal of* [illegible]

[illegible] (1980). Mechanisms of action of the ben[illegible] *Federation Proceedings*, 39, [illegible]

[illegible] (1983). Benzodiazepine dependency [illegible] *Drugs*, 45, 85–95.

[illegible] Benzodiazepine receptors in [illegible] *Nature*, 266, 732–[illegible]

[illegible] Muscle damage and alcoholism. *British Medical* [illegible]

[illegible] *benzodiazepine dependence*. Unpub[illegible]

[illegible] The benzodiazepine with[illegible] *Journal of Affective Disorders*, [illegible]

Tyrer, [illegible] Gradual withdrawal of [illegible] *Lancet*, 1, 1402–1406.

Tyrer, [illegible] & [illegible] T. (1981). Benzodiazepine [illegible] propranolol. *Lancet*, 1, 520–522.

Winokur, [illegible] Greenblatt, D.J., Snyder, P.J., & Schatz, [illegible] from long-term low dosage ad[illegible] *Archives of General Psychiatry*, 37, [illegible]

Young, [illegible] immunohistochemical localisa[illegible] rat brain. *Journal of Phar*[illegible] 337–346.

Z[illegible] The hospital anxiety and de[illegible] *Acta Psychiatrica Scandinavica*, 67, [illegible]