Benzodiazepine Side Effects: Role of Pharmacokinetics and Pharmacodynamics

Abstract
Benzodiazepines have a wide variety of indications. However, CNS and psychiatric adverse reactions, tolerance, and withdrawal effects of benzodiazepines are becoming increasingly recognized and must be better understood for proper drug use. Certain benzodiazepines are associated with memory impairment and other cognitive defects and hyperexcitability phenomena during treatment (early-morning insomnia, daytime anxiety) and following withdrawal (rebound insomnia and anxiety, seizures). Elimination half-life, receptor-binding affinity, effects on the locus coerulescens-norepinephrine (LC-NE) and hypothalamic-pituitary-adrenal (HPA) axes, and the interaction of these factors appear to be major determinants of frequency and severity of these untoward effects. Rapid drug elimination and high receptor-binding affinity were initially suggested as primary underlying factors which determine frequency, severity, and type of the side effects of benzodiazepines during administration and withdrawal. Newer data and information on triazolobenzodiazepines indicate that these psychiatric adverse reactions also relate to whether the benzodiazepine has strong direct effects on the LC-NE and HPA systems. Initial suppression of the LC-NE and HPA systems is followed, on an interdose basis, by a significant rebound and activation. This repetitive pattern of suppression followed by rebound results in a neurophysiologic and behavioral sensitization (kindling) of the limbic system and consequently contributes to central nervous system and psychiatric adverse reactions. The tendency of certain of these side effects to worsen over time supports empirically this neurophysiologic and biochemical model.
Benzodiazepines have achieved extensive worldwide use and a remarkable safety record [1]. They have a wide spectrum of central nervous system (CNS) activity and an extraordinary safety margin in all species. The wide margin between their tranquilizing and hypnotic doses in animals and their minimal effects on autonomic, respiratory, and cardiovascular systems partially account for their strong acceptance. However, tolerance, psychiatric adverse reactions, withdrawal effects, drug dependence, and drug-taking behavior, especially with newer benzodiazepines, are becoming increasingly recognized and can limit their usefulness.

The first benzodiazepines introduced (1,4-benzodiazepines), e.g., diazepam and flurazepam, had similar pharmacokinetics (relatively slow elimination rate) and pharmacodynamics (low receptor-binding affinity/low potency; table 1) [2]. The most frequent side effect of these benzodiazepines was excessive daytime sleepiness.

Late in the 1970s, additional 1,4-benzodiazepines were introduced, e.g., lorazepam and flunitrazepam, which were more rapidly eliminated [3] and more potent [4]. The use of these benzodiazepines was associated not only with more potent anxiolytic and hypnotic effects, but also with more rapid development of tolerance, significant withdrawal difficulties such as rebound insomnia and anxiety following termination of treatment [5], and other 'unexpected' side effects such as memory impairment during drug administration [6].

In the late 1970s and early 1980s, a new class of benzodiazepines with even greater potency and more rapid elimination was introduced, the triazolobenzodiazepines. This new class differed chemically from the classical 1,4-benzodiazepines in that it included a triazolo ring attached to the basic diazepine structure. Based on this chemical structure, the triazolobenzodiazepines have been promoted for their unique clinical effects. For example, triazolam has been marketed as a potent hypnotic with few side effects (especially lack of sedation the following day because of extremely rapid elimination) and alprazolam as an antianxiolytic drug with additional potential antidepressant effects. However, these pharmacological properties also appear to be responsible for frequent and severe CNS and psychiatric adverse reactions that occur with triazolobenzodiazepines in three major categories: (1) amnesia and other cognitive impairments [7, 8]; (2) daytime anxiety, tension or panic, and early-morning insomnia [9, 10], and (3) withdrawal difficulties such as rebound insomnia, anxiety, and seizures [5, 7, 11].

Accordingly, the goals of this review are: (1) to examine systematically the relationship between benzodiazepine side effects and their pharmacokinetics and pharmacodynamics as well as any special characteristics of their

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Table 1. Pharmacokinetics and pharmacodynamics of benzodiazepines [from refs 3 and 4]

<table>
<thead>
<tr>
<th>Drug</th>
<th>t_{1/2}, h</th>
<th>( K_t )</th>
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<tbody>
<tr>
<td>Midazolam</td>
<td>1–3</td>
<td>0.4</td>
</tr>
<tr>
<td>Triazolam</td>
<td>2–4</td>
<td>0.4</td>
</tr>
<tr>
<td>Brotizolam</td>
<td>4–8</td>
<td>0.9</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>5–15</td>
<td>17.2</td>
</tr>
<tr>
<td>Temazepam</td>
<td>6–16</td>
<td>23.0</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>9–15</td>
<td>4.8</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>10–15</td>
<td>4.8</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>10–20</td>
<td>3.8</td>
</tr>
<tr>
<td>Flunitrazepam</td>
<td>10–25</td>
<td>3.8</td>
</tr>
<tr>
<td>Estazolam</td>
<td>9–27</td>
<td>17.0</td>
</tr>
<tr>
<td>Nitrazeplam</td>
<td>20–50</td>
<td>11.5</td>
</tr>
<tr>
<td>Diazepam</td>
<td>26–50</td>
<td>9.6</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>24–56</td>
<td>0.5</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>40–120</td>
<td>17.2</td>
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<tr>
<td>Quazepam</td>
<td>40–200</td>
<td>–</td>
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chemical structure and (2) to propose a neurochemical and neurophysiologic model explaining the differential side effect profiles of various benzodiazepines.

Benzodiazepine-Induced CNS and Psychiatric Adverse Reactions

Daytime Sedation

Manifestations of CNS-depressant effects of benzodiazepines, such as daytime drowsiness, hangover, and dizziness, generally are considered to be more prevalent with drugs that have long elimination half-lives. These findings are derived mainly from specially designed performance studies which showed that daytime psychomotor impairment is greater with the slowly eliminated agents [12–15]. In clinical use, however, the actual prevalence of hangover and other side effects related to daytime sedation surprisingly does not appear to differ considerably among benzodiazepine hypnotics, although they have very different rates of elimination [16–19]. For example, the overall prevalence of drowsiness reported in new drug applications was 11.4% with flurazepam and 14.0% with triazolam [18].

One explanation for the similarity in frequency of reporting daytime sedation for drugs with different half-lives is that this side effect, when assessed subjectively in clinical trials or in clinical use, may be underestimated [20]. However, when assessed objectively as in the many sleep laboratory studies of long half-life hypnotics, e.g., flurazepam and quazepam, daytime sedation is the major side effect noted [21–23]. Daytime sedation is more frequent, intense, and prolonged with high doses and in the elderly [22]. However, with continued use of these drugs, tolerance appears to develop to this side effect [24].

Memory Impairment/Amnesia

Most benzodiazepines are associated with anterograde amnesia shortly after administration of the drug, i.e., at its peak concentration [25]. Memory-imparing effects of benzodiazepines are limited to failures in explicit memory for recent events [25] and are dependent on potency and route of administration [26]. For example, while anterograde amnesia often results from intravenous administration of diazepam, it is much less frequent with intramuscular administration of the drug and rare with the oral route [26]. In contrast, potent benzodiazepines appear to be associated with a high degree of memory impairment with oral administration. For example, it has been shown that lorazepam [27–29] and flunitrazepam [30], benzodiazepines with relatively high potency, cause more amnesia following oral administration than benzodiazepines with less potency, such as diazepam and flurazepam. Also, controlled studies have shown that triazolam, a highly potent triazolobenzodiazepine, shortly after administration, when drug or active metabolite is at high concentration, causes significantly more memory impairment than other benzodiazepine hypnotics such as flurazepam [29, 31, 32] or temazepam [31, 33]. The factors underlying these differences remain controversial or unknown. Some authors have hypothesized that increased sedation associated with increased potency of benzodiazepines accounts for the greater memory loss [29, 31].

However, memory impairment with the absence of sedation has been demonstrated in a number of studies suggesting that the effect of the benzodiazepines on memory is specific [25, 34–36]. For example, it has been shown that caffeine attenuates sedation, but not memory impairment following benzodiazepine administration [35]. Also, experimental studies have shown that memory impairment
caused by intravenous administration of diazepam was not reversed despite the blockade of sedation following the use of a benzodiazepine antagonist [25]. Moreover, in addition to memory impairment associated with benzodiazepine use at peak concentration, triazolam, which is very rapidly eliminated, has been associated with high rates of next-day memory impairment when most of the drug should have been eliminated from the system [33, 37]. Thus, these findings do not support the view that memory impairment is directly correlated with the degree of sedation.

The clinical relevance of benzodiazepine-induced anterograde amnesia is underscored by the fact that benzodiazepine-treated subjects may often be unaware of their memory impairment. This was confirmed in two studies [36, 38] where triazolam-treated and lorazepam-treated subjects considerably underestimated the degree of their memory impairment.

**Tolerance, Daytime Anxiety, and Other Hyperexcitability Phenomena**

All benzodiazepines, especially after prolonged use, are associated with development of tolerance. However, benzodiazepines differ significantly with regard to degree and rapidity of development of tolerance [39, 40]. Flurazepam [41], quazepam [41, 42], diazepam [43], and clonazepam [44], all of which are more slowly eliminated, remain efficacious with continued use over a period of up to 1 month. In contrast, triazolam [7, 45, 46], alprazolam [47], temazepam [42, 48], and lorazepam [49], all of which are more rapidly eliminated, quickly lose much of their initial efficacy. Rapid development of tolerance occurs even over a period of continued use of only 1 week [10, 47, 49] (fig. 1, 2).

Another adverse reaction observed with continued use of rapidly eliminated benzodiazepines is hyperexcitability manifested as
early-morning insomnia and daytime anxiety, tension, or panic. In 1982, Morgan and Oswald [9] and, subsequently, Adam and Oswald [50] reported that continued use of triazolam was associated with significantly and progressively increased levels of daytime anxiety during the administration period. These results are consistent with findings from the recent reanalysis by the FDA of 25 NDA studies of triazolam which showed that 0.5 mg, and even 0.25 mg, of triazolam was associated with an increased risk of dropouts due to daytime anxiety with longer drug administration [51].

Also in support of the findings of hyperexcitability phenomena occurring with continued use of rapidly eliminated benzodiazepines are the findings of Kales et al. [10]. These authors reported that early-morning insomnia, a significant increase in wakefulness during the final hours of drug nights, occurred after 1 or 2 weeks of nightly administration of benzodiazepine hypnotics with ultrashort elimination half-lives. In particular, midazolam and triazolam were associated with early-morning insomnia, in contrast to flurazepam and quazepam which remained efficacious during the last 2 h of the night’s recording. Also in this study, triazolam and midazolam were associated with increased levels of daytime anxiety and nervousness. The observation of early-morning insomnia was reported in several additional studies [52–54]. However, some other studies failed to show this finding, either because the nightly recording time was ad libitum [55] or because of lack of statistical power [56]. In the latter study [56], it was reported that early-morning awakening was nonsignificantly increased as compared with baseline at the end of 3 weeks of drug administration. In another study [57], there was a slight increase in anxiety as compared with baseline associated with a loss of initial efficacy for early final awakening after only 2 weeks of administration. From a clinical standpoint, hyperexcitability phenomena following nightly use of hypnotics can lead to drug-taking behavior and drug dependence [58]. This was clearly shown in a recently published study [59] which reported daytime consumption of triazolam by patients in order to treat daytime anxiety that developed following the nighttime use of this short-acting, highly potent benzodiazepine.

Similar hyperexcitability phenomena have been described with other relatively rapidly eliminated and potent benzodiazepines such as alprazolam [47], lorazepam [49], and brotizolam [60]. In particular, alprazolam, another potent triazolobenzodiazepine, has been frequently reported to be associated with hyperexcitability phenomena during drug administration, such as interdose rebound anxiety, disinhibition, panic attacks, and even episodes of mania [61–66].

From these data, it appears that tolerance and hyperexcitability phenomena (daytime anxiety and early-morning insomnia during drug administration) are interrelated. However, the exact relationship between tolerance and hyperexcitability phenomena has not been systematically investigated.

Withdrawal Phenomena (Rebound Insomnia and Anxiety)

It has long been recognized that continued use of large doses of nonbenzodiazepine sedative hypnotics for prolonged periods of time leads to dependence and a fully developed withdrawal syndrome [67–74]. Also, there have been numerous reports on withdrawal reactions with benzodiazepine anxiolytics and hypnotics as well [75–85]. In most cases, fully developed withdrawal reactions with benzodiazepines have also followed their prolonged use in high doses. Such withdrawal syndromes have even been noted after use of relatively low doses of benzodiazepines, but
for extended periods [75–77, 83, 84]. These observations have been extended through the striking finding that certain withdrawal difficulties (rebound insomnia and anxiety) may occur not only with discontinuation of a low daily dose of a drug, but even after relatively short periods of drug administration [5, 86, 87].

Separate studies, in our sleep laboratory, of 12 benzodiazepine hypnotics and anxiolytics showed that withdrawal of drugs with rapid or intermediate elimination rates, such as lorazepam, triazolam, and midazolam, resulted in rebound insomnia at night and, in a number of instances, anxiety during the day [6, 7, 42, 43, 49, 88]. In contrast, withdrawal of benzodiazepines with long half-lives, such as flurazepam and quazepam, was not associated with rebound insomnia or rebound anxiety (fig. 3) [12, 21, 23, 42, 57, 89, 90].

These is general agreement that sleep withdrawal difficulties are frequently present, and to a high degree, with rapidly eliminated drugs [6, 12, 56, 57, 60, 89, 91–93] and by contrast infrequently present and, if so, to a much milder degree with slowly eliminated drugs [12, 57, 89, 90]. In fact, no investigator has objectively demonstrated rebound insomnia (as defined by group mean values) following withdrawal of flurazepam or quazepam. In three studies that reported sleep disturbance following withdrawal of slowly eliminated drugs, only mild degrees of sleep disturbance were noted that were not sufficient in degree to be qualified as rebound insomnia [21, 94, 95].

Of considerable clinical interest was the recent finding with rapidly eliminated benzodiazepines that rebound insomnia can occur even under conditions of brief intermittent use and withdrawal. One study [96] showed that triazolam is associated with rebound insomnia even after a single night’s dose. In another study [97], triazolam and, to a much lesser degree, temazepam produced rebound insomnia after only 1 or 2 nights of administration. This side effect makes intermittent use, which is the most preferred form of treatment for insomniacs, of rapidly eliminated hypnotics problematic, as it predisposes to drug-taking behavior and increases the potential for drug dependence [97].
Factors Determining Severity and Frequency of Adverse Drug Reactions

Several factors have been proposed as significant in the etiology of benzodiazepine-induced CNS and psychiatric adverse reactions. Some of them such as dose and duration of administration are common to all of the drugs, while other factors such as elimination rate, receptor-binding affinity, and benzodiazepine effects on sympathetic nervous system and hypothalamic-pituitary-adrenal (HPA) axis are characteristic of individual drugs. There has been a controversy about the relative weight of these factors underlying the causes of benzodiazepine adverse reactions. At present, almost all investigators agree that dose and elimination rate are important factors determining benzodiazepine adverse reactions.

However, the importance of two other factors, i.e., binding affinity and the triazolostructure and its effects on the sympathetic nervous system and HPA axis, has been largely ignored in several reviews [98–100]. In this paper we review evidence that supports the contributing role of these two factors in the production of specific side effects. For example, daytime anxiety is determined not only by elimination rate, but also by the presence of triazolostructure and high binding affinity. Also, with next-day memory impairment, all three factors (rapid elimination, binding affinity, and triazolo structure) appear to play important roles.

Dose

Both clinicians and researchers recognized early on the role of dose in benzodiazepine-induced side effects. In sleep laboratory studies in humans, frequency and severity of side effects such as daytime sedation or rebound insomnia have been shown to be dose related [22, 88, 101]. However, investigators are divided about the importance of this factor in the side-effect profile of benzodiazepines when used in clinical doses. According to some investigators, dose is the primary or even the only factor that can explain differences in the side effect profile among benzodiazepines [102, 103]. For example, there have been claims that reported differences among benzodiazepines with regard to amnesia were due to the comparison of nonequivalent doses [104]. Further, it has been suggested that considerable side effects can be avoided by using the lowest effective dose [103]. However, these views cannot account for the significantly different side effect profiles of benzodiazepines when used in clinical doses as recommended by the pharmaceutical companies and regulatory agencies such as the FDA.

Furthermore, the definition of an equipotent dose is frequently a source of confusion. Some researchers use data from animal studies or in vitro binding-affinity studies. Also, it has been shown that on a milligram per milligram basis triazolam was over 150 times more potent than flurazepam (i.e., triazolam 0.5 mg produced 250% greater impairment of free recall than flurazepam 30 mg) [105]. Some have then extrapolated these values of equipotency for amnesia to equipotency for efficacy. In our view, it appears appropriate that equipotency for efficacy should be defined only by the clinically desirable effect which, in the case of hypnotics, is sleep induction and maintenance as objectively measured in the sleep laboratory.

Elimination Rate

To explain intensity and severity of rebound insomnia found in the early benzodiazepine studies in which only single doses of the drugs were administered nightly, we utilized findings on pharmacokinetics of these drugs as well as information concerning specific benzodiazepine receptors in the brain [5,
The intense rebound insomnia that follows the withdrawal of rapidly eliminated benzodiazepines is attributed to the much shorter duration of action of these drugs. Conversely, the absence of rebound insomnia after slowly eliminated benzodiazepines are withdrawn is attributed to their having active metabolites with long half-lives (table 1).

The discovery of benzodiazepine receptors in the brain suggests the presence of endogenous benzodiazepine-like molecules, the production of which would be regulated by concentrations of the circulating molecules or a feedback mechanism [5, 86]. Production of endogenous benzodiazepine-like molecules would be decreased if active exogenous benzodiazepine drugs or metabolites were introduced. We hypothesized that abrupt withdrawal of those benzodiazepine drugs with a relative short duration of action results in an intense form of rebound insomnia because of a lag in production and replacement of endogenous benzodiazepine-like compounds [5, 86]. However, when benzodiazepines with long-acting metabolites are withdrawn, the effects on benzodiazepine receptors are less abrupt because endogenous benzodiazepine-like compounds may be partially restored before active metabolites of the exogenously administered drugs are completely eliminated. The ability to produce endogenous benzodiazepine-like compounds within the time these long-acting metabolites are eliminated may also be a function of dosage and duration of drug administration [5]. Thus, this model does not preclude the possibility that rebound insomnia may develop in response to benzodiazepines with long-acting metabolites that are taken for lengthy periods and/or in high doses.

Since this early hypothesis with regard to the underlying mechanism of rebound insomnia, many studies have shown that the elimination rate of parent compound and active metabolites appears to be a critical factor that determines whether a benzodiazepine produces rebound insomnia after relatively short periods of administration. Following withdrawal of benzodiazepines with short elimination half-lives, there is a frequent, intense, and immediate degree of rebound insomnia [7, 56, 60, 86, 88, 91, 93, 96, 97, 106]. After withdrawal of intermediate half-life benzodiazepines, rebound insomnia occurs somewhat less frequently, is of moderate degree, and may be delayed in appearance [42, 48, 97, 107]. With the benzodiazepines having a longer half-life, withdrawal sleep disturbances occur even less frequently, are delayed in appearance, and are milder [5, 41, 43, 45, 89, 93, 108].

Receptor-Binding Affinity

With the accumulation of information on the withdrawal patterns of the newer potent benzodiazepines, it appeared that, although rates of elimination are important in determining a drug's potential for rebound insomnia, other factors, i.e., high receptor-binding affinity, are also involved. Thus, we proposed that rebound insomnia is related to at least two mechanisms: (1) rapid elimination and (2) high receptor-binding affinity [39, 40, 44]. When both factors are present, e.g., with triazolam, rebound insomnia is more frequent, immediate, and of greater severity [7, 45, 84]. When neither factor is present, as is the case for both flurazepam and quazepam which are slowly eliminated and have moderately low receptor-binding affinity, rebound insomnia is infrequent, delayed, and mild in severity [21, 108]. When only one of the two factors is present (e.g., temazepam is relatively rapidly eliminated but has low receptor-binding affinity), rebound insomnia is more likely to be less frequent and milder in severity [42, 48, 97].
These two mechanisms (rapid elimination and high receptor-binding affinity) appear also to determine to a large extent tolerance and hyperexcitability phenomena which occur after drug administration. Numerous studies have shown more rapid development of tolerance with benzodiazepines of short to intermediate half-life and moderate to high potency such as triazolam, brotizolam, midazolam, lorazepam, and alprazolam [7, 10, 45, 47, 49, 50, 57, 60]. Rapidly eliminated benzodiazepines, when given in single nightly doses, may result in a daily withdrawal syndrome (early-morning insomnia, daytime anxiety), the severity of which is significantly affected by the potency of the drugs as well as by their duration of administration.

It also appears that receptor-binding affinity is a major factor in the propensity of some benzodiazepines to cause significant anterograde amnesia after oral administration. Benzodiazepines with a high or a relatively high binding affinity, e.g., lorazepam [6, 49], flunitrazepam [26], triazolam [7, 8, 33, 37], and midazolam [88], have been frequently associated with amnesia following oral administration. In contrast, benzodiazepines with a low or a relatively low binding affinity, e.g., temazepam, flurazepam, and quazepam, have been infrequently associated with anterograde amnesia [29, 33, 37].

**Benzodiazepine Effects on the LC-NE and HPA Axes**

The greater intensity and frequency of CNS and psychiatric adverse reactions associated with the triazolobenzodiazepines, such as daytime anxiety [9, 46, 50–54, 109], next-day memory impairment [8, 33, 37, 110], and withdrawal difficulties [45, 56, 57, 92, 93, 96, 97, 111, 112] with triazolam and daytime interdose rebound anxiety, panic, mania [62–66], disinhibition [61], and withdrawal difficulties [11, 47] with alprazolam, are not adequately explained and understood only by the mechanisms of elimination rate and binding receptor affinity [39, 40].

The unique chemical structure of triazolobenzodiazepines and, more specifically, their direct effects on the LC-NE and the HPA axes shed more light on understanding the underlying mechanisms of these CNS and psychiatric adverse reactions associated with the use of these drugs.

The clinical and laboratory reports on benzodiazepine withdrawal reviewed in this paper described symptoms such as anxiety, insomnia, and other hyperexcitability phenomena which suggested increased adrenergic activation. These reports prompted investigators to explore potential effects of benzodiazepines on NE levels. Biochemical studies in both humans and in animals showed that acute and long-term use of benzodiazepines was associated with decreased levels of NE and its metabolites, while benzodiazepine withdrawal was associated with increased NE levels [113–124]. Although it is not known exactly how 1,4-benzodiazepines affect NE, it has been proposed that these benzodiazepines affect the regulation of noradrenaline release indirectly through γ-aminobutyric acid which is the primary inhibiting neurotransmitter system in the brain [121, 125–127].

Also, both in animal and human studies, benzodiazepine use and withdrawal have been associated with cortisol suppression and rebound, respectively [56, 128–131]. Further experimental findings in rats have shown that classic benzodiazepines, e.g., diazepam, suppress the central corticotropin-releasing hormone (CRH) secretion, while benzodiazepine inverse agonists are potent stimulators of the CRH secretion [132].

In addition to this indirect effect of benzodiazepines on NE system and HPA axis, which is expected to be related to the potency or binding affinity of the drugs, triazoloben-
zodiazepines appear to exert a direct potent effect on the LC-NE system and HPA axis. Triazolobenzodiazepines activate α2-adrenoceptors [133–136], inhibit platelet-activating factor (PAF) [137–140], and do not appear to have total cross-tolerance with other benzodiazepines [141, 142]. In addition, triazolobenzodiazepines have an increased capacity relative to other benzodiazepines to suppress the CRH neuron in the LC which is followed by an overactivation of the CRH neuron after drug withdrawal [143–145].

α2-Receptors are mainly located in the brain stem and have an inhibiting effect on the LC-NE system [122, 133, 146]. Also, PAF activates CRH which in turn has an activating effect on the LC-NE system [146]. Therefore, triazolobenzodiazepines by activating α2-adrenoceptors, inhibiting PAF, and suppressing CRH seem to have a direct suppressant effect on the LC-NE-CRH system. Based on this direct effect on the LC-NE-CRH system, some investigators have attempted to explain both the antipanic and antidepressant effects of the triazolobenzodiazepines [134, 143, 147].

However, this same direct pharmacologic effect on the LC-NE-CRH system, when associated with rapid drug elimination, can explain the adverse reactions associated with triazolobenzodiazepines. It is likely that the initial dampening or suppression of the LC-NE system and HPA axis is followed by a significant rebound and activation of the LC-NE system and HPA axis when the drug is rapidly eliminated from the system. We have speculated that this repetitive daily pattern of suppression followed by activation can lead to a chemical overactivation of the LC-NE system and HPA axis and a neurophysiological and behavioral sensitization (kindling phenomenon) of various parts of the limbic system of the brain [39, 40].

Many experimental and clinical findings support our hypothesis for the role of the LC-NE system and HPA axis as significant factors in the development of the following: (1) frequent memory impairment which has been observed during both the presence as well as the absence of the drug; (2) rapid development of tolerance and occurrence of daytime anxiety and other hyperexcitability phenomena during drug administration, and (3) withdrawal difficulties (rebound insomnia, anxiety, and seizures) even after short-term use.

Memory Impairment/Amnesia during Drug Administration. Several studies have shown that memory impairment may occur during both the suppression and the activation of the LC-NE system. It has been demonstrated that norepinephrine’s dose-effect curve on memory has an inverted U shape, i.e., decreased or increased norepinephrine levels can cause memory impairment [148]. Also, clinical studies of antihypertensive drugs that act primarily through the noradrenergic system (α-methyldopa, propranolol, and clonidine) have shown that these drugs are associated with memory impairment [149–155]. In addition, experimental studies have shown that β-adrenergic blockade affects memory in a way which is similar to the memory impairment caused by benzodiazepines [156]. Furthermore, NE is decreased in Korsakoff’s syndrome which is associated with memory impairment of a similar type to the one caused by benzodiazepines (explicit or episodic memory impairment) [157–159].

The role of the HPA axis in memory impairment is supported by several animal and human studies [146, 160, 161]. In animal experiments, it has been shown that CRH administration has an inverted U dose-response effect on learning and performance [146]. In addition, in humans it has been shown that the hippocampus is rich in corticosterone receptors which are selectively acti-
vated during stress [160, 161]. In turn, an increase in corticosteroid levels can suppress hippocampal function and thus cause amnesia.

Tolerance, Daytime Anxiety and Other Hyperexcitability Phenomena during Drug Administration. Both animal and human studies have provided evidence for a role of the noradrenergic system in the development of tolerance and hyperexcitability. Studies in mice have indicated that brain noradrenergic systems are important for tolerance to hypnotic and sedative effects of barbiturates and ethanol [162, 163]. Also, in animals, anxiogenic substances (B-carbolines, inverse benzodiazepine receptor agonists) activate noradrenergic neurons [164, 165]. In humans, hyperexcitability phenomena such as anxiety, panic, or mania have been associated with increased noradrenergic activity [133, 134, 147, 166]. Also, more recently, challenge studies have shown the importance of the noradrenergic system on the genesis of anxiety and panic. For example, clonidine, an $\alpha_2$-agonist, has anxiolytic-sedative effects, while yohimbine, an $\alpha_2$-antagonist, is anxiogenic [133].

The HPA axis has also been shown to be activated in stressful anxiogenic situations. In humans, chronic stress and anxiety or panic disorder are associated with hyperactivation of the HPA axis [146, 167]. In rats, administration of CRH is associated with 'anxious' behavior opposite to that observed in rats treated with benzodiazepines [146].

Withdrawal Difficulties (Rebound Insomnia and Anxiety). The role of the noradrenergic system in production of a full withdrawal syndrome after long-term use of benzodiazepines has been well established in many studies [113, 114, 116, 117, 119, 121, 122, 124]. Also, drugs with a strong direct effect on LC-NE activity have a higher potential for tolerance and withdrawal effects [168]. For example, antihypertensive medication with direct effects on the NE system such as clonidine or methyldopa, may, when abruptly withdrawn, cause rebound hypertension and adrenergic hyperactivity [169]. Also, $\alpha_2$-adrenoceptors and NE significantly modulate limbic seizures. In animal studies, chemically induced limbic seizures are attenuated with $\alpha_2$-adrenergic agonists (clonidine), while $\alpha_2$-antagonists (yohimbine) potentiate these seizures [170].

Because many signs and symptoms observed in animals and humans after abrupt discontinuation of benzodiazepines resemble the stress response, investigators have explored the effects of benzodiazepine withdrawal on CRH neurons and HPA axis. In fact, experiments in humans and animals have shown a profound activation of CRH neurons and HPA axis following withdrawal of triazolobenzodiazepines [56, 143, 145]. Furthermore, CRH administered intracerebroventricularly produces seizures [171]. Investigators have conceptualized a continuum of CRH-induced changes, depending on the dose, that progress from a mild increase in aroused behavior to anxiety-like behavior and, with the largest doses, aggressive behavior and ultimately limbic-types seizures [171]. At a more clinical level, the strong, direct, and repetitive effect of alprazolam on both the LC-NE and HPA axes can explain the much more severe, frequent, and sustained withdrawal reactions associated with even the gradual withdrawal of this drug [11, 172] as compared with lorazepam which has a half-life and binding affinity similar to alprazolam [173].

Other Postulated Mechanisms

In this section, we briefly review and critique other theoretical models proposed to explain the side effect profile of benzodiazepines. Some investigators have postulated that triazolam is an anomalous ligand or that
it has qualities of an inverse benzodiazepine agonist [50]. There is, however, little experimental evidence to support such speculations. Significant differences among benzodiazepines do exist in quantitative, but not qualitative, affinity characteristics [174].

Other investigators have reported that low doses of alprazolam upregulate benzodiazepine receptors, postulating that this ‘anomalous’ behavior of alprazolam could explain difficulties with tapering the dose of this drug [175, 176]. However, this finding cannot explain the initial effectiveness of the drug in small doses, the frequent hyperexcitability phenomena observed in patients adequately dosed, or the fact that frequency and severity of withdrawal difficulties are directly related to the dose used.

Finally, it is unlikely that these differences reflect differential effects on specific receptors subtypes (BZ₁ and BZ₂) because: benzodiazepines such as triazolam, temazepam, and flurazepam, with very different side effect profiles, are not known to differ in terms of their effects on these receptor subtypes, and benzodiazepines such as quazepam, with known selective effects on these receptors (preferentially interacting with BZ₁), exhibit a side effect profile (daytime sedation) readily understood from their pharmacokinetics (slow elimination) [177].

It should be noted that the debate on the potential importance of differential effects on specific receptor subtypes in the clinical profile of benzodiazepines has been rekindled by introduction of newer nonbenzodiazepines, zopiclone and zolpidem, which presumably bind preferentially to BZ₁. There have been claims that these two short-acting hypnotics are as efficacious as benzodiazepines and have better profiles for adverse events. However, these drugs have not been studied in the sleep laboratory as thoroughly as others, and their withdrawal period has often not been thoroughly and adequately assessed [178–184]. Nevertheless, two of five studies that assessed adequately withdrawal of zolpidem reported rebound insomnia [185, 186], while the other three did not [185, 187, 188]. With zopiclone, one study [189] reported no rebound insomnia, while another [190] suggested the presence of strong sleep disturbance following withdrawal of the drug.

Also, with both zopiclone and zolpidem, there are a number of clinical reports of serious paradoxical or unexpected adverse events, e.g., psychotic reactions associated with their use [191–194]. Although both drugs are of rather low binding affinity (zolpidem has 10 and 30 times less binding affinity than flunitrazepam and triazolam, respectively), zolpidem appears to exhibit an increased intrinsic activity [195], and their potency varies in different brain areas [196]. These characteristics may explain the nature of their adverse reactions which are usually associated with benzodiazepines possessing high binding affinity.

Concluding Remarks

In conclusion, rapid elimination, high receptor-binding affinity, and direct effects on the LC-NE and HPA axes appear to influence substantially severity and frequency of the three major CNS and psychiatric adverse drug reactions associated with the use and withdrawal of benzodiazepines. In relation to amnesia/memory impairment and other cognitive impairments, a high receptor binding affinity has a major role, while with hyperexcitability phenomena (daytime anxiety and early-morning insomnia during drug use and rebound insomnia and anxiety following drug cessation), rapid drug elimination is a major factor.
These factors, combined with only once per day administration of these drugs when used as hypnotics, can lead to a repetitive, intermittent activation of these two systems that increases with continued use of the medication (kindling or behavioral sensitization phenomenon) [171]. Further, the adverse reactions of cognitive impairments and hyperexcitability phenomena are marked in both frequency and severity with the use of triazolobenzodiazepines as a consequence of their direct effects on the LC-NE system and HPA axis [39, 40]. Additional empirical support for this model is provided by the finding of progressively increased memory impairment [38, 51] and daytime anxiety [9, 50, 51] with continued use of triazolam.

From a practical standpoint, based on the accumulated information reviewed in this article, prescribing physicians should take into consideration not only the dose, but the pharmacokinetics and pharmacodynamics of benzodiazepines, in order to understand and avoid psychiatric side effects associated with this class of drugs. Specifically, the use of benzodiazepines with rapid elimination, high binding affinity, and/or triazolo structure is associated with a much higher risk for the development of frequent and more severe psychiatric side effects.

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