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Clinical Pharmacology, Clinical Efficacy, and Behavioral Toxicity of Alprazolam: A Review of the Literature

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ABSTRACT

Alprazolam is a benzodiazepine derivative that is currently used in the treatment of generalized anxiety, panic attacks with or without agoraphobia, and depression. Alprazolam has a fast onset of symptom relief (within the first week); it is unlikely to produce dependency or abuse. No tolerance to its therapeutic effect has been reported. At discontinuation of alprazolam treatment, withdrawal and rebound symptoms are common. Hence, alprazolam discontinuation must be tapered.

An exhaustive review of the literature showed that alprazolam is significantly superior to placebo, and is at least equally effective in the relief of symptoms as tricyclic antidepressants (TCAs), such as imipramine. However, although alprazolam and imipramine are significantly more effective than placebo in the treatment of panic attacks, Selective Serotonin Reuptake Inhibitors (SSRIs) appear to be superior to either of the two drugs. Therefore, alprazolam is recommended as a second line treatment option, when SSRIs are not effective or well tolerated.

In addition to its therapeutic effects, alprazolam produces adverse effects, such as drowsiness and sedation. Since alprazolam is widely used, many clinical studies investigated its cognitive and psychomotor effects. It is evident from these studies that alprazolam may impair performance in a variety of skills in healthy volunteers as well as in patients. Since the majority of alprazolam users are outpatients, this behavioral impairment limits the safe use of alprazolam in patients routinely engaged in potentially dangerous daily activities, such as driving a car.

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INTRODUCTION

Alprazolam, 8-chloro-1-methyl-6-phenyl-4H-s-triazolo [4,3-α] (1,4) benzodiazepine, is a benzodiazepine derivative used in the treatment of a variety of disorders, including panic attacks, generalized anxiety, and depression. Since its introduction in the 1960s, alprazolam became one of the most used drugs in the USA and is currently the most often prescribed psychoactive drug.

The first section of this review article summarizes clinical pharmacology of alprazolam. In the second section its clinical use is discussed. The therapeutic efficacy of alprazolam is compared with the alternative pharmacological treatments that have been introduced over the years. The ideal drug should be clinically effective and should not produce adverse effects that interfere with daily activities, such as driving a car. Since the majority of alprazolam users are outpatients, many experimental studies have been conducted to investigate the behavioral effects of this drug. The results from these studies are summarized in the third section of this article. The fourth section discusses the future prospects for alprazolam.

CLINICAL PHARMACOLOGY

Alprazolam is a 1,4-triazolobenzodiazepine analog. The chemical structure of alprazolam differs from that of classical benzodiazepines such as diazepam by the presence of the triazole ring.

Greenblatt and colleagues studied pharmacokinetics of alprazolam during the 1980s and 1990s (108,109). At 1 to 2 h after administration (T_{max}) of a single 1 mg dose of alprazolam the peak plasma concentration (C_{max}) ranged between 12 and 22 μg/L, the volume of distribution (VD) from 0.8 to 1.3 L/kg, the elimination half-life ($t_{1/2}$) from 9 to 16 h and the clearance from 0.7 to 1.5 mL/min/kg. After oral administration, approximately 90% of alprazolam was absorbed and bound to plasma proteins (the fraction of unbound alprazolam is approximately 30%). The absorption rate was independent of the administered dose. However, plasma levels of alprazolam (and its metabolites) were linearly related to the administered dose (45). A steady state condition was reached after 2 to 3 days, independent of the dosage schedule.

Alprazolam is metabolized in the liver by hepatic microsomal oxidation. This process is mediated by cytochrome P4503A isoforms (CYP3A4). Up to now, 29 metabolites of alprazolam have been identified. Alprazolam's two principle metabolites, 4-hydroxy alprazolam and α-hydroxy alprazolam, are present at low plasma concentrations and show much less benzodiazepine receptor affinity than alprazolam. Hence, these metabolites are unlikely to contribute to the clinical effects of alprazolam. Approximately 80% of alprazolam is excreted by the kidney as unchanged drug.

Factors that Influence the Pharmacokinetics of Alprazolam

A comparison of pharmacokinetics of alprazolam (1 mg) after oral and sublingual routes in 12 healthy male volunteers (233) showed that peak plasma levels are reached significantly later after sublingual (2.8 h) than after oral administration (1.8 h). Other pharmacokinetic parameters do not differ significantly between these routes of adminis-

tration. Another study by the same author reported no significant differences (232). Pharmacokinetics after intravenous administration did not differ from that after oral administration, except for a faster T_{max} (0.48 h) after intravenous administration (250). The onset of alprazolam-induced sedation was more rapid after intravenous (10 to 20 min) than after oral administration (40 min).

The pharmacokinetics of alprazolam is not significantly influenced by gender (140, 150) or menstrual cycle (140,176). However, oral contraceptives have been reported to affect pharmacokinetics of alprazolam (151). In pregnant women alprazolam appears to increase the risk of congenital abnormalities when used during the first trimester (127). Alprazolam and 4-hydroxy-alprazolam have been found in breast milk (194). Pharmacokinetics of alprazolam in breast milk is similar to that in blood plasma of lactating women, suggesting that alprazolam readily passes the blood-milk barrier. Hence, alprazolam is classified as a pregnancy category D drug and lactating women are advised to stop breastfeeding if they are treated with alprazolam.

In elderly, peak plasma levels of alprazolam are higher than in young subjects. Furthermore, alprazolam clearance is reduced in older subjects resulting in a prolonged elimination half-life (104,106,182).

Alprazolam pharmacokinetics is similar in healthy volunteers and patients. In elderly depressed patients, pharmacokinetics of alprazolam did not change significantly from day 1 (starting dose of 0.5 mg) up to day 42 (mean daily dose of 1.6 mg). Metabolites of alprazolam do not accumulate after repeated dosing (63). In another study there was also no significant difference in the pharmacokinetics of alprazolam in healthy volunteers as compared to patients with panic disorder (134).

Since alprazolam is metabolized in the liver, patients with hepatic diseases should be carefully monitored when treated with the drug. The clearance of alprazolam is significantly reduced and elimination half-life significantly increased in patients with liver cirrhosis (131). Renal disease may also reduce alprazolam clearance leading to accumulation of alprazolam and its metabolites. Increased levels of free alprazolam have been reported in patients receiving either hemodialysis or Continuous Ambulatory Peritoneal Dialysis (CAPD) as compared to healthy controls (235). CAPD patients also showed a tendency to increased T_{max}, clearance and prolonged elimination half-life of alprazolam. Metabolism is significantly slowed by obesity (1), whereas smoking has been reported to accelerate alprazolam elimination (123,197,251). No significant changes in the pharmacokinetics of either drug have been observed during co-administration of alprazolam and buspirone to healthy male volunteers (35).

Drugs that inhibit cytochrome P450 enzymes are likely to alter the pharmacokinetics of alprazolam. Inhibitors of CYP3A4 may increase elimination half-life and elevate peak plasma concentrations of this drug, whereas other drugs may enhance alprazolam metabolism. Changes in the pharmacokinetics of alprazolam have been produced by drugs that alter CYP3A4 metabolism. They have been reported for erythromycin (285), ketoconazole (111), itraconazole (286), venlafaxine (3), nefazodone (112,154), fluoxetine (107, 160), fuvoxamine (91), carbamazepine (97), cimetidine (1,207), and propoxyphene (2). However, other substrates for CYP3A4 such as grapefruit juice (287) and sertindole (281) did not significantly alter alprazolam metabolism.

Because immediate release tablets are clinically effective for 3 to 6 h, alprazolam must be administrated several times during the day. This can result in fluctuations in plasma levels, which may affect clinical efficacy. Sustained release (SR) formulations reduce

interdose variability in plasma levels of alprazolam and its adverse effects (5). Hence, SR formulations may improve treatment compliance. SR formulations have a considerably lower absorption rate, resulting in peak plasma concentrations that are half those observed with immediate-release formulation of alprazolam and a T_{max} of 8 to 12 h (38). Therefore, it has been suggested that sedative effects of alprazolam SR may be less pronounced than those with the immediate release tablets. A study on the pharmacokinetics of alprazolam SR at single doses of 2, 4, 8, and 10 mg reported a linear increment in peak plasma concentrations of alprazolam and its metabolites with increasing doses (283). Anxious patients, who were switched from immediate release tablets (first 2 weeks) to extended release alprazolam tablets (second 2 weeks), showed gradual clinical improvement during the study. However, patients reported a significant increase in sedation and anxiety symptoms during the first days after switching (271).

MECHANISM OF ACTION

Alprazolam easily crosses the blood brain barrier and enters central nervous system (CNS). Although the exact mechanism of action of benzodiazepines is unknown, alprazolam binds nonselectively to the gamma-amino butyric acid$_A$ ($GABA_A$)-benzodiazepine receptor complex. Most $GABA_A$ receptors are composed of three classes of subunits with several variants (α_{1-6}, β_{1-3}, γ_{1-3}). Benzodiazepine receptors can be differentiated based upon their subunit structure: type 1 receptors are composed of $\alpha_1\beta_{1-3}\gamma_2$ subunits whereas type 2 receptors have $\alpha_{2,3,5}\beta_{1-3}\gamma_2$ subunits. The functional significance of these subunits is still under investigation, but it has been established that sedation and anterograde amnesia are mediated by α_1 subunits, whereas α_2 subunits mediate anxiolytic effects (59,65,226, 231). Benzodiazepine α_1 subunits are found in high density in the cerebellum and in low density in hippocampus. Benzodiazepine α_2 subunits are abundantly present in hippocampus, striatum, and spinal cord.

At the receptor complex, alprazolam facilitates the binding of GABA and increases the influx of chloride ions. The presence of GABA, in turn, inhibits the action of several connected brain structures. It is, however, difficult to limit the action to "therapeutic meaningful" sites of action: GABA binds nonselectively to more than 30% of all brain synapses. The inhibition exerted by GABA results in a general slowing of brain activity, known as sedation. Further, the GABA system interacts with other neurotransmitter systems, including noradrenergic, serotonergic, cholinergic, and opioidergic systems. Especially alprazolam's interactions with the serotonergic and noradrenergic pathways to the limbic system and brain stem structures (e.g., locus coeruleus) contribute to its clinical effectiveness in the treatment of anxiety and depression.

CLINICAL EFFICACY OF ALPRAZOLAM

Generalized Anxiety Disorder (GAD)

During the 1980s and 1990s a number of studies investigated the efficiency of alprazolam in the treatment of GAD. The efficacy of alprazolam during 4 to 8 weeks-long periods of therapy was determined by means of anxiety symptom scales such as the Hamilton

Rating Scale for Anxiety (HAM-A). The average alprazolam dosage used in GAD ranged from 0.5 to 3.0 mg. Relative to placebo, most studies reported significant clinical improvement during alprazolam treatment (4,49,61,62,75,83,170,171,177,181,213). However, some studies failed to demonstrate any significant difference between alprazolam and placebo (40,95). This was probably caused by a significant clinical improvement during placebo treatment. As in panic disorder studies, global improvement rates of 50% and higher after placebo treatment has been reported in GAD patients.

Alprazolam has been shown to be at least equally effective in the treatment of GAD as other benzodiazepines, such as oxazepam (218,272), diazepam (4,49,61,62,71,83,95,171, 213), lorazepam (50,51,119,269), clobazam (40,118), etizolam (19,30,200), bromazepam (19), and the partial benzodiazepine agonist abecarnil (170). Alprazolam has also been shown to be at least equally effective as TCAs, such as imipramine (121,178). Alprazolam was more effective than imipramine in the relief of somatic symptoms, whereas imipramine had a positive effect on psychic symptoms such as dysphoria and negative anticipatory thinking.

In a 6-week double-blind placebo-controlled study in 94 outpatients with GAD (75) alprazolam (1.9 mg daily) was equally effective as buspirone (18.7 mg daily). However, the onset of clinical improvement was much faster with alprazolam (within the first week) than with buspirone (gradual improvement over weeks). Another study reported that alprazolam was at least equally as effective as buspirone in the treatment of anxious outpatients (51). Buspirone produced significantly fewer adverse effects when compared to alprazolam. However, dropout rate during buspirone treatment was rather high, since the therapeutic effect was apparent only at 2 to 4 weeks after the start of therapy.

Alprazolam was found to be as effective as diazepam in the treatment of moderate to severe anxiety during alcohol withdrawal in alcoholics (145). Also, 98% of GAD patients with comorbid irritable bowel syndrome showed a significant reduction in anxiety and 89% reported a reduction of gastrointestinal complaints after 4 weeks of alprazolam therapy. These benefits were maintained during a 4-week tapering period and were also present at 4 weeks after discontinuation of therapy (268). In the treatment of anxiety associated with cancer alprazolam has been reported to produce significant improvement that was evident within one week of treatment and was maintained thereafter. However, in similar studies clinical improvement was also achieved with muscle relaxants (122) and even with placebo (276).

Panic Disorder (PD)

During the eighties two large-scale international multi-center studies, the first and second Cross-National Collaborative Panic Study (CNCPS I and II), were initiated to examine the efficacy of alprazolam in the treatment of PD. The first CNCPS was a multicenter study performed in the USA, Canada, and Australia (11,142,165,190,203). Patients with PD or agoraphobia with panic attacks (Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, DSM III, criteria) were included. Patients received either placebo or alprazolam for 8 weeks. Daily dosages were increased to reach 6 mg alprazolam after 3 weeks of treatment. The mean (±SD) daily alprazolam dose was 4.2 ± 1.1 mg after 3 weeks and 5.7 mg $\pm$ 2.3 mg after 8 weeks of treatment. Results showed that after 4 weeks alprazolam was significantly more effective than placebo. However, after 8 weeks the dif-

ference between alprazolam and placebo was only moderate and all therapeutic gains disappeared after discontinuation of alprazolam.

Clinical improvement was maximal when alprazolam plasma levels ranged from 20 to 40 ng/mL (110). However, plasma levels and corresponding treatment responses showed great individual differences and there was no linear relationship between plasma levels and clinical improvement (280). Therefore, individual dose adjustments are necessary to gain optimal treatment benefits with alprazolam (166).

With few exceptions (99,270), other placebo-controlled studies also reported clinical superiority of alprazolam as compared to placebo (48,68,162,169,186,238,266,267). However, there were high rates of noncompliance in the placebo groups. This was also a problematic issue in the first CNCPS trial when approximately 50% of patients that received placebo dropped out of the study between weeks 4 and 8. It is likely that a large number of noncompleters affected the study outcome. Hence, the results from the first CNCPS have been a matter of debate (172). Several relatively small studies compared the efficacy of alprazolam with that of other benzodiazepines. For example, double-blind studies showed that alprazolam was at least as effective in the treatment of PD as diazepam (68,192,278), etizolam (179), clonazepam (266,267), adinazolam (208), or lorazepam (43,237). Alprazolam was also superior to non-benzodiazepine drugs such as propranolol (186,209). Unlike alprazolam, trazodone (42) and ibuprofen (243) were ineffective.

The traditional treatment in PD is imipramine, a TCA. The largest study comparing the effects of imipramine and alprazolam versus placebo was the second CNCPS (55). A total of 1168 PD patients were randomly assigned to one of the treatment groups. During an 8-week, double blind treatment period, clinical changes were recorded. The onset of clinical improvement was faster in the alprazolam group (week 1) as compared to the imipramine group (week 4). After 8 weeks, both drugs were equally effective, and both were superior to placebo. The average daily dose was 5.7 mg of alprazolam and 155 mg of imipramine. The number of patients that did not complete the study was considerably higher in the placebo (43%) and imipramine groups (30.2%) than in the alprazolam group (17.4%).

Several smaller double-blind studies compared the efficacy of alprazolam (at doses ranging from 2 to 6 mg) with that of imipramine (at doses ranging from 100 to 150 mg); the treatment periods in these trials ranged from 8 to 12 weeks (42,48,58,162,163,219, 245,265,270). In line with the CNCPS, these studies consistently showed that in the treatment of PD alprazolam was at least as effective as imipramine. Again, the onset of the therapeutic effect of alprazolam (week 1) was significantly faster than that of imipramine (weeks 2 to 4). Symptoms of the disease often exacerbated during the first weeks of therapy with imipramine. Due to its anticholinergic side effects, imipramine was not well tolerated by a substantial number of patients. As a result, dropout rates in patients receiving imipramine were higher than with alprazolam.

Long-term (8 months) treatment of PD patients with alprazolam showed that clinical improvement was maintained without significant dose changes. However, the number of completers in patients receiving the active drug was twice that in the placebo group. At 1.5 years after participation in a 6-week clinical trial (267) 78% of PD patients continued using alprazolam without dosage increments and most of these patients continued to benefit from long-term therapy with alprazolam (205). Long-term efficacy of alprazolam was also reported in other studies (135,136,216,239,246). Nevertheless, many patients still had occasional panic attacks or agoraphobia. Hence, long-term therapy with alprazolam does not cure panic patients, but only reduces the symptoms of PD.

Klosko and colleagues (143) treated patients with PD over a period of 15 weeks with alprazolam (mean dose, 4.6 mg), behavioral therapy, or placebo; one group of patients received no treatment at all. These authors reported that behavioral therapy was significantly more effective than placebo or no treatment. Although in both groups of patients clinical improvement was observed, there was no significant difference in the improvement of alprazolam- and placebo-treated patients. In 1992, a meta-analysis comparing the effectiveness of treatments in PD with agoraphobia revealed that alprazolam was effective for the treatment of panic and anxiety symptoms, whereas behavioral treatment (exposure therapy) was significantly more effective for phobia (53).

The London/Toronto study in 154 PD patients with agoraphobia compared the effects of combined treatment with alprazolam (5 mg/day) and exposure therapy, alprazolam and relaxation therapy (a psychological placebo), placebo and exposure therapy, and placebo and relaxation therapy (173). Patients received 8 weeks of treatment, followed by a tapering period of 8 to 16 weeks and follow-up visits until week 43. Unlike in the CNCSP studies, placebo dropout percentage in the London/Toronto study was low. Clinical improvement was shown in all four groups, but the onset was faster with alprazolam than with exposure therapy. In contrast to the results from the 1992 meta-analysis (53), exposure therapy was significantly more effective than alprazolam and placebo. Improvement after alprazolam did not differ significantly from that after placebo. Thus, regarding clinical efficacy, the advantage of alprazolam or exposure therapy in the treatment of PD is not yet obvious.

The improvement with the combination of alprazolam and exposure therapy was not significantly greater than after exposure therapy combined with placebo. Furthermore, in contrast to those patients receiving exposure therapy, sedation was reported up to week 8 during alprazolam treatment. Taking into account these adverse effects, exposure therapy may be regarded more favorably than treatment with alprazolam.

An 8-week double-blind study in 92 PD patients showed that alprazolam was significantly superior to buspirone or placebo. Moreover, buspirone was not superior to placebo in the treatment of PD (244).

Selective Serotonin Reuptake Inhibitors (SSRIs) were introduced more recently as an alternative treatment option for PD. Unfortunately, up to now, no direct comparison of the therapeutic efficacy of alprazolam and any of the SSRIs has been made. A meta-analysis of 27 clinical studies in PD patients showed that SSRIs (including paroxetine, fluvoxamine, zimelidine and clomipramine) were significantly superior ($p < 0.0004$) to alprazolam (mean dosage of 4 mg/day), imipramine (mean dosage of 150 mg/day) or placebo (29). Although there was a significant relationship between dose and the magnitude of the effect for either alprazolam or imipramine, SSRIs were also superior to higher dosages of alprazolam and imipramine. There was no significant difference between imipramine and alprazolam ($p < 0.11$). Nevertheless, both treatments were significantly superior to placebo in alleviating panic symptoms. Taken together, these results suggest that SSRIs should be viewed as the first-line treatment of panic disorder. Alprazolam may be used as a second-line treatment, if SSRIs prove to be ineffective or are not tolerated well.

Depression

Although alprazolam use has been associated with suicide ideation, a review of the literature (149) and a meta-analysis of 22 studies in depressed patients (130) showed that al-

prazolam use is not associated with an increased risk of suicide. Moreover, in contrast to other benzodiazepines, alprazolam is known for its antidepressant properties.

First-line treatments in depression are tricyclic antidepressants (TCAs). Clinical studies in depressed patients showed that alprazolam is at least equally effective as TCAs, such as amitriptyline (13,66,76,126,157,249), imipramine (84,86,87,180,212,277), dosulepine (41), desipramine (85,210), or doxepin (9). However, other studies reported that, although alprazolam provided symptom relief, amitriptyline (124,159,227) and imipramine (103,161) were significantly more effective. Analyses of early dropouts revealed that whether alprazolam or TCAs are the most favorable treatment choice depends on the diagnosis of depression (mild versus severe) (199). Early dropouts were most frequently observed during imipramine treatment (in patients with severe depression). Imipramine, however, seems to be more efficacious in the long run in patients that remain in treatment (patients with mild depression). Patients with severe depression seem to benefit most from alprazolam treatment. Meta-analyses confirmed that alprazolam is significantly superior to placebo and is as effective as TCAs (204,256).

Premenstrual Dysphoric Disorder (PDD)

Most women experience mild to moderate premenstrual symptoms during their lifetime, but 3 to 5% of women experience a severe syndrome, referred to in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) as Premenstrual Dysphoric Disorder or PDD (146). Double blind placebo-controlled studies in women with PDD showed that alprazolam caused improvement during the luteal phase, but had no postmenstrual effects (64,115,253). Other studies reported, however, no significant improvement with alprazolam as compared to placebo in any phase of the menstrual cycle (234). Mixed results, depending on the presence of mild anxiety or depression, were reported for alprazolam, 0.75 mg/day. (18). Conflicting reports are not surprising, since in the treatment of PDD the placebo effect is rather high, providing at least 50% symptom relief in 20 to 60% of patients (93), independent of the time spent with the physician (94).

Studies with SSRIs have shown that drugs such as fluoxetine (201,257,258) or sertraline (288,289) are highly effective in the treatment of PDD, without producing adverse CNS effects of alprazolam. Hence, SSRIs are recommended as the first-line treatment strategy in PDD. Alprazolam may be considered in case SSRIs do not provide sufficient relief.

Other Therapeutic Areas

A placebo-controlled study investigated the effects of alprazolam (0.5 to 1.5 mg) on tinnitus over a 12-week period (128). In thirteen out of 17 patients suffering from tinnitus alprazolam, 1.5 mg/day reduced the intensity of tinnitus, while at 0.5 mg alprazolam was effective in only 4 patients. It appears that more crossover studies are needed to confirm the effectiveness of alprazolam (125,248).

Alprazolam has also been examined in the treatment of Post Traumatic Stress Disorder (PTSD), but found to be ineffective. Although improvement in anxiety related symptoms was evident, specific PTSD symptoms remained unimproved (32).

In flight phobia, a single dose of alprazolam, 1 mg, (but not placebo) significantly reduced anxiety but increased heart rate and respiratory rate during flight. Patients treated

with alprazolam during one flight expected to be less anxious on future flights. This expectation did not, however, materialize. If the patients were not medicated, rebound anxiety, panic attacks and physiological responses were observed during the second flight (279).

In a more recent study six patients suffering from seasonal affective disorder were treated successfully with alprazolam, 1.2 to 2.4 mg/day for 2 weeks (284). Since the number of patients in this study was limited, the results will have to be confirmed by future placebo-controlled and active treatment-controlled (light therapy) studies. When co-administered with haloperidol in the treatment of schizophrenia, alprazolam reduced symptoms of excitement and uncooperativeness in 28 psychotic patients (15). Alprazolam has also been reported to be effective in the treatment of primary fibrositis/fibromyalgia syndrome when co-administered with ibuprofen (229). Its effectiveness has been described in essential tremor (113), social phobia (99), and in patients with disruptive behavioral episodes (44).

Adverse Events

A post-marketing study in the UK, involving almost 10,000 patients treated with alprazolam, reported no serious adverse events. The most commonly reported adverse events were drowsiness and sedation (70). A literature review including 3574 patients that participated in the active drug-controlled studies reported similar results (129).

In the London/Toronto study significantly more adverse effects were reported after alprazolam than after placebo (195). Generally, adverse effects diminished during treatment, but were still present at the end of the study. Analysis of the number of adverse events reported in the second CNCPS showed marked differences between the treatments (39). Patients using alprazolam reported an increment in typical adverse effects of benzodiazepines, such as sedation, fatigue, weakness, memory problems, ataxia and slurred speech, whereas patients using imipramine reported an increment in anticholinergic adverse effects such as blurred vision, tachycardia, palpitations, insomnia, nervousness, malaise, dizziness, headache, nausea, vomiting, and decreased appetite. In patients that received placebo anxiety symptoms were the most reported adverse events. In total, alprazolam produced less adverse effects than either imipramine or placebo. The number of adverse events decreased over time with either of the treatments. Clinical improvement was not correlated with either number or severity of adverse effects.

Withdrawal and Rebound Effects after Discontinuation of Therapy

Discontinuation of daily alprazolam use is preferably tapered to reduce rebound symptoms. During tapering over a period of several weeks or months the daily dosage is gradually decreased to zero.

In the London/Toronto study, the therapeutic benefits from alprazolam were lost during tapering and follow-up, whereas the gains from exposure therapy continued. The results from this study enhanced the debate on alprazolam's efficacy in the treatment of PD (173,174,175,254). With few exceptions (164), other studies also showed that treatment of PD with benzodiazepines is followed by withdrawal and rebound symptoms (anxiety scores higher than baseline), especially if the drugs are discontinued abruptly. High rates (50% or more) of symptomatic withdrawal and rebound effects have been reported

after 4 to 8 weeks of successful treatment with alprazolam, followed by a rather short (several weeks) tapering period (69,202,215,239). However, also after much longer tapering periods rebound effects were still present in a substantial number of patients. Rebound anxiety has been often reported with the dose reduction from 1 to 0 mg. Hence, a slower tapering period from 1 to 0 mg (in gradually lower dosages over several weeks) seems necessary to avoid the occurrence of rebound symptoms. In this context, it is important to note that an effective tapering period could last longer than the duration of the actual alprazolam treatment.

In contrast, discontinuation effects are not observed after buspirone (214), imipramine (215), SSRIs, or cognitive-behavioral therapy (173). Withdrawal and rebound effects during alprazolam tapering are not reduced by concurrent therapy with a non-benzodiazepine, such as the 5-HT_3 receptor antagonist ondansetron (224). Combining alprazolam tapering with cognitive behavioral therapy reduces withdrawal symptoms and thus facilitates alprazolam discontinuation (198,255).

Frequency of panic attacks or of episodes of phobia before the start of therapy did not predict recurrent pathology after long-term (4 years) treatment with alprazolam (136). However, other studies showed that baseline levels of anxiety can predict treatment outcome. Age over 40, low levels of baseline anxiety (282), or reduced anxiety and panic symptoms during treatment (33) correlated with less rebound and withdrawal effects. The severity of rebound phenomenon differs among benzodiazepines and seems to be related to the half-life of the drug. For example, rebound and withdrawal effects after alprazolam are more severe than after diazepam, which has a much longer half-life (191).

Dependence, Addiction, and Abuse Liability

In contrast to general beliefs, and taking into account a huge number of prescriptions for alprazolam, the incidence of abuse and dependence in the patient population is very low (221,223,241). However, like other benzodiazepines, alprazolam is abused for nonmedical reasons, often in combination with alcohol, drugs of abuse and/or other prescription medications. Alprazolam is used by drug addicts and has become a popular party drug during the last decade.

Mood changes associated with abuse liability in subjects with a history of drug abuse have been assessed with the Addiction Research Center Inventory (ARCI). The following factors are assessed by the ARCI questionnaire: euphoria, dysphoria, sedation, intellectual efficacy and energy, and activation. Studies have consistently shown that the use of alprazolam is accompanied by a dose-dependent sedation (37,77,78,183,184,185,228,291) and euphoria (46,47,185,291). Especially the euphoric effects of alprazolam may reinforce usage of the drug by subjects with a history of drug abuse. In contrast, in healthy volunteers and patients the sedative effects of alprazolam are more pronounced. Decreased intellectual efficacy and energy (185,291) and increased dysphoria (37) have been reported. It has been shown that patients' tendency to consume drugs more frequently predicts dependence to a much greater extent than the preference for aprazolam (drug liking) (196). Thus, the simple fact of increased "drug liking" or euphoria does not correlate well with the risk for alprazolam abuse.

BEHAVIORAL EFFECTS

Brain Activity

Cerebral blood flow (CBF) and brain activation were found to be decreased after alprazolam. By intravenous administration alprazolam caused an acute decrease in whole-brain CBF of 25 to 30% (225). More specifically, cerebral blood flow was significantly decreased (>15%) in the left lateral superior and right medial inferior frontal areas as well as in the cingulate cortex (259).

The decrease in brain activity after administration of alprazolam has also been demonstrated by studies recording event-related potentials. For example, significantly reduced N1 and P1 amplitudes have been found after alprazolam administration (6,25,242), reflecting the inhibitory activity of alprazolam. Significantly decreased P300 amplitude and a prolonged P300 latency have also been shown (187,242). The reduction of P300 amplitude reflects a worsening of cognitive functioning, reduction in information processing, and the quality of processing. The prolonged P300 latency implicates a prolonged stimulus evaluation time. In line with these changes in P300 activity, performance on a reaction speed test was significantly impaired. In this context, it has been shown that the P300 correlates highly to alprazolam's effects on a choice reaction time (117).

Acute Effects of Aprazolam in Healthy Volunteers

Psychomotor performance

The majority of behavioral studies were performed in healthy volunteers after a single dose of aprazolam. Table 1 provides an overview of the results from these studies.

The doses of alprazolam in these studies ranged from 0.25 to 2.0 mg, reflecting those used in clinical practice. Studies in Table 1 are double blind and placebo-controlled. They were designed as crossover or comparison group trials. Acute administration of alprazolam led to a general slowing of performance expressed in increased reaction speed on the tests. The performance impairing effects are significantly different from placebo at doses of 0.5 mg and higher. Performance impairment is not limited to specific skills or abilities. The effects of alprazolam are evident in all tests.

Some remarks must be made regarding the clinical relevance of the findings summarized in Table 1. That is, several of the studies were performed with a limited number of subjects. Hence, the results have low statistical power and their reliability is questionable. Furthermore, most tests do not represent daily activities. For example, the Digit Symbol

TABLE 1. Psychomotor performance after acute administration of alprazolam

Alprazolam dosage (mg)	0.25	0.50	0.75	1.0	1.5	2.0
% of tests showing impairment	13.0	28.6	66.7	84.2	92.9	75.0
Total number of tests	23	28	15	38	14	12

Data are from references 10,17,22–25,54,60,72–74,78,89,92,105,114,116,120,133,137,147, 155,160, 167,187–189,206,211,228,230,233,240,250,261,263,273–274,283. Tests included reaction time tests, tapping, cancellation, tracking, DSST, symbol copying, CFFT, card sorting, vigilance, stroop, and balance tests. A detailed summary of study results can be obtained upon request from the authors.

Substitution Test (DSST), Cancellation Test (CT), and Symbol Copying Test (SCT) are very popular in human psychopharmacology. Their popularity is probably due to the fact that they are cheap, easy to apply, and of short duration (1 to 3 min). Their results are readily obtained by counting the number of correct digit-symbol pairs (DSST), cancelled items (CT), or copied symbols (SCT). Unfortunately, these tests have no clear theoretical background. That is, it is unclear what is actually measured by these tests, and as a result interpretation of the data differs greatly among investigators. Tests such as the DSST measure several skills and abilities simultaneously resulting in a global measure of response (98), which in turn cannot be related easily to distinct brain regions or specific neurotransmitter systems.

Performance on these tests is also very sensitive to learning effects. Despite exhaustive training sessions, significant performance improvement on subsequent test sessions can be observed. Unfortunately, learning effects are not always taken into account and other studies do not report whether subjects were trained to a baseline performance level before the start of the study.

Whereas it is likely that performance decrement in short cognitive and performance tests (usually 5 to 10 min) can be compensated by increased effort and alertness during test performance, this is generally not true in tests of longer duration (>30 min). In this context, performance of daily activities, such as highway driving, requires sustained attention over a long period of time (vigilance). Benzodiazepines are known to affect vigilance performance by producing gradual performance decrement (144). At 0.5 mg alprazolam impaired performance in a 60 minutes vigilance test (147,148) and at 0.8 mg it reduced speed and accuracy in a 20 min visual vigilance test at 3.5 h after its administration (263).

As a consequence of the limitations observed in the majority of studies summarized in Table 1, one should be cautioned about making judgments regarding real-life performance based upon results from psychomotor test batteries. This is particularly true since daily activities often represent overlearned skills or abilities, whereas laboratory tests are more often of an artificial nature and are not practiced on a daily basis. In addition, daily activities such as driving a car are examples of complex behavior. Individually tested skills and abilities related to driving may be unimpaired, whereas results on a driving test may show significant impairment. Also, the severity of impairment found in laboratory tests does not predict to what extent daily activities will be impaired. For example, in a study which showed both significant impairment in laboratory tests and in actual driving performance after acute alprazolam treatment, a comparative analysis showed that results of laboratory tests measuring skills and abilities related to driving do not accurately predict actual driving performance in normal traffic (274).

Driving ability

Driving is an example of complex, skilled behavior practiced on a daily basis. Epidemiological evidence showed that benzodiazepine users have an increased risk of traffic accidents (16). A review showed that benzodiazepine hypnotics significantly impaired driving ability during normal traffic the day following bedtime administration (275). Although the effect of benzodiazepines on driving performance depends on various factors, such as the dose of the drug, time after drug intake, or gender, driving impairment due to benzodiazepines is generally higher than observed with blood alcohol concentrations of 0.05% (the legal limit for driving in The Netherlands).

Recently, Verster and colleagues examined the acute effects of alprazolam (1 mg) on driving ability (274). Twenty healthy volunteers performed an on-the-road driving test during normal traffic, one hour after treatment administration. Subjects were instructed to drive with a steady lateral position and a constant speed (60 mph) over a 100 km highway circuit. The Standard Deviation of Lateral Position (SDLP, cm) and speed variability (SD Speed, km/h) were the primary and secondary parameters of the test, expressing the amount of vehicle control of the subjects. Driving performance was severely impaired after alprazolam. That is, performance on the test was characterized by significantly increased side-to-side weaving of the car, repeated excursions out-of-lane into both the adjacent traffic lane and the road shoulder and significantly increased speed variability. Hence, vehicle control was seriously affected. SDLP increment after alprazolam (1 mg) was equal to that observed after blood alcohol levels of 0.15%, clearly above the legal limit of driving, and corresponding to a significantly increased traffic accident risk. Moreover, after alprazolam six out of twenty subjects had to stop their driving test before completion, because they fell asleep behind the steering wheel. In conclusion, driving is unsafe after acute administration of alprazolam.

Effect on memory

Brain structures involved in memory processes (cerebellum, hippocampus, amygdala and cerebral cortex) have a high affinity for alprazolam, due to the abundant presence of $GABA_A$ benzodiazepine receptor complexes. Several reviews concerning the effects of benzodiazepines on memory have pointed to the dose-related impairment of acquisition (56,100) and retrieval (262) of newly learned information, whereas previous learned information (i.e., before drug administration) remains intact. The results from studies with alprazolam are summarized in Table 2. The effects of alprazolam were similar to those of other benzodiazepines.

Immediate and delayed recall, and recognition are impaired by alprazolam at doses of 0.5 mg and higher. In contrast, working memory is not significantly affected after administration of this drug. Although studies using the Sternberg Memory Scanning Test, Digit Span and Mental Arithmetic showed significant impairment, this impairment involves reaction speed parameters, and not the accuracy of test performance. Hence, impairments in these tests do not indicate an effect on memory processes, but suggest only slower responsiveness (reaction speed) after alprazolam.

TABLE 2. Memory functioning after acute administration of alprazolam

Alprazolam dosage (mg)	0.25	0.50	0.75	1.0	1.5	2.0
% of tests showing impairment	11.8	36.4	53.3	75.0	85.7	100.0
Total number of tests	17	22	15	24	7	2

Data from references 14,22,23,52,60,92,105,114,116,120,137,155,167,187,206,228,230,233,260, 263,273–274. Tests included immediate and delayed recall, recognition, digit span, arithmetics, Sternberg memory scanning, and story recall. A detailed summary of study results can be obtained upon request from the authors.

Dose dependency of the effects

It is evident from Tables 1 and 2 that with increased alprazolam blood levels impairment in memory and psychomotor tests are reported more often. Also, the impairment is more severe with higher doses of the drug. Behavioral and adverse effects of alprazolam are less pronounced after small and more frequent dosing (252).

Interestingly, Bourin and colleagues (28) reported that alprazolam at a low dose (0.125 mg b.i.d. for 14 days) improved performance in DSST, picture recall, choice reaction time test and the Critical Flicker Fusion Test (CFFT). The authors reported that the test performance was trained to baseline before the start of the study. The placebo group showed less improvement in the performance than the alprazolam group. However, the clinical relevance of the effects of alprazolam at such a low dose is questionable.

Routes of administration

By either oral or sublingual routes of administration alprazolam produced similar impairment in the DSST, a reaction time test, and in immediate and delayed recall tests (233). DSST and performance on a perceptual speed test, measured at 1.25 to 12.5 h after drug administration, were equally affected by alprazolam, by either oral or intravenous routes (250). These data suggest that alprazolam impairs performance independent of its route of administration. However, due to the differences in the pharmacokinetic parameters the time of maximal effects of the drug may vary substantially with the route of administration.

Interactions with alcohol

Interactions between alprazolam and alcohol are important to address since many patients with anxiety or panic disorder self-medicate with alcohol. Bond and colleagues (24) examined the acute effects of alprazolam (1 mg) and alcohol (0.5 g/kg) alone and in combination in a variety of psychological tests. Alprazolam caused significant impairment in all tests. The impairment after alcohol was less pronounced. The effects of both drugs administrated simultaneously were not greater than predicted from the sum of the single dose effects, suggesting no interaction (25). With higher doses of alcohol, impairment in combination with alprazolam was greater than with either drug alone (167,228). Alprazolam and alcohol combination increased behavioral aggression and irritability in moderately drinking healthy volunteers and in patients with panic disorder more than would have been predicted from the sum of single effects (26,27).

Interactions with CYP3A4 inhibitors

Erythromycin did not modify the acute effects of alprazolam (0.8 mg) in DSST performance (285). DSST performance worsened significantly when alprazolam was co-administered with ketoconazole, but immediate and delayed word recall test after alprazolam was not affected by ketoconazole (111). Inhibition of alprazolam metabolism by itraconazole significantly impaired performance in the DSST (286). DSST and symbol copying were not affected by alprazolam and venlafaxine combined (3). Test performance (DSST and RT tasks) after alprazolam are worsened by drugs that alter CYP3A4 metabolism, including nefazodone (112,154), fluoxetine (107,160), fluvoxamine (91), carbamazepine (97), cimetidine (1,207), and propoxyphene (2).

Acute tolerance

It has been shown that after a single dose of benzodiazepines, including alprazolam, psychomotor impairment in simple tests such as the DSST, symbol copying and tracking is greater during the absorption phase than at a later time point after acute administration, even if blood levels of a drug are similar (72,73,74,105,152,155,252,283). This effect, called proteresis, suggests the development of acute tolerance and many authors support this conclusion. However, because these tests are known to be very sensitive to learning and practice effects the "tolerance" may also reflect a practice effect.

Repeated Administration to Healthy Volunteers

The effects of aprazolam by chronic administration were initially studied in healthy volunteers. Tables 3 and 4 summarize the results of these studies.

It is evident from Tables 3 and 4 that after 1 to 3 weeks of daily administration of alprazolam, the drug produced no significant impairment in most of the tests. In contrast, Tables 1 and 2 show that in the same tests a single dose of alprazolam produced significant impairment of performance. Hence, many authors concluded that tolerance to the performance impairing effects of alprazolam was evident. However, as discussed earlier, learning effects can also cause the absence of impairing effects in these tests.

Fleishaker and colleagues (90) reported that sedation scores after three days of therapy with alprazolam were independent of the dose of the drug (1, 3, or 6 mg daily, sustained release) and were lower than after a single dose of alprazolam. Alprazolam's blood levels after 3 days of therapy were, however, 1.5 times higher than after a single dose of the drug.

This finding may be explained by the results of a study that measured changes in $GABA_A$ benzodiazepine receptor density with single photon emission computed tomography. During 24 days of daily alprazolam administration (2 mg) to healthy volunteers receptor density decreased (96). At the baseline, and at 3, 10, 17, and 24 days after the start of therapy, sedation was measured and the Hopkins verbal learning test was per-

TABLE 3. Psychomotor performance after repeated administration of alprazolam

Alprazolam dosage (mg)	0.25	0.50	0.75	1.0	1.5	2.0
% of tests showing impairment	0.0	0.0	14.3	0.0	0.0	66.7
Total number of tests	3	3	7	7	4	3

Data from references 10,28,116,132,156,160,206,240,252,261. Tests included reaction time tests, DSST, symbol copying, card sorting, tracking, vigilance, and the CFFT. A detailed summary of study results can be obtained upon request from the authors.

TABLE 4. Memory functioning after repeated administration of alprazolam

Alprazolam dosage (mg)	0.25	0.50	0.75	1.0	1.5	2.0
% of tests showing impairment	0.0	0.0	0.0	0.0	50.0	0.0
Total number of tests	2	2	2	2	2	2

Data from references 28, 96,116,156,206. Tests included immediate and delayed recall, and recognition. A detailed summary of study results can be obtained upon request from the authors.

formed. Results were compared with $GABA_A$ receptor density. Sedation was associated with 16% receptor occupancy, but tolerance developed on day 17. This rather low occupancy rate had significant performance effects. After 3 and 10 days of therapy delayed recall was significantly worse as compared to baseline. After 24 days, delayed recall performance returned to the baseline performance level, suggesting the development of tolerance. Immediate recall was unaffected at all measurements. Correlation between tolerance effects in sedation and memory tests and receptor density was poor, suggesting the involvement of other mechanisms.

In this context, it is important to note that tolerance lasts only as long as drug therapy is continued on a daily basis. Patients requiring chronic drug treatment comply poorly with treatment instructions (21) and often use the drug only if needed, use other medication concurrently, or change dosages depending on their health complaints (222). In such instances, tolerance to the impairing effects of alprazolam will not develop easily, and patients are still at risk that behavioral impairments will compromise their daily activities.

Gender

None of the behavioral studies summarized in Tables 1 to 4 reported significant gender differences in the test performance. Also, menstrual cycle phases did not affect performance during alprazolam therapy. Progesterone did not affect performance in alprazolam-treated patients. DSST and card sorting test were equally impaired during the luteal and follicular menstrual cycle phases (176). However, women using oral contraceptives were more sensitive to alprazolam-induced impairment in the DSST, an aiming test, and a reaction time test. The increased impairment did not, however, correlate well with the pharmacokinetic parameters (151).

Age

Elderly

Old age is associated with an increased sensitivity to pharmacodynamic and behavioral effects of benzodiazepines. That is, at a given alprazolam plasma concentration performance will be more impaired in older than in young subjects. However, the relationship between pharmacokinetic differences and behavioral effects does not always correlate well, and some studies failed to find pharmacokinetic and pharmacodynamic differences between young and old subjects (133). In a study comparing young and elderly healthy volunteers, the elderly showed a longer duration of performance impairment, as measured by DSST and tracking tests (188). The difference between young and elderly subjects was more pronounced with increased task difficulty. By intravenous administration to young and elderly healthy volunteers alprazolam had a significant sedative effect. Elderly subjects were more impaired in the card sorting test and DSST, but there was no significant difference in the performance of elderly and younger subjects in the cancellation as well as in the immediate and delayed recall tests (20).

Children

Alprazolam is not frequently prescribed to children and behavioral studies in the pediatric population are scarce. In an open trial with alprazolam (88) twelve children with overanxious disorders received placebo (week 1), alprazolam (4 weeks), and post-drug

placebo treatment (2 weeks). Children were subjected to a continuous performance task, a paired associate learning test, a semantic word processing task, and a test to assess visuomotor performance. No significant performance decrement was reported during alprazolam treatment. On the contrary, performance improved in most tests, probably due to practice effect.

In another study the effects of alprazolam (mean dose 1.57 mg/day) were studied in children and adolescents with overanxious and avoidance disorders (mean age 12.6 years). After 1 week of placebo, followed by 4 weeks of alprazolam, there was no significant change in performance in the continuous performance test and visual matching task that assess long-term memory. However, in the Sternberg memory scanning test, children in the placebo group performed significantly worse than those on alprazolam (247). Based upon these limited results, it seems that the behavioral effects of alprazolam in children and adults are similar.

Current or Past Drug Abusers

Mumford and colleagues (184) investigated the single-dose effects of alprazolam (0.5, 1.0, and 2.0 mg) in 14 male subjects who met the DSM-III-R diagnosis for psychoactive substance dependence. Urine drug tests revealed that subjects were drug-free on test days. Tests included DSST, balance, a choice reaction time test, and immediate and delayed picture recall and recognition. After 2 mg of alprazolam the subjects showed significantly greater impairment than with placebo in all tests. At lower doses alprazolam produced no significant impairment of performance, except in the choice reaction time test. In similar studies with polydrug users the same authors reported significant impairment in digit span, balance, DSST and choice reaction tests after a single dose of alprazolam (37,77, 183,185).

Light, moderate and heavy drinkers are at increased risk to abuse benzodiazepines. Women are more vulnerable to this effect than men. Moderately drinking women reported equally increased alprazolam and buspirone liking when compared to light drinking women. Although alprazolam produced a dose-dependent impairment in performance tests, including DSST, a word learning test, divided attention, and tracking, drug liking was independent of the dose of alprazolam (82). Females with a paternal history of alcoholism performed significantly worse in the DSST and immediate word recall test than control subjects (81).

Behavioral Effects in the Patient Population

The presence of pathology is known to affect human behavior. For example, it has been shown that anxiety and depression itself significantly impair cognitive and psychomotor performance (31,36,67,101,139,141,220,264). However, the number of studies that investigated possible impairment caused by the illness itself is limited and the results are often conflicting.

For example, in a direct comparison (67), 14 panic patients in a non-panic state (background anxiety) performed worse than healthy controls in a variety of psychological tests, including immediate and delayed recall, digit span, DSST, symbol copying, digit cancellation test, and a reaction time test. Panic patients in the non-panic state are physiologically more aroused and reported significantly higher levels of anxiety than the healthy

controls. However, performance differences in the tests reached significance only for immediate and delayed recall tests. In contrast, in another study with 69 patients with mild to moderate panic disorder, there was no significant impairment in similar tests (101).

In patients with unipolar and bipolar depression, significant impairment was found in laboratory tests assessing motor speed (reaction time and tapping tests) and visual tracking (trial making and dot replacement tests) (264). There was no significant difference in the impairment of patients with unipolar as compared to bipolar depression. In contrast, another study reported that patients with unipolar or bipolar depression had no significant impairment in a laboratory test battery, including tests of executive functioning, verbal and visual memory, attention, intelligence, psychomotor speed, and sensory-perceptual skills, than matched control subjects (220). However, memory functioning in patients scoring high on depression was significantly worse than those having mild depression.

A study examining memory functioning in 3999 Vietnam veterans (141) reported that those experiencing depressive symptoms (without anxiety) had significantly impaired immediate recall on the California Verbal Learning Test. The veterans experiencing anxiety (without depression) had no significant impairments. However, veterans suffering from both, anxiety and depression, had immediate recall impairment and were significantly worse on the retrieval of newly learned information than control subjects.

These studies illustrate that it is important to take comorbidity into account when discussing possible impairments accompanying panic disorder, anxiety, or depression. Taking into account the mixed and conflicting results described above, more studies are needed to get a better understanding of the impact of the pathology itself on human performance.

The complex interaction between therapeutic effects (presumably improving performance) and adverse effects (presumably worsening performance) of alprazolam cannot easily be predicted from studies with healthy volunteers. However, these studies will examine the adverse drug effects of alprazolam, without interference of changes in the pathology itself. Since alprazolam's activity may be modified by the disease, it is important to perform these studies in a patient population as well.

A limited number of studies investigated the effects of alprazolam on cognitive and psychomotor performance in patients. For example, patients receiving hemodialysis or continuous peritoneal dialysis performed significantly worse on the DSST, choice reaction and short-term memory tests suggesting that patients with renal dysfunction are more sensitive to some of the psychomotor and memory effects of alprazolam (236).

Behavioral effects after acute administration of alprazolam (0.25, 0.5, 0.75 mg) and placebo have been investigated during the premenstrual and postmenstrual phases in women with premenstrual syndrome (79,80). Performance tests were performed at 0.5 to 4 h after treatment; they included DSST, balance, divided attention, repeated acquisition, and word learning tests. Relative to placebo, alprazolam produced significant dose-related decreases in performance on all tasks regardless of menstrual cycle phase. However, significant practice effects were found in the DSST and repeated acquisition test.

A study comparing the performance impairing effects of a single dose of alprazolam (1 mg) in healthy volunteers and PD patients showed that alprazolam significantly impaired DSST performance in both groups. The difference between patients and healthy volunteers was not significant (134).

A controlled longitudinal study (57) examined memory functions in PD patients from the London Toronto Study. The patients received alprazolam, placebo, and/or psychologi-

cal therapy (exposure or relaxation). Patients were treated for 8 weeks with alprazolam (mean daily dose of 5.25 mg in week 8) or placebo and tested at baseline (week 0), after chronic treatment (week 8), and during follow-up period (24 weeks after the start of the study). As compared to placebo, alprazolam significantly impaired free word recall after 8 weeks. After 24 weeks, performance in alprazolam-treated patients returned to the baseline, whereas performance in the placebo-treated patients improved. There was no significant difference in the performance of alprazolam- and placebo-treated patients in digit span, news recall and psychomotor tests (cancellation and tapping speed). Psychological therapy had no significant effects on test performance. A 3.5-year follow-up of these patients showed that the test performance of PD patients that belonged to the alprazolam treated group was similar to that in the placebo-treated group (138). Performance in both groups was equal to the pre-treatment level. The authors concluded that their post-treatment findings after 24 weeks should be explained as practice effects rather than drug-induced effects.

Gladsjo and colleagues (102) investigated neuropsychological functioning of PD patients treated for six weeks with alprazolam (4 mg/day, extended release) or placebo in combination with cognitive-behavioral therapy. Relative to baseline, both groups showed significant improvement on tests measuring attention, executive functioning (Card Sorting Test), psychomotor speed (Trial Making Test, Finger Tapping Test), and visual memory tests. No significant improvement was found on tests measuring learning, verbal memory and reaction time. However, these effects were caused by a practice effect on the tests, making the results of this study hard to interpret.

Like alprazolam (274), driving ability after diazepam can be severely impaired (193). Driving ability after chronic alprazolam treatment has not been investigated in patients. A 4-week study (158) examined the effects on actual driving performance in anxious outpatients treated with buspirone (15 mg daily) or diazepam (15 mg daily). Chronic treatment with buspirone did not significantly impair driving performance. In contrast, diazepam significantly impaired driving performance during the first three weeks of treatment. In addition, speed control after diazepam was significantly impaired during the first treatment week. From these results it could be expected that driving will be significantly impaired after chronic administration of alprazolam as well. It is, therefore, important to investigate whether alprazolam would affect performance of PD patients in the-road driving test and whether tolerance develops to driving impairment that is evident after acute alprazolam administration (274).

A study that examined the effects of long-term (8 years) benzodiazepine therapy on DDST performance and a Symbol copying test before, during, and after discontinuation of the therapy showed that performance of PD patients, who were successfully tapered off from alprazolam therapy, significantly improved as compared to patients continued on alprazolam (217). An earlier study (168) compared cognitive and psychomotor performance in anxious outpatients who were treated with benzodiazepines (including alprazolam) and those who received no pharmacological treatment. Performance in benzodiazepine-treated patients was significantly worse in the Critical Flicker Fusion Test (CFFT), but no significant differences were observed on the DSST, symbol copying, letter cancellation and immediate and delayed recall tests. However, after acute administration of benzodiazepines to these patients, performance in the DSST significantly improved, whereas delayed recall was significantly impaired. Treated patients were also tested at 4 to 8 days after discontinuation of therapy (during benzodiazepine withdrawal). In comparison with their base-

line performance, there were no significant differences in the test results, except for an increase in CFF threshold. Furthermore, patients reported significantly increased sedation and less feelings of tranquilization.

DISCUSSION

This exhaustive literature review shows that alprazolam is effective in the treatment of panic disorder, generalized anxiety and depression. The major conclusion from the studies discussed is that alprazolam is as effective as TCAs, such as imipramine, in the relief of symptoms. However, in panic disorder SSRIs appear to be significantly superior to alprazolam, as well as TCAs, and should, therefore, be viewed as the first line therapy of this disorder.

In panic attacks alprazolam produces rapid clinical improvement during the first week of therapy, reducing anxiety, depressive symptoms and frequency of the attacks. TCAs and SSRIs, in contrast, may worsen the symptoms initially and may become effective only after 2 to 4 weeks of continuous administration. Patients receiving psychological therapy reported no worsening at the onset, but it took several weeks before clinical improvement was established. The aggravation of symptoms or slow onset of action has serious implications for compliance and may result in premature discontinuation of therapy. Hence, alprazolam treatment is favored, if rapid relief of symptoms is required.

During treatment, alprazolam is safe and well tolerated. No dose increments are necessary and the risks of dependence and abuse are small in the patient population. However, like other benzodiazepines, when treatment is discontinued, alprazolam causes withdrawal and rebound effects; the symptoms that were reduced or absent during treatment may reappear. The rebound symptoms may be more severe than prior to therapy. Furthermore, it has been reported that all advantages of alprazolam therapy are lost after discontinuation of the drug. In contrast, improvement remains stable long after discontinuation of psychological therapy. However, psychological treatment is effortful, time-consuming and costly.

Alprazolam produces a variety of unwanted effects of which drowsiness and sedation are the most prominent. As reviewed above, aprazolam at clinically effective doses produces significant behavioral toxicity. The results summarized in Tables 1 and 2 show that a single dose of alprazolam can impair memory and psychomotor performance. As summarized in Tables 3 and 4, after repeated administration of the drug tolerance develops to the performance impairing effects of alprazolam. However, it must be taken into account that the tests used in these studies (e.g., the DSST) are known for persistent learning and practice effects. Hence, it cannot be ruled out that improvement in the performance after repeated administration of the drug is caused by practice effects. Moreover, a large number of patients use alprazolam not on a daily basis, but only as needed. In such cases, tolerance to alprazolam's impairing effects does not develop easily. This becomes evident from the few behavioral studies conducted in patients. Although some of these studies reported learning and practice effects, others reported significant performance impairment after long-term therapy with alprazolam. It can be questioned whether at higher doses of alprazolam the therapeutic effect of alprazolam outweighs its adverse effects.

In conclusion, the impairing effects on daily activities such as driving a car limit the safe use of alprazolam in outpatients. Taking into account alprazolam's effects after treatment discontinuation (withdrawal and rebound effects) and its adverse effect profile

(drowsiness and sedation), it is not surprising that alprazolam is not recommended as first-line therapy in panic disorder (12), generalized anxiety (7,12) or depression (8). However, alprazolam may be considered as a second-line treatment if SSRIs are not effective or tolerated well.

Prescribers may prefer a combination therapy of SSRIs and alprazolam. It is known that SSRIs have a slow onset of action (several weeks) and may produce initial symptom worsening. The co-administration of alprazolam may provide adequate symptom relief during the first 6 to 8 weeks after the start of the therapy. Alprazolam can be gradually withdrawn when SSRIs become clinically effective (290). The combination therapy with alprazolam will presumably enhance treatment compliance.

A recent study in 443 panic patients reported that despite efforts to promote the use of SSRIs in the treatment of panic disorder only a modest increase in their use took place (34). Despite all recommendations to use SSRIs instead of alprazolam in the therapy of panic disorder, the use of alprazolam remained stable over the past decade. The prescribers are apparently conservative in changing their treatment regimen, despite clear evidence that SSRIs have a greater clinical efficacy combined with a favorable adverse effect profile when compared to alprazolam.

REFERENCES

1. Abernethy DR, Greenblatt DJ, Divoll M, Moschitto LJ, Harmatz JS, Shader RI. Interaction of cimetidine with the triazolobenzodiazepines alprazolam and triazolam. *Psychopharmacology* 1983;80:275–278.
2. Abernethy DR, Greenblatt DJ, Morse DS, Shader RI. Interaction of propoxyphene with diazepam, alprazolam and lorazepam. *Br J Clin Pharmacol* 1985;19:51–57.
3. Achmin J, Zarycranski W, Taylor KP, Albano D, Klockowski PM. Effects of venlafaxine on the pharmacokinetics of alprazolam. *Psychopharmacol Bull* 1998;34:211–219.
4. Aden GC, Thein SG. Alprazolam compared to diazepam and placebo in the treatment of anxiety. *J Clin Psychiatry* 1980;41:245–248.
5. Alexander PE. The need for extended-release medications. *Curr Ther Res* 1995;56:940–946.
6. Allen D, Curran HV, Lader M. The effects of repeated doses of clomipramine and alprazolam on physiological, psychomotor and cognitive functions in normal subjects. *Eur J Clin Pharmacol* 1991;40:355–362.
7. American Psychiatric Association (APA). Practical guideline for the treatment of patients with panic disorder. *Am J Psychiatry* 1998;155:1–34.
8. Anderson IM, Nutt DJ, Deakin FW. Evidence-based guideline for treating depressive disorders with antidepressants: A revision of the 1993 British Association for Psychopharmacology guidelines. *J Psychopharmacol* 2000;14:3–20.
9. Ansseau M, Ansoms C, Beckers G, et al. Double-blind clinical study comparing alprazolam and doxepin in primary unipolar depression. *J Affect Disord* 1984;7:287–296.
10. Aranko K, Mattila MJ, Bordignon D. Psychomotor effects of alprazolam and diazepam during acute and subacute treatment, and during the follow-up phase. *Acta Pharmacol Toxicol* 1985;56:364–372.
11. Ballenger JC, Burrows GD, DuPont RL, et al. Alprazolam in panic disorder and agoraphobia: Efficacy in short-term treatment. *Arch Gen Psychiatry* 1988;45:413–422.
12. Bandelow B, Zohar J, Hollander E, Kasper S, Möller H-J. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders. *World Biol Psychiatry* 2002;3:171–199.
13. Banerji JR, Brantingham P, McEwan GD, et al. A comparison of alprazolam with amitriptyline in the treatment of patients with neurotic or reactive depression. *Irish J Med Sci* 1989;158:110–113.
14. Barbee JG, Black FW, Kehoe CE, Todorov AA. A comparison of the single-dose effects of alprazolam, buspirone, and placebo upon memory function. *J Clin Psychopharmacol* 1991;11:351–356.
15. Barbee JG, Mancuso DM, Freed CR, Todorov AA. Alprazolam as a neuroleptic adjunct in the emergency treatment of schizophrenia. *Am J Psychiatry* 1992;149:506–510.
16. Barbone F, McMahon AD, Davey PG, et al. Association of road-traffic accidents with benzodiazepine use. *Lancet* 1998;352:1331–1336.

17. Berg F van den, Tulen JHM, Boomsma F, Noten JBGM, Moleman P, Pepplinkhuizen L. Effects of alprazolam and lorazepam on catecholaminergic and cardiovascular activity during supine rest, mental load and orthostatic challenge. *Psychopharmacology* 1996;128:21–30.
18. Berger CO, Presser B. Alprazolam in the treatment of two subsamples of patients with late luteal phase dysphoric disorder: A double-blind, placebo-controlled crossover study. *Obstet Gynecol* 1994;84:379–385.
19. Bertolino A, Mastucci E, Porro V, et al. Etizolam in the treatment of generalized anxiety disorder: A controlled clinical trial. *J Int Med Res* 1989;17:455–460.
20. Bertz RJ, Kroboth PD, Kroboth FJ, et al. Alprazolam in young and elderly men: Sensitivity and tolerance to psychomotor, sedative and memory effects. *J Pharmacol Exp Ther* 1997;281:1317–1329.
21. Blackwell B. Compliance. *Psychother Psychosomatics* 1992;58:161–169.
22. Block RI, Berchou R. Alprazolam and lorazepam effects on memory acquisition and retrieval processes. *Pharmacol Biochem Behav* 1984;20:233–241.
23. Blom MW, Bartel PR, de Sommers K, Van der Meyden CH, Becker PJ. The effects of alprazolam, quazepam and diazepam on saccadic eye movements, parameters of psychomotor function and the EEG. *Fund Clin Pharmacol* 1990;4:653–661.
24. Bond A, Silveira JC, Lader M. Effects of single doses of alprazolam and alcohol alone and in combination on psychological performance. *Hum Psychopharmacol* 1991;6:219–228.
25. Bond AJ, Silveira JC, Lader MH. The effects of alprazolam alone and in combination with alcohol on central integrative activity. *Eur J Clin Pharmacol* 1992;42:495–498.
26. Bond AJ, Silveira JC. The combination of alprazolam and alcohol on behavioral aggression. *J Stud Alcohol* 1993;11(Suppl):30–39.
27. Bond AJ, Curran HV, Bruce MS, O'Sullivan G, Shine P. Behavioural aggression in panic disorders after 8 weeks' treatment with alprazolam. *J Affect Disord* 1995;35:117–123.
28. Bourin M, Colombel M, Guitton B. Alprazolam 0.125 mg twice a day improves aspects of psychometric performance in healthy volunteers. *J Clin Psychopharmacol* 1998;18:364–372.
29. Boyer W. Serotonin uptake inhibitors are superior to imipramine and alprazolam in alleviating panic attacks: A meta-analysis. *Int Clin Psychopharmacol* 1995;10:45–49.
30. Bramanti P, Ricci RM, Rifici C, et al. Etizolam: A controlled study versus alprazolam in the treatment of generalized anxiety disorder with minor associated depressive symptoms. *Curr Ther Res* 1990;48:369–377.
31. Brand N, Jolles J. Information procesing in depression and anxiety. *Psychol Med* 1987;17:97–105.
32. Braun P, Greenberg D, Dasberg H, Lerer B. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. *J Clin Psychiatry* 1990;51:236–238.
33. Bruce TJ, Spiegel DA, Gregg SF, Nuzzarello A. Predictors of alprazolam discontinuation with and without cognitive behavior therapy in panic disorder. *Am J Psychiatry* 1995;152:1156–1160.
34. Bruce SE, Vasile RG, Goisman RM, et al. Are benzodiazepines still the medication of choice for patients with panic disorder with or without agoraphobia? *Am J Psychiatry* 2003;160:1432–8.
35. Buch AB, van Harken DR, Seidehamel RJ, Barbhaiya RH. A study of pharmacokinetic interaction between buspirone and alprazolam at steady state. *J Clin Pharmacol* 1993;33:1104–1109.
36. Burt DB, Zembar MJ, Niederehe G. Depression and memory impairment: A meta-analysis of the association, its pattern, and specificity. *Psychol Bull* 1995;117:285–305.
37. Busto U, Kaplan HL, Zawertailo L, Sellers EM. Pharmacologic effects and abuse liability of bretazenil, diazepam, and alprazolam in humans. *Clin Pharmacol Ther* 1994;55:451–463.
38. Busto UE, Kaplan HL, Wright CE, et al. A comparative pharmacokinetic and dynamic evaluation of alprazolam sustained-release, bromazepam, and lorazepam. *J Clin Psychopharmacol* 2000;20:628–635.
39. Cassano GB, Toni C, Petracca A, et al. Adverse effects associated with the short-term treatment of panic disorder with imipramine, alprazolam or placebo. *Eur Neuropsychopharmacol* 1994;4:47–53.
40. Castillo A, Sotillo C, Mariategui J. Alprazolam compared to clobazam and placebo in anxious outpatients. *Neuropsychobiology* 1987;18:189–194.
41. Češková E, Švestka K, Náhunek K, Obrovská V. Double blind comparison of alprazolam with dosulepine in endogenous depression. *Activ Nerv Super* 1989;31:290–291.
42. Charney DS, Woods SW, Goodman WK, et al. Drug treatment of panic disorder: The comparative efficacy of imipramine, alprazolam, and trazodone. *J Clin Psychiatry* 1986;47:580–586.
43. Charney DS, Woods SW. Benzodiazepine treatment of panic disorder: A comparison of alprazolam and lorazepam. *J Clin Psychiatry* 1989;50:418–423.
44. Christensen DB, Benfield WR. Alprazolam as an alternative to low-dose haloperidol in older, cognitively impaired nursing facility patients. *J Am Geriatr Soc* 1998;46:620–625.
45. Ciraulo DA, Antal EJ, Smith RB, et al. The relationship of alprazolam dose to steady-state plasma concentrations. *J Clin Psychopharmacol* 1990;10:27–32.

46. Ciraulo DA, Barnhill JG, Ciraulo AM, et al. Alternations in pharmacodynamics of anxiolytics in abstinent alcoholic men: Subjective reponses, abuse liability, and electroencephalographic effects of alprazolam, diazepam, and buspirone. *J Clin Psychopharmacol* 1997;37:64–73.
47. Ciraulo DA, Knapp CM, LoCastro J, Greenblatt DJ, Shader RI. A benzodiazepine mood effect scale: Reliability and validity determined for alcohol-dependent subjects and adults with a parental history of alcoholism. *Am J Drug Alcohol Abuse* 2001;27:339–347.
48. Clark DB, Taylor CB, Roth WT, et al. Surreptitious drug use by patients in a panic disorder study. *Am J Psychiatry* 1990;147:507–509.
49. Cohn JB. Multicenter double-blind efficacy and safety study comparing alprazolam, diazepam and placebo in clinically anxious patients. *J Clin Psychiatry* 1981;42:347–351.
50. Cohn JB, Wilcox CS. Long-term comparison of alprazolam, lorazepam and placebo in patients with an anxiety disorder. *Pharmacotherapy* 1984;4:93–98.
51. Cohn JB, Wilcox CS. Low-sedation potential of buspirone compared with alprazolam and lorazepam in the treatment of anxious patients: A double-blind study. *J Clin Psychiatry* 1986;47:409–412.
52. Coldwell SE, Milgrom P, Getz T, Ramsay DS. Amnestic and anxiolytic effects of alprazolam in oral surgery patients. *J Oral Maxillofac Surg* 1997;55:1061–1070.
53. Cox BJ, Endler N, Lee PS, Swinson RP. A meta-analysis of treatments for panic disorder with agoraphobia: Imipramine, alprazolam and *in vivo* exposure. *J Behav Ther Exp Psychiatry* 1992;23:175–182.
54. Crombez G, Kupers R, Adriaensen H. The effects of a single oral dose of lorazepam and alprazolam on reaction times in young healthy volunteers. *Acta Anaesthesiol Belg* 1991;42:79–84.
55. Cross-National Collaborative Panic Study, Second Phase Investigators. Drug treatment of panic disorder: Comparative efficacy of alprazolam, imipramine, and placebo. *Br J Psychiatry* 1992;160:191–202.
56. Curran HV. Benzodiazepines, memory and mood: A review. *Psychopharmacology* 1991;105:1–8.
57. Curran HV, Bond A, O'Sullivan G, et al. Memory functions, alprazolam and exposure therapy: A controlled longitudinal study of agoraphobia with panic disorder. *Psychol Medi*cine 1994;24:969–976.
58. Curtis GC, Massana J, Udina C, Ayuso JL, Cassano GB. Maintenance drug therapy of panic disorder. *J Psychiat Res* 1993;27(Suppl 1):127–142.
59. Dämgen K, Lüddens H. Zaleplon displays a selectivity to recombinant $GABA_A$ receptors different from zolpidem, zopiclone and benzodiazepines. *Neurosci Res Commun* 1999;25:139–148.
60. Danjou P, Warot D, Hergueta T, Lacomblez L, Bouhours P, Puech AJ. Comparative study of the psychomotor and antistress effects of ritanserin, alprazolam and diazepam in healthy subjects: Some trait anxiety-independent responses. *Int Clin Psychopharmacol* 1992;7:73–79.
61. Davison K, Farquharson RG, Kahn MC, et al. A double-blind comparison of alprazolam, diazepam and placebo in the treatment of anxious out-patients. *Psychopharmacology* 1983;80:308–310.
62. Davison K, Farquharson RG, Kahn MC, et al. A double-blind comparison of alprazolam, diazepam and placebo in the treatment of anxious out-patients. *Br J Clin Pharmacol* 1985;19(Suppl 1):37S–43S.
63. Dehlin O, Kullingsjö H, Lidén A, Agrell B, Moser G, Olsen I. Pharmacokinetics of alprazolam in geriatric patients with neurotic depression. *Pharmacol Toxicol* 1991;68:121–124.
64. Diegoli MSC, da Fonseca AM, Diegoli CA, Pinotti JA. A double-blind trial of four medications to treat severe premenstrual syndrome. *Int J Gynecol Obstet* 1998;62:63–67.
65. Doble A. New insights into the mechanisms of action hypnotics. *J Psychopharmacol* 1999;13(Suppl 4): S11–S20.
66. Draper RJ, Daly I. Alprazolam and amitriptyline: A double blind comparison of anxiolytic and anti-depressant activity. *Irish Med J* 1983;76:453–456.
67. Dratcu L, Bond A. Panic patients in the non-panic state: Physiological and cognitive dysfunction. *Eur Psychiatry* 1998;3:18–25.
68. Dunner DL, Ishiki D, Avery DH, Wilson LG, Hyde TS. Effects of alprazolam and diazepam on anxiety and panic attacks in panic disorder: A controlled study. *J Clin Psychiatry* 1986;47:458–460.
69. DuPont RL, Swinson RP, Ballenger JC, et al. Discontinuation of alprazolam after long-term treatment of panic-related disorders. *J Clin Psychopharmacol* 1992;12:352–354.
70. Edwards JG, Inman WHW, Pearce GL, Rawson NSB. Prescription-event monitoring of 10895 patients treated with alprazolam. *Br J Psychiatry* 1991;158:387–392.
71. Elie R, Lamontagne Y. Alprazolam and diazepam in the treatment of generalized anxiety. *J Clin Psychopharmacol* 1984;4:125–129.
72. Ellinwood EH, Heatherly DG, Nikaido AM, Bjornsson TD, Kilts C. Comparative pharmacokinetics and pharmacodynamics of lorazepam, alprazolam and diazepam. *Psychopharmacology* 1985;86:392–399.
73. Ellinwood EH, Nikaido AM, Heatherly DG, Bjornsson TD. Benzodiazepine pharmacodynamics: Evidence for biophase rate limiting mechanisms. *Psychopharmacology* 1987;91:168–174.

74. Ellinwood EH, Nikaido AM, Gupta SK, Heatherly DG, Hege S. Comparison of the relationship between structure and CNS effects for lorazepam, clonazepam and alprazolam. *J Psychopharmacol* 1993;7:24–32.
75. Enkelman R. Alprazolam versus buspirone in the treatment of outpatients with generalized anxiety disorder. *Psychopharmacology* 1991;105:428–432.
76. Eriksson B, Nagy A, Starmark J-E, Thelander U. Alprazolam compared to amitriptyline in the treatment of major depression. *Acta Psychiatr Scand* 1987;75:656–663.
77. Evans SM, Troisi JR, Griffiths RR. Tandospirone and alprazolam: Comparison of behavioral effects and abuse liability in humans. *J Pharmacol Exp Ther* 1994;271:683–694.
78. Evans SM, Foltin RW, Levin FR, Fischman MW. Behavioral and subjective effects of DN-2327 (pazinaclone) and alprazolam in normal volunteers. *Behav Pharmacol* 1995;6:176–186.
79. Evans SM, Haney M, Levin FR, Foltin RW, Fischman MW. Mood and performance changes in women with premenstrual dysphoric disorder: Acute effects of alprazolam. *Neuropsychopharmacology* 1998;19: 499–516.
80. Evans SM, Foltin RW, Fischman MW. Food "cravings" and the acute effects of alprazolam on food intake in women with premenstrual dysphoric disorder. *Appetite* 1999;32:331–349.
81. Evans SM, Levin FR, Fischman MW. Increased sensitivity to alprazolam in females with a paternal history of alcoholism. *Psychopharmacology* 2000;150:150–162.
82. Evans SM, Levin FR. The effects of alprazolam and buspirone in light and moderate female social drinkers. *Behav Pharmacol* 2002;13:427–439.
83. Fabre LF, McLendon D. Alprazolam efficacy in anxiety. *Clin Pharmacol Ther* 1979;25:233.
84. Farbe LF, McLendon DM. A double-blind study comparing the efficacy and safety of alprazolam with imipramine and placebo in primary depression. *Curr Ther Res* 1980;27:474–482.
85. Fawcett J, Kravitz HM, Howard HM, Jeffriess H. Alprazolam: An antidepressant? Alprazolam, desipramine, and an alprazolam-desipramine combination in the treatment of adult depressed outpatients. *J Clin Psychopharmacol* 1987;7:295–310.
86. Feighner JP, Aden GC, Farbe LF, Rickels K, Smith WT. Comparison of alprazolam, imipramine, and placebo in the treatment of depression. *JAMA* 1983;249:3057–3064.
87. Feighner JP, Meredith CH, Frost NR, Chammas S, Hendrickson G. A double-blind comparison of alprazolam vs. imipramine and placebo in the treatment of major depressive disorder. *Acta Psychiatr Scand* 1983; 68:223–233.
88. Ferguson HB, Simeon JG. Evaluating drug effects on children's cognitive functioning. *Prog Neuropsychopharmacol Biol Psychiatry* 1984;8:683–686.
89. Fernandez-Guardiola A, Jurado JL, Aguilar-Jimenez E. Evaluation of the attention and sleepiness states by means of a psychophysiological test of reaction time and time estimate in man: Effects of psychotropic drugs. *Curr Ther Res* 1984;35:1000–1009.
90. Fleishaker JC, Phillips JP, Eller MG, Smith RB. Pharmacokinetics and pharmacodynamics of alprazolam following single and multiple oral doses of a sustained-release formulation. *J Clin Pharmacol* 1989;29: 543–549.
91. Fleishaker JC, Hulst LK. A pharmacokinetic and pharmacodynamic evaluation of the combined administration of alprazolam and fluvoxamine. *Eur J Clin Pharmacol* 1994;46:35–39.
92. Fleishaker JC, Garzone PD, Chambers JH, Sirocco K, Weingartner H. Comparison of the spectrum of cognitive effects of alprazolam and adinazolam after single doses in healthy subjects. *Psychopharmacology* 1995;120:169–176.
93. Freeman EW, Rickels K. Characteristics of placebo responses in medical treatment of premenstrual syndrome. *Am J Psychiatry* 1999;156:1403–1408.
94. Freeman EW, Rickels K, Sondheimer SJ, Polansky M. A double-blind trial of oral progesterone, alprazolam, and placebo in treatment of severe premenstrual syndrome. *JAMA* 1995;274:51–57.
95. Friedman MJ, Stolk JM, Harris PQ, et al. Serum dopamine-β-hydroxylase activity in depression and anxiety. *Biol Psychiatry* 1984;19:557–570.
96. Fujita M, Woods SW, Verhoef NPLG, et al. Changes of benzodiazepine receptors during chronic benzodiazepine administration in humans. *Eur J Pharmacol* 1999;368:161–172.
97. Furukori H, Otani K, Yasui N, et al. Effect of carbamazepine on the single oral dose pharmacokinetics of alprazolam. *Neuropsychopharmacology* 1998;18:364–369.
98. Gaillard AWK. The evaluation of drug effects in laboratory tasks. In: Hindmarch I, Aufdembrinke B, Ott H, Eds. *Psychopharmacology and Reaction Time*. New York: Wiley Medical Publication,1988.
99. Gelernter CS, Uhde TW, Cimbolic P, et al. Cognitive-behavioral and pharmacological treatments of social phobia. A controlled study. *Arch Gen Psychiatry* 1991;48:938–945.

100. Ghoneim MM, Mewaldt SP. Benzodiazepines and human memory: A review. *Anesthesiology* 1990;72: 926–938.
101. Gladsjo JA, Rapaport MH, McKinney R, et al. A neuropsychological study of panic disorder: Negative findings. *J Affect Disord* 1998;49:123–131.
102. Gladsjo JA, Rapaport MH, McKinney R, et al. Absence of neuropsychologic deficits in patients receiving long-term treatment with alprazolam-XR for panic disorder. *J Clin Psychopharmacol* 2001;21:131–138.
103. Goldberg SC, Ettigi P, Schulz PM, Hamer RM, Hayes PE, Friedel RO. Alprazolam versus imipramine in depressed out-patients with neurovegetative signs. *J Affect Disord* 1986;11:139–145.
104. Greenblatt DJ, Divoll M, Abernethy DR, Moschitto LJ, Smith RB, Shader RI. Alprazolam kinetics in the elderly. *Arch Gen Psychiatry* 1983;40:287–290.
105. Greenblatt DJ, Harmatz JS, Dorsey C, Shader RI. Comparative single-dose kinetics and dynamics of lorazepam, alprazolam, prazepam, and placebo. *Clin Pharmacol Ther* 1988;44:326–334.
106. Greenblatt DJ, Harmatz JS, Shader RI. Clinical pharmacokinetics of anxiolytics and hypnotics in the elderly. *Clin Pharmacokinet* 1991;21:165–177.
107. Greenblatt DJ, Preskorn SH, Cotreau MM, Holst WD, Harmatz JS. Fluoxetine impairs clearance of alprazolam but not of clonazepam. *Clin Pharmacol Ther* 1992;52:479–486.
108. Greenblatt DJ, Wright E. Clinical pharmacokinetics of alprazolam. Therapeutic implications. *Clin Pharmacokinet* 1993;24:453–471.
109. Greenblatt DJ, von Moltke LL, Harmatz JS, Ciraulo DA, Shader RI. Alprazolam pharmacokinetics, metabolism, and plasma levels: Clinical implications. *J Clin Psychiatry* 1993;54(Suppl 10):4–11.
110. Greenblatt DJ, Harmatz JS, Shader RI. Plasma alprazolam administrations. Relation to efficacy and side effects in the treatment of panic disorder. *Arch Gen Psychiatry* 1993;50:715–722.
111. Greenblatt DJ, Wright CE, von Moltke LL, et al. Ketoconazole inhibition of triazolam and alprazolam clearance: Differential kinetic and dynamic consequences. *Clin Pharmacol Ther* 1998;64:237–247.
112. Greene DS, Salazar DE, Dockens RC, Kroboth P, Barbhaiya RH. Coadministration of nefazodone and benzodiazepines. III A pharmacokinetic interaction study with alprazolam. *J Clin Psychopharmacol* 1995;15: 399–408.
113. Gunal DI, Afsar N, Bekiroglu N, Aktan S. New alternative agents in essential tremor therapy: Double-blind placebo-controlled study of alprazolam and acetazolamide. *Neurol Sci* 2000;21:315–317.
114. Haney M, Foltin RW, Fischman MW. Behavioral contingencies modulate alprazolam self-administration by humans. *Behav Pharmacol* 1997;8:82–90.
115. Harrison WM, Endicott J, Nee J. Treatment of dysphoria with alprazolam. A controlled study. *Arch Gen Psychiatry* 1990;47:270–275.
116. Hart RP, Colenda CC, Hamer RM. Effects of buspirone and alprazolam on the cognitive performance of normal elderly subjects. *Am J Psychiatry* 1991;148:73–77.
117. Hayashi R. Correlation between coefficient of variation of choice reaction time and components of event-related potentials (P300): Effect of a benzodiazepine. *J Neurol Sci* 2000;178:52–56.
118. Hayoun H, Hirigoyen M-F, Prigent Y, et al. Double-blind, comparative, multicenter study of two benzodiazepines in 117 outpatients: Alprazolam versus clobazam. *Psychiat Psychobiol* 1987;2:202–213.
119. Hecquet S, Puech AJ, Lecrubier Y. Double-blind study, alprazolam versus lorazepam in ambulatory anxious patients. *Therapie* 1984;39:253–261.
120. Hindmarch I. Measuring the side-effects of psychoactive drugs: A pharmacodynamic profile of alprazolam. *Alcohol Alcoholism* 1983;18:361–367.
121. Hoehn-Saric R, McLoad DR, Zimmerli WD. Differential effects of alprazolam and imipramine in generalized anxiety disorder: Somatic versus psychic symptoms. *J Clin Psychiatry* 1988;49:293–301.
122. Holland JC, Morrow GR, Schmale A, et al. A randomized clinical trial of alprazolam versus progressive muscle relaxation in cancer patients with anxiety and depressive symptoms. *J Clin Oncol* 1991;9: 1004–1011.
123. Hossain M, Wright E, Baweja R, Ludden T, Miller R. Nonlinear mixed effects modeling of single dose and multiple dose data for an immediate release (IR) and a controlled release (CR) dosage form of alprazolam. *Pharmac Res* 1997;14:309–315.
124. Hubain PP, Castro P, Mesters P, De Maertelaer V, Mendlewicz J. Alprazolam and amitriptyline in the treatment of major depresssive disorder: A double-blind clinical and sleep EEG study. *J Affect Disord* 1990;18:67–73.
125. Huynh L, Fields S. Alprazolam for tinnitus. *Ann Pharmacother* 1995;29:311–312.
126. Imlah NW. An evaluation of alprazolam in the treatment of reactive or neurotic (secondary) depression. *Br J Psychiatry* 1985;146:515–519.
127. Iqbal MM, Sobhan T, Ryals T. Effects of commonly used benzodiazepines on the fetus, the neonate, and the nursing infant. *Psychiatr Serv* 2002;53:39–49.

128. Johnson RM, Brummett R, Schleuning A. Use of alprazolam for relief of tinnitus. A double-blind study. *Arch Otolaryngol Head Neck Surg* 1993;119:842–845.
129. Jonas JM, Cohon MS. A comparison of the safety and efficacy of alprazolam versus other agents in the treatment of anxiety, panic, and depression: A review of the literature. *J Clin Psychiatry* 1993;54 (Suppl 10):25–45.
130. Jonas JM, Hearron AE. Alprazolam and suicidal ideation: A meta-analysis of controlled trials in the treatment of depression. *J Clin Psychopharmacol* 1996;16:208–211.
131. Juhl RP, van Thiel DH, Dittert LW, Smith RB. Alprazolam pharmacokinetics in alcohol liver disease. *J Clin Pharmacol* 1984;24:113–119.
132. Jurado JL, Fernández-Mas R, Fernández-Guardiola A. Effects of 1 week administration of two benzodiazepines on the sleep and early daytime performance of normal subjects. *Psychopharmacology* 1989;99: 91–93.
133. Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Harmatz JS, Shader RI. Single-dose pharmacokinetics and pharmacodynamics of alprazolam in elderly and young subjects. *J Clin Pharmacol* 1997;38: 14–21.
134. Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Harmatz JS, Shader RI. Differences in pharmacodynamics but not pharmacokinetics between subjects with panic disorder and healthy subjects after treatment with a single dose of alprazolam. *J Clin Psychopharmacol* 2000;20:338–346.
135. Katschnig H, Amering M, Stolk JM, et al. Long-term follow-up after a drug trial for panic disorder. *Br J Psychiatry* 1995;167:487–494.
136. Katschnig H, Amerig M, Stolk JM, Ballenger JC. Predictors of quality of life in a long-term followup study in panic disorder patients after a clinical drug trial. *Psychopharmacol Bull* 1996;32:149–155.
137. Kelly TH, Foltin RW, Serpick E, Fischman MW. Behavioral effects of alprazolam in humans. *Behav Pharmacol* 1997;8:47–57.
138. Kiliç C, Curran HV, Noshirvani H, Marks IM, Başoğlu M. Long-term effects of alprazolam on memory: A 3.5 year follow-up of agoraphobia/panic patients. *Psychol Med* 1999;29:225–231.
139. Kindermann SS, Brown GG. Depression and memory in the elderly: A meta-analysis. *J Clin Exp Neuropsychol* 1997;19:625–642.
140. Kirkwood C, Moore A, Hayes P, DeVane CL, Pelonero A. Influence of menstrual cycle and gender on alprazolam pharmacokinetics. *Clin Pharmacol Ther* 1991;50:404–409.
141. Kizilbash AH, Vanderploeg RD, Curtiss G. The effects of depression and anxiety on memory performance. *Arch Clin Neuropsychol* 2002;17:57–67.
142. Klerman GL. Overview of the cross-national collaborative panic study. *Arch Gen Psychiatry* 1988;45: 407–412.
143. Klosko JS, Barlow DH, Tassinari R, Cerny JA. A comparison of alprazolam and behavioral therapy in treatment of panic disorder. *J Consult Clin Psychol* 1990;58:77–84.
144. Koelega HS. Benzodiazepines and vigilance performance: A review. *Psychopharmacology* 1989;98: 145–156.
145. Kolin IS, Linet OI. Double-blind comparison of alprazolam and diazepam for subchronic withdrawal from alcohol. *J Clin Psychiatry* 1981;42:169–173.
146. Korzekwa MI, Steiner M. Assessment and treatment of premenstrual syndromes. *Prim Care Update Obstet Gynecol* 1999;6:153–162.
147. Kožená L, Frantik E, Horváth M. Vigilance impairment after a single dose of benzodiazepines. *Psychopharmacology* 1995;119:39–46.
148. Kožená L, Frantik E, Horváth M. Pharmacologically induced decrease in vigilance measured by two different psychological methods. *Homeostasis* 1997;38:64–65.
149. Kravitz HM, Fawcett J, Newman AJ. Alprazolam and depression: A review of risks and benefits. *J Clin Psychiatry* 1993;54(Suppl 10):78–84.
150. Kristjánsson F. Disposition of alprazolam in human volunteers. Differences between genders. *Acta Pharm Nord* 1991;3:249–250.
151. Kroboth PD, Smith RB, Stoehr GP, Juhl RP. Pharmacodynamic evaluation of the benzodiazepine-oral contraceptive interaction. *Clin Pharmacol Ther* 1985;38:525–532.
152. Kroboth PD, Smith RB, Erb RJ. Tolerance to alprazolam after intravenous bolus and continuous infusion: Psychomotor and EEG effects. *Clin Pharmacol Ther* 1988;43:270–277.
153. Kroboth PD, McAuley JW, Smith RB. Alprazolam in the elderly: Pharmacokinetics and pharmacodynamics during multiple dosing. *Psychopharmacology* 1990;100:477–484.
154. Kroboth PD, Folan MM, Lush RM, et al. Coadministration of nefazodone and benzodiazepines. I. Pharmacodynamic assessment. *J Clin Psychopharmacol* 1995;15:306–319.

155. Kroboth PD, Folan MM, Bauer KS, Tullock W, Wright CE, Sweeney JA. Do alprazolam-induced changes in saccadic eye movement and psychomotor function follow the same time course. *J Clin Pharmacol* 1998; 38:337–346.
156. Kumar R, Mac DS, Gabrielli WF, Goodwin DW. Anxiolytics and memory: A comparison of lorazepam and alprazolam. *J Clin Psychiatry* 1987;48:158–160.
157. Laakman G, Faltermaier-Temizel M, Bossert-Zaudig S, Baghai T, Lorkowski G. Treatment of depressive outpatients with lorazepam, alprazolam, amitriptyline and placebo. *Psychopharmacology* 1995;120: 109–115.
158. Laar van MW, Volkerts ER, Willigenburg van APP. Therapeutic effects and effects on actual driving performance on chronically administered buspirone and diazepam in anxious outpatients. *J Clin Psychopharmacol* 1992;12:86–95.
159. Lappiere YD, Browne M, Oyewumi K, Sarantidis D. Alprazolam and amitriptyline in the treatment of moderate depression. *Int Clin Psychopharmacol* 1994;9:41–45.
160. Lasher TA, Fleishaker JC, Steenwyk RC, Antal EJ. Pharmacokinetic pharmacodynamic evaluation of the combined administration of alprazolam and fluoxetine. *Psychopharmacology* 1991;104:323–327.
161. Lenox RH, Shipley JE, Peyser JM, Williams JM, Weaver LA. Double-blind comparison of alprazolam versus imipramine in the inpatient treatment of major depressive illness. *Psychopharmacol Bull* 1984;20: 79–82.
162. Leon CA, DeArango MV, Arevallo W, et al. On treatment of panic disorder in Cali, Columbia: A comparison between alprazolam, and imipramine-administered samples, and a placebo-administered control group. *Acta Psiquiatr Psicol Am Lat* 1990;36:59–72.
163. Lepola U, Heikkinen H, Rimon R, Riekkinen P. Clinical evaluation of alprazolam in patients with panic disorder: A double-blind comparison with imipramine. *Hum Psychopharmacol* 1990;5:159–164.
164. Lepola UM, Rimon RH, Riekkinen PJ. Three-year follow-up of patients with panic disorder after short-term treatment with alprazolam and imipramine. *Int Clin Psychopharmacol* 1993;8:115–118.
165. Lesser IM, Rubin RT, Pecknold JC, et al. Secondary depression in panic disorder and agoraphobia: Frequency, severity, and response to treatment. *Arch Gen Psychiatry* 1988;45:437–443.
166. Lesser IM, Lydiard RB, Antal E, Rubin RT, Ballenger JC, DuPont R. Alprazolam plasma concentrations and treatment response in panic disorder and agoraphobia. *Am J Psychiatry* 1992;149:1556–1562.
167. Linnoila M, Stapleton JM, Lister R, et al. Effects of single doses of alprazolam and diazepam, alone and in combination with ethanol, on psychomotor and cognitive performance and on autonomic nervous system reactivity in healthy volunteers. *Eur J Clin Pharmacol* 1990;39:21–28.
168. Lucki I, Rickels K, Geller AM. Chronic use of benzodiazepines and psychomotor and cognitive test performance. *Psychopharmacology* 1986;88:426–433.
169. Lydiard RB, Lesser IM, Ballenger JC, Rubin RT, Laraia M, DuPont R. A fixed-dose study of alprazolam 2 mg, alprazolam 6 mg, and placebo in panic disorder. *J Clin Psychopharmacol* 1992;12:96–103.
170. Lydiard RB, Ballenger JC, Rickels K. A double-blind evaluation of the safety and efficacy of abecarnil, alprazolam, and placebo in outpatients with generalized anxiety disorder. *J Clin Psychiatry* 1997;58 (Suppl 11):11–18.
171. Maletzky BM. Anxiolytic efficacy of alprazolam compared to diazepam and placebo. *J Int Med Res* 1980;8:139–143.
172. Marks IM, De Albuqueque A, Cottraux J, et al. The "efficacy" of alprazolam in panic disorder and agoraphobia: A critique of recent reports. *Arch Gen Psychiatry* 1989;46:668–672.
173. Marks IM, Swinson RP, Başoğlu M, et al. Alprazolam and exposure alone and combined in panic disorder with agoraphobia. A controlled study in London and Toronto. *Br J Clin Psychiatry* 1993;162:776–787.
174. Marks IM, Swinson RP, Başoğlu M, et al. Reply to comment on the London/Toronto study. *Br J Psychiatry* 1993;162:790–794.
175. Marks IM, Başoğlu M, Noshirvani H, Greist J, Swinson RP, O'Sullivan G. Drug treatment of panic disorder. *Br J Psychiatry* 1993;162:795–796.
176. McAuley JW, Friedman CI. Influence of endogenous progesterone on alprazolam pharmacodynamics. *J Clin Psychopharmacol* 1999;19:233–239.
177. McLendon DM, Fabre LF. A double-blind comparison of the efficacy of alprazolam, chlordiazepoxide hydrochloride and placebo in the chronic withdrawal period from alcohol. *Curr Ther Res* 1980;28:447–455.
178. McLoad DR, Hoehn-Saric R, Zimmerli WD, et al. Treatment effects of alprazolam and imipramine: Physiological v subjective changes in patients with generalized anxiety disorder. *Biol Psychiatry* 1990;28: 849–861.
179. Meco G, Capriani C, Bonifati U, et al. Etizolam: A new therapeutic possibility in the treatment of panic disorder. Advances in Therapy 1989;6:196–206.

180. Mendels J, Schless AP. Comparative efficacy of alprazolam, imipramine, and placebo administered once a day in treating depressed patients. *J Clin Psychiatry* 1986;47:357–361.
181. Möller H-J, Volz H-P, Reimann IW, Stoll K-D. Opipramol for the treatment of generalized anxiety disorder: A placebo-controlled trial including an alprazolam-treated group. *J Clin Psychopharmacol* 2001;21:59–65.
182. Mühlberg W, Rieck W, Arnold E, Ott G, Lungershausen E. Pharmacokinetics of alprazolam in elderly patients with multiple diseases. *Arch Gerontol Geriatr* 1997;25:91–100.
183. Mumford GK, Evans SM, Fleishaker JC, Griffiths RR. Alprazolam absorption kinetics affects abuse liability. *Clin Pharmacol Ther* 1995;57:356–366.
184. Mumford GK, Rush CR, Griffiths RR. Alprazolam and DN-2327 (Pazinaclone) in humans: Psychomotor, memory, subjective, and reinforcing effects. *Exp Clin Psychopharmacol* 1995;3:39–48.
185. Mumford GK, Rush CR, Griffiths RR. Abecarnil and alprazolam in humans: behavioral, subjective and reinforcing effects. *J Pharmacol Exp Ther* 1995;272:570–580.
186. Munjack DJ, Crocker B, Cabe D, et al. Alprazolam, propanolol, and placebo in the treatment of panic disorder and agoraphobia with panic attacks. *J Clin Psychopharmacol* 1989;9:22–27.
187. Münte TF, Gehde E, Johannes S, Seewald M, Heinze H. Effects of alprazolam and bromazepam on visual search and verbal recognition memory in humans: A study with event-related brain potentials. *Neuropsychobiology* 1996;34:49–56.
188. Nikaido AM, Ellinwood EH, Heatherly DG, Gupta SK. Age-related increase in CNS sensitivity to benzodiazepines as assessed by task difficulty. *Psychopharmacology* 1990;100:90–97.
189. Norman TR, Burrows GD, McIntyre IM. Pharmacokinetic and pharmacodynamic effects of a single nocturnal dose of alprazolam. *Int Clin Psychopharmacol* 1990;5:111–117.
190. Noyes R, DuPont RL, Pecknold JC, et al. Alprazolam in panic disorder and agopraphobia: Patient acceptance, side effects, and safety. *Arch Gen Psychiatry* 1988;45:423–428.
191. Noyes R, Garvey MJ, Cook B, Suelzer M. Controlled discontinuation of benzodiazepine treatment for patients with panic disorder. *Am J Psychiatry* 1991;148:517–523.
192. Noyes R, Burrows GD, Reich JH, et al. Diazepam versus alprazolam for the treatment of panic disorder. *J Clin Psychiatry* 1996;57:349–355.
193. O'Hanlon JF, Haak TW, Blaauw GJ, et al. Diazepam impairs lateral position control in highway driving. *Science* 1982;217:79–81.
194. Oo CY, Kuhn RJ, Wright CE, McNamara PJ. Pharmacokinetics in lactating women: Prediction of alprazolam transfer into milk. *Br J Clin Pharmacol* 1995;40:231–236.
195. O'Sullivan GH, Noshirvani H, Başoğlu M, et al. Safety and side effects of alprazolam. Controlled study in agoraphobia with panic disorder. *Br J Psychiatry* 1994;165:79–86.
196. Oswald LM, Roache JD, Rhoades HM. Predictors of individual differences in alprazolam self-medication. *Exp Clin Psychopharmacol* 1999;7:379–390.
197. Otani K, Yasui N, Kaneko S, et al. Effects of genetically determined s-mephentoin 4-hydroxylation status and cigarette smoking on the single-dose pharmacokinetics of oral alprazolam. *Neuropsychopharmacology* 1997;16:8–14.
198. Otto MW, Pollack MH, Sachs GS, Reiter SR, Meltzer-Brody S, Rosenbaum JF. Discontinuation of benzodiazepine treatment: Efficacy of cognitive-behavioral therapy for patients with panic disorder. *Am J Psychiatry* 1993;150:1485–1490.
199. Overall JE, Donachie ND, Faillace LA. Implications of restrictive diagnosis for compliance to antidepressant drug therapy: Alprazolam versus imipramine. *J Clin Psychiatry* 1987;48:51–54.
200. Pariante F, Cadeo S, Ecari U. Etizolam in the treatment of generalized anxiety disorder associated with depressive symptoms. *Curr Med Res Opin* 1989;11:543–549.
201. Pearlstein TP, Stone AB. Longterm fluoxetine treatment of late luteal phase dysphoric disorder. *J Clin Psychiatry* 1994;55:332–335.
202. Pecknold JC, Swinson RP. Taper withdrawal studies with alprazolam in patients with panic disorder and agoraphobia. *Psychopharmacol Bull* 1986;22:173–176.
203. Pecknold JC, Swinson RP, Kuch K, Lewis CP. Alprazolam in panic disorder and agoraphobia: Discontinuation effects. *Arch Gen Psychiatry* 1988;45:429–436.
204. Petty F, Trivedi MH, Fulton M, Rush AJ. Benzodiazepines as antidepressants: Does GABA play a role in depression? *Biol Psychiatry* 1995;38:578–591.
205. Pollack MH, Otto MW, Tesar GE, Cohen LS, Meltzer-Brody S, Rosenbaum JF. Long-term outcome after acute treatment with alprazolam or clonazepam for panic disorder. *J Clin Psychopharmacol* 1993;13: 257–263.
206. Pomara N, Tun H, DaSilva D, Hernando R, Deptula D, Greenblatt DJ. The acute and chronic performance effects of alprazolam and lorazepam in the elderly: Relationship to duration of treatment and self-rated sedation. *Psychopharmacol Bull* 1998;34:139–153.

207. Pourbaix S, Desager JP, Hulhoven R, Smith RB, Harvengt C. Pharmacokinetic consequences of long term coadministration of cimetidine and triazolobenzodiazepines, alprazolam and triazolam, in healthy subjects. *Int J Clin Pharmacol Ther Toxicol* 1985;23:447–451.
208. Pyke RE, Greenberg HS. Double-blind comparison of alprazolam and adinazolam for panic and phobic disorders. *J Clin Psychopharmacol* 1989;9:15–21.
209. Ravaris CL, Friedman MJ, Hauri PJ, McHugo GJ. A controlled study of alprazolam and propanolol in panic-disordered and agoraphobic outpatients. *J Clin Psychopharmacol* 1991;11:344–350.
210. Remick RA, Keller FD, Buchanan RA, Gibson RE, Fleming JAE. A comparison of the efficacy and safety of alprazolam and desipramine in depressed outpatients. *Can J Psychiatry* 1988;33:590–594.
211. Riba J, Rodriguez-Fornells A, Urbano G, Morte A, Antonijoan R, Barbanoj MJ. Differential effects of alprazolam on the baseline and fear-potentiated startle reflex in humans: A dose response study. *Psychopharmacology* 2001;157:358–367.
212. Rickels K, Cohen D, Csanalosi I, Harris H, Koepke H, Werblowsky J. Alprazolam and imipramine in depressed outpatients: A controlled study. *Curr Ther Res* 1982;32:157–164.
213. Rickels K, Csanalosi I, Greisman P, et al. A controlled clinical trial of alprazolam for the treatment of anxiety. *Am J Psychiatry* 1983;140:82–85.
214. Rickels K, Schweizer E, Csanalosi I, Case W, Chung H. Long-term treatment of anxiety and risks of withdrawal. Prospective comparison of clorazepate and buspirone. *Arch Gen Psychiatry* 1988;45:444–450.
215. Rickels K, Schweizer E, Weiss S, Zavodnick S. Maintenance drug treatment for panic disorder. II. Short- and long-term outcome after drug taper. *Arch Gen Psychiatry* 1993;50:61–68.
216. Rickels K, Schweizer E. Panic disorder: long-term pharmacotherapy and discontinuation. *J Clin Psychopharmacol* 1998(Suppl 2):12S–18S.
217. Rickels K, Lucki I, Schweizer E, Garcia-Espana F, Case WG. Psychomotor performance of long-term benzodiazepine users before, during, and after benzodiazepine discontinuation. *J Clin Psychopharmacol* 1999; 19:107–113.
218. Rimon R, Kultalahti E-R, Kalli A, et al. Alprazolam and oxazepam in the treatment of anxious out-patients with depressive symptoms: A double-blind multicenter study. *Pharmacopsychiatry* 1991;24:81–84.
219. Rizley R, Kahn RJ, McNair DM, Frankenthaler BA. A comparison of alprazolam and imipramine in the treatment of agoraphobia and panic disorder. *Psychopharmacol Bull* 1986;22:167–172.
220. Rohling ML, Green P, Allen III LM, Iverson GL. Depressive symptoms and neurocognitive test scores in patients pasing symptom validity tests. *Arch Clin Neuropsychol* 2002;17:205–222.
221. Romach MK, Busto UE, Sobell LC, Sobel MB, Somer GR, Sellers EM. Long-term alprazolam use: Abuse, dependence or treatment? *Psychopharmacol Bull* 1991;27:391–395.
222. Romach MK, Somer GR, Sobell LC, Sobell MB, Kaplan HL, Sellers EM. Characteristics of long-term alprazolam users in the community. *J Clin Psychopharmacol* 1992;12:316–321.
223. Romach M, Busto U, Somer G, Kaplan HL, Sellers E. Clinical aspects of chronic use of alprazolam and lorazepam. *Am J Psychiatry* 1995;152:1161–1167.
224. Romach MK, Kaplan HL, Busto UE, Somer G, Sellers EM. A controlled trial of ondansetron, a 5-HT_3 antagonist, in benzodiazepine discontinuation. *J Clin Psychopharmacol* 1998;18:121–131.
225. Roy-Byrne P, Fleishaker J, Arnett C, et al. Effects of acute and chronic alprazolam treatment on cerebral blood flow, memory, sedation, and plasma catecholamines. *Neuropsychopharmacology* 1993;8:161–169.
226. Rudolph U, Crestani F, Möhler H. $GABA_A$ receptor subtypes: Dissecting their pharmacological functions. *Trends Pharmacol Sci* 2001;22:188–194.
227. Rush AJ, Erkman MK, Schlesser MA, et al. Alprazolam vs amitriptyline in depressions with reduced REM latencies. *Arch Gen Psychiatry* 1985;42:1154–1159.
228. Rush CR, Griffiths RR. Acute participant-rated and behavioral effects of alprazolam and buspirone, alone and in combination with ethanol, in normal volunteers. *Exp Clin Psychopharmacol* 1997;5:28–38.
229. Russell IJ, Fletcher EM, Michalek JE, McBroom PC, Hester GG. Treatment of primary fibrositis/fibromyalgia syndrome with ibuprofen and alprazolam. *Arthr Rheum* 1991;34:552–560.
230. Saletu B, Grünberger J, Linzmayer L, Semlitsch HV, Anderer P, Chwatal K. Pharmacokinetic and-dynamic studies with a new anxiolytic, suriclone, utilizing EEG mapping and psychometry. *Br J Clin Pharmacol* 1994;37:145–156.
231. Sanger DJ, Benavides J, Perrault G, et al. Recent developments in the behavioral pharmacology of benzodiazepine (ω) receptors: Evidence for the functional significance of receptor subtypes. *Neurosci Biobehav Rev* 1994;18:355–372.
232. Scavone JM, Greenblatt DJ, Shader RI. Alprazolam kinetics following sublingual and oral administration. *J Clin Psychopharmacol* 1987;7:332–334.

233. Scavone JM, Greenblatt DJ, Goddard JE, Friedman H, Harmatz JS, Shader RI. The pharmacokinetics and pharmacodynamics of sublingual and oral alprazolam in the post-prandial state. *Eur J Clin Pharmacol* 1992;42:439–443.
234. Schmidt PJ, Grover GN, Rubinow DR. Alprazolam in the treatment of premenstrual syndrome. A double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 1993;50:467–473.
235. Schmith VD, Piraino, Smith RB, Kroboth PD. Alprazolam in end-stage renal disease. I. Pharmacokinetics. *J Clin Pharmacol* 1991;31:571–579.
236. Schmith VD, Piraino B, Smith RB, Kroboth PD. Alprazolam in end-stage renal disease. II. Pharmacodynamics. *Clin Pharmacol Ther* 1992;51:533–540.
237. Schweizer E, Pohl R, Balon R, Fox I, Rickels K, Yeragani VK. Lorazepam vs. alprazolam in the treatment of panic disorder. *Pharmacopsychiatry* 1990;23:90–93.
238. Schweizer E, Patterson W, Rickels K, Rosenthal M. Double-blind, placebo-controlled study of a once-a-day, sustained-release preparation of alprazolam for the treatment of panic disorder. *Am J Psychiatry* 1993; 150:1210–1215.
239. Schweizer E, Rickels K, Weiss S, Zavodnick S. Maintenance drug treatment of panic disorder. I. Results of a prospective, placebo-controlled comparison of alprazolam and imipramine. *Arch Gen Psychiatry* 1993; 50:51–60.
240. Seidel WF, Cohen L, Wilson L, Dement WC. Effects of alprazolam and diazepam on the daytime sleepiness of non-anxious subjects. *Psychopharmacology* 1985;87:194–197.
241. Sellers EM, Ciraulo DA, DuPont RL, et al. Alprazolam and benzodiazepine dependence. *J Clin Psychiatry* 1993;54(Suppl 10):64–75.
242. Semlitsch HV, Anderer P, Saletu B. Acute effects of the anxiolytics suriclone and alprazolam on cognitive information processing utilizing topographic mapping of event-related brain potentials (P300) in healthy subjects. *Eur J Clin Pharmacol* 1995;49:183–191.
243. Sheehan DV, Coleman JH, Greenblatt DJ, et al. Some biochemical correlates of panic attacks with agoraphobia and their response to a new treatment. *J Clin Psychopharmacol* 1984;4:66–75.
244. Sheehan DV, Raj AB, Harnett-Sheehan K, Soto S, Knapp E. The relative efficacy of high-dose buspirone and alprazolam in the treatment of panic disorder: A double-blind placebo-controlled study. *Acta Psychiatr Scand* 1993;88:1–11.
245. Sheikh JI, Swales JI. Treatment of panic disorder in older adults: A pilot study comparison of alprazolam, imipramine and placebo. Int J Psychiatr Med 1999;29:107–117.
246. Shelton RC, Harvey DS, Stewart PM, Loosen PT. Alprazolam in panic disorder: A retrospective analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 1993;17:423–434.
247. Simeon JG, Ferguson HB, Knott V, et al. Clinical, cognitive, and neurophysiological effects of alprazolam in children and adolescents with overanxious and avoidant disorders. *J Am Acad Child Adolesc Psychiatry* 1992;31:29–33.
248. Simpson JJ, Davies WE. Recent advances in the pharmacological treatment of tinnitus. *Trends Pharmacol Sci* 1999;20:12–18.
249. Singh AN, Nair NPV, Suranyi-Cadotte B, Schwartz G, Lizondo E. A double blind comparison of alprazolam and amitriptyline hydrochloride in the treatment of nonpsychotic depression. *Can J Psychiatry* 1988; 33:218–222.
250. Smith RB, Kroboth PD, Vanderlught JT, Philips JP, Juhl RP. Pharmacokinetics and pharmacodynamics of alprazolam after oral and IV administration. *Psychopharmacology* 1984;84:452–456.
251. Smith RB, Gwilt PR, Wright CE. Single and multiple dose pharmacokinetics of oral alprazolam in healthy smoking and nonsmoking men. *Clin Pharmacy* 1983;2:139–143.
252. Smith RB, Kroboth PD. Influence of dosing regimen on alprazolam and metabolite serum concentrations and tolerance to sedative and psychomotor effects. *Psychopharmacology* 1987;93:105–112.
253. Smith S, Rinehart JS, Ruddock VE, Schiff I. Treatment of premenstrual syndrome with alprazolam: Results of a double-blind, placebo-controlled, randomized crossover clinical trial. *Obstet Gynecol* 1987;70:37–43.
254. Spiegel DA, Roth SM, Weissman M, Lavori P, Gorman J, Ballenger J. Comment on the London/Toronto study of alprazolam and exposure in panic disorder with agoraphobia. *Br J Psychiatry* 1993;162:788–789.
255. Spiegel DA. Psychological strategies for discontinuing benzodiazepine treatment. *J Clin Psychopharmacol* 1999;19:17S-22S.
256. Srisurapanont M, Boonyanaruthee V. Alprazolam and standard antidepressants in the treatment of depression: A meta-analysis of the antidepressant effect. *J Med Ass Thai* 1997;80:183–188.
257. Steiner M, Steinberg S, Stewart D, et al. Fluoxetine in the treatment of premenstrual dysphoria. *N Engl J Med* 1995;332:1529–1534.
258. Steiner M, Korzekwa M, Lamont J, Wilkins A. Intermittent fluoxetine dosing in the treatment of women with premenstrual dysphoria. *Psychopharmacol Bull* 1997;33:771–774.

259. Streeter CC, Ciraulo DA, Harris GJ, et al. Functional magnetic resonance imaging of alprazolam-induced changes in humans with familial alcoholism. *Psychiatry Res Neuroimaging* 1998;82:69–82.
260. Streufert S, Satish U, Pogash R, et al. Effects of alprazolam on complex human functioning. *J Appl Soc Psychol* 1996;26:1912–1930.
261. Subhan Z, Harrison Ch, Hindmarch I. Alprazolam and lorazepam. Single and multiple-dose effects on psychomotor skills and sleep. *Eur J Clin Pharmacol* 1986;29:709–712.
262. Sumner DD. Benzodiazepine-induced persisting amnestic disorder: Are older adults at risk? *Arch Psychiat Nursing* 1998;12:119–125.
263. Suzuki M, Uchiumi M, Murasaki M. A comparative study of the psychological effects of DN-2327, a partial benzodiazepine agonist, and alprazolam. *Psychopharmacology* 1995;121:442–450.
264. Swann AC, Katz MM, Bowden CL, Berman NG, Stokes PE. Psychomotor performance and monoamine function in bipolar and unipolar affective disorders. *Biol Psychiatry* 1999;45:979–988.
265. Taylor CB, Hayward C, King R, et al. Cardiovascular and symptomatic reduction effects of alprazolam and imipramine in patients with panic disorder: Results of a double-blind, placebo-controlled trial. *J Clin Psychopharmacol* 1990;10:112–118.
266. Tesar GE, Rosenbaum JF, Pollach MH, et al. Clonazepam versus alprazolam in the treatment of panic disorder: Interim analysis of data from a prospective, double-blind, placebo-controlled trial. *J Clin Psychiatry* 1987;48(Suppl 10):16–19.
267. Tesar GE, Rosenbaum JF, Pollach MH, et al. Double-blind, placebo-controlled comparison of clonazepam and alprazolam for panic disorder. *J Clin Psychiatry* 1991;52:69–76.
268. Tollefson GD, Luxenberg M, Valentine R, Dunsmore G, Tolefson SL. An open label trial of alprazolam in comorbid irritable bowel syndrome and generalized anxiety disorder. *J Clin Psychiatry* 1991;52:502–508.
269. Torres-Ruiz AT. A double-blind study of alprazolam and lorazepam in the treatment of anxiety. *J Clin Psychiatry* 1983;44:60–62.
270. Uhlenhuth EH, Matuzas W, Glass RM, Easton C. Response of panic disorder to fixed doses of alprazolam or imipramine. *J Affect Disord* 1989;17:261–270.
271. Uhlenhuth EH, Alexander PE, Dempsey GM, Jones W, Coleman BS, Swiontek AM. Medication side effects in anxious patients: Negative placebo responses? *J Affect Disord* 1998;47:183–190.
272. Väissänen E, Jalkanen E. A double-blind study of alprazolam and oxazepam in the treatment of anxiety. *Acta Psychiatr Scand* 1987;75:536–541.
273. Vermeeren A, Jackson JL, Muntjewerff ND, Quint PJ, Harrison EM, O'Hanlon JF. Comparison of acute alprazolam (0.25, 0.50 and 1.0 mg) effects versus those of lorazepam 2 mg and placebo on memory in healthy volunteers using laboratory and telephone tests. *Psychopharmacology* 1995;118:1–9.
274. Verster JC, Volkerts ER, Verbaten MN. Effects of alprazolam on driving ability, memory functioning and psychomotor performance: A randomized, placebo-controlled study. *Neuropsychopharmacology* 2002;27: 260–269.
275. Verster JC, Verbaten MN, Volkerts ER. Next-day residual effects of sleeping medicine on driving ability: A review of the literature. In: Lader M, Pandi-Perumal SR, Cardinali OP, Eds. Sleep and sleep disorders: A neuropsychopharmacological approach. Landes Bioscience, in press.
276. Wald TG, Kathol RG, Noyes R, Carrol BT, Clamon GH. Rapid relief of anxiety in cancer patients with both alprazolam and placebo. *Psychosomatics* 1993;34:324–332.
277. Weissman MM, Prusoff B, Sholomskas AJ, Greenwald S. A double-blind clinical trial of alprazolam, or placebo in the depressed elderly. *J Clin Psychopharmacol* 1992;12:175–182.
278. Wilcox JA. An open comparison of diazepam and alprazolam. *J Psychoact Drugs* 1986;18:159–160.
279. Wilhelm FH, Roth WT. Acute and delayed effects of alprazolam on flight phobics during exposure. *Behav Res Ther* 1997;35:831–841.
280. Wincor MZ, Munjack DJ, Palmer R. Alprazolam levels and response in panic disorder: Preliminary results. *J Clin Psychopharmacol* 1991;11:48–51.
281. Wong SL, Locke C, Staser J, Granneman GR. Lack of multiple dosing effects of sertindole on the pharmacokinetics of alprazolam in healthy volunteers. *Psychopharmacology* 1998;135:236–241.
282. Woodman CL, Noyes R, Ballenger JC, Lydiard RB, Sievers G, Mihalko D. Predictors of response to alprazolam and placebo in patients with panic disorder. *J Affect Disord* 1994;30:5–13.
283. Wright CE, Lasher Sisson T, Fleishaker JC, Antal EJ. Pharmacokinetics and psychomotor performance of alprazolam: Concentration-effect relationship. *J Clin Pharmacol* 1997;37:321–329.
284. Yamadera H, Okawa M, Takahashi K. Open study of effects of alprazolam on seasonal affective disorder. *Psychiatr Clin Neurosci* 2001;55:27–30.
285. Yasui N, Otani K, Kaneko S, et al. A kinetic and dynamic study of oral alprazolam with and without erythromycin in humans: *In vitro* evidence for the involvement of CYP3A4 in alprazolam metabolism. *Clin Pharmacol Ther* 1996;59:514–519.

286. Yasui N, Kondo T, Otani K, et al. Effect of itraconazole on the single oral dose pharmacokinetics and pharmacodynamics of alprazolam. *Psychopharmacology* 1998;139:269–273.
287. Yasui N, Kondo T, Furukori H, et al. Effects of repeated ingestion of grapefruit juice on the single and multiple oral-dose pharmacokinetics and pharmacodynamics of alprazolam. *Psychopharmacology* 2000;150: 185–190.
288. Yonkers KA, Halbreich U, Freeman E, et al. Symptomatic improvement of premenstrual dysphoric disorder with sertraline treatment. *JAMA* 1997;278:983–988.
289. Young SA, Hurt PH, Benedek DM, Howard RS. Treatment of premenstrual dysphoric disorder with sertraline during the luteal phase: A randomized, placebo-controlled crossover trial. *J Clin Psychiatry* 1998;59: 76–80.
290. Zamorski MA, Albucher RC. What to do when SSRIs fail: Eight strategies for optimizing treatment of panic disorder. *Am Fam Physician* 2002;66:1477–84.
291. Zawertailo LA, Busto U, Kaplan HL, Sellers EM. Comparative abuse liability of sertraline, alprazolam, and dextroamphetamine in humans. *J Clin Psychopharmacol* 1995;15:117–124.