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Treatment of Alprazolam Withdrawal With Chlordiazepoxide Substitution and Taper

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Abstract— We describe the first case series ($n = 6$) of using chlordiazepoxide to accomplish a rapid, well-tolerated withdrawal from alprazolam. After abruptly discontinuing alprazolam, we substituted a 50-mg dose of chlordiazepoxide for each 1 mg of alprazolam (except for one elderly patient where we substituted 25 mg) and gave additional chlordiazepoxide doses (25–50 mg every 4–6 hours) as needed for the first 1–2 days of hospitalization. With this approach, the mean “substitution ratio” of chlordiazepoxide to alprazolam was 86 to 1. We then tapered chlordiazepoxide by an average of 10% each day over a 7- to 14-day period according to the symptoms manifested and tolerated by individual patients. No seizures or other serious side effects occurred. Incomplete cross-dependence, as described elsewhere in the literature, was not observed. The rapidity and familiarity of the method are advantages for inpatient units, but careful titration of dosage, diagnostic clarity, and extended follow-ups are necessary when applying this approach.

Keywords— alprazolam; chlordiazepoxide; benzodiazepines; substance withdrawal; substance dependence.

INTRODUCTION

ALPRAZOLAM IS A BENZODIAZEPINE MEDICATION that is highly effective and well studied for treating panic disorder (Schweizer, Rickels, Weiss, & Zavadnick, 1993). Panic disorder results in significant disability (Markowitz, Weissman, Ouellette, Lish, & Klerman, 1989) and may increase the risk for suicide (Noyes, 1991). Although other therapies are available (Gelder, 1991), alprazolam often works more quickly and has fewer side effects and greater patient acceptance (Schweizer et al., 1993). Given the benefits of alprazolam and the

importance of treating panic disorder, physicians will likely continue prescribing it in the near future.

Alprazolam, like other benzodiazepines, has definite abuse liability (American Psychiatric Association, 1990; Ciraulo & Sarid-Segal, 1991; Juergens, 1991). Here, abuse refers to taking alprazolam for its nonmedical, euphoric effects despite harmful consequences. The vast majority of treated patients do not abuse benzodiazepines (American Psychiatric Association, 1990; Woods, Katz, & Winger, 1988). A prior history of substance abuse, abusing other substances such as alcohol or opioids, and a family history of alcoholism may all increase the risk for benzodiazepine abuse (Ciraulo & Sarid-Segal, 1991; Woods et al., 1988).

Apart from its abuse potential, physical dependence on alprazolam develops frequently (Fyer et al., 1987;

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Rickels, Schweizer, Weiss, & Zavodnick, 1993). Physical dependence refers to the appearance of withdrawal symptoms upon reducing or discontinuing drug use. Physical dependence on alprazolam occurs even with controlled use of therapeutic doses. In studies of gradual alprazolam discontinuation in panic-disordered patients, 53–63% of them had moderate to severe withdrawal symptoms after taking therapeutic doses for 3–10 months (Fyer et al., 1987; Rickels et al., 1993).

Some evidence suggests that withdrawal from alprazolam may be more difficult than withdrawal from some other benzodiazepines, because of its higher potency and shorter duration of action (Noyes, Garvey, Cook, & Suelzer, 1991). Withdrawal symptoms include agitation, anxiety, depersonalization and derealization, depression, diaphoresis, difficulty concentrating, dizziness, headaches, increased perceptual acuity for sights and sounds, insomnia, light-headedness, loss of appetite, malaise, muscular pains, nausea, poor coordination, restlessness, tachycardia, tremor, and weakness (Fyer et al., 1987; Pecknold, Swinson, Kuch, & Lewis, 1988; Rickels et al., 1993). Symptoms may begin within 1 day of stopping alprazolam, peak within 3 days to 2 weeks, and generally subside by 2–4 weeks (American Psychiatric Association, 1990; Fyer et al., 1987; Pecknold et al., 1988; Rickels et al., 1993). At worst, seizures, delirium, and psychosis can occur during alprazolam withdrawal (Browne & Hauge, 1986; Warner, Peabody, Boutros, & Whiteford, 1990; Zipursky, Baker, & Zimmer, 1985), so abrupt or rapid discontinuation without other pharmacological intervention is clearly contraindicated.

The manufacturer recommends a reduction in alprazolam of not more than 0.5 mg every 3 days. Although this recommendation provides a maximal rate, many patients do not tolerate a taper this rapid, especially toward the end of their tapers, and so optimal rates of reduction are usually slower. Even if one assumes the maximal rate, a taper from 6 mg would take 36 days. Patients and physicians sometimes desire more rapid techniques, especially in chemical dependency treatment settings.

Substitution strategies make rapid discontinuation possible. Typically, alprazolam is discontinued abruptly, and a long-acting sedative is substituted to suppress harmful withdrawal symptoms, after which the latter sedative is tapered completely over 1–2 weeks. Phenobarbital (Juergens & Morse, 1988; Ravi, Maany, Burke, Dhopes, & Woody, 1990) and the benzodiazepines, clonazepam (Albeck, 1987; Patterson, 1990), diazepam (Harrison, Busto, Naranjo, Kaplan, & Sellers, 1984), and chlordiazepoxide (Juergens & Morse, 1988), have all been used this way. Other classes of medications such as carbamazepine (Ries, Roy-Byrne, Ward, Neppe, & Cullison, 1989; Schweizer, Rickels, Case, & Greenblatt, 1991) and clonidine (Fyer et al., 1988) have been

used adjunctively to facilitate the rate of alprazolam reduction with varying degrees of success.

After a patient on our unit suffered a seizure during alprazolam reduction without substitution, we developed a protocol for chlordiazepoxide substitution and taper. We reasoned that chlordiazepoxide had the advantage of familiarity on our treatment unit, where we regularly employed it to treat alcohol withdrawal.

METHOD

Patients

The sample consisted of consecutively admitted inpatients to our chemical dependency unit from 1987 to 1989 whose primary diagnosis was alprazolam dependence, and who had a history of withdrawal symptoms upon discontinuation. During this period, we treated six patients for alprazolam withdrawal (Table 1). The charts of our six patients were retrospectively reviewed for demographics, alprazolam history, diagnoses, and hospital course.

Treatment Procedures

On admission all patients received complete medical, psychiatric, substance use, and laboratory evaluations. For treatment of alprazolam withdrawal, a modification of our alcohol detoxification protocol was implemented. Except for one case, we substituted 50 mg of chlordiazepoxide for each 1 mg of alprazolam reported, and we gave this amount orally as a regular divided dosage (3–4 times daily). Our exceptional case was an elderly patient (72 years old) for whom we substituted 25 mg of chlordiazepoxide for each 1 mg of alprazolam. In addition, we gave each patient supplemental doses of chlordiazepoxide by mouth: 25–50 mg every 4–6 hours as needed to suppress withdrawal symptoms. The next scheduled dose was held if the patient was drowsy. If withdrawal symptoms worsened on the second day, then we allowed an additional 24-hour period of “as-needed” dosing in addition to the regular dosing. The total 24-hour dosage of chlordiazepoxide (regular plus supplemental amounts) needed to suppress withdrawal was regarded to be equivalent to the patient’s daily alprazolam dosage. We then decreased chlordiazepoxide at an average rate of 10% per day (range 7.7%–14.3%). The rate of taper was individualized as determined by each patient’s symptom profile. In sum, we took 1–2 days to establish a substitution dose, and then tapered the substituted dose over the next 7–14 days.

After the taper was finished, patients were expected to complete a 2-week program of chemical dependency rehabilitation. We made follow-up observations during this time.

TABLE 1
Medications Used

Patient	Alprazolam Dose ^a (mg/d)	Duration of Alprazolam (mo)	Chlordiazepoxide Dose ^b (mg)	Chlordiazepoxide Duration ^c (days)	Substitution Ratio ^d
1	6.0 (12)	4	300	9	50.00
2	4.0	72	350	15	87.50
3	3.0	48	195	15	65.00
4	4.0	72	225	10	56.25
5	2.0 (10)	60	350	9	175.00
6	5.0	48	400	9	80.00

^aAlprazolam dosage on admission. For cases 1 and 5, value in parentheses is dose from which outpatient taper began prior to hospitalization.

^bTotal 24-hr dosage needed to suppress withdrawal symptoms.

^cTotal days of chlordiazepoxide administration, including substitution and taper.

^dChlordiazepoxide dosage in column 4 divided by alprazolam dosage in column 2.

RESULTS

The mean age of our patients was 44.8 years (range 23–72), and five patients were female. The primary indications for initially prescribing alprazolam were panic disorder in five patients (two of whom had additional admitting diagnoses of either generalized anxiety or social phobia) and generalized anxiety by itself in one patient. Discharge diagnoses included alprazolam dependence ($n = 6$), major depression ($n = 1$), mixed personality disorder ($n = 1$), alcohol dependence ($n = 1$), alcohol and cannabis dependence ($n = 1$), and bulimia ($n = 1$). Patients' daily alprazolam dose at time of admission ranged from 2 to 6 mg ($M = 4.0$ mg), and the duration of use ranged from 4 to 72 months ($M = 52.7$) (Table 1). For each patient, we calculated the "substitution ratio" of chlordiazepoxide to alprazolam as the total 24-hour dosage of chlordiazepoxide given before tapering, divided by the admission dosage of alprazolam (Table 1). The mean substitution ratio was 85.6 (range 50–175). The mean number of days on chlordiazepoxide was 11.2 (range 9–15 days), and the mean number of days to taper chlordiazepoxide was 9.5 (range 7–13 days). All patients remained in treatment for the duration of the taper.

Discontinuation symptoms during chlordiazepoxide administration included anxiety ($n = 6$), insomnia ($n = 4$), high blood pressure ($n = 4$), tachycardia ($n = 3$), irritability ($n = 2$), tremor ($n = 2$), depersonalization or derealization ($n = 2$), sweatiness ($n = 1$), and aches ($n = 2$). One panic attack was noticed in one patient. After chlordiazepoxide was discontinued, we recorded follow-up observations for the remainder of hospitalization. One patient was admitted for detoxification only and was discharged without symptoms 2 days after stopping chlordiazepoxide. Another patient was asymptomatic for 5 days but then left against medical advice before completing the rehabilitation program because of a relationship conflict. The other

four patients were followed for 12, 14, 15, and 48 days, respectively, and received regular discharges. During the follow-up periods for the six patients, we observed the following symptoms: anxiety ($n = 4$), insomnia ($n = 3$), high blood pressure ($n = 2$), tachycardia ($n = 1$), irritability ($n = 1$), tremor ($n = 1$), depersonalization or derealization ($n = 1$), and headache ($n = 1$). No panic attacks were observed during the follow-up period. No seizures, episodes of delirium, or psychosis occurred in any patient during the entire course of observation.

Two patients (cases 1 and 3) had residual symptoms at the time of discharge. One patient continued to have decreased sleep (<5 hr/night), and the other complained of mild anxiety. Both patients had complicating psychiatric and medical problems requiring medications (major depression, mixed personality disorder, sustained hypertension, coronary artery disease, chronic obstructive pulmonary disease, irritable bowel syndrome, and fibromyositis). We attributed the two patients' residual symptoms to coexisting diagnoses rather than to poorly treated alprazolam withdrawal.

DISCUSSION

To our knowledge, this is the first reported case series in which chlordiazepoxide was used successfully to treat inpatients for physical withdrawal from alprazolam. Early reports cautioned that incomplete cross-dependence between alprazolam and either chlordiazepoxide or diazepam might result in seizures and delirium (Browne & Hauge, 1986; Kantor, 1986; Zipursky et al., 1985). None of our patients manifested seizures, delirium, or psychosis. None of them left treatment during the taper, and all of them completed the taper without difficulty. In short, we did not observe evidence for a lack of cross-dependence between alprazolam and chlordiazepoxide in our six patients.

The early reported failures with diazepam (Zipursky et al., 1985) and chlordiazepoxide (Kantor, 1986) may have resulted from drug interactions, insufficient dosing, or coexisting diagnoses. We are aware of only three cases in the literature in which chlordiazepoxide was substituted for treating alprazolam withdrawal (Albeck, 1987; Juergens & Morse, 1988; Kantor, 1986). In the case reported by Kantor (1986), a dose of 150 mg did suppress withdrawal symptoms from a daily 2-mg dose of alprazolam, but the authors were then unable to taper the chlordiazepoxide because of "severe agitation and crippling back spasm." They eventually substituted diazepam and tapered it over 19 weeks. A diagnosis of major depression and concurrent phenelzine administration may have complicated this case. Albeck (1987) substituted 300 mg of chlordiazepoxide for a daily consumption of 10–35 mg of alprazolam, and the patient remained tremulous with tachycardia, high blood pressure, diaphoresis, vomiting, formication, and headache. This was an insufficient chlordiazepoxide dosage compared with our cases. Eventually, 10 mg of clonazepam was substituted successfully, which has two to four times the potency of alprazolam (American Psychiatric Association, 1990; Smith & Seymour, 1991). Finally, Juergens and Morse (1988) used chlordiazepoxide successfully over a 7-day period in a patient who was taking 8 mg of alprazolam, but they did not report chlordiazepoxide dosage.

One milligram of alprazolam is generally considered equivalent to 20 or 25 mg of chlordiazepoxide (American Psychiatric Association, 1990; Smith & Seymour, 1991). This 20–25:1 ratio contrasts with our mean substitution ratio of 86:1, but it is closer to the 100:1 ratio published by Harrison et al. (1984). Nevertheless, Harrison et al. (1984) recommended substituting diazepam in a loading dose that was 40% of reported daily consumption, which amounts to a 40:1 ratio in chlordiazepoxide equivalents. Only 1 of 23 patients in their case series was alprazolam-dependent, and the authors did not specify if that case was successfully treated or 1 of the 4 patients who left against medical advice within 6 days (Harrison et al., 1984). Smith and Seymour (1991) observed that their conversion factors (25:1 for chlordiazepoxide to alprazolam) might be low when treating alprazolam withdrawal. We suspect that higher ratios are needed when substituting chlordiazepoxide for alprazolam for the purpose of a rapid taper, because steady-state concentrations of chlordiazepoxide are not achieved by the time chlordiazepoxide tapering begins (1–2 days after its substitution).

Smith and Seymour (1991) argued against "as-needed" dosing in order to avoid drug-seeking behavior by sedative-dependent patients. One could argue that the higher ratios required by our patients resulted from our responding to drug seeking with "as-needed" doses. Although clinicians must guard against inadvertently intoxicating their patients, flexible dosing has

two important advantages. First, it allows for individual differences, and we found a wide range of substitution ratios (Table 1). Second, patients do not always know or reliably report how much alprazolam and other sedatives they are taking. Indeed, our patient who suffered a seizure when we attempted reduction without chlordiazepoxide substitution later told us she took twice the daily dosage that she reported on admission. Providing nursing staff with the discretion to administer "as-needed" doses allows for necessary, upward adjustment of dosing in a timely fashion. Doses were withheld if patients showed signs of toxicity such as drowsiness, ataxia, slurred speech, double vision, and dizziness. Thus, our procedure prevented both over- and undermedication problems, as we carefully titrated the dosage according to individual need.

We were hesitant to employ the higher (50:1) substitution ratio of chlordiazepoxide to alprazolam in our elderly patient (case 1), because the patient's age raised concerns about the accumulation of a long-acting medication (Closser, 1991). Although we conservatively employed a 25:1 substitution ratio, our patient ultimately required a 50:1 substitution ratio after we included the "as-needed" doses in our calculation (Table 1). Interestingly, we did not find a significant correlation between age and substitution ratio ($r_s = -0.43$, $p = 0.40$).

Our cases were confined to inpatients whose daily alprazolam dosage ranged from 2 to 6 mg. We cannot recommend this procedure for outpatients at this time, nor do we know if our substitution ratios apply to patients taking more than 6 mg of alprazolam daily. In the substitution and taper method of Smith and Seymour (1991), a maximum daily dosage of 500 mg of phenobarbital (the equivalent of about 420 mg of chlordiazepoxide) is recommended, regardless of the sedative amount the patient used.

Our mean follow-up period (2 weeks) was too short to observe the full course of withdrawal (2–4 weeks) to determine relapse rates and to rule out completely a recurrent panic disorder in need of further treatment. Nevertheless, withdrawal symptoms do peak, and alprazolam-related seizures occur, within 2 weeks of discontinuation (American Psychiatric Association, 1990; Warner et al., 1990). Moreover, our immediate outcomes were favorable in contrast to previous reports of chlordiazepoxide substitution (Albeck, 1987; Kantor, 1986). Finally, all inpatients require continued monitoring for diagnostic and treatment purposes following discharge. Another limitation of our retrospective study was the lack of structured rating scales for withdrawal symptoms, which made it difficult to distinguish withdrawal symptoms from symptoms of a recurrent anxiety disorder. Finally, we did not conduct a controlled, comparison study, so we do not know if patients would have done as well or better with other withdrawal techniques. However, our main in-

terest was in determining the dosing of, and feasibility of using, chlordiazepoxide for alprazolam withdrawal.

In conclusion, we found that inpatients on a chemical dependency unit successfully tolerated rapid withdrawal from alprazolam in doses of 2–6 mg daily when chlordiazepoxide was substituted in adequate doses and then tapered over 1–2 weeks. When the amount of chlordiazepoxide was individualized, cross-dependence occurred, and seizures were prevented. Chlordiazepoxide has the advantage of familiarity on treatment units that regularly use it for alcohol withdrawal. The rapid attainment of a drug-free state facilitates entry into drug rehabilitation when indicated. Future studies should employ a prospective, comparative design with structured rating scales and diagnostic assessments, and a longer follow-up period.

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