Alprazolam and Standard Antidepressants in the Treatment of Depression: A Meta-analysis of the Antidepressant Effect

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Abstract

Alprazolam differs from other benzodiazepines by the incorporation of a triazolo ring in the basic chemical structure. Several lines of evidence have supported that alprazolam and standard antidepressants have some similar actions, such as beta-adrenergic receptor down-regulation, antipanic effect. Because of the difference in opinions pertaining to the antidepressant effect of alprazolam, this issue could not reach a firm conclusion. In the present analysis, we carried out a meta-analysis of 11 random controlled studies that compared the antidepressant effect of alprazolam and standard antidepressants in depressed patients. The results showed that the weighted mean effect size d (d_w) is equal to 0.06. In conclusion, the antidepressant effect of alprazolam is comparable to that of low-dose tricyclic antidepressants. Very few studies have investigated severely depressed patients. Also, in long-term administration, the lack of a long-term treatment study makes the isssue of alprazolam's benefits and disadvantages still undetermined.

Alprazolam differs from other benzodiazepines by the incorporation of a triazolo ring in the basic chemical structure. Several lines of evidence have supported that alprazolam and standard antidepressants have some similar actions. Both of them are able to down-regulate postsynaptic beta-adrenergic receptors[1,2] and are effective for the treatment of panic disorder[3,4].

Because of the troubling adverse effects and slow onset of action of standard antidepressants, alternatives have been extensively investigated. Since the result of an open study showed that alprazolam appeared to have an antidepressant effect[5], numerous studies have been carried out for investigating the efficacy of alprazolam in the treatment of depression. So far, the antidepressant effect of alprazolam has not reached a firm conclusion. On one hand, alprazolam is "effective (for outpatients)"[6], "at least comparable in efficacy to other medications for the treatment of depression-related disorders"[7], or "considered equal to that of tricyclic antidepressant in depressed outpatients without retardation and/or suicidal ideation"[8]. On the other hand, others viewed that "alprazolam's

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therapeutic value appears to be less than that of the tricyclics...these issues remain to be resolved by further laboratory studies and clinical trials"[9]. In clinical practice, alprazolam is not on the list of drugs used for the treatment of major depressive disorder[10].

Meta-analysis is a method that has been used to aggregate information systematically[11]. To find out the conclusion of different opinions, we therefore carried out a meta-analysis of the existing literature of random controlled trials in which alprazolam was compared with standard antidepressants.

Method

With the purpose of answering the question of "Is the antidepressant effect of alprazolam comparable to that of standard antidepressants?", criteria for inclusion the study are as follows:

1. Depression (without anxiety disorders) as defined in studies.
2. Investigating both alprazolam and standard antidepressants.
3. Random controlled trials.
4. Double-blind studies.
5. Measuring the severity of depression with a standard scale.
6. Presenting the means of the endpoint scores.

By Medline Computerized Literature Search (up to June, 1995), to find the original articles, we used the following headings and terms: depressive disorder-drug therapy; alprazolam, antidepressants, and randomized-controlled-trial. Eight

Table 1. Random controlled trials of alprazolam and tricyclic antidepressants in the treatment of depression.

Authors	Characteristics of patients.	No. of wks	Mean dose (mg/d)		No. of patients (endpoint)		X_1-X_2 (SD_p)	No. of dropouts		θ
			ALP	TCAs	ALP	TCAs		ALP	TCAs	
Draper & Daly 1983	HRSD≥17 OP	6	2.15	85.0	10	5	3.50 (5.75)	5	5	-0.17
Ansseau et al 1984	HRSD≥18 OP	6	2.70	137.5	52	63	0 (NA)	7	4	0.06
Remick et al 1985	HRSD≥21 OP	6	3.47	201.4	16	18	-4.20 (NA)			
Remick et al 1985	HRSD≥21 IP	6	4.15	225.0	13	7	3.00 (NA)	6	6	-0.02
Rickels et al 1985	HRSD≥18 OP	6	3.00	148.0	104	90	-1.18 (NA)	24	34	-0.08
Rush et al 1985	HRSD≥18 OP=32 IP=17	6	4.40	190.0	13	16	5.80 (7.22)	12	8	0.15
Eriksson et al 1987	HRSD≥18 OP	6	3.05	130.0	30	31	-3.0 (NA)	11	5	0.13
Fawcett et al 1987	HRSD≥20 OP	6	4.60	229.8	18	20	0.6 (7.96)	9	8	0.04
Rickels et al 1987	HRSD≥18 OP	6	3.10	143.0	39	37	1.3 (NA)	19	26	-0.08
Banerji et al 1989	RDS≥6 OP	4	1.80	63.8	36	38	3.3 (NA)	15	15	0.01
Weissman et al 1992	RDS≥7 OP	6	2.20	97.5	7	7	1.9 (NA)	3	6	-0.16
Lapierre et al 1994	HRSD≥18 OP	6	3.20	115.0	20	18	6.47 (7.75)	3	2	0.03

ALP = alprazolam; TCAs = tricyclic antidepressants.
X_1 = mean of HRSD endpoint score for alprazolam-treated group; X_2 = mean of HRSD endpoint score for antidepressant-treated group; SD_p = pooled standard deviation.
θ = rate difference of dropouts.
OP = outpatients; IP= inpatients.

studies which met the first three criteria were found. Of these, 4 studies met all 6 criteria[12-15]. With cross-reference manual search, we found the other seven studies[16-22]. Details of these 11 studies are presented in Table 1 (see Table 1). Because either 17- or 21- item of Hamilton Rating Scale for Depression (HRSD) was used in all studies, HRSD scores of each study were examined.

The effect of treatment in each report was computed using the effect size (d) according to Equation 1[23].

$$d = X_1 - X_2/SD_p \qquad \text{Eq. 1}$$

Where X_1 and X_2 are the means of HRSD endpoint scores for alprazolam- and antidepressant-treated groups, respectively. SD_p is the pooled standard deviation of HRSD endpoint scores. In cases where the means of HRSD endpoint scores were not available[13,17], the subtracting of the mean change scores from the initial scores will be used as endpoint scores. Because the standard deviations of HRSD endpoint scores were available in 4 studies[15,16,19,21], the average of the standard deviations of alprazolam-treated groups and antidepressant-treated groups of these 4 studies were applied to the other 7 studies[12-14,17,18,20,22]. For interpretation, the higher the effect size (d), the more favor the antidepressant effect of standard antidepressants. It should be noted that, in a study that those alprazolam, amitriptyline, and doxapine were investigated[18], only the comparison of alprazolam- and amitriptyline-treated groups were analysed.

Because correlation coefficient (r) is the effect size estimate of choice, the effect size (d) in each study was converted to correlation coefficient (r) by using Equation 2[23].

$$r = d/\sqrt{d^2 + 4} \qquad \text{Eq.2}$$

The standard normal deviation Z used for combing the studies can be yielded from each correlation coefficient (r) by using Equation 3[23].

$$Z = 1/2 \log_e [(1+r)(1-r)] \qquad \text{Eq. 3}$$

The weight (by df) mean Z (Z_w) could then be computed by using Equation 4[23].

$$Z_w = \Sigma df_j Z_j / \Sigma df_j \qquad \text{Eq.4}$$

The homogeneity of Zs was tested by the using of Equation 5[23].

$$Q = \Sigma (Z-Z_w)^2 \qquad \text{Eq.5}$$

Where Q lesser than χ^2 value with degree of freedom (df) = K-1 is considered as no significant heterogeneity of Zs[24]. In this case, K is the number of Zs from independent studies.

The rate difference (θ) of dropouts in each study can be computed by the using of Equation 6[25].

$$\theta = p_1 - p_2 \qquad \text{Eq.6}$$

Where $p_1 = d_1/n_1$ and $p_2 = d_2/n_2$. d_1 and d_2 are the numbers of dropouts in alprazolam- and standard antidepressant-treated groups, respectively, and the corresponding sample sizes are n_1 and n_2.

The weighted mean θ (θ_w) can be yielded by using Equation 7[25].

$$\theta_w = \Sigma\omega\theta/\Sigma\omega \qquad \text{Eq.7}$$

Where $\omega = S^{-1}$ and $S = [p_1 (1-p_1)/n_1] + [p_2 (1- p_2)/n_2)$.

The homogeneity of θs was tested by the using of Equation 8[25].

$$Q = \Sigma\omega(\theta-\theta_w)^2 \qquad \text{Eq.8}$$

Where Q lesser than χ^2 value with degree of freedom (df) = K-1 is considered as no significant heterogeneity of θs[24]. In this case, K is the number of θs from independent studies.

The 95 per cent confidential interval (CI) of the weighted mean Z (Z_w) and weighted mean θ (θ_w) were computed. The weighted mean r (r_w) and weighted mean d (d_w) were derived from the weighted mean Z (Z_w), respectively.

RESULTS

From 11 random controlled trials, the antidepressant effects of alprazolam and standard antidepressants were examined in 472 and 469 depressed patients, respectively. Because the standard antidepressants in all studies were tricyclic antidepressants (TCAs) which used in the same dose (100-300 mg/d)[10], mean dosage of TCAs in all 11 studies could be able to be computed

Table 2. Summary of the effect size (d), correlation coefficient (r), and standard normal deviation (Z) in each study.

Authors	N	df	d	r	Z
Draper & Dely 1983	15	13	0.61	0.29	0.30
Ansseua et al 1984	115	113	0	0	0
Remick et al 1985 (OP)[a]	34	32	-0.58	-0.28	-0.29
Remick et al 1985 (IP)[b]	20	18	0.42	0.21	0.21
Rickels et al 1985	194	192	-0.16	-0.08	-0.08
Rush et al 1985	29	27	0.80	0.37	0.39
Eriksson et al 1987	61	59	-0.41	-0.20	-0.20
Fawcett et al 1987	38	36	0.08	0.04	0.04
Rickel et al 1987	76	74	0.18	0.09	0.09
Banerji et al 1989	74	72	0.45	0.22	0.22
Weissman et al 1992	14	12	0.26	0.13	0.13
Lapierre et al 1994	38	36	0.83	0.38	0.40

[a] OP = outpatient study; [b] IP = inpatient study

together. The mean TCA dosage was 147.17 mg/d, while that for alprazolam was 3.15 mg/d. The effect size (d), correlation coefficient (r), and standard normal deviation (Z) of each study are presented in Table 2 (see Table 2). The weighted mean Z (Z_w) with S.D. was 0.03±0.22. The 95 per cent CI of the weighted mean Z (Z_w) was between -0.45 and 0.51. From the Equation 5, Zs of all studies were not found to have significant heterogeneity (Q = 0.586, lesser than 19.68 of χ^2 with 11 df at $p<0.05$). The weighted mean r (r_w) and the weighted mean d (d_w) were 0.03 and 0.06, respectively.

Rate differences (θ) of dropouts were also examined. The weighted mean θ (θ_w) with S.D. was 0.003±0.338. The 95 per cent CI of the weighted mean θ (θ_w) was between -0.224 to 0.230. From the Equation 8, θs of all studies were not found to have significant heterogeneity (Q = 8.983, lesser than 18.31 of χ^2 with 10 df at $p<0.05$).

DISCUSSION

Since the weighted mean d (d_w) of 0.06 is smaller than the small effect size described by Cohen[26], it could be interpretated that the antidepressant effect of alprazolam is comparable to that of standard antidepressants. In an endpoint analysis like this, the rate differences (θ) of dropouts have to be considered simultanously with the comparison of the effectiveness to rule out the effect of dropouts on the results. With the weighted mean θ (θ_w) (95% CI) of 0.003 (-0.224 to 0.230), the rate differences of dropouts in both treated groups were not significant difference.

Since there are several limitations of included studies, the equally therapeutic effect in the present analysis should be viewed with caution. First, the results can be applied to only mildly to moderately depressed outpatients because alprazolam was studied in very few severely depressed inpatients. Second, with the mean dosage of tricyclic antidepressants of 147.17 mg/d, more explicitly, the antidepressant effect of alprazolam is comparable to that of low dose tricyclic antidepressants. In the treatment of depression, a low dosage of tricyclic antidepressants is significantly less effective than high dosage regimen[27,28]. We did not exclude a study of tricyclic antidepressant used in low dose (<100 mg/d) because it was investigated in elderly patients[14] in which that dosage is acceptable in such patients. Third, although the results of long-term study is desperately needed for the treatment planning of depression, the duration of all alprazolam studies were not more than 6 weeks. Not only the lack of long-term benefit evidence but also the risk of benzodiazepine abuse and dependence should be considered in the long-term treatment.

It should be mentioned that some studies with a large number of subjects were excluded from this present meta-analysis. Some of them did not meet the inclusion criteria because of no presented means of endpoint scores in figure[29,30].

Also, we excluded a nonrandom controlled trial[31].

While other benzodiazepines are "not effective in combating symptoms of endogenous depression"[32] or "certainly inferior to the tricyclic antidepressants"[33], the antidepressant effect of alprazolam should be viewed as somewhat successful. In the future, the knowledge gained from this sort of study may bring us an alternative approach in the treatment of depression.

SUMMARY

The results of the present meta-analysis showed that the antidepressant effect of alprazolam is comparable to that of low dose tricyclic antidepressants. Alprazolam was studied in very few severely depressed inpatients. The benefits and disadvantages of long-term treatment of alprazolam also have not been extensively investigated. To be used as an antidepressant, the aforementioned limitations of alprazolam should be taken into account.

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การรักษาอาการซึมเศร้าด้วยอัลพราโซแลมและยาต้านซึมเศร้ามาตรฐาน: มหวิเคราะห์ในด้านฤทธิ์ต้านซึมเศร้า

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Alprazolam มีความแตกต่างจากยาเบนโซไดอะซิพีนตัวอื่น คือ ยานี้จะมีการรวมเอาวงแหวน triazolo (triazolo ring) ไว้ในโครงสร้างพื้นฐาน จนถึงปัจจุบันมีหลักฐานจำนวนมากที่สนับสนุนว่า alprazolam และยาต้านซึมเศร้ามาตรฐาน (standard antidepressants) มีการออกฤทธิ์ที่คล้ายกัน เช่น beta-adrenergic receptor down-regulation, ฤทธิ์ต้านอาการแพนิค (antipanic effect) อย่างไรก็ตามความเห็นเกี่ยวกับฤทธิ์ต้านซึมเศร้า (antidepressant effect) ของ alprazolam ยังเป็นที่ถกเถียงกันอยู่ ในการวิเคราะห์นี้ ผู้นิพนธ์ได้ทำมหวิเคราะห์ (meta-analysis) การศึกษาชนิดที่มีการควบคุมและสุ่มตัวอย่าง (random controlled studeis) เป็นจำนวน 11 การศึกษา ซึ่งการศึกษาทั้งหมดได้ทำการเปรียบเทียบฤทธิ์ต้านซึมเศร้าของ alprazolam กับยาต้านซึมเศร้ามาตรฐานในผู้ป่วยซึมเศร้า ผลการวิเคราะห์พบว่าขนาดเฉลี่ยของประสิทธิผลเมื่อมีการให้น้ำหนักแล้ว (weighted mean effect size) เท่ากับ 0.06 สรุปได้ว่าฤทธิ์ต้านซึมเศร้าของ alprazolam เทียบเท่ากับฤทธิ์ต้านซึมเศร้าของยาต้านซึมเศร้ามาตรฐานในขนาดยาที่ต่ำ อย่างไรก็ตาม การศึกษาในผู้ป่วยซึมเศร้ารุนแรงยังมีน้อยมาก นอกจากนี้ในด้านของการใช้ยาในระยะยาวก็ยังไม่มีการศึกษาวิจัยอย่างกว้างขวางทำให้ยังไม่ทราบถึงประโยชน์และโทษของ alprazolam ในแง่มุมนี้

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