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Brief report

Is antidepressant–benzodiazepine combination therapy clinically more useful? A meta-analytic study

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Abstract

Background: Anxiety frequently coexists with depression, and benzodiazepines are often prescribed together with antidepressants. However, benzodiazepines themselves have little or no antidepressive effects and we lack firm evidence for or against this combination therapy. We therefore conducted a meta-analysis of relevant randomized controlled trials to date. *Methods*: All randomized controlled trials that compared antidepressant–benzodiazepine treatment with antidepressant alone for adult patients with major depression were sought by electronic searches of Medline and several other databases (January 1972 to December 1998), combined with hand searching, reference searching and SciSearch. Two reviewers independently assessed the eligibility and quality of the studies. Relative risks were estimated with random effects model. *Results*: Aggregating nine studies with a total of 679 patients, the combination therapy group was 37% (95%CI: 19–51%) less likely to drop out than the antidepressant alone group. The intention-to-treat analysis showed that the former were 63% (18–127%) to 38% (15–66%) more likely to show response (defined as 50% or greater reduction in the depression scale from baseline) up to 4 weeks. *Limitations*: None of the included RCTs followed the patients beyond 8 weeks. *Conclusions*: The potential benefits of adding a benzodiazepine to an antidepressant must be balanced judiciously against possible harm, including development of dependence and accident proneness, on the one hand, and against continued suffering following no response and drop-out, on the other.

Keywords: Major depression; Drug Therapy; Antidepressants; Benzodiazepines

1. Introduction

Anxiety frequently coexists with depression. Reviews of randomized clinical trials show, however, that anxiolytic benzodiazepines, with the possible exception of some triazolo-benzodiazepines for mild

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to moderate depression, are less effective than standard antidepressants in treating major depression (Birkenhager et al., 1995). There then remains a clinical question if adding benzodiazepines to antidepressants can bring about any advantage over antidepressants alone in the treatment of depression. We therefore conducted a systematic overview of the available RCTs. The objectives of the present meta-analysis were:

1. To determine whether combining antidepressants with benzodiazepines confers any benefit over and above treatment with antidepressants alone among adult patients with major depression in terms of the speed and magnitude of symptomatic recovery and the side-effects profile.
2. To conduct subgroup analyses based on severity of comorbid anxiety and on types of co-administered benzodiazepines.

2. Methods

All randomized controlled trials meeting the following criteria were included. (1) Participants were adults (age 18 or older) with major depression, diagnosed according to any one of the operationalized criteria such as the Research Diagnostic Criteria, Diagnostic and Statistical Manual of Mental Disorders 3rd, 3rd Revised or 4th Edition or International Classification of Diseases, 10th Revision. (2) The comparisons were between any combination of antidepressants plus benzodiazepines vs. antidepressants alone.

The details of the study selection and data extraction procedures are reported elsewhere (Furukawa et al., 2000). The present brief report will summarize the methodological procedures and concentrate on the clinically relevant issues.

Relevant trials were identified by searching the following databases for studies since January 1972, when the operationalized diagnoses were first introduced: Medline, Embase, International Pharmaceutical Abstracts, Biological Abstracts, Lilacs, PsycLIT, and the trials register of the Cochrane Depression, Anxiety and Neurosis Group. The references of the selected studies were also inspected for citations of other published and unpublished studies. All the selected articles were used as a citation in the Scisearch in order to identify more studies.

Two independent reviewers assessed the eligibility and the methodologic quality of the selected trials, blind to the authors, institution, journal of publication and results of the study. The quality assessment was based on the adequacy of randomization concealment: (A) adequate concealment, (B) unclear concealment, and (C) inadequate concealment. The inter-rater agreement with regard to the six criteria for eligibility was excellent with quadratic weighted κ values between 0.77 and 1.0 (mean: 0.88). That for the validity criteria was a weighted κ of 1.0.

Dichotomous outcome variables were combined using the relative risk (RR) by DerSimonian and Laird random effects model. We employed random effects model because this tends to produce wider confidence intervals and is hence more conservative than the Mantel–Haenzel fixed effects model (Berlin et al., 1989). Dropouts were assigned to the least favorable outcome group. We used REVIEWMANAGER software developed by the Cochrane Collaboration.

3. Results

All in all, we included 679 patients from nine studies (Feighner et al., 1979; Dominguez et al., 1984; Feet et al., 1985; Scharf et al., 1986; Fawcett et al., 1987; Ordonez et al., 1992; Nolen et al., 1993; Yamaoka, 1994; Smith et al., 1998) in the present meta-analysis (Table 1). Two of the nine studies were rated A and the others B with regard to adequacy of randomization concealment. Sensitivity analyses excluding studies with lower ratings did not affect the conclusions. Funnel plot analyses of response rates were not suggestive of publication bias. In the following we will therefore report the overall results from the nine studies.

3.1. Acceptability of treatment

Premature drop out from the treatment for any reason was taken as a surrogate measure of acceptability of treatment. The pooled RR shows that patients allocated to the combination treatment were 0.63 (95%CI: 0.49–0.82) times less likely to drop out from the treatment than those on antidepressant

Table 1
Characteristics of eight studies included in the present meta-analysis

Study	Setting	Total number of subjects included	Baseline depressive severity (mean±SD)	Antidepressant	Benzodiazepine	Duration of combined treatment	Co-intervention allowed
Feighner, 1979	Psychiatric OP?	190	35.2±8.8 on HRSD-24	amitriptyline 75–150 mg	chlordiazepoxide 30–60 mg	4	NS
Dominguez, 1984	Advertise-ment OP	126	26.6±5.3 on HRSD-21	imipramine 100–145 mg	triazolam 0.5 mg h.s.	4	NS
Feet, 1985	Psychiatric OP	42	4.0±1.1 on CPRS–VAS	imipramine 138–200 mg	diazepam 10 mg	8	flunitrazepam (2 mg) pm for insomnia
Scharf, 1986	Psychiatric	20	24.3±5.4 on HRSD	amitriptyline 50–150 mg	chlordiazepoxide 20–60 mg	8	NS
Fawcett, 1987	Psychiatric OP	52	24.1±5.6 on HRSD-21	desipramine 100–300 mg	alprazolam 2–6 mg	6	No supplementary psychotropic drug
Ordonez, 1991	Psychiatric OP & IP	83	28.5±5.5 on HRSD-21	clomipramine 100–150 mg	bentazepam 75 mg	6	Additional hypnotic for 1 patient in the combination treatment and 11 patients in the antidepressant alone treatment
Nolen, 1993	Psychiatric IP	53	27.5±4.7 on HRSD-17	maprotidine 160 mg or nortriptyline 150 mg	flunitrazepam 2 mg or lormetazepam 2 mg h.s.	4	No supplementary psychotropic drug
Yamaoka, 1994	Psychiatric OP	32	26.1±8.8 on HRSD-24	mianserin 30–60 mg	mexazolam 3 mg	4	NS
Smith, 1998	Psychiatric OP	81	22.1±2.9 on HRSD-17	fluoxetine 20–40 mg	clonazepam 0.5–1 mg	5	NS

OP = outpatient, IP = inpatient, NS = not specified, HRSD = Hamilton Rating Scale for Depression, CPRS–VAS = Comprehensive Psychiatric Rating Scale–Visual Analog Scale. Please see text for ratings under allocation concealment and double blinding.

alone. The test of heterogeneity was not significant ($\chi^2 = 6.78$, df = 7, $P = 0.45$).

We consider that this much unbalanced drop out from two treatment arms is of paramount pragmatic importance and that it poses a serious threat to internal validity if comparisons of outcomes are made on a per protocol (completer) basis or by the last-observation-carried-forward method only. In the following we will therefore concentrate on the dichotomous outcome of response based on the intention-to-treat analysis (worst case scenario).

3.2. Depression

The combination therapy group was 1.63 (1.18–2.27) times at 1 week, 1.41 (1.14–1.76) times at 2 weeks, 1.38 (1.15–1.66) times at 4 weeks, and 1.06 (0.76–1.49) times at 6–8 weeks more likely to show greater than 50% reduction from their baseline depressive severity than the antidepressant alone group. Neither statistical test of heterogeneity nor graphical inspection showed heterogeneity among the studies combined.

3.3. Subgroup analyses

We could not find enough trials for our first subgroup analysis with regard to comorbid anxiety. Only one study (Feighner et al., 1979) specifically targeted subjects with moderate to severe anxiety, while only one other (Feet et al., 1985) was conducted with patients with mild to moderate anxiety. The former showed superiority of combination therapy at 1 and 2 weeks, while the latter did not find any statistically significant difference between the two groups throughout their 8-week trial. Note that the latter trial allowed flunitrazepam 2 mg prn for insomnia as co-intervention. These two studies are

not mutually incompatible as all the 95%CIs of their RRs easily overlap with each other.

Our second subgroup analysis led to some more interpretable findings. Pooling two studies (Dominguez et al., 1984; Nolen et al., 1993) which used a short-acting benzodiazepine at bedtime produced RRs of 1.65 (0.69–3.99) at 1 week, 1.14 (0.67–1.96) at 2 weeks, and 1.43 (0.68–3.03) at 4 weeks for depression improvement. A meta-analysis excluding these two studies produced RRs of 1.63 (1.15–2.32) at 1 week, 1.47 (1.16–1.87) at 2 weeks, 1.39 (1.13–1.72) at 4 weeks, and 1.06 (0.76–1.49) at 6–8 weeks.

4. Discussion

The results of a meta-analysis expressed as RR will become clinically more interpretable and meaningful if we transform them into the number needed to treat (NNT) (Sackett et al., 1997), because it expresses the number of patients that a clinician must treat with the experimental treatment in order to create one good outcome or to prevent one bad outcome in comparison with the control treatment. The NNT therefore conveniently summarizes the investment of time, energy and resources that clinicians and patients must make in order to achieve a specific therapeutic goal.

Taking the average control event rate of the included RCTs, the obtained RRs in the present meta-analysis can be translated into NNT as follows. The NNT for preventing a premature dropout was 8 (95%CI: 6–17). In other words, only 8 patients need to be placed on an antidepressant alone, rather than on the combination therapy, for one of them drop out of treatment prematurely and unnecessarily within 4–8 weeks. The NNT for improvement in depression was 12 (6– 42) at 1 week, 9 (5–27) at 2 weeks and 7 (4–18) at 4 weeks. This means that one needs to treat only seven patients with an antidepressant plus a benzodiazepine for 4 weeks in order to make one additional patient to show 50% or greater reduction in his/her depressive severity from baseline. The baseline comorbid anxiety level or the types of benzodiazepine co-administered did not appear to influence these general findings.

These are clinically meaningful figures. For example, chlorpromazine prevents one patient out of fourteen from dropping out of treatment, and promotes global improvement in one out of seven people with schizophrenia who are treated with it instead of placebo (Thornley et al., 1998). The NNT of selective serotonin-reuptake inhibitors for major depression is about 5 against placebo (Trindade and Menon, 1997). Combining a benzodiazepine with an antidepressant is as effective as chlorpromazine over placebo for acute schizophrenia, and nearly as effective as SSRI over placebo for major depression. The benefits of adding a benzodiazepine to an antidepressant must therefore be balanced judiciously against possible harm, including development of dependence (Schweizer and Rickels, 1998), accident proneness (Neutel, 1995) and cost amongst others. Whether or not the potential difficulties encountered with benzodiazepines are important enough to offset the benefits of the combination therapy as found in the present meta-analysis requires deliberation on the part of both the physician and the patient.

The present meta-analysis could not elucidate whether the observed advantage of the combination therapy in terms of the global depression severity might be due only to its effects on sleep and anxiety, which typically accompany major depression, or to some synergistic effect on core depressive symptoms. We would need individual patient data to answer this question definitively. Another weakness of the present meta-analysis is that none of the included trials followed the patients beyond 8 weeks.

The implications of the present findings for research are clear. We need a long-term, pragmatic RCT to compare the combination therapy (preferably involving two prescription patterns, one for continued combination and another withdrawing the benzodiazepine within a month or so) against the monotherapy of antidepressant in major depression.

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