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Efficacy of Org 3770 (Mirtazapine) vs Amitriptyline in Patients with Major Depressive Disorder: A Meta-Analysis

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Results are presented from a meta-analysis performed on short-term efficacy data from five randomized, double-blind, amitriptyline-controlled studies of Org 3770. All participating patients ($n=814$) had a DSM III diagnosis of moderate or severe Major Depressive Episode, and the majority of them was hospitalized. Efficacy of treatments was compared on an Intent-to-Treat basis; 732 patients were available for this type of analysis. Primary efficacy variables were changes from baseline in group mean 17-item HAMD scores and percentages of responders. The results of the meta-analysis are in agreement with those from individual studies, consistently showing that there are no statistically nor clinically relevant differences in efficacy of Org 3770 and amitriptyline throughout the study period and at endpoint.

KEY WORDS—Org 3770; mirtazapine; amitriptyline; major depression

INTRODUCTION

Org 3770 is a new antidepressant with a unique and specific mechanism of action on both the noradrenergic and serotonergic neurotransmitter systems (de Boer, Nefkens and van Helvoirt, 1994). This particular pharmacological profile could be best summarized as Noradrenergic and Specific Serotonergic Antidepressant—the NaSSA (de Boer and Ruigt, in press). In clinical trials to date, Org 3770 has demonstrated efficacy superior to placebo (Bremner, in press; Claghorn, in press; Smith *et al.*, 1990) or trazodone (van Moffaert *et al.*, 1995), and comparable to commonly used TCAs such as amitriptyline (Bremner, in press; Mullin *et al.*, submitted; Smith *et al.*, 1990; Zivkov and de Jongh, 1995), clomipramine (Richou *et al.*, in press), or doxepin (Marttila *et al.*, in press). In all these active-controlled studies, Org 3770 had a more favorable side-effect profile than the comparator drug.

This publication presents the results of a meta-analysis of the efficacy data from randomized, double-blind, short-term amitriptyline-controlled studies of Org 3770, performed in hospitalized and outpatients with DSM III (APA, 1980) diagnosis

of Major Depressive Episode. Amitriptyline is still regarded as a 'gold standard' in antidepressant drug trials, with undisputed efficacy, particularly in difficult-to-treat patients where efficacy has to be maximized (Anderson and Tomeson, 1994). The meta-analysis was performed to obtain pooled, and hence more precise, estimates of the treatment difference and 95% confidence intervals (Whitehead and Whitehead, 1991). This statistical technique is of value not only because it helps determine whether a particular treatment produces a reliable therapeutic effect, but also because it permits an empirical assessment of its magnitude.

METHODS

Design

Efficacy data are available for 7 randomized, double-blind, short-term amitriptyline-controlled studies with Org 3770. The selection of studies for the meta-analysis was based on the approach suggested by Peto (1987), Bullpitt (1988) and Schmidt *et al.* (1991), that:

- selection of trials should be independent of results;
- the selected trials should not be biased, i.e. only properly randomized and blinded trials are to be considered;

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Table 1. Amitriptyline-controlled efficacy and safety studies of Org 3770 included in the meta-analysis

Study	Number of patients		Dose range		Design	Group mean 17-item HAM-D scores at baseline	
	Org 3770	Amitriptyline	Org 3770	Amitriptyline		Org 3770	Amitriptyline
1. Bremner, J.D., in press	50	50	5-35 mg/day	40-280 mg/day	double-blind, randomized, placebo-controlled, dose-titration, 6-week study in outpatients, weekly efficacy assessments	28.3 ± 4.0	27.6 ± 4.4
2. Smith <i>et al.</i> , 1990	50	50	5-35 mg/day	40-280 mg/day	double-blind, randomized, placebo-controlled, dose-titration 6-weeks study in outpatients, weekly efficacy assessments	23.4 ± 3.5	23.6 ± 3.8
3. Zivkov and de Jongh, in press	125	126	20-60 mg/day	75-225 mg/day	multicentre, randomized, double-blind, dose-titration, 6-week study in hospitalized patients, biweekly efficacy assessments	25.9 ± 4.7	25.7 ± 4.5
4. Mullin <i>et al.</i> , submitted	79	77	20-60 mg/day	75-225 mg/day	double-blind, dose-titration, 5-week study in hospitalized and outpatients, biweekly efficacy assessments	22.5 ± 3.9	22.6 ± 4.1
5. Gueffi <i>et al.</i> , data on file	103	104	20-60 mg/day	75-225 mg/day	multicentre, randomized, double-blind, dose-titration, 6-weeks study in hospitalized and outpatients, HAM-D assessed at baseline and Day 42	27.1 ± 4.2	27.1 ± 4.2

- the trials should address the same therapeutic issue in a well-defined patient population, with similar design and outcome variables.

Five out of the seven randomized, double-blind, amitriptyline-controlled studies were sufficiently similar regarding study design, inclusion/exclusion criteria, response variables, assessment schedule and dosages used to be included in the meta-analysis. Two studies were excluded from the meta-analysis: an efficacy and safety study in the elderly depressed patients (Høyberg *et al.*, in press), while in the other study Hamilton Depression Rating Scale-HAMD ratings (Hamilton, 1960) were not used (Ruimy *et al.*, data on file, N.V. Organon). Table 1 gives a summary of included trials, with respect to the numbers of patients, dosages used, patient status, efficacy assessment schedule and group mean 17-item HAMD scores at baseline.

Protocols for all the above mentioned studies were approved by responsible ethics committees and regulatory authorities, and all participating patients gave informed written consent. The studies were performed in full accordance with the Declaration of Helsinki and its later revisions. Participating patients had a DSM III diagnosis of Major Depressive Episode (single or recurrent), and a baseline 17-item HAMD score of ≥ 18 (Bremner; in press; Smith *et al.*, 1990) or 21-item HAMD score of ≥ 18 (Hamilton 1960, 1967) (Zivkov and de Jongh, in press; Mullin *et al.*, submitted; Guelfi *et al.*, data on file, N.V. Organon).

The duration of the present depressive episode should be between 14 days and 6 months, and patients should have had less than 6 depressive episodes requiring hospitalisation in the past. The patients with more than 25% decrease in total HAMD score during the placebo-washout period; those with a history of schizophrenia or other psychoses, atypical depression, adjustment disorder, drug or alcohol abuse; drug overdose in the previous 4 months, and active suicidal tendencies were excluded from the studies. Patients with clinically relevant renal, cardiovascular, respiratory or cerebrovascular diseases, prostatic hypertrophy, narrow angle glaucoma, urinary retention, unstable diabetes, seizure disorder or clinically relevant EEG changes were not eligible for the participation in the studies as well. At baseline, the patients could have a maximum of 3 abnormal laboratory variables.

None of the patients had been treated with ECT in the previous 3 months, or with an adequate dose of an antidepressant (≥ 150 mg amitriptyline or equivalent for at least 6 weeks) in a month preceding the trial. Concomitant use of other psychotropic medication was prohibited, except for chloral hydrate (max. 3000 mg/day, during the whole study period). In 3 studies (Guelfi *et al.*, data on file, N.V. Organon; Mullin *et al.*, submitted; Zivkov and de Jongh, in press) short acting benzodiazepines such as lorazepam, oxazepam and triazolam were permitted only during the first 14 days of the study for night-time sedation. Women of child-bearing potential had to be adequately protected against pregnancy, while mothers, either breast-feeding or within 6 months post-partum, were excluded from the studies.

The studies were randomized, double-blind, flexible dose comparisons between Org 3770 and amitriptyline. The study duration was 6 weeks except for Mullin *et al.* (submitted), which was a 5-week study. Bremner (in press) and Smith *et al.* (1990) were also placebo-controlled. Upon entry, current psychotropic medication was withdrawn (if applicable), and patients were assessed on the 17-item or 21-item HAMD before and after a 3–7 day placebo-washout period. Eligible patients were then randomized to treatment with Org 3770 or amitriptyline prepared as indistinguishable-looking capsules packed in coded packages. Lists for randomisation were centrally prepared using random number tables and the randomisation was stratified for investigator. The dosage was flexible in all studies; respective dose ranges used per study are given in Table 1. During the first three study weeks daily doses could be increased at the discretion of the investigator, but were preferably kept constant during the remainder of the study period. Daily doses could be decreased only in case of intolerable adverse effects.

Evaluation of the patient's response to drug treatment was based on weekly or biweekly use of the HAMD. A complete physical examination was performed at screening and after 6 (5 in case of Mullin *et al.*, submitted) weeks of treatment. Vital signs (heart rate, blood pressure and body temperature) and body weight were recorded at all visits; laboratory tests (hematology, blood chemistry, urinalysis and pregnancy test) were performed at screening, at baseline and after 3 and 6(5) weeks of treatment, and ECG at screening, and after 3 and 6(5) weeks of treatment. Adverse drug experiences were recorded at each visit and

whenever otherwise reported by the patient. Overall safety aspects will be discussed in detail elsewhere.

STATISTICAL ANALYSIS

Overall group comparability at baseline (demographic characteristics, psychiatric history and depressive symptomatology) was evaluated using appropriate summary statistics. Differences were statistically evaluated using tests of significance at a level of 5% (t-test for continuous variables, and Fisher's exact test for dichotomous characteristics).

The statistical analysis was performed on an Intent-to-Treat basis, including all patients randomized and treated for whom the baseline and at least one post-baseline assessment on the HAMD were available. Efficacy analyses were performed for the individual studies and a meta-analysis was used to obtain pooled results. Main efficacy variable was change from baseline in the total score on the 17-item HAMD rating scale, analyzed per assessment point (Observed Case analysis), using analysis of variance (ANOVA) with treatment and investigator as main effects. In addition, an endpoint analysis was performed for each study separately and for pooled results, with endpoint defined as the last available assessment of a patient within the time frame of the study (Last Observation Carried Forward analysis). The resulting estimates of the mean difference between treatments (Org 3770 minus amitriptyline) and their 95% confidence intervals are presented by study and assessment. The estimates based on the ANOVA per study were pooled with weights inversely proportional to their standard errors. Thus, the larger studies and the ones showing smaller inter-individual variation received the largest weight, thus resulting in a minimum variance for the pooled estimate. The estimates and 95% confidence intervals are presented by assessment, including endpoint.

To test if the estimates of treatment difference were similar for the different studies a test for homogeneity was performed (Whitehead and Whitehead, 1991). The results of this test are presented (for week 6 and endpoint results). The pooled estimates and 95% confidence intervals were then based on the random effects model.

The second measure of efficacy analyzed were responder rates, i.e. the percentages of patients

with a reduction from baseline of at least 50% on the total score of the 17-item HAMD rating scale. Per study and assessment (including endpoint), percentages of responders on Org 3770 and amitriptyline were compared by means of 95% confidence intervals on the relative response rate, i.e. the percentage of responders on Org 3770 divided by the percentage responders on amitriptyline. The estimated relative response rates and the confidence intervals for each study and assessment separately were obtained using the Cochran-Mantel-Haenszel method with investigators as strata. This is in line with the randomization, which was stratified by investigator.

The meta-analysis to obtain pooled estimates of the relative response rates was based on the Cochran-Mantel-Haenszel method, but now using studies as strata. The per study estimates of the response rate as well as the pooled estimates and 95% confidence intervals are presented by assessment, including endpoint.

RESULTS

Group comparability at baseline

A total of 814 patients entered the studies (Org 3770 $n=407$, amitriptyline $n=407$). Three hundred and sixty-four Org 3770- and 368 amitriptyline-treated patients were acceptable for efficacy analysis on an Intent-to-Treat basis. Both groups were comparable at baseline regarding gender distribution, mean age, percentages of patients with a diagnosis of a single or recurrent major depressive episode and mean group 17-item HAMD scores (Table 2). The majority of patients were females (74% and 73% in the Org 3770 and amitriptyline group, respectively). Mean age was 45.5 ± 11.6 years in the Org 3770 group and 45.2 ± 11.8 years in the amitriptyline group. The patient's age ranged between 18 and 73 years in the Org 3770-treated patients, and between 18 and 93 years in the amitriptyline-treated patients. Similar proportions of patients were diagnosed as having a recurrent major depressive episode (58% and 61% in the Org 3770 and amitriptyline groups, respectively). Two studies were performed in outpatients (Bremner, in press; Smith *et al.*, 1990), two in hospitalized patients (Zivkov *et al.*, in press; Guelfi *et al.*, data on file) while in one study (Mullin *et al.*, submitted) approximately 25% of patients were hospitalized and the rest were outpatients. Mean group baseline 17-item

Table 2. Baseline demographic characteristics and mean group rating scale scores

	Org 3770	Amitriptyline
Gender		
female	74%	73%
male	26%	27%
Age (years)		
range	18-73	18-93
mean	45.5 ± 11.6	45.2 ± 11.8
DSM III diagnosis		
296.2 (single episode)	42%	39%
296.3 (recurrent)	58%	61%
17-item HAMD	25.5 ± 4.6	25.4 ± 4.6

HAMD scores were ≥ 25 , suggesting that the majority of patients were assessed by the investigators as being severely depressed at baseline.

Doses

In all studies a flexible dosage regimen was used. Investigators had an option to up-titrate daily dosages of study medication within the dose ranges foreseen by the protocol. Table 3 shows the mean daily dosages of Org 3770 and amitriptyline used during each week of treatment. The dosages used are within the recommended dose ranges for both drugs.

Drop-out rates

Approximately 80% of the patients in both groups completed the whole study period. Similar percentages of patients prematurely withdrew due to drug-related reasons (lack of efficacy, adverse events and lack of efficacy combined with adverse events): 13.3% in the Org 3770 and 13.0% in the amitriptyline treatment groups.

Efficacy

For this meta-analysis, main efficacy variables were changes from baseline in 17-item HAMD scores and percentage of responders, i.e. patients with at least 50% decrease from baseline in the 17-item HAMD score. The homogeneity across the 5 amitriptyline studies was investigated, and the results confirmed that for comparisons with amitriptyline there were no statistical objections against the estimation of the relative treatment effect of Org 3770 using a meta-analysis (Table 4).

Throughout the treatment period, mean group 17-item HAMD scores progressively decreased in both treatment groups. At the end of the treatment period, mean change from baseline was 16.0 ± 7.9 points in the Org 3770-treated group, and 16.2 ± 7.8 in the amitriptyline group; respective reductions at endpoint were 13.6 ± 8.7 and 14.0 ± 8.6 points (Figure 1). In addition, for each assessment point estimated treatment differences and corresponding 95% confidence intervals were calculated. At all weekly assessments and at endpoint there were no statistically significant differences between treatments with Org 3770 and amitriptyline (Table 5). These results are in line with those of the individual studies, which also show no statistically significant differences between Org 3770 and amitriptyline (Table 4 and Figure 2). The meta-analytical estimate of the difference between Org 3770 and amitriptyline on the change from baseline for the 17-item HAMD at endpoint is 0.6 (95% CI: -0.6; 1.7). Thus, if there would be a difference in efficacy between Org 3770 and amitriptyline, this is with 95% confidence a small difference which can be considered to be clinically irrelevant (Montgomery, 1994).

Corroborative evidence for efficacy of Org 3770 in the treatment of patients with major depressive disorder was provided by analysis of responder rates. Similar percentages of patients in both treatment groups responded to treatment at all weekly assessments and at endpoint (Table 6).

Table 3. Mean daily doses of study medication (pooled data)

	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Org 3770	22.0 mg/day	27.5 mg/day	33.5 mg/day	39.1 mg/day	41.5 mg/day	42.0 mg/day
Amitriptyline	92.0 mg/day	112.7 mg/day	136.7 mg/day	156.0 mg/day	163.6 mg/day	173.0 mg/day

Table 4. Estimated treatment differences and 95% confidence intervals at the last week of treatment and endpoint: individual studies and meta-analysis

Study	Assessment point	Estimated treatment difference	95% confidence intervals	P-value	P-value for homogeneity
Bremner	Week 6	-1.54	-5.02; 1.95	0.382	N.A.
	Endpoint	-1.74	-4.99; 1.51	0.290	
Smith	Week 6	0.16	-3.35; 3.66	0.930	N.A.
	Endpoint	1.81	-1.39; 5.00	0.263	
Zivkov and de Jongh	Week 6	0.32	-1.95; 2.59	0.781	N.A.
	Endpoint	-0.21	-2.61; 2.20	0.864	
Mullin	Week 5	1.13	-1.05; 3.31	0.306	N.A.
	Endpoint	1.26	-0.82; 3.34	0.232	
Guelfi	Week 6	1.10	-1.51; 3.71	0.406	N.A.
	Endpoint	1.10	-1.51; 3.71	0.406	
Pooled	Week 6	0.21	-1.18; 1.61	0.763	0.692
	Endpoint	0.58	-0.57; 1.73	0.324	0.466

N.A. = not applicable

After 4 weeks of treatment approximately 50% of patients in either treatment groups were responders. After 6 weeks of treatment responder rates were also equally high (70.3% and 73.2% in

the Org 3770 and amitriptyline treatment group, respectively); at endpoint, responder rates were 61.3% in the Org 3770- and 63.9% in the amitriptyline treatment group. The relative response rates and the corresponding 95% confidence intervals confirmed that the difference between the percentages of patients responding to treatment with either Org 3770 or amitriptyline is negligible and clinically irrelevant (Table 6; Figure 3).

Figure 1. Changes from baseline in the 17-item HAMD scores during treatment with either Org 3770 or amitriptyline (BL = baseline; EP = endpoint)

DISCUSSION

The aim of the present meta-analysis was to assess the efficacy of Org 3770 in the short-term treatment of patients with an DSM III diagnosis of Major Depressive Episode, in 5 randomized, double-blind, amitriptyline-controlled studies. The overall methodology of these studies was sufficiently similar, and they could therefore be included in the meta-analysis. This analysis could provide a more precise estimate of the difference in efficacy between Org 3770 and amitriptyline than the individual studies. Moreover, it is sufficiently precise to demonstrate that both compounds have clinically equivalent efficacy.

Table 5. Changes from baseline in the amitriptyline-controlled studies (meta-analysis); estimated treatment differences, 95% confidence intervals

Day of treatment	Org 3770		Amitriptyline			Estimated treatment difference	95% confidence interval	p-value
	Number of patients	Total score $\pm$ SD	Change from baseline $\pm$ SD	Number of patients	Total score $\pm$ SD	Changes from baseline $\pm$ SD		
Baseline	364	25.5 $\pm$ 4.6		368	25.4 $\pm$ 4.6			
Week 1	220	21.9 $\pm$ 6.1	-4.0 $\pm$ 4.37	220	22.0 $\pm$ 6.3	-3.7 $\pm$ 4.6	-1.21; 0.20	0.162
Week 2	280	17.7 $\pm$ 6.5	-7.3 $\pm$ 5.6	278	17.1 $\pm$ 6.5	-7.7 $\pm$ 5.8	-0.48; 1.28	0.242
Week 3	205	16.0 $\pm$ 7.1	-9.9 $\pm$ 6.4	203	15.1 $\pm$ 6.8	-10.5 $\pm$ 6.3	-0.50; 1.94	0.394
Week 4	268	13.8 $\pm$ 7.3	-11.3 $\pm$ 7.1	260	13.3 $\pm$ 7.2	-11.8 $\pm$ 7.0	-0.59; 1.71	0.754
Week 5	246	11.6 $\pm$ 6.9	-13.6 $\pm$ 7.0	241	11.3 $\pm$ 7.2	-13.8 $\pm$ 7.2	-0.80; 1.61	0.867
Week 6	246	10.4 $\pm$ 7.7	-16.0 $\pm$ 7.9	254	10.1 $\pm$ 7.5	-16.2 $\pm$ 7.8	-1.18; 1.61	0.692
Endpoint	364	11.8 $\pm$ 8.5	-13.6 $\pm$ 8.7	368	11.4 $\pm$ 8.3	-14.0 $\pm$ 8.6	-0.57; 1.73	0.466

Figure 2 Changes from baseline in the 17-item HAM-D scores: 95% Confidence Intervals for the estimates of treatment differences

All participating patients had a DSM III diagnosis of Major Depressive Episode, with similar baseline severity. The number of patients per study was at least 50 per treatment group, ranging up to 123 per group. The majority of patients in both treatment groups were females. The treatment groups were of similar mean age, and approximately 60% in each treatment group were diagnosed as having

recurrent major depressive episode. The majority of patients were hospitalized.

The meta-analysis was performed on pooled data from all patients on an Intent-to-Treat basis, for all assessment points and endpoint. The following efficacy variables were analyzed: changes from baseline in the group mean 17-item HAM-D scores, and responder rates. The individual

Table 6. Responder rates, estimated relative response rates and 95% confidence intervals

	17-HAM-D responders ¹		Relative response rates Org 3770/amitriptyline	
	Org 3770 (%)	Amitriptyline (%)	Estimate ²	95% Confidence interval
Week 1	4.5	5.9	0.76	0.34-1.68
Week 2	20.0	23.0	0.86	0.64-1.17
Week 3	33.7	36.9	0.92	0.71-1.19
Week 4	47.0	48.5	0.97	0.81-1.16
Week 5	59.8	63.1	0.95	0.83-1.09
Week 6	70.3	73.2	0.95	0.85-1.05
Endpoint	61.3	63.9	0.95	0.85-1.05

¹A responder is defined as a patient with a $\geq 50\%$ decrease from baseline on the 17-item HAM-D.

²Based on Cochran-Mantel-Haenszel correction with studies as strata.

Figure 3 Responder rates: 95% confidence intervals for the estimates of treatment differences

studies did not show any difference in efficacy between both compounds and their homogeneity was sufficient to allow a meta-analysis. The results of the meta-analysis of both efficacy variables were in line with results from individual studies, consistently showing that there are no statistically significant nor clinically relevant differences between efficacy of Org 3770 and amitriptyline at any assessment point nor at endpoint. The meta-analysis showed that the treatment difference is small (0.6 at endpoint) and could be precisely estimated due to narrow confidence interval (-0.57; 1.73). This indicates that any true difference that might exist between treatments is small and clinically unimportant (Montgomery, 1994). Since possible influence of the confounding factors such as randomization and blinding (Schulz *et al.*, 1995) in this meta-analysis was minimal, the results should be regarded as a reliable evidence of an equivalent efficacy of both compounds.

In all the studies included in the present meta-analysis, a flexible dosage regimen was applied. Dosages were tailored on individual patients needs, based on their clinical response. Dosage ranges of both compounds were somewhat lower in the US studies than in the European ones. The daily doses of both drugs reached a level within

recommended and clinically considered as optimal dose ranges.

The question regarding the comparative efficacy of newer antidepressants, mainly SSRIs, versus TCAs in the treatment of hospitalized depressed patients was raised recently (Vestergaard *et al.*, 1993; Andersen and Thomsen, 1994). Hospitalized patients are not systematically studied as a distinct patient population, but they are generally regarded by clinicians as having more worrying or more difficult to treat depressive illness due to factors other than severity alone (Costello, 1990; Ansseau, 1992). These factors are presence of suicide risk, treatment resistance, personality problems or interpersonal problems. The results of comparative studies performed in hospitalized depressed patients unequivocally demonstrated superior efficacy of the TCA clomipramine over the SSRIs citalopram and paroxetine and the MAOI moclobemide (DUAG, 1986; 1990; 1993). A recently published meta-analysis comparing efficacy of SSRIs and TCAs in depression showed that there is poor evidence for efficacy of SSRIs in hospitalized patients (Anderson and Thomsen, 1994). Furthermore, the currently advocated clinical approach is to use TCAs and not SSRIs in

severely depressed or hospitalized depressed patients (Vestergaard *et al.*, 1993; Brown and Kahn, 1994; Goodwin, 1994). However, for the novel antidepressant Org 3770, the results of two large comparisons of Org 3770 and amitriptyline in hospitalized patients (Guelfi *et al.*, data on file; Zivkov *et al.*, in press; total number of patients: Org 3770 $n=228$, amitriptyline $n=230$) consistently demonstrate that both drugs were of equal efficacy in the treatment of hospitalized depressed patients.

The questions of comparative tolerability of Org 3770 and amitriptyline are not addressed in this paper, but they are going to be discussed *in extenso* elsewhere. Data from reported individual studies are favoring Org 3770 over amitriptyline and other commonly used antidepressants, such as clomipramine, doxepin or trazodone. We conclude that the meta-analysis has clearly demonstrated that Org 3770, a NaSSA, is an antidepressant proven to be equally effective as amitriptyline in the treatment of both outpatients and hospitalized depressed patients.

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