A Randomized, Double-Blind, Placebo-Controlled Trial of Moclobemide in Patients With Chronic Fatigue Syndrome

Ian B. Hickie, M.D., F.R.A.N.Z.C.P.; Andrew J. Wilson, F.R.A.N.Z.C.P.; J. Murray Wright, F.R.A.N.Z.C.P.; Barbara K. Bennett, B.Sc. (Hons); Denis Wakefield, M.D., F.R.A.C.P., F.R.C.P.A.; and Andrew R. Lloyd, M.D., F.R.A.C.P.

Background: Chronic fatigue syndrome is characterized by prolonged and disabling fatigue and a range of neuropsychiatric symptoms including depressed and/or irritable mood. To date, no medical or psychotropic therapies have provided clear symptomatic benefit.

Method: Ninety patients with chronic fatigue syndrome, diagnosed with our system that approximates CDC criteria, participated in a randomized, placebo-controlled, double-blind trial of 450 to 600 mg/day of moclobemide, a novel reversible inhibitor of monoamine oxidase-A.

Results: Fifty-one percent (24/47) of patients receiving moclobemide improved compared with 33% (14/43) of patients receiving placebo (odds ratio = 2.16, 95% confidence interval [CI] = 0.9 to 5.1). Drug response was best characterized symptomatically by an increase in the subjective sense of vigor and energy rather than a reduction in depressed mood. The effect of moclobemide on subjective energy was detectable within the first 2 weeks of treatment and increased across the course of the study. The greatest reduction in clinician-rated disability was in patients with concurrent immunologic dysfunction (mean difference in standardized units of improvement = 0.8, 95% CI = 0.03 to 1.6).

Conclusion: Moclobemide produces some improvement in key symptoms experienced by patients with chronic fatigue syndrome. This effect is not dependent on the presence of concurrent psychological distress and is likely to be shared with other monoamine oxidase inhibitors.

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Received Nov. 4, 1999; accepted May 17, 2000. From the School of Psychiatry (Professor Hickie) and the Inflammation Research Unit, School of Pathology (Associate Professor Wakefield and Dr. Lloyd), University of New South Wales; the Academic Department of Psychiatry (Professor Hickie, Dr. Wilson, and Ms. Bennett), St. George Hospital and Community Health Service; and the Department of Liaison Psychiatry, Royal North Shore Hospital (Dr. Wright), Sydney, Australia.

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Reprint requests to: Ian B. Hickie, M.D., Academic Department of Psychiatry, St. George Hospital and Community Health Service, 7 Chapel St., Kogarah, NSW 2217, Australia (e-mail: i.hickie@unsw.edu.au).

Chronic fatigue syndrome (CFS) is characterized by profound mental and physical fatigue and a range of other nonspecific neuromuscular and neuropsychiatric symptoms.[1] Although cognitive-behavioral approaches appear to result in long-term benefits,[2,3] no effective psychotropic treatments have yet been identified.[4] Importantly, up to two thirds of patients with CFS also meet criteria for lifetime major depression,[5–8] and patients with CFS closely resemble patients with atypical depression, a syndrome characterized by a preferential response to monoamine oxidase inhibitors (MAOIs).[9,10] As prolonged fatigue syndromes appear to have unique genetic risk factors[11,12] and longitudinal course,[13,14] the pursuit of specific treatments remains an important clinical goal.[15]

Few controlled studies have been published of antidepressant agents in patients with CFS. Vercoulen et al.[16] reported no specific benefit from 20 mg/day of fluoxetine, a selective serotonin reuptake inhibitor (SSRI), a result consistent with our own experiences with this agent.[17] In an open evaluation,[18] patients treated with nefazodone, an antagonist of the serotonin-2 (5-HT_2) receptor, reported some benefit. Natelson et al.[19] reported symptomatic improvement, but little reduction in disability in patients receiving low-dose phenelzine (an older MAOI). Moclobemide has been reported to be of some benefit in patients with CFS in 2 uncontrolled studies.[17,20] On the basis of prevalence of depressive syndromes in patients with CFS, the syndromal overlap with atypical depression, the re-

sults of our open study,[17] and the relative safety of moclobemide compared with older MAOIs (i.e., lack of adverse interactions with foods containing tyramine and fewer drug interactions), we proceeded to conduct a randomized controlled trial of moclobemide.

METHOD

Subjects from 18 to 65 years of age were recruited from infectious diseases and immunology outpatient clinics of Prince Henry and Prince of Wales Hospitals in Sydney, Australia. Subjects were considered eligible for the trial if they fulfilled diagnostic criteria for CFS according to Lloyd et al.[21] Clinically, these criteria approximate those compiled later by the Centers for Disease Control[1] and include (1) chronic, persisting, or relapsing fatigue present for greater than 6 months and (2) neuropsychiatric dysfunction including impairment of concentration and/or new onset of short-term memory impairment. Exclusion criteria included (1) a physician's diagnosis of an alternative medical illness; (2) a psychiatrist's diagnosis of an alternative major psychiatric disorder (besides major depression) or suicidal risk; (3) use of steroid medication or other immunomodulatory agents; (4) hepatic dysfunction; (5) recent alcohol or substance abuse; and (6) for female subjects, pregnancy or breastfeeding or being of childbearing age and not using a reliable form of contraception. Prior to entry, the nature of the study was explained, and written consent obtained from all subjects. The study was approved by the institutional ethics committee.

Assessment at trial entry included (1) the Structured Clinical Interview for DSM-III-R depressive, anxiety, and somatoform disorders (SCID)[22]; (2) a semistructured interview for CFS to confirm the diagnosis (available on request); (3) the investigator-rated Karnofsky Performance Index (KPI)[23] to assess the level of physical disability; (4) the self-report Profile of Mood States (POMS) questionnaire[24] to assess the severity of subjective fatigue, vigor, and depressed mood; and (5) the 30-item General Health Questionnaire (GHQ)[25] to determine cases of general psychological distress (scores > 4). Cell-mediated immune function was assessed by enumeration of T-lymphocyte subclasses (CD4, CD8) and by delayed-type hypersensitivity skin testing using a standardized commercial kit (CMI Multitest, Institut Merieux, Paris, France). A patient was considered to have abnormal cell-mediated immune function if the CD4 count was $< 0.70 \times 10^9$/L, CD8 count was $< 0.30 \times 10^9$/L (only seen in less than 5% of normal subjects in our reference laboratory), or their delayed-type hypersensitivity skin response was hypoergic or anergic (typically seen in less than 10% of healthy Australian adults). A normal delayed-type hypersensitivity response was scored for men with a total induration diameter of 10 mm or greater and for women with 5 mm or greater.

Each patient was reassessed clinically at 2-week intervals during the trial with the POMS and the KPI administered on each occasion. At trial completion, the immunologic measures were again taken, and patients completed a subjective global outcome scale (separating degrees of "improvement" from "no improvement").

A randomization list (by blocks of 10) as well as packaging and labeling were produced by Hoffman-LaRoche (Sydney, Australia). The trial medication was dispensed in bottles labeled "moclobemide/placebo preparation." Moclobemide was prescribed as 150-mg tablets. The moclobemide/placebo was initially administered at a dose of one 150-mg tablet twice per day after meals. After 1 week, the dose was increased to 2 tablets in the morning and 1 tablet at night for a total dose of 450 mg/day. This dose was increased to 600 mg/day if tolerated by the subject. Intermittent night dosages of a short-acting benzodiazepine were allowed for insomnia.

On the basis of our previous open study[17] and the likelihood of a significant placebo response rate in patients with CFS,[4,26] we predicted a 66% response rate in those receiving moclobemide versus 33% among the placebo recipients. For 90 enrolled subjects (assume 45 per group, Cohen[27] effect size [h] = 0.67, $\alpha = .05$ [2-tailed]), we therefore had statistical power of 0.88. All analyses were conducted on an intent-to-treat basis, with the last recorded value on each outcome measure being carried forward to the end of the trial. Response was assessed in terms of (1) standardized units of improvement for the relevant continuous variables and (2) percentage of patients classifying themselves as significantly improved on the global outcome scale. Standardized units of improvement are calculated as (pretreatment score – posttreatment score)/standard deviation of the mean pretreatment score. One standardized unit of improvement for the KPI, therefore, represents a reduction in pretreatment KPI of 1 standard deviation. In clinical trials, effect sizes greater than 0.5 are typically considered clinically significant. Here we report the mean differences between these standardized units for those receiving moclobemide versus those receiving placebo and the 95% confidence intervals (CI) for those differences. A 95% CI that is positive on both ends is indicative of a statistically significant result.

Since the diagnosis of CFS depends on a cluster of nonspecific symptoms,[1] certain other illness characteristics may indicate the presence of relevant subgroups. These include the presence of concurrent psychological disturbance (notably in the form of major depression), the duration of illness, the total number of medically unexplained somatic symptoms,[26,28] and the presence of cell-mediated immune dysfunction.[29–31] Consequently, we planned subanalyses to examine whether response rates to moclobemide varied across these subgroups. These analyses were conducted in patients who (1) were classified by the GHQ as likely cases of psychological disorder (i.e.,

Table 1. Sociodemographic, Illness, and Immunologic Characteristics of Patients Receiving Moclobemide or Placebo[a]

Characteristic	Moclobemide (N = 47)	Placebo (N = 43)	Statistic t or χ^2
Sociodemographic/illness			
Age, y	42.3 ± 13.4	44.9 ± 12.8	0.98
Gender, N (%) female	25 (53)	24 (56)	0.06
Duration of illness, wk	84.2 ± 78.2	90.9 ± 74.0	0.42
Initial KPI score (disability)	74.3 ± 5.0	75.9 ± 4.5	1.66
POMS subscale scores			
Fatigue	18.0 ± 5.6	18.0 ± 5.8	0.02
Vigor	8.2 ± 5.3	8.8 ± 5.1	0.57
Depression	12.9 ± 13.4	14.1 ± 12.2	0.42
Cases of current major depression (DSM-III-R), N (%)	14 (30)	17 (40)	0.94
Cases of psychological distress (GHQ score > 4), N (%)	32 (68)	29 (67)	0.00
Immunologic			
CD4 T cell count × 10^9/L[b]	0.87 ± 0.31	0.95 ± 0.34	1.00
CD8 T cell count × 10^9/L[b]	0.83 ± 0.26	0.51 ± 0.15	–0.40
Abnormal delayed-type hypersensitivity skin response, N (%)[c]	16 (36)	11 (31)	1.65

[a]Abbreviations: GHQ = General Health Questionnaire, KPI = Karnofsky Performance Index, POMS = Profile of Mood States. All values expressed mean ± SD unless otherwise indicated.
[b]N = 44 for moclobemide-treated group, N = 34 for placebo-treated group.
[c]N = 44 for moclobemide-treated group, N = 35 for placebo-treated group.

score > 4; N = 61), (2) met DSM-III-R criteria for a current major depressive episode (N = 31), or (3) demonstrated a reduced delayed-type hypersensitivity skin response or reduced CD4 or CD8 cell counts at the initial assessment interview (N = 36).

RESULTS

Ninety subjects were enrolled; 77 completed the 6-week trial period. The sociodemographic, illness, and immunologic characteristics of patients allocated to the moclobemide- and placebo-treatment groups are shown in Table 1. Among the 13 subjects who left the study prior to the 6-week endpoint, 6 had received placebo and 7, moclobemide. Two subjects refused ongoing treatment without explanation. Side effects reported by those who withdrew included agitation (N = 5), headache (N = 2), insomnia (N = 6), gastrointestinal problems (N = 5), increased malaise (N = 4), and anxiety (N = 3). One patient receiving moclobemide developed psychotic symptoms.

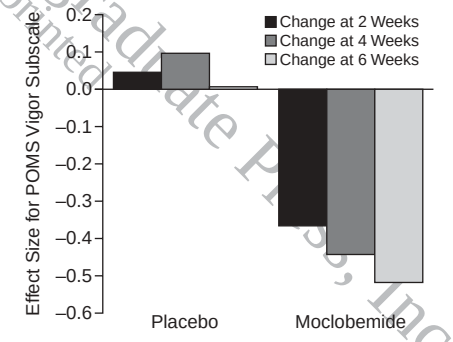
In evaluating the efficacy of moclobemide, it is important to note the size of the response to placebo (Table 2). For the clinician-rated KPI, a standardized unit of improvement of 0.58 was achieved, consistent with considerable clinical improvement. Correspondingly, 33% (14/43) of patients receiving placebo reported themselves as substantially improved at 6 weeks, again demonstrating that despite the duration of illness and degree of disability reported by these patients, the nonspecific treatment response was significant.[4] Among those patients receiving moclobemide, 51% (24/47) reported subjective improvement at 6 weeks, while there was a significant improvement in subjective vigor as rated by the POMS and a weak trend toward greater improvement in KPI score (see Table 2). The pattern of change in standardized units of improvement for the vigor subscale (Figure 1) across the

Table 2. Changes in Clinical and Immunologic Measures in Response to Treatment With Moclobemide or Placebo (Intent-to-Treat Analyses With Last Observation Carried Forward) for the Whole Sample[a]

Measure	Moclobemide (N = 47)	Placebo (N = 43)	OR (95% CI)[b]
Clinical			
Globally improved cases (patient-rated), N (%)	24 (51)	14 (33)	2.16 (0.9 to 5.1)
	Standardized Units of Improvement		Mean Difference Between Groups
KPI score (disability)	0.86 ± 1.2	0.58 ± 1.3	0.28 (–0.2 to 0.8)
POMS subscale scores			
Fatigue	–0.05 ± 0.4	–0.01 ± 0.3	0.04 (–0.2 to 0.1)
Vigor	0.51 ± 1.2	0.00 ± 1.1	0.51 (0.1 to 1.0)
Depression	–0.06 ± 1.0	–0.08 ± 0.7	0.02 (–.3 to 0.5)
Immunologic	Mean Values[c]		
Change in CD4 T cell count × 10^9/L	0.03 ± 0.29	0.07 ± 0.32	0.04 (–0.2 to 0.1)
Change in CD8 T cell count × 10^9/L	0.01 ± 0.19	0.03 ± 0.12	0.02 (–0.1 to 0.04)
Change in size of delayed-type hypersensitivity skin response, mm	0.00 ± 0.73	–0.10 ± 0.56	0.10 (–0.2 to 0.4)

[a]Abbreviations: CI = confidence interval, KPI = Karnofsky Performance Index, OR = odds ratio, POMS = Profile of Mood States. All values expressed mean ± SD unless otherwise indicated.
[b]Where the 95% CI of the mean difference between groups ranged from negative to positive values, the difference was not statistically significant.
[c]The change in immunologic measures within each subject was calculated (time 1 – time 2), and the means of these change values were then compared between groups.

Figure 1. The Time Course of Response to Moclobemide Over the 6-Week Trial as Illustrated by the Change in the Vigor Subscale Score (Standardized Units) of the Profile of Mood States Questionnaire (POMS)[a]



[a]The linear trend in differences between the active drug– and placebo-treated groups was significant ($p < .05$).

Table 3. Patterns of Clinical Response to Moclobemide or Placebo in Patients With General Psychological Distress, Current Major Depression, or Reduced Immune Responsiveness[a]

Patient Group	Variable	Moclobemide	Placebo	OR (95% CI)
General psychological distress[b]	N	32	29	
	Globally improved cases, N (%)	15 (47)	7 (24)	2.77 (0.92 to 8.31)
		Standardized Units of Improvement		Mean Difference Between Groups
	KPI score (disability)	0.84 ± 1.2	0.43 ± 1.2	0.41 (–0.2 to 1.0)
	POMS subscale scores			
	Fatigue	–0.06 ± 1.3	0.03 ± 0.3	0.09 (–0.3 to 0.1)
	Vigor	0.62 ± 1.1	–0.17 ± 1.0	0.79 (0.3 to 1.3)
	Depression	–0.07 ± 1.2	–0.10 ± 0.9	0.03 (–0.5 to 0.6)
Major depression[c]	N	14	17	
	Globally improved cases, N (%)	8 (57)	8 (47)	1.50 (0.4 to 6.2)
		Effect Size Changes		Mean Difference
	KPI score (disability)	1.11 ± 1.2	0.97 ± 1.3	0.14 (–0.8 to 1.1)
	POMS subscale scores			
	Fatigue	–0.17 ± 0.4	–0.01 ± .33	–0.16 (–0.4 to 0.1)
	Vigor	0.93 ± 1.1	0.08 ± 1.0	0.85 (0.1 to 1.6)
	Depression	–0.39 ± 1.5	–0.19 ± 0.9	0.20 (–1.1 to 0.7)
Reduced immune responsiveness[d]	N	16	20	
	Globally improved cases, N (%)	6 (38)	6 (30)	1.4 (0.4 to 5.6)
		Standardized Units of Improvement		Mean Difference
	KPI score (disability)	1.16 ± 1.2	0.36 ± 1.0	0.80 (0.03 to 1.6)
	POMS subscale scores			
	Fatigue	–0.05 ± 0.4	0.03 ± 0.3	–0.08 (–0.3 to 0.2)
	Vigor	0.40 ± 1.3	–0.04 ± 0.8	0.44 (–0.3 to 1.2)
	Depression	0.16 ± 0.6	–0.17 ± 0.8	0.33 (–0.2 to 0.8)

[a]Abbreviations are defined in the first footnote to Table 1. All values expressed mean ± SD unless otherwise indicated.
[b]General psychological distress was defined as a General Health Questionnaire score > 4.
[c]Major depression diagnosed according to DSM-III-R criteria.
[d]A patient was considered to have reduced immune responsiveness if CD4 count was $< 0.70 \times 10^9$/L, CD8 count was $< 0.30 \times 10^9$/L, or delayed-type hypersensitivity (DTH) skin response was hypoergic or anergic. A normal DTH response was scored for men with a total induration diameter of 10 mm or greater and for women with 5 mm or greater.

6 weeks of the trial indicates that this sense of increased energy both was apparent early in treatment with moclobemide and continued to improve with ongoing treatment (multivariate analysis of variance, $p < .05$).

With regard to specific subgroup analyses, patients with significant psychological distress, as determined by the GHQ, demonstrated a pattern of response to moclobemide similar to that of the whole sample (Table 3). Although the subsample was relatively small, a diagnosis of concurrent major depression was not associated with higher response rates to the active drug (see Table 3). By contrast, patients with impaired immune responsiveness demonstrated the most impressive drug-placebo difference on the clinician-rated KPI (see Table 3). Among patients receiving moclobemide, the only significant correlate of increases in vigor and KPI was a higher POMS depression subscale score at baseline ($r = –0.28$, $p = .05$ for both measures). Other potential factors such as age, sex, duration of symptoms, and number of unexplained somatic symptoms were not associated with drug response.

Moclobemide did not appear to have any direct effect on immunologic function (see Table 2), but in patients who improved clinically, that improvement was accompanied by improvement in the delayed-type hypersensitivity skin response (for improvers, mean ± SD change = 0.22 ± 0.58 mm versus for nonimprovers, –0.26 ± 0.61 mm, $t = 3.14$, $p < .01$). The change in vigor scores was specifically correlated with the improvement in CD8 counts ($r = –0.30$, $p = .012$), but not with the change in delayed-type hypersensitivity scores ($r = 0.17$) or CD4 counts ($r = –0.16$).

DISCUSSION

Moclobemide appears to result in some improvement in a key clinical feature of patients with CFS, namely the sense of subjective energy. This change is accompanied by a trend toward global improvement as rated by the patients themselves. Although the overall effect of 6 weeks of moclobemide treatment on functional status was more limited, the relatively low doses of moclobemide utilized, the large degree of improvement achieved by the placebo group, and the restricted range of KPI scores in ambulatory patients may have all contributed to the smaller drug-placebo difference noted on this investigator-rated instrument. Longer periods of drug treatment, possibly at higher doses (600–900 mg/day, as is now commonly used

for patients with major depression) and in combination with appropriate cognitive-behavioral approaches,[32,33] may be required to achieve more significant reductions in disability.

Although clinical improvement was associated with improvements in cell-mediated immune function, change in immunologic function did not appear to be a direct consequence of moclobemide treatment (see Table 2). This result suggests that no benefits of moclobemide in patients with CFS are secondary to unexpected direct effects on immunologic function. It is likely that moclobemide, via its effects on central nervous system factors, leads primarily to an improvement in global functioning, which then promotes improved cell-mediated immune function. The effect of moclobemide on subjective energy is apparent soon after commencing drug treatment. This early shift in feelings of energy and vigor can be utilized to facilitate cognitive-behavioral approaches, which encourage gradually increasing levels of social and physical activity.[34]

While the severity of initial depressive symptoms weakly predicted the degree of response to the drug, our subgroup analyses suggested that the use of moclobemide should not be restricted to patients with concurrent major depression. This result is somewhat different from results of an open-label study, which suggested greater benefit in those with comorbid major depression.[20] In the clinical practice of psychiatrists and other mental health professionals, patients with CFS will commonly have major depression. The subsample reported here is too small to allow confidence about the relative predictive importance of concurrent major depression. The beneficial effects of moclobemide, however, did not appear to be secondary to reduction in depressed mood, since the POMS depression subscale scores showed little change during the trial. This suggests that the concept of energy or vigor in patients with CFS is not simply a function of mood state.

We assume that fatigue in these patients is a consequence of some other mood-independent perceptual factor, an interpretation that is consistent with findings with regard to other cognitive symptoms in patients with CFS.[35] It is also consistent with our earlier open comparison of moclobemide and fluoxetine in which the reversible inhibitor of monoamine oxidase-A (RIMA) demonstrated considerable advantages over the SSRI.[17] If improvement in subjective energy was a consequence of mood-altering effects, then we would not have expected to find such a difference. From a biochemical perspective, this finding might suggest that agents that impact preferentially on noradrenergic and/or dopaminergic (rather than serotonergic) systems are to be preferred in prolonged fatigue states. In countries where RIMAs are not available, we would expect similar response profiles following treatment with conventional MAOIs or other noradrenergic and/or dopaminergic agents. Clearly, when patients with CFS do have concurrent mood disturbance, the argument for initial treatment with such agents is even stronger.

The only patient subgroup that appeared to have a particularly favorable pattern of drug response was that with impaired immune responsiveness. We have suggested previously that such immunologic measures may help to define a more homogeneous subgroup of patients with CFS,[29] and this finding now requires further exploration.

As would be expected in a double-blind, placebo-controlled study, the overall response rate for moclobemide (51%) was lower than that in our open study (69%).[17] Importantly, however, the placebo response rate (33%) was consistent with that expected in a clinically credible antidepressant trial. Our pretrial calculations of statistical power had assumed that the drug-placebo difference in response rates would approximate 66% versus 33%. Since the observed drug-placebo response rates were 51% versus 33%, we eventually had less power to detect real drug-placebo differences (51% versus 33%; $h = 0.36$, $N = 90$ [assume 45 per group], $\alpha = .05$ [2-tailed], power = 0.43). This is further complicated by the inevitable heterogeneity of cohorts of patients with a nonspecific clinical syndrome such as CFS.[26] The overall pattern of drug response observed, however, does suggest a possible clinical role for moclobemide in patients with CFS.

Drug names: fluoxetine (Prozac), nefazodone (Serzone), phenelzine (Nardil).

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