REVIEW PAPER

Continuation and Maintenance Treatments in Major Depression: The Neglected Role of Monoamine Oxidase Inhibitors

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The importance of continuation and maintenance antidepressant therapy has been increasingly recognized, but usually focuses on tricyclic and selective serotonin reuptake inhibitor (SSRI) antidepressants. This review examines the evidence in support of classical monoamine oxidase inhibitor (MAOI) agents and the selective reversible monoamine oxidase type A inhibitor moclobemide in continuation and maintenance therapy. Phenelzine and tranylcypromine have demonstrated long-term efficacy but often cause intolerable side effects. Moclobemide is a well-tolerated alternative antidepressant, but there is a need for prospective controlled trials to evaluate its long-term efficacy.

Key Words: monoamine oxidase inhibitors, moclobemide, continuation therapy, maintenance, long-term treatment, major depression

INTRODUCTION

Relatively little has been written about the long-term use of classical or reversible MAOI therapies (Pare 1985; Nutt and Glue 1989; Kennedy and Glue 1994) despite the facts that increased attention has been devoted to continuation and maintenance treatments with tricyclic and SSRI antidepressants (World Health Organization Mental Health Collaborating Centres 1989; Kupfer 1993; Montgomery and others 1994), that classical MAOIs have experienced a resurgence of interest, particularly in the treatment of refractory depression (Amsterdam 1991), and that the selective and reversible inhibitor of monoamine oxidase-A (RIMA), moclobemide, has become established in Australia, Europe, and Canada as an effective antidepressant (Fitton and others 1992; Roth and Guelfi 1992; Williams and others 1993; UK Moclobemide Study Group 1994).

MAOI uncertainties

A series of uncertainties has plagued clinical and research interest in MAOIs. Failure to demonstrate efficacy in a widely publicized clinical trial in the United Kingdom (Medical Research Council 1965), exaggerated concerns about adverse food and drug interactions (Shulman and others 1989), and persistent attempts to define therapeutic niches for phenelzine and tranylcypromine in subpopulations of depression have all contributed to the reluctance of many clinicians to learn how to use these drugs. This has also

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produced a carry-over effect among partially informed clinicians who equate RIMA drugs with their more potent and potentially hazardous ancestors, resulting in underprescribing of both MAOI and RIMA therapies.

This brief review is based on reported findings about continuation and maintenance trials, dosage reduction and discontinuation trials, and case reports on the intermediate and long-term efficacy of MAOI and RIMA therapies.

Continuation and maintenance trials with classical MAOIs

Only 2 groups of investigators (Georgotas and others 1989; Robinson and others 1991) have reported results from randomized, placebo-controlled comparative trials involving both continuation and maintenance treatment with classical MAOI therapies. Georgotas and associates (1989) compared phenelzine and nortriptyline during a 1-y maintenance trial in elderly depressed patients. Following a double-blind, placebo-controlled acute phase of treatment (7 to 9 weeks) in which there was no difference in treatment response between nortriptyline and phenelzine and both were significantly better than placebo (60% versus 10%), responders entered a double-blind continuation phase for at least 4 mo. Again, there was no difference in response rates to either phenelzine or nortriptyline. To evaluate the effects of maintenance treatment for a further year, approximately half the patients in each of the 2 active treatment groups were switched to placebo, leaving 15 patients on phenelzine, 13 on nortriptyline, and 23 on placebo, all under double-blind conditions. The recurrence rate among those patients who received maintenance treatment with phenelzine was 13%, which contrasts the 54% recurrence rate for those on nortriptyline and the 65% rate for the placebo group. These authors paid careful attention to adequacy of dosing for both groups, according to plasma levels of nortriptyline and degree of platelet monoamine oxidase inhibition in phenelzine-treated patients. In an attempt to explain the superior effect of phenelzine, the authors suggested that long-term maintenance therapy with nortriptyline may be adversely affected by the accumulation of 10-hydroxynortriptyline, a metabolite of nortriptyline. They also acknowledged a greater number of prior episodes in the nortriptyline group.

In the 2nd maintenance study, also involving phenelzine, Robinson and colleagues (1991) carried out a double-blind randomization to phenelzine or placebo after open-label acute and 16-week continuation phases of treatment with phenelzine up to a dose of 90 mg/d. During the 2-y maintenance phase, patients were randomly assigned to phenelzine 60 mg/d (n = 19), phenelzine 45 mg/d (n = 12), or placebo (n = 16). There was a 50% recurrence rate in the placebo group within 3 mo, compared with 13% in the combined phenelzine groups. Of the 25 patients who remained in remission (n = 14, 8, and 3 in the 3 subgroups, respectively), however, 12 had discontinued the drug treatment prematurely because of side effects—most commonly weight gain, ankle edema, and muscle twitching—highlighting concerns about the clinical utility of maintenance therapy with phenelzine.

The efficacy of continuation but not maintenance therapy was evaluated by 3 additional groups of investigators. In a pilot study to examine the effect of continuation treatment with phenelzine in chronic depression, Harrison and colleagues (1986) reported on the outcome of phenelzine treatment for up to 6 mo in a small group of patients who 1) met criteria for DSM-III dysthymic disorder and 2) were considered responders after 12 weeks of phenelzine treatment. All 7 patients who had been randomized to placebo relapsed, while only 1 of the 5 patients who continued to receive phenelzine treatment relapsed during the 6-mo follow-up.

Himmelhoch and associates (1991) monitored the outcome of continuation therapy for 10 weeks in anergic, depressed bipolar patients who had responded to a 6-week, double-blind trial of imipramine or tranylcypromine. Response was sustained in 70% of the MAOI group compared with only 20% of the tricyclic treated group. Similarly, Liebowitz and colleagues (1988) reported a significantly better response to phenelzine than imipramine among atypical depressed patients who were responders after a 6-week, double-blind, placebo-controlled trial that was followed by a further 6-week continuation phase of treatment. Although not the focus of this review, it is important to remember that the claim for superiority of phenelzine in "atypical depressives" is based mainly on studies conducted at Columbia University (Quitkin and others 1988, 1989) involving relatively small numbers of subjects and predating the availability of SSRI and RIMA antidepressants.

Continuation and maintenance trials with RIMA

Despite a comprehensive series of reports documenting the efficacy, safety, and tolerability of moclobemide as an antidepressant in acute depression (Fitton and others 1992; Roth and Guelfi 1992; Williams and others 1993; UK Moclobemide Study Group 1994), there are few published reports on the continuation and maintenance effects of this drug. Guelfi and colleagues (1994) reported on the efficacy and safety of moclobemide (400 mg) during a 6-mo, open-label treatment trial involving 381 patients. Reasons for discontinuation during this open-label trial were as follows: failure to respond (28%); adverse events (11%); recovery (4%). A further 10% declined participation in the double-blind maintenance phase of treatment, leaving 155 patients who had remained well for at least the last 3 mo of moclobemide and were randomly allocated to receive either moclobemide or placebo for a further 12 mo. Further results of this trial have not yet been reported. Lonnqvist and colleagues (1995) reported equivalent efficacy with moclobemide and fluoxetine, including measures of quality of life in a 12-week continuation phase following a 6-week initial trial. Using

rigorous criteria for response (Hamilton Depression Rating Scale [HDRS] ≤ 7), the moclobemide group showed an increase in responders from 55% to 65% between the 6th and 18th week compared with an increase from 33% to 57% in the fluoxetine group. These differences were not statistically significant. Health status and quality of life also improved equally in both groups during continuation treatment, but the study suffered from a greater than 50% dropout rate between the acute and continuation phases of treatment.

Following a double-blind trial with moclobemide administered in 3 different dosage regimens, Gagiano and colleagues (1995) reported on the outcome of continuation therapy with moclobemide 150 mg administered twice daily in an open-label design for up to 18 weeks. This continuation trial was not restricted to those patients who were classified as responders after 6 weeks of treatment. The response rate increased from 63% (week 6) to 84% (week 24) according to the HDRS (Hamilton 1960); most of the increase occurred by week 12, and there was no evidence of adverse events leading to termination.

In a metaanalysis of 50 studies involving 1120 patients who continued treatment with moclobemide for more than 44 d, Moll and associates (1994) included an evaluation of 485 patients from 1 large, open, long-term trial. Rates of response, relapse, and recurrence were presented for up to 18 mo. Conclusions are of limited value because of the lack of controlled conditions, but the reported recurrence rates of 15% after 12 mo and an additional 12% after 18 mo of moclobemide therapy are comparable to rates reported with other agents. Similarly, there is preliminary open-label evidence of long-term efficacy for up to 1 y with another RIMA agent, brofaromine, which is not available for routine use (Moller and Volz 1992).

Dosage reduction and discontinuation trials

The effects of both abrupt and progressive discontinuation of phenelzine have been evaluated in depressed patients. When Tyrer (1984) abruptly discontinued phenelzine treatment in a "depressive neurosis" population of outpatients, 30% met criteria for relapse after only 4 weeks, and in over 50%, it was felt necessary to restart phenelzine by 3 mo. A lower relapse rate (approximately 25%) was reported for similar patients who had discontinued tricyclic maintenance therapy. Davidson and Raft (1984) compared the effects of leaving the dose of phenelzine constant with progressive dose reduction during continuation treatment in a group of depressed patients who had responded to acute phenelzine treatment and remained well for 4 weeks. In this double-blind continuation trial, the dose of phenelzine was decreased by 15 mg each month (and a placebo capsule was substituted). Based on relapse criteria, all patients in the reducing-dose group had relapsed (100%) by the 3rd month, compared with 14% in the constant-dose group.

The question of discontinuation in MAOI combination treatments has also been addressed. In an attempt to evaluate the need for maintenance isocarboxazid in a combined isocarboxazid–amitriptyline treatment for previously refractory depressive patients who responded to this combination, Berlanga and Ortega-Soto (1995) systematically discontinued isocarboxazid every 6 mo and recorded the number of reinstatements of isocarboxazid after 2 to 4 weeks on each occasion. At the end of the 1st 6 mo, all patients relapsed after isocarboxazid discontinuation and responded again within 1 week of its reintroduction. By 36 mo, 50% were judged still to require the combination, 33% were well on amitriptyline alone, and 17% had relapsed despite reintroduction of the combination. Following withdrawal of l-tryptophan for regulatory reasons, Ferrier and colleagues (1990) documented the relapse of all 11 patients with a diagnosis of refractory depression who had responded to a serotonin "cocktail" of phenelzine, lithium, and l-tryptophan. Reinstatement of tryptophan was effective in only 6 of the 11 patients. Both of these reports support the need to continue all the ingredients of an initially effective combination therapy during continuation and maintenance phases of treatment.

Tolerance and loss of efficacy

Finally, the issue of tolerance to MAOI treatment and loss of efficacy has been addressed only in the form of case reports. Donaldson (1989) presented details of 3 patients in whom an initially favorable response to phenelzine "wore off" during the 1st year of treatment and dose increments were limited by side effects. Similar findings have been reported by Cohen and Baldessarini (1985) involving both tricyclic and MAOI therapies. Persad and Oluboka (1995) raised a similar issue with respect to moclobemide. There is no systematic evidence, however, to suggest that this phenomenon occurs with greater frequency during RIMA or MAOI therapies than with other antidepressants.

CONCLUSIONS

Despite the paucity of controlled trials to examine continuation and maintenance treatments involving MAOI and RIMA agents, there is limited but consistent evidence to suggest that these drugs have long-term efficacy in adult and elderly depressive patients and that treatment should be continued for 6 to 12 mo or longer in the case of refractory depression. Discontinuation should be done gradually and in various drug combinations for refractory depression involving MAOIs: there is a need to maintain the full "cocktail" during long-term treatment. Tolerability of classical MAOIs is usually the limiting factor in therapy, while effectiveness is less of an issue. Clinical experience is supported by the observation of Robinson and colleagues (1991) that high rates of side effects persist with ongoing phenelzine treatment. Often, the dilemma for the patient is to decide whether the therapeutic benefits outweigh unwelcome side effects.

While the reversible and selective MAOI moclobemide is a better-tolerated drug than the classical MAOIs, more rigorous evidence of its effectiveness over the long term is required from double-blind maintenance trials. There is no current evidence to support its role in previously treatment-refractory depression, but rather there is evidence to suggest that its niche may lie in the treatment of overlapping anxiety and depression states, including social phobia (Versiani and others 1992). With the ascendency of SSRIs and related classes of antidepressants, it will be important to include both classical MAOI and RIMA drugs in comparative outcome trials, particularly during continuation and maintenance phases of treatment and in trials where atypical, bipolar, and other depressive subtypes are included.

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