CLOMIPRAMINE AUGMENTATION IN TREATMENT-RESISTANT DEPRESSION

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In depression that is resistant to tricyclic antidepressant (TCA) therapy, the substitution of a selective serotonin re-uptake inhibitor (SSRI), clomipramine, or a monoamine oxidase (MAO) inhibitor has been recommended. However, adding an additional antidepressant medication from a different drug class may produce even more rapid efficacy. In this regard, the combination of a MAO inhibitor or a SSRI plus a TCA has been shown to be of value in treatment-resistant depression (TRD).

In this report, we examined the efficacy of clomipramine augmentation in 20 patients who failed to respond to either a MAO inhibitor or fluoxetine therapy for at least a 6-week period, and compared this to a third group given MAO inhibitor plus a conventional TCA.

Two out of 9 (22%) MAO inhibitor/clomipramine patients and 4 out of 11 (36%) fluoxetine/clomipramine patients improved (Fisher's Exact test, P = ns), compared to 3 out of 7 (43%) patients taking MAO inhibitor/TCA (P = ns). However, the MAO inhibitor/clomipramine group experienced significantly more adverse events which necessitated stopping treatment (56%) when compared to the fluoxetine/clomipramine (9%) and compared to the MAO inhibitor/TCA group (0%) (χ^2 = 8.9, df = 2, P < 0.05). These adverse events included several cases of serotonin syndrome of mild to moderate severity. These observations indicate that clomipramine augmentation of a failed MAO inhibitor trial is of marginal efficacy (compared to augmentation with a conventional TCA) and should be employed with extreme caution. Depression and Anxiety 5:84–90, 1997. © *1997 Wiley-Liss, Inc.*

Key words: *clomipramine; MAO inhibitor; tricyclic antidepressant; refractory depression; serotonin syndrome; drug interaction*

INTRODUCTION

Advances is psychopharmacologic treatment of mood disorders have contributed to improved response rates in patients with treatment-resistant depression (TRD). Using currently accepted strategies of antidepressant drug combinations and augmentations, as many as 85% of patients with major depression will demonstrate a satisfactory treatment outcome. There remains, however, a significant number of patients (15%) who have persistent, treatment-refractory depression. Even after controlling for important factors such as duration of treatment, medication dosage, diagnostic issues (e.g., co-morbid diagnoses), and pharmacokinetic issues (e.g., plasma drug concentrations, variance in drug metabolism, etc.), a substantial percentage of patients still fail to respond to what appears to be an "adequate" antidepressant drug trial. A variety of treatment algorithms have been proposed using drug combinations and augmentation strategies (Nierenberg and Amsterdam, 1990; Amsterdam and Hornig-Rohan, 1996). Unfortunately, there is a paucity of systematic data available to compare between the bewildering number of drug combinations and augmentation strategies. While there are some data to suggest that particular antidepressants may demonstrate a preferential response in patients with specific diagnostic subtypes of major depression (Liebowitz et al., 1984; Himmelhoch et al., 1991; Nierenberg et al., 1994), comparative antidepressant efficacy rates in treatment-refractory depression are rare. In this context, we (Nierenberg and Amsterdam, 1990; Am-

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sterdam and Hornig-Rohan, 1996) and others (Himmelhoch et al., 1991; Thase et al., 1992) have suggested that some TRD patients with unipolar or bipolar depression may demonstrate a preferential response to either a MAO inhibitor or a mixed serotonin/noradrenalin re-uptake inhibitor. Although there are some data to support the contention that these drug classes may be superior to conventional TCAs (Quitkin et al., 1979; Himmelhoch et al., 1991; Thase et al., 1992; Nierenberg et al., 1994), there is less information available on comparative efficacy of combination drug therapy (e.g., the addition of a TCA) in either MAO inhibitor or SSRI treatment failure.

In TRD patients for whom standard antidepressant therapy has failed, and in whom there is a substantial likelihood of morbidity and/or mortality from suicide, it is justified for physicians to take cautiously measured risks. In this context, the risk-to-benefit ratio for patients with treatment-resistant depression must extend beyond the issue of efficacy vs. side effects to include factors such as the risk of suicide and the relative risk of "therapeutic decrement" after repeated treatment failures (Amsterdam and Maislin, 1994; Amsterdam and Hornig-Rohan, 1996). While the use of drug combinations and augmentation strategies in TRD is not without potential risks, a more comprehensive understanding of the relative risk-to-benefit ratio of specific treatment strategies can result in an enhanced therapeutic outcome with fewer adverse events.

Clomipramine is a unique TCA which differs from conventional TCAs, and possesses substantial inhibition of serotonin (5HT) re-uptake (Carlsson et al., 1969). It has recently been shown to be of value in patients with TRD (Trimble, 1990). In fact, some investigators have suggested that augmentation with clomipramine may result in an enhanced efficacy of the existing antidepressant therapy (Pandy et al., 1991).

In the present report, we examined the comparative efficacy and safety of adding clomipramine to a failed trial of either (1) a MAO inhibitor or (2) fluoxetine in patients with TRD, and compared this treatment to (3) augmentation of a failed MAO inhibitor with a conventional TCA.

METHODS

SUBJECTS

Twenty outpatients with TRD from the Depression Research Unit at the Hospital of the University of Pennsylvania received clomipramine augmentation therapy: 14 women and 6 men with a mean (±SD) age of 42 ± 12 years (range 23 to 69 years). All patients met DSM-III-R criteria (American Psychiatric Association, 1988) for major depression and had moderate to severe symptoms with a Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) score ≥21 on the 20-item scale prior to initiating clomipramine augmentation. Demographic features are displayed in Table 1. All patients had previously failed to respond to at least a 6-week prospective trial of either a MAO inhibitor or fluoxetine (Amsterdam and Hornig-Rohan, 1996) immediately prior to clomipramine augmentation (Table 1). Patients with psychotic features or a diagnosis of schizophrenia, organic

TABLE 1. Patient characteristics and outcome for clomipramine (CMI) augmentation[a]

Patient no.	Age	Gender	No. prior trials	Last trial	Max CMI (mg) augmentation dose	Treatment outcome
1	40	M	13	MAOI	250	–
2	56	M	10	FLU	100	–
3	48	F	7	FLU	300	–
4	27	F	3	MAOI	25	s.e.
5	37	M	12	FLU	300	–
6	26	F	13	FLU	150	s.e.
7	36	F	4	MAOI	50	s.e.
8	47	F	3	FLU	250	+
9	56	M	8	FLU	300	–
10	56	F	5	MAOI	250	+
11	40	F	3	FLU	175	+
12	34	F	5	FLU	125	+
13	39	F	4	MAOI	25	–
14	45	F	2	FLU	200	–
15	23	F	2	MAOI	50	s.e.
16	42	F	3	FLU	50	+
17	69	F	16	MAOI	50	+
18	28	M	4	MAOI	100	s.e.
19	57	F	2	FLU	25	–
20	33	M	2	MAOI	25	s.e.

[a]*MAOI = monoamine oxidase inhibitor; FLU = fluoxetine; + = full response as defined in text; – = no or minimal response; s.e. = side effects necessitating cessation of trial.*

affective disorder, dysthymia, or characterologic disorder were not included.

Seven additional patients (3 women and 4 men) with a mean age of 41 ± 14 years (range 26 to 69 years) who had failed to respond to a previous MAO inhibitor trial, and who received augmentation with a conventional TCA, were also examined for comparison with the clomipramine augmentation groups (Table 2).

All patients had received a complete medical evaluation prior to augmentation therapy, and all were physically healthy and without meaningful laboratory test abnormalities.

PROCEDURES

A retrospective review of treatment outcome was conducted on patients who had either (1) clomipramine augmentation of a failed MAO inhibitor trial (n = 9) or (2) clomipramine augmentation of a failed fluoxetine trial (n = 11). These groups were then compared to (3) patients who received conventional TCA augmentation of a failed MAO inhibitor trial (n = 7). All patients were treated in an open, naturalistic fashion. Clomipramine augmentation was initiated at 25 mg daily and was gradually titrated upward (as tolerated) to a maximum daily dose of 300 mg. Patients who tolerated clomipramine augmentation remained on combination MAO inhibitor/clomipramine therapy for at least 4 additional weeks for assessment of treatment outcome. Clinical ratings were obtained for efficacy (Hamilton, 1960) with "response"' defined as a ≥50% reduction in the baseline HDRS score and a final HDRS score ≤9. In those cases where severe side effects necessitated discontinuation of treatment, appropriate documentation was obtained in order to determine the nature of the treatment-emergent adverse events.

STATISTICAL PROCEDURES

Because the data were derived from an open, unrandomized, naturalistic setting, we considered the sample to include all 27 subjects. Categorical variables were assessed using the chi-square or Fisher's Exact test (where appropriate). ANOVAs and unpaired *t*-tests were used to examine continuous variables. Statistical significance was set at the $P = 0.05$ level.

RESULTS

EFFICACY

ANOVAs demonstrated no difference in age ($F = 0.46$, df = 2,26; P = ns) or the number of prior drug trials ($F = 0.69$, df = 2,26; P = ns) across the three treatment groups. Two out of 9 patients (22%) taking a MAO inhibitor, and 4 out of 11 patients (36%) taking fluoxetine, responded to clomipramine augmentation (Fisher's Exact test, P = ns). Similarly, 3 out of 7 MAO inhibitor patients (43%) responded to augmentation with a conventional TCA (vs. 2 of 9 receiving clomipramine augmentation) (Fisher's Exact test, P = ns) (Tables 1 and 2). The mean daily clomipramine augmentation dose was 150 ± 90 mg (range 50 to 250 mg) in the responders and 136 ± 113 mg (range 25 to 300 mg) in the nonresponders ($t = 0.28$, df = 18, P = ns).

ADVERSE EVENTS

While most patients experienced some mild side effects from the addition of clomipramine to their existing drug therapy, only those adverse events that were severe enough to warrant cessation of treatment were considered for the purposes of statistical analysis (Table 3). Overall, 6 out of 9 patients (67%) receiving clomipramine augmentation experienced severe side effects. Five of these patients (56%) were taking a MAO inhibitor and received a mean daily clomipramine dose of 50 ± 31 mg (range 25 to 100 mg). Side effects were usually characterized by symptoms of serotonin syndrome (e.g., restlessness, agitation, anxiety, nervousness, diaphoresis, muscle fasiculations and myoclonic discharge, hyperreflexia, tremor, and occasionally mental confusion). One patients had symptoms severe enough to require hospitalization, while two others required immediate medical attention at a hospital emergency room. Serotonin-related side effects typically occurred within 4 to 48 h of adding clomipramine to the MAO inhibitor treatment, and in one subject symptoms began within 2 h of receiving a single 25-mg clomipramine tablet (Table 3). In contrast, only one of 11 patients (9%) receiving the combination of fluoxetine and clomipramine developed severe side affects (Fisher's Exact test, P = 0.05). Significantly, none of the patients who re-

TABLE 2. Patient characteristics and outcome for tricyclic-MAOI augmentation[a]

Patient no.	Age (years)	Gender	No. prior trials	Last trial	Max TCA augmentation dose (mg)	Treatment outcome
1	41	F	5	Phenelzine	DMI 200	–
2	37	M	6	Phenelzine	AMI 150	–
3	69	F	2	Phenelzine	DMI 150	+
4	44	F	4	Phenelzine	IMI 300	–
5	26	M	6	Tranylcypromine	DMI 200	+
6	38	M	2	Isocarboxid	DMI 150	+
7	33	M	3	Phenelzine	NTP 100	–

[a]*DMI = desipramine; NTP = nortriptylene; IMI = imipramine; + = full reponse as defined in text; – = no or minimal response.*

TABLE 3. Characteristics of patients who discontinued due to side effects[a]

Patient	Age (years)	Gender	MAO inhibitor	CMI dosage (mg)	Side effect	Outcome
1	27	F	TCP	25	5 HT syndrome	Hospitalized
2	26	F	FLU	150	Jittery/ hypersomnia	Recovered
3	36	F	ISO	50	5 HT syndrome	Emergency room
4	23	F	ISO	50	5 HT syndrome	Emergency room
5	28	M	TCP	50	5 HT syndrome	Recovered
6	33	M	ISO	25	5 HT syndrome	Recovered

[a]*TCP = tranylcypromine; ISO = isocarboxide; PLZ = phenelzine; FLU = fluoxetine.*

ceived TCA augmentation of their MAO inhibitor developed severe side effects or needed to discontinue the trial (Fisher's Exact test, $P < 0.05$).

Finally, a chi-square analysis was performed among the three augmentation treatment groups by the categories of (1) response, (2) nonresponse, and (3) severe side effects ($\chi^2 = 9.0$, df = 4, $P < 0.06$) (Table 4). While there did not appear to be a significant difference in efficacy among the three treatment groups, there was a significant difference in the rate of severe side effects with substantially more events observed in the MAO inhibitor/clomipramine treatment group ($\chi^2 = 8.9$, df = 2, $P < 0.05$).

DISCUSSION

As many as 30% of depressed patients fail to respond to treatment with a tricyclic antidepressant (TCA) and at least 60–75% may fail to achieve complete remission (Roose et al., 1986). In its broadest form, TRD may characterize the majority of depressed patients in therapy and substantially contribute to the overwhelming morbidity and mortality associated with this syndrome (Keller et al., 1982, 1986; Keller, 1988). The paucity of attention given to the systematic treatment of TRD has led to inconsistent and haphazard treatment approaches. Moreover, treatment algorithms suggesting the step-wise selection of medication with optimal dosage and duration of administration have often led to confusion regarding what constitutes "adequate" therapy for TRD. Thus, prior to the advent of SSRIs, treatment of MDD usually began with a TCA. Non-response rates were substantial (about 20–30%) with causes variously attributed to sub-optimal dosing and treatment length (Keller et al., 1982), variability in TCA metabolism (Glassman et al., 1977; Amsterdam et al., 1979), or inadequate drug concentrations (Asberg, 1976; Amsterdam et al., 1980). This scenario has not substantially changed with the introduction of SSRIs (Fava et al., 1994). While some clinicians have advocated switching from the failed antidepressant to another agent in a different chemical class (e.g., a TCA to a SSRI or MAO inhibitor), the empirical justification for this strategy is limited (Nystrom and Hallstrom, 1987; Nolen et al., 1988a,b). Moreover, there is also evidence that the use of high-dose therapy with some antidepressants may reverse what appears to be TRD without the necessity of switching to a new antidepressant (Amsterdam et al., 1979; Amsterdam, 1991; Fava et al., 1994).

More recently, SSRIs have been used in the treatment of TRD (Tyrer et al., 1987; Amsterdam and Maislin, 1994), and as adjunctive therapy in patients who have failed to respond to a TCA (Rosenthal et al., 1991). However, even after an adequate trial of fluoxetine at 20 mg daily for up to 3 months, remission rates (final HDRS score ≤7) were only 56% in patients with a prior history of TRD (Amsterdam and Maislin, 1994).

In lieu of TCAs and SSRIs for the treatment of TRD, some investigators have reported MAO inhibitors to be superior in many patients resistant to other antidepressants (McGrath et al., 1987; Nolen et al., 1988a; Amsterdam, 1991; Thase et al., 1992). But what does one do when a MAO inhibitor fails? In patients who do not respond to MAO inhibitor therapy,

TABLE 4. Rates of response and adverse events during CMI and TCA augmentation[a] (%)

	MAOI/CMI (n = 9)	FLU/CMI (n = 11)	MAOI/TCA (n = 7)
Responders	22 (2)	36 (4)	43 (3)
Nonresponders	22 (2)	55 (6)	57 (4)
Adverse events	56 (5)	9 (1)	0 (0)

[a]*CMI = clomipramine; FLU = fluoxetine; TCA= tricyclic antidepressant;* $\chi^2 = 9.0$, *df = 4*, P < *0.06.*

some investigators have suggested augmenting with an additional antidepressant like lithium, (Nelson and Byck, 1982), L-tryptophan (Pare, 1963), or the cautious administration of a TCA (Davidson, 1982; Amsterdam and Hornig-Rohan, 1996). However, concerns over drug interactions have limited the use of MAO inhibitor augmentation strategies.

In the present study, we examined the relative safety and efficacy of augmenting a failed fluoxetine or MAO inhibitor trial with adjunctive clomipramine, a potent re-uptake site inhibitor of 5HT (as well as NA). We then compared these treatment groups to a separate group of TRD patients receiving a MAO inhibitor, which was augmented with a conventional TCA (excluding clomipramine). We observed no overall difference in efficacy among the three treatment groups (χ^2 = 0.83, P = ns), although there were significantly more serious side effects observed in the MAO inhibitor/clomipramine group (56%) compared to the fluoxetine/clomipramine group (9%) (Fisher's Exact test, $P < 0.05$). Interestingly, there were no serious adverse events necessitating cessation of treatment in the MAO inhibitor/TCA group. Thus, we observed a substantial risk-to-benefit ratio for MAO inhibitor/clomipramine combination compared to that of MAO inhibitor/TCA combination to such an extent (Table 4) that we would suggest dropping clomipramine augmentation of a failed MAO inhibitor trial from treatment algorithms for TRD. In contrast, to the high side effect rate with MAO inhibitor/clomipramine therapy, we observed no adverse events severe enough to warrant treatment cessation with the MAO inhibitor/TCA combination. This observation comports well with earlier reports documenting the relative safety of this drug combination in TRD. In this regard, several investigators reported similar rates of side effects in patients taking a combination of MAO inhibitor/TCA compared to 150 patients receiving either a MAO inhibitor or TCA alone (Spiker and Pugh, 1976; Davidson et al., 1987). On the other had, the substantial number of potentially serious serotonin-related side effects resulting from clomipramine augmentation of a MAO inhibitor strengthens prior observations indicating that clomipramine is pharmacologically distinct from other TCAs and should not be viewed as a conventional TCA with relatively weak 5HT re-uptake inhibition (Insel et al., 1982). Reports of similar side effects as those experienced in the MAO inhibitor/clomipramine group have been reported with the addition of L-tryptophan (Glassman and Plattman, 1969) and, more recently, with fluoxetine (Beasley et al., 1993). These similarities in side effects between clomipramine and other 5HT enhancing compounds strongly suggest that the adverse events observed in the present study with MAO inhibitor/clomipramine augmentation result from enhancement of 5HT neurotransmission. Moreover, we observed this effect after a single, low dose of clomipramine in one patient, and similar observations have been reported with clomipramine (Insel et al., 1982) and fluoxetine (Beasley et al., 1993). Therefore, when assessing treatment options in TRD, the risk-to-benefit ratio of clomipramine augmentation should be carefully analyzed before adding clomipramine with extreme caution to an existing MAO inhibitor trial.

Several caveats should be considered in the interpretation of the present results. The use of MAO inhibitor/CMI combination in the present report was undertaken before the extreme dangers of this drug combination were generally appreciated. Although case reports of 5HT syndrome had been reported as early as the 1970s (Beaumont, 1973; Marley and Wozniak, 1984; Blackwell, 1991; Stern et al., 1992), there have been no systematic comparisons of patients treated with the combination of an MAO inhibitor plus CMI vs. an MAO inhibitor plus conventional TCA.

Additionally, there are obvious limitations to the naturalistic, retrospective design of this study. This factor, together with the lack of a comparable patient group receiving placebo augmentation places constraints upon the conclusions that can be drawn about the relative clomipramine efficacy of the three treatments for TRD. The use of a placebo control group might have enhanced the present study design, as a modest reduction in depressive symptomatology can be expected in some depressed patients treated with placebo. However, the use of a placebo control might raise ethical concerns in patients with TRD (Stanley, 1988). In addition, the limited sample size of each treatment cell detracts from the ability to distinguish statistical significance and limits the inferences that can be drawn from the present results.

The assessment of prior drug non-response, although made prospectively, was naturalistic in context and not part of a controlled drug trial. Consequently, documentation of the ''adequacy'' of prior drug therapy with either fluoxetine, a TCA or a MAO inhibitor must be considered as questionable in the absence of a prospective treatment study. Thus, it is possible that some of the patients characterized as TRD might have responded if they had prospectively received treatment. In the present study, we defined an "adequate" prior treatment to be at least 6 weeks. However, this time frame may have been too short to truly estimate a TRD status (Greenhouse et al., 1987). In this regard, prior studies (Georgotas et al., 1987; Greenhouse et al., 1987; Schweizer et al., 1990) suggest that a proportion of patients thought to have TRD may actually be responders with "pseudo-TRD."

In summary, we found no statistically significant difference in efficacy among the three treatment TRD groups. However, the combination of MAO inhibitor/clomipramine caused significantly more serious adverse events necessitating treatment cessation (56%) when compared to the fluoxetine/clomipramine (9%) (Fisher's Exact test, $P < 0.05$) or MAO inhibitor/TCA combination (0%). Finally, we observed a marginally

significant association ($P < 0.06$) between response and side effects among the three treatment groups, indicating that while there was not a significant difference in efficacy among the three treatment groups, there was a significant difference in the rate of severe side effects with substantially more events observed in the MAO inhibitor/clomipramine treatment group. The substantial risk of serotonin-related adverse events with clomipramine in combination with a MAO inhibitor strongly suggests that this drug combination be used with extreme caution in treating patients refractory to a MAO inhibitor alone.

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