CME

Combining Antidepressants for Treatment-Resistant Depression: A Review

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Objective: Many patients with depression remain poorly responsive to antidepressant monotherapy. One approach for managing treatment-resistant depression is to combine antidepressants and to capitalize on multiple therapeutic mechanisms of action. This review critically evaluates the evidence for efficacy of combining antidepressants.

Method: A MEDLINE search of the last 15 years (up to June 2001), supplemented by a review of bibliographies, was conducted to identify relevant studies. Criteria used to select studies included (1) published studies with original data in peer-reviewed journals, (2) diagnosis of depression with partial or no response to standard treatments, (3) any combination of 2 antidepressants with both agents used to enhance antidepressant response, (4) outcome measurement of clinical response, and (5) sample size of 4 or more subjects.

Results: Twenty-seven studies (total N = 667) met the inclusion criteria, including 5 randomized controlled trials and 22 open-label trials. In the 24 studies (total N = 601) reporting response rates, the overall mean response rate was 62.2%. Methodological limitations included variability in definitions of treatment-resistant depression and response to treatment, dosing of medications, and reporting of adverse events.

Conclusion: There is limited evidence, mostly in uncontrolled studies, supporting the efficacy of combination antidepressant treatment. Further randomized controlled trials with larger sample sizes are required to demonstrate the efficacy of a combination antidepressant strategy for patients with treatment-resistant depression.

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Despite the number of available and effective antidepressants, many patients continue to respond poorly to treatment. It is well recognized that up to 50% of depressed patients have an inadequate response to antidepressant monotherapy,[1–3] and as many as 20% have chronic courses, remaining depressed despite multiple interventions.[4,5]

Unfortunately, there is still little consensus about the definition and characterization of refractory, or treatment-resistant, depression.[1,3,6] Varying opinions on treatment adequacy, as indicated by dose, duration, number and type of previous trials, and treatment sequencing, have resulted in a lack of consensus on formal operational criteria for response.[7–9] Consequently, it is difficult to compare treatment studies for patients with treatment-resistant depression (TRD). For consistency, the term *TRD* will be used in this review to denote any partial response or nonresponse to antidepressant treatment.

Optimizing antidepressant use by ensuring that patients receive an adequate dose for an adequate length of time is usually the first recommended strategy for managing poor response.[10] Beyond optimization, however, there is limited evidence to guide clinical decisions in managing TRD. Medication strategies include switching to another antidepressant, both within class and not, augmenting the antidepressant with a medication that itself does not have

an antidepressant effect (e.g., lithium or triiodothyronine), or combining with another recognized antidepressant.[10]

Combining antidepressants for patients with TRD was first described in the early 1960s with monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs).[11] Clinicians were often reluctant to combine older antidepressants, however, because the compounds either had similar mechanisms of action (e.g., combining 2 TCAs) or had potentially hazardous interactions (e.g., MAOI + TCA combinations). More recently, antidepressants with very distinct neurochemical actions have become available. Combining these antidepressants allows the possibility of enlisting multiple therapeutic mechanisms of action to achieve clinical response in patients who have not responded to a single-mechanism medication.

Beyond the possibility of a synergistic effect, combination antidepressant treatment has other potential advantages when compared with switching to another monotherapy. Continuing the first medication means that the patient avoids possible discontinuation symptoms and the demoralizing aspects of "giving up" on the first medication. The addition of another antidepressant can build on a partial response by targeting specific residual symptoms. It may be possible to use lower doses of each antidepressant, thereby decreasing the overall side effect burden. A second drug may "treat" or improve some side effects associated with the first drug. It is also possible that adding a second drug may result in a faster onset of response than switching to another monotherapy.

There are also potential disadvantages to combination treatment. A clinical maxim is to use the simplest treatment whenever possible; a single drug regimen is simpler than polypharmacy. When combining antidepressants, one can never be sure that the patient would not simply respond to monotherapy with the second agent. Using 2 or more medications may reduce compliance, lead to additive side effects, or result in drug-drug interactions. In addition, the cost of combination treatment may be higher than that of monotherapy.

Regardless of these potential disadvantages, strategies involving multiple medications, or polypharmacy, appear to increasingly be used for the management of TRD. The objective of this article is to review the evidence for the efficacy of antidepressant combinations in patients with TRD resistant to monotherapy, focusing on the newer, novel-action antidepressants.[12]

METHOD

A computerized search on MEDLINE was performed of all literature published in English in the last 15 years up to June 2001 using the Medical Subject Heading terms *combination therapy*, *antidepressive agents*, and *depressive disorders*, as well as any variant of the words *combination*, *treatment-resistant*, and *refractory*. The bibliographies of relevant articles were also manually searched. Articles were included if they met the following criteria: (1) published studies with original data in peer-reviewed journals; (2) involved patients with a diagnosis of major depressive disorder who had partial or no response to standard treatments; (3) described a combination of 2 antidepressants where both agents were used to enhance antidepressant response, and not just to treat side effects; (4) used an outcome measurement of clinical response; and (5) had a sample size of 4 or more subjects. The data were extracted systematically and categorized into specific combination categories.

RESULTS

Overall, 27 studies were identified (Table 1) involving a total of 667 patients. In 14 studies, patients had at least 2 unsuccessful trials of antidepressant monotherapy and/or 1 trial plus augmentation; the rest included patients with only 1 failed trial. The most frequently employed outcome measures were the Hamilton Rating Scale for Depression (HAM-D) and the Clinical Global Impressions scale (CGI). The Montgomery-Asberg Depression Rating Scale (MADRS) was used in 3 studies, while in 7 studies only subjective impressions were used to assess response. A positive response was usually defined as a 50% reduction in HAM-D or MADRS score from baseline, a statistically significant reduction in the depression scores, or 2 levels of improvement in the CGI. Marked response or remission rates were also included in 6 studies that defined more stringent criteria for response. These criteria included either a longer period of sustained improvement (5 weeks to 6 months) or posttreatment HAM-D scores within the normal range (i.e., 7 or less). Results from each combination category are summarized.

MAOI + TCA

The MAOI plus TCA combination for patients with TRD has been described in an open trial[13] and a retrospective case series.[14] In these studies, greater than 70% of the 106 patients reported clinical improvement, with side effects similar to those seen with monotherapy. A later study[15] reported that 12 (48%) of 25 patients with TRD responded to an acute trial of isocarboxazid plus amitriptyline. This study was one of the few studies reporting longer-term outcome: a 3-year follow-up found that only 6 of 12 patients continued to respond to the combination. In a naturalistic study of nonresponders to MAOIs,[16] only 5 (31%) of 16 patients responded to MAOI plus TCA combination. Moreover, in patients treated with MAOI plus clomipramine, 6 of 9 had severe serotonergic side effects that required discontinuation of treatment. In the same study,[16] a cohort of patients treated with fluoxetine

Table 1. Summary of Combination Antidepressant Studies[a]

Study	N	Design/Sample	Drug/Dose (mg/day)	Outcome Measure/ Response Criteria	Results/Comments[b]
MAOI + TCA					Overall Response: 75/135 (56%)
Amsterdam et al, 1997[16]	27	Open trial; NR; MAOI/CMI = 9, FLU/CMI = 11, MAOI/TCA = 7	CMI = 25–300, DMI, AMI, IMI; NTP = 100–300; MAOI = TD	≥ 50% reduction in the baseline HAM-D and a final HAM-D score ≤ 9	Responded: 5/16, MAOI/CMI = 2/9, MAOI/TCA = 3/7; D/C due to SEs: MAOI/CMI = 5/9, MAOI/TCA = 1/7
Berlanga and Ortega-Soto, 1995[15]	25	Open trial; NR	Mean dose: ISO = 28; AMI = 132	≥ 50% reduction in the baseline HAM-D and a score of 1 or 2 in the PGI-RS	Responded: 12/25; D/C due to SEs: 5/25; at 36 mo: 6/12 required maintenance combination therapy
Davidson et al, 1978[17]	17	RCT; Bilateral ECT = 9; AMI/PHE = 8	Mean dose: AMI = 71; PHE = 34; ECT = 5.4 treatments	Statistically significant change in HAM-D, BDI, SAI; plasma levels	ECT > AMI/PHE[c]
Schmauss et al, 1988[14]	94	Case series; NR	TCP (mean) = 13; TCA = TD	Subjective clinical criteria	Responded: 64/94
Sethna, 1974[13]	12	Open trial; AMI/PHE = 12	PHE = 45; AMI = 75 (50 for 2 intolerant patients)	Statistically significant reduction in HAM-D, HAM-A; clinical impressions	AMI/PHE > Previous treatments[d]; 9/12 required maintenance combination therapy
SSRI + TCA/HCA					Overall Response: 85/139 (61%)
Amsterdam et al, 1997[16]	27	Open trial; NR; MAOI/CMI = 9, FLU/CMI = 11, MAOI/TCA = 7	CMI = 25–300, DMI, AMI, IMI; NTP = 100–300, FLU = TD	≥ 50% reduction in the baseline HAM-D and a final HAM-D score ≤ 9	Responded: 4/11; D/C due to SEs: 1/6
Fava et al, 1994[24]	41	RCT; blinded; NR; ↑FLU = 15, FLU/DMI = 12, FLU/LI = 14	↑FLU = 40–60, DMI = 25–50, LI = 300–600, FLU = 20	A final HAM-D score ≤ 7; plasma levels	Responded: FLU/CMI = 3/12, ↑FLU = 8/15, FLU/LI = 4/14; plasma levels did not predict response
Levitt et al, 1999[23]	13	Open trial; NR	DMI/IMI (mean) = 70, FLU (mean) = 44	≥ 40% reduction in the baseline HAM-D; CGI-S, plasma levels	Responded: 7/13; plasma levels may predict response in combination treatments
Seth et al, 1992[26]	8	Case series; NR	NTP = 25–75, SRT = 50–100, FLU = 20	≥ 3 levels decrease and a final value of ≤ 3 in CGI-S	Responded: 8/8
Weilburg et al, 1989[19]	30	Case series; NR	IMI equivalents = 0–250, FLU = 20–60	Subjective clinical criteria	Responded: 26/30; 8/12 required maintenance combination therapy
Weilburg et al, 1991[20]	20	Open trial; NR	DMI/NTP = 10–50, FLU = 20–40	≥ 2 levels decrease in CGI-S and a final CGI-S of ≤ 2	Responded: 13/20; overall, response was rapid and sustained (at least 6 wk)
Zajecka et al, 1995[27]	25	Open trial; NR + PR	Mean dose: HCA = 113, FLU = 73	≥ 50% reduction in HAM-D and a final CGI-I of ≥ 2	Responded: 12/25; 5/12 are partial responders with further improvement
Nierenberg et al, 1992[28]	8	Case series; PR	Mean dose: FLU = 32, TRZ = 97	Subjective clinical criteria	Responded: 3/8
SSRI + SSRI					Overall Response: 12/13 (92%)
Bondolfi et al, 1996[29]	7	Open trial; NR	CIT = 40, FLV = 50–100	≥ 50% reduction in MADRS and a final score ≤ 13; plasma levels	Responded: 6/7; FLV stereo-selectively increases plasma concentrations of S-CIT vs R-CIT
Hunchak, 1997[30]	6	Case report; NR	Various SSRIs = TD	Subjective clinical criteria	Responded: 6/6; overall, response was rapid and sustained (> 9 mo for some)

continued

Table 1. Summary of Combination Antidepressant Studies[a] (cont.)

Study	N	Design/Sample	Drug/Dose (mg/day)	Outcome Measure/ Response Criteria	Results/Comments[b]
RIMA + TCA					Overall Response: 13/23 (57%)
Konig and Wolfersdorf, 1997[36]	23	Open trial; NR	Mean dose: TMI = 179, AMI = 150, MAP = 100, MIA = 78, MOC = 30	≥ 50% reduction in HAM-D; BPRS	Responded: 13/23
RIMA + SSRI					Overall Response: 14/30 (47%)
Hawley et al, 1996[35]	19	Open trial; NR	MOC = 150–600, FLU, PXT = 20	MADRS final score ≤ 11; CGI-S, CGI-I	Responded: 6/19; D/C due to SEs: 4/19
Joffe and Bakish, 1994[31]	11	Open trial; NR	MOC = 452, SRT = 125, FLV = 130	Subjective clinical criteria	Responded: 8/11 (some remissions)
BUP + SSRI/SNRI (venlafaxine)					Overall Response: 35/46 (76%)
Bodkin et al, 1997[38]	27	Case series; PR	Mean dose: BUP = 243, FLU = 31	Subjective clinical criteria	Responded: 19/27; D/C due to SEs: 4/27
Kennedy et al, 2002[41]	18	Open trial; NR + PR	BUP = 150; Mean dose: VEN = 244, FLU = 44, PXT = 45, SRT = 125	Statistically significant reduction in HAM-D and CGI; Sex-Fx; plasma levels	Responded: 15/18; Improvement in sexual function; Increase in mean VEN levels
Marshall and Liebowitz, 1996[39]	4	Open trial; NR	BUP = 300–450, SRT = 50–150	Subjective clinical criteria	Responded: 4/4
Spier, 1998[40]	25	Open trial; NR + PR	Mean dose: BUP = 230, FLU = 20, SRT = 55, PXT = 25, VEN = 131	≥ 2 levels decrease in CGI sustained for ≥ 3 mo	Responded: 12/15; overall, response was sustained for > 3 mo
NRI (reboxetine) + SSRI					Overall Response: 4/4 (100%)
Devarajan and Dursun, 2000[42]	4	Case report; NR	CIT = 20–60, REB = 4–6	≥ 50% reduction in HAM-D	Responded: 4/4
NaSSA + TCA					Overall Response: N/A
Medhus et al, 1994[49]	37	RCT; blinded; NR; TCA/placebo = 19, TCA/MIA = 18	AMI, CMI, NTP, DOX, TMI, IMI = 75–225, MIA = 30–60	Statistically significant reduction in MADRS and GAS	Responded: TCA/MIA > TCA/placebo[e]
NaSSA + SSRI					Overall Response: 37/62 (60%)
Ferreri et al, 2001[47]	104	RCT; blinded; MIA/placebo = 34, MIA/FLU = 32, FLU/placebo = 38	MIA = 60, FLU = 20	≥ 50% reduction in HAM-D and a final score ≤ 8; HARD; modified CGI-I	Responded: 20/32; D/C due to SEs: 7/32; greater response and lower adverse effects for combination than switching
Maes et al, 1999[46]	31	RCT; blinded; FLU/placebo = 11, FLU/PIN = 10, FLU/MIA = 10	FLU = 20, PIN = 7.5, MIA = 30	≥ 50% reduction in HAM-D; rapid onset is ≥ 4 decrease in HAM-D	Responded: 6/10; response was most rapid for MIA/FLU
Carpenter et al, 1999[45]	20	Open trial; NR	MIR = 15–30, SSRIs, VEN, DMI/BUP, or SSRI/VEN = TD	Final CGI-I ≥ 2	Responded: 11/20; D/C due to SEs: 3/11
SNRI (venlafaxine) + TCA					Overall Response: 9/11 (82%)
Gómez Gómez and Perramón, 2000[50]	11	Open trial; PR	Mean dose: IMI = 217, CMI = 202, VEN = 192	≥ 50% reduction in HAM-D and reduction in CGI-S for > 6 mo; plasma levels	Responded: 9/11; full remission: 7/11; minimal change in TCA levels

[a]Abbreviations: AMI = amitriptyline, BDI = Beck Depression Inventory, BPRS = Brief Psychiatric Rating Scale, BUP = bupropion, CGI = Clinical Global Impressions scale, CGI-I = CGI-Improvement scale, CGI-S = CGI-Severity of Illness scale, CIT = citalopram, CMI = clomipramine, D/C = discontinued, DMI = desipramine, DOX = doxepin, ECT = electroconvulsive therapy, FLU = fluoxetine, FLV = fluvoxamine, GAS = Global Assessment Scale, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression, HARD = Humeur–Angoisse–Ralentissement–Danger [Mood–Anxiety–Retardation–Depression] diagram scale, HCA = heterocyclic antidepressant, IMI = imipramine, ISO = isocarboxazid, LI = lithium, MADRS = Montgomery Asberg Depression Rating Scale, MAOI = monoamine oxidase inhibitor, MAP = maprotiline, MIA = mianserin, MIR = mirtazapine, MOC = moclobemide, NaSSA = noradrenergic and specific serotonergic antidepressant, NR = nonresponse, NRI = norepinephrine reuptake inhibitor, NTP = nortriptyline, PGI-RS = Patient Global Impression Rating Scale, PHE = phenelzine, PIN = pindolol, PR = partial responders, PXT = paroxetine, RCT = randomized controlled trial, REB = reboxetine, RIMA = reversible inhibitor of monoamine oxide type A, SAI = State Anxiety Inventory, SEs = side effects, Sex-Fx = Sexual Function Questionnaire, SNRI = serotonin-norepinephrine reuptake inhibitor, SRT = sertraline, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TCP = tranylcypromine, TD = therapeutic dose, TMI = trimipramine, TRZ = trazodone, VEN = venlafaxine. Symbol: ↑ = increased dose (of FLU).

[b]Evaluable patients were included in either the efficacy analysis or intent-to-treat population (last observation carried forward).

[c]$p < .02$. [d]χ^2 test significance at 5%. [e]$p = .01$.

plus clomipramine had a response rate of 36% (4 of 11 patients). In the only randomized controlled trial that examined MAOI plus TCA combinations,[17] patients with TRD randomly assigned to 4 to 10 treatments of bilateral electroconvulsive therapy (ECT) had significantly more rapid and greater improvement in HAM-D, Beck Depression Inventory (BDI), and State Anxiety Inventory (SAI) scores than those who received combination phenelzine and amitriptyline. Low doses of amitriptyline (mean = 71 mg/day) and phenelzine (mean = 34 mg/day) were administered due to concerns of tolerability in some patients, and although a 78% inhibition of MAOI was achieved in the drug group (64%–97%), none of the patients had achieved therapeutic plasma tricyclic levels.[17]

SSRI + TCA/HCA

Early studies examining β-adrenergic receptors predicted the possibility that fluoxetine may potentiate response to desipramine by accelerating β-adrenergic receptor down-regulation, thereby enhancing serotonergic activity.[18] This combination was first reported as a retrospective case series and subsequently in open trials.[19–21] In total, 73 (65%) of 112 patients were classified as responders in these open studies. In one report,[19] responders to the combination showed relapse when one of the antidepressants was discontinued, but responded again when the medication was restarted. In general, the combinations have been well tolerated.

Since selective serotonin reuptake inhibitors (SSRIs) can inhibit cytochrome P450 isoenzymes that metabolize TCAs, some investigators have suggested that the higher response rates to this combination treatment are due to SSRI-induced elevation in plasma levels of the TCA.[22] In one open study,[23] significant increases in plasma desipramine levels were found after fluoxetine addition, in some cases 2.5 times higher than one would expect, even with average desipramine doses of no more than 38 to 68 mg/day. Additionally, higher plasma TCA levels were seen in responders compared with partial responders and nonresponders, and a significant correlation was found between depression scores and TCA levels in the responders to combination treatment.[23]

In the only randomized controlled trial involving this combination,[24] 41 patients who had less than 50% reduction in HAM-D score and a score of 10 or more after 8 weeks of fluoxetine, 20 mg/day, were randomly assigned to 4 weeks of treatment with 40 to 60 mg/day of fluoxetine, 20 mg/day of fluoxetine plus 25 to 50 mg/day of desipramine, or 20 mg/day of fluoxetine plus 300 to 600 mg/day of lithium. The high-dose fluoxetine group had superior response rates (50%) compared with the desipramine combination (25%) and the lithium augmentation (25%). It was suggested that the poor response was due to doses of desipramine inadequate to achieve therapeutic levels.[25] However, open trials have found therapeutic plasma levels of desipramine and good response rates at doses of 38 to 68 mg/day.[23] In an earlier report,[21] clinical improvement was detected even when differences in desipramine levels between the combination and monotherapy were not significant. In fact, 2 weeks after fluoxetine addition, higher serum levels of desipramine were actually associated with less favorable HAM-D and CGI ratings.[21]

In separate studies, clomipramine and nortriptyline have also been combined with SSRIs to enhance response in patients with TRD with beneficial results.[16,26] Side effects were generally mild, but 1 patient treated with clomipramine developed severe side effects suggestive of serotonin syndrome.[16] A number of TCAs were combined with fluoxetine in 25 patients who had not adequately responded to at least 4 weeks of fluoxetine treatment; the response rate with combined treatment was 35%.[27] Of these patients, 71% had not responded to previous monotherapy with the same TCA that they responded to when combined with fluoxetine.

The heterocyclic antidepressant (HCA) trazodone was combined with fluoxetine in a small sample (N = 8) of patients who reported fluoxetine-associated insomnia or partial response to fluoxetine.[28] Only 3 of 8 patients showed sustained improvement; the remainder either had no response or were unable to tolerate the combination.[28] The poor response may be due to the low doses of trazodone used, as only 3 patients received doses greater than 100 mg/day.

SSRI + SSRI

Patients who are partial responders or who are intolerant to high doses of an SSRI may benefit from the addition of another SSRI. Rather than losing any potential gains by switching to another SSRI, adding the second SSRI may help therapeutic response without adding to the side effect burden. There are 2 reports of dual SSRI combinations.[29,30] In the first,[29] for patients who had no response to 3 weeks of citalopram at 40 mg/day, fluvoxamine, 50 to 100 mg/day, was added. Six (85.7%) of the 7 patients responded to this combination by the third week. Some patients exhibited minor side effects such as nausea and tremor, but generally the combination was well tolerated. In the second report,[30] 6 patients who had not responded to an SSRI showed a positive response within 2 weeks to the addition of a second SSRI.

RIMA + SSRI/TCA

Irreversible MAOIs are associated with potentially fatal interactions with dietary tyramine and serotonergic medications such as SSRIs.[31,32] Moclobemide, a reversible inhibitor of monoamine oxidase A (RIMA), does not require the same dietary restrictions as the MAOIs, although it may have the same potential for serotonin syndrome when combined with serotonergic drugs. Placebo-

controlled studies, however, have shown no serious adverse effects when moclobemide and SSRIs are carefully administered.[33,34] In one case series,[31] 8 of 11 patients who were resistant to treatment with SSRIs responded after the addition of moclobemide, 150 to 800 mg/day. The combination was well tolerated with few side effects and no serious adverse events. However, another study (N = 19) using similar doses found that RIMA plus SSRI combinations resulted in high rates of side effects, including 1 patient with symptoms suggestive of serotonin syndrome.[35] These side effects limited the overall response rate to 32%.

Moclobemide has also been used in combination with trimipramine, amitriptyline, and maprotiline to treat TRD in an open trial.[36] Thirteen (57%) of 23 patients responded to the combination; however, 65% of the patients were also receiving medium- or high-potency antipsychotics or benzodiazepines.

Bupropion + SSRI/Venlafaxine

Although the mechanism of action of bupropion is not well understood, it is known to modulate norepinephrine activity and weakly inhibit dopamine reuptake.[37] This novel mechanism of action provides a rationale for combining it with SSRIs. Two case series (total N = 31)[38,39] have examined the effectiveness of the combination. Both studies found the combination to be superior to monotherapy with an average response rate of 74%. However, only 5 of the total 31 patients were nonresponders to previous separate trials of both bupropion and an SSRI; the rest were partially responsive to at least 1 of the 2 agents. Side effects encountered for both studies were similar, but there were some clear differential effects that were specific to each drug type. It appears that the energy level, cognition, and motivation were substantially improved with bupropion, either in combination with SSRIs or alone.[38] Conversely, anxiety and obsessive-compulsiveness were target symptoms preferentially improved by the SSRIs.[38]

Two additional studies involved bupropion plus SSRI or bupropion plus venlafaxine (a serotonin-norepinephrine reuptake inhibitor [SNRI]) combinations.[40,41] In the first study, 15 patients with an inadequate response to an SSRI, venlafaxine, or bupropion monotherapy, and 10 patients who were intolerant of SSRI side effects despite positive response received combination treatment. Eighty percent of patients in the former group exhibited a response as defined by 2 or greater levels of improvement on the CGI, while only 20% in the latter group experienced resolution of their side effects.[40] In the second study,[41] 18 patients received combination therapy with bupropion sustained release after showing inadequate response and unacceptable sexual dysfunction following a minimum of 6 weeks of treatment with an SSRI or venlafaxine. Fifteen (83%) of 18 partial or nonresponders reported a clinically significant benefit, while 6 (33%) of 18 patients achieved full remission (defined as 17-item HAM-D score of 7). Plasma monitoring data indicated a 3-fold increase in venlafaxine but not in SSRI levels after adding bupropion, which suggests an effect of bupropion sustained release on the pharmacokinetics of venlafaxine but not SSRIs.[41]

Reboxetine + SSRI

A small preliminary report[42] examined the combination of reboxetine, a norepinephrine reuptake inhibitor (NRI), with citalopram, an SSRI. All 4 patients who were unresponsive to a number of treatments, including ECT, responded to the combination, which was also well tolerated. Although this combination strategy appears very similar in mechanism to an SNRI (venlafaxine), its side effect profile may be different.

NaSSA + SSRI/TCA

Mianserin (not available in North America) and mirtazapine are related medications known as noradrenergic and specific serotonergic antidepressants (NaSSAs). These drugs antagonize presynaptic α_2-adrenoceptor activity, thereby enhancing noradrenergic neurotransmission via autoreceptor antagonism and enhancing serotonergic neurotransmission via heteroreceptor antagonism.[43] Mirtazapine also blocks postsynaptic 5-HT_2 and 5-HT_3 receptors. It has been postulated that this α_2-adrenoceptor antagonism may complement the action of serotonin and norepinephrine reuptake inhibitors to achieve greater clinical response.[44] In an open study of mirtazapine combinations,[45] 20 patients not achieving adequate response to at least 4 weeks of treatment with high doses of standard antidepressants had mirtazapine added. After 4 weeks, 55% of the patients were responders, and 15% discontinued due to side effects.

Two randomized controlled trials[46,47] examined mianserin combined with fluoxetine. In both instances the addition of mianserin to fluoxetine significantly enhanced and accelerated clinical response compared with fluoxetine alone. In the smaller study,[46] 31 patients who were unresponsive to a prior adequate trial of an antidepressant were randomly assigned to receive fluoxetine, 20 mg/day; fluoxetine, 20 mg/day, plus pindolol, 7.5 mg/day; or fluoxetine, 20 mg/day, plus mianserin, 30 mg/day. Sixty percent of patients responded to fluoxetine plus mianserin treatment compared with 9% to fluoxetine alone.[46] Using a higher dose of mianserin (60 mg/day), the second randomized controlled trial[47] involved a double-blind design with 3 parallel groups. One hundred four depressed patients who had not responded to at least 6 weeks of treatment with fluoxetine at 20 mg/day were randomly assigned to switch to mianserin (N = 34), add mianserin to fluoxetine (N = 32), or continue the fluoxetine (N = 38) for a further 6 weeks. This study design ensures that any superiority of combination treatment is not due solely to the second agent alone. The combination mianserin/

fluoxetine group had significantly greater reduction in HAM-D scores compared with the fluoxetine alone group. Response rates were also numerically greater in the mianserin plus fluoxetine group (63%) than in the mianserin alone (49%) and fluoxetine alone groups (37%), but these comparisons did not reach statistical significance.[47] Combination treatment was also as well tolerated as monotherapy. Moreover, the increased response of the combined treatment was not likely due to pharmacokinetic interaction between mianserin and fluoxetine, as neither drug increases the plasma level of the other during coadministration.[48]

Combinations of mianserin and TCAs may also be beneficial in patients with TRD. In a randomized controlled trial,[49] 37 patients with no response to various TCAs at doses of at least 150 mg/day were randomly assigned to either TCA plus placebo or TCA plus mianserin, 60 mg/day. The mianserin plus TCA group had significantly lower MADRS scores at completion than the TCA alone group ($p = .01$), while there were no significant differences in adverse effects. Unfortunately, response rates were not reported in this study.

Venlafaxine + TCA

A preliminary case series[50] was reported for the SNRI venlafaxine combined with TCAs in depressed patients who had achieved only partial remission to TCAs alone. The serum levels of TCAs were maintained at greater than 250 ng/mL for 2 months in most patients before 75 to 300 mg/day of venlafaxine was added. Nine (82%) of 11 patients had a positive response, while 7 (64%) of 11 achieved full clinical remission. Tolerability was good, but venlafaxine was used in low doses (75–150 mg/day) in 5 of the 11 patients.

DISCUSSION

This review highlights the limitations of the evidence base for efficacy of combination antidepressant treatment. There are very few randomized controlled trials (3 of which involve mianserin, currently not available in North America), and sample sizes are small. Most studies use open-label treatment so that nonspecific or placebo effects cannot be ruled out. There may also be publication bias, in that open studies with positive results are more likely to be submitted and published than those with negative results. Additionally, the study samples consisted of patients with different definitions of treatment resistance and different treatments prior to the combination. The studies also use different outcome measures and definitions of clinical response. Finally, the dose and duration of drugs used in combination treatment are also highly variable between studies. All of these factors make it difficult to compare a particular combination treatment with monotherapy, with validated treatments such as lithium or triiodothyronine augmentation, or with other combinations. Also, ECT should always be considered in any algorithm for TRD, given the ample evidence for efficacy in refractory populations, as well as its superiority over combined MAOI plus TCA in 1 early randomized controlled trial.[17]

Due to these limitations, combining antidepressants cannot be recommended as a first-line treatment for TRD. However, given that the overall response rate (liberally defined), summing all studies, is in the range of 60% and that combination antidepressants are generally well tolerated with sustained beneficial effects in some patients who have been unresponsive to monotherapy, it is likely that some patients may do well with combination treatment. Unfortunately, the scarcity of data comparing combination treatment with other medication strategies (e.g., switching, augmentation) makes it impossible to address when, or which, combination treatment should be applied in the sequencing of treatments for management of TRD. Furthermore, there are no existing data that address whether combination treatment is required for the maintenance phase of treatment, and if it is, the optimal duration of maintenance. Hence, the decision to employ a particular combination must be based on an evaluation of the individual patient's clinical status, including an assessment of the possible benefits and risks of using a combination versus those of alternative strategies.

If antidepressants are combined, the clinician must monitor for additive side effects and be aware of potential drug-drug interactions, especially when using medications that affect the cytochrome P450 system. Some SSRI plus TCA combinations, for example, may lead to elevated plasma TCA levels that can result in cardiotoxicity, seizures, or delirium.[51] Starting with low TCA doses and regularly monitoring plasma TCA levels are important when using this combination. Other combinations (for example, the use of moclobemide + SSRI) require close monitoring for symptoms of serotonin syndrome.

Given the high rates of inadequate response to current treatments for depression, it is important to better evaluate the efficacy of combination antidepressant treatment. Future randomized controlled trials should incorporate study designs that are most likely to determine efficacy versus monotherapy with the second drug. For example, an optimal design requires at least 3 parallel treatment groups: first drug plus placebo, first drug plus second drug, and second drug plus placebo. Ensuring adequate statistical power to detect small but clinically important differences between conditions requires very large sample sizes; these types of studies can usually be conducted only in multicenter clinical research networks.[52] A crossover phase (from the first drug to the second drug and vice versa) may provide additional data on the relative efficacy of switching versus combination strategies, and studies of longer duration may provide relevant insight into the long-term outcomes of combination treatment. Other

methodological suggestions to enhance comparisons of studies include using standardized assessments of prior treatment (e.g., the Antidepressant Treatment History Form[9]), a consistent definition of response, and systematic evaluation of adverse events.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin and others), citalopram (Celexa), desipramine (Norpramin and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), mirtazapine (Remeron), nortriptyline (Pamelor and others), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), tranylcypromine (Parnate), trimipramine (Surmontil), venlafaxine (Effexor).

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