Review

Combination pharmacotherapy in unipolar depression

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It is estimated that between 60 and 80% of those with major depressive disorder do not achieve full symptomatic remission from first-line antidepressant monotherapy. Residual depressive symptoms substantially impair quality of life and add to the risk of recurrence. It is now clear that depression would benefit from more vigorous treatment, in order to ameliorate its disease burden. While there are established algorithms in situations of treatment resistance, the use of combination pharmacotherapy in unipolar depression is a relatively under-investigated area of treatment and may be an effective and tolerable strategy that maximizes the available resources. This paper reviews the current evidence for combination pharmacotherapy in unipolar depression and discusses its clinical applications.

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Depressive disorders are increasingly recognized as a major cause of illness burden in the modern world. In the WHO Global Burden of Disease study in 2000, the 12-month prevalence of depression was estimated at 5.8% for men and 9.5% for women, and unipolar depression was the leading cause of disease burden in terms of years lived with disability (YLD) [1]. Both the early age of onset and the chronic, recurrent course of major depressive disorder contribute to its heavy burden. A large-scaled national epidemiological study from the USA reported a mean age of 30.4 years for the onset of major depressive disorder, a mean of 4.7 episodes in the course of a lifetime and a median duration of 24.3 weeks for the longest episode [2]. Despite its magnitude and impact, major depressive disorder remains under-diagnosed and under-treated, with an estimate of over half of the cases being untreated [3]. Vos and colleagues, using a simulation model, demonstrated that optimal episodic treatment and long-term maintenance treatment of major depressive disorder could significantly alleviate the disease burden [4]. However, most of those with major depressive disorder, between 60 and 80%, are not expected to achieve full symptomatic remission from first-line antidepressant monotherapy [5]. There is clearly a need for a more aggressive treatment approach, incorporating all aspects of the biopsychosocial framework to address the heterogeneous and pleomorphic nature of depression.

From a psychopharmacological viewpoint, the treatment algorithm after unsuccessful antidepressant monotherapy has been poorly substantiated by evidence base, even though this scenario is commonly encountered in clinical practice. This may be partly explained by the exclusion of treatment-resistant depression from most antidepressant clinical trials [6], the wide variability of clinical practice, and the evidence base that is heavily weighted to registration type trials that favor monotherapeutic strategies. Nevertheless, research into combination and augmentation therapies is gathering momentum, fuelled by increasing interest in the neurobiology of depression and more sophisticated selection of psychopharmacological agents based on their specific neuropharmacological actions.

This paper aims to review the current evidence for combination therapy in unipolar major depression. The scope is limited to discussion of unipolar depression, as bipolar

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depression is regarded as a separate entity, the treatment of which, especially the role of antidepressants [7], requiring different considerations. Combination pharmaco-psychotherapy is also a treatment option for the acute and maintenance phases of depression [8], but is not the focus of the current review. The term combination therapy often describes the concomitant use of two or more antidepressants, and is differentiated from augmentation therapy, which refers to the addition of a nonantidepressant pharmacological agent to an antidepressant with the goal of enhancing the antidepressant effect [9]. Such distinction, based on the artificial categorization of psychopharmacological agents into classes according to their main indications, is at risk of becoming meaningless in the face of current trends towards a more precise classification based on pharmacodynamic profiles. In this paper, both strategies are discussed under the broad heading of combination therapy. Specifically, only antidepressant combinations and antidepressant-atypical antipsychotic combinations will be discussed, as they mirror the emerging clinical trends, yet are poorly explored in research, and as augmentation strategies, such as lithium, triiodothyronine and β-blockers already have an established literature base.

Methods

A search of the published literature up to February 2006 was conducted using PubMed. Key terms used in various combinations were major depressive disorder, major depression, unipolar depression, depression, treatment-resistant depression, refractory, combination therapy, combination, polypharmacy, antidepressant combinations, antidepressant, atypical antipsychotic, trials, randomized, controlled, placebo and names of individual antidepressants and atypical antipsychotics. Original studies were selected, ranging from case reports to randomized controlled trials. Additional studies were identified by searching the reference sections of original studies, review articles and book chapters.

Results

The use of antidepressant combination therapies in depression was represented by a limited research base, which mostly consisted of data invested with low levels of evidence. In fact, only 12 randomized controlled trials were identified [10–21]. These used different combinations and yielded diverging results.

The evidence for antidepressant-atypical antipsychotic combinations was even more wanting, a situation that probably arose from their relatively short periods of availability, costs and prescription restrictions. The emerging studies of atypical antipsychotics have a greater emphasis on their efficacy in bipolar and schizoaffective disorders than in unipolar depression.

An area of discrepancy among these studies was the variation in level of treatment resistance in the populations, which complicated the interpretation and comparability of their results. Treatment-resistant depression has been variously defined, including one of failure to respond to adequate trials of two antidepressants from different classes [22] and the nonresponse or lack of remission despite administration of an adequate dose of an antidepressant for sufficient duration with good treatment adherence [5]. Such variability highlights the difficulties of reaching a unified definition of a clinical phenomenon that belies a multitude of causative factors.

Another limitation to the comparability of the data related to the outcomes under study, which could be one of response, commonly defined as a reduction of symptoms by at least 50%, or remission, usually defined as the virtual absence of symptoms [23]. Whilst remission should be the treatment goal, in view of the disability that would ensue from residual symptoms, most studies have designated response as the study outcome measure.

Antidepressant combinations

Randomized controlled trials

All studies combined antidepressants with different mechanisms of action, under the guiding rationale of broadening the neuropharmacological effects. In reflection of the contemporary range of antidepressants, the earlier trials studied tricyclic antidepressant (TCA) and monoamine oxidase inhibitor (MAOI) combinations [10–13], while later trials used selective serotonin reuptake inhibitors (SSRIs) and mirtazapine in combination with TCAs and mianserin [14–21].

Of the three TCA–MAOI combination trials, none demonstrated any benefit of combination therapies over antidepressant monotherapies, and none demonstrated serious adverse effects, although increased anticholinergic side effects were noted with TCA and combination therapies [10–12]. Young and colleagues randomized 135 out-patients with mild-to-moderate, not necessarily treatment-resistant, depression to five 6-week treatment groups, using trimipramine (50–150 mg/day, mean 106 mg/day; n = 34), phenelzine (15–60 mg/day, mean 45 mg/day; n = 25), isocarboxazid (10–30 mg/day, mean 32 mg/day; n = 25), trimipramine plus phenelzine (mean 102 mg/day and 44 mg/day, respectively; n = 26) and trimipramine plus isocarboxazid (mean 96 mg/day and 30 mg/day, respectively; n = 25) [10]. Trimipramine was statistically more effective than both MAOIs and both combination therapies as measured by the Hamilton Rating Scale for Depression (HAMD), an overall rating of depression severity, Medical Research Council UK (MRC) total score, MRC anxiety, insomnia and lack of energy scales. The trials conducted by Razani and colleagues [11] and O'Brien and colleagues [12] compared the combination of amitriptyline and tranylcypromine with each drug used alone in patients with major depression. In the former study, 60 severely depressed patients (mean HAMD score = 26) were assigned to treatment over 4 weeks with either amitriptyline (300 mg/day), tranylcypromine (40 mg/day) or the combination of both (150 mg/day of amitriptyline and 20 mg/day of tranylcypromine). All treatment groups improved with no significant intergroup differences in HAMD, Hamilton Rating Scale for Anxiety (HAMA), and the Zung Self-Rating

Depression Scale. O'Brien and colleagues replicated similar findings in their cohort of 80 nontreatment-resistant in-patients studied over 6 weeks [12]. These concordant results were notable for demonstrating the safety of TCA–MAOI combinations, and for showing a lack of advantage in efficacy of using combination therapy over TCA and MAOI monotherapies. TCAs and MAOIs have broad pharmacological actions and efficacies unsurpassed by newer antidepressants [24], but any advantage of combining the two cannot be discerned from these studies, given that the populations were not necessarily treatment-resistant.

In their comparison of TCA–MAOI combination therapy with electroconvulsive therapy (ECT), Davidson and colleagues randomly allocated a sample of 17 patients with severe, refractory depression to either a combination of phenelzine (15–45 mg/day, mean 34 mg/day) and amitriptyline (≤100 mg/day, mean 71 mg/day; n = 8) or a course of 4–10 ECT (mean 5.4; n = 9) [13]. Over the study period of 5 weeks, the ECT group improved significantly as measured by their scores on the HAMD, whereas no statistically significant improvement was found in the phenelzine–amitriptyline group. The inclusion of psychotic depression in this study could have a biased outcome in favor of ECT, although the superior efficacy of ECT over pharmacotherapy in the treatment of major depression has been well established [25].

The eight trials using newer antidepressant combinations produced less consistent results. Three randomized trials studied the combination of fluoxetine, one of the earliest SSRIs, and desipramine, the most noradrenergic of the TCAs. In their study of 41 depressed patients who had partial or no response to an 8-week trial of 20 mg/day of fluoxetine, Fava and colleagues randomly assigned them to three 4-week treatment groups consisting of higher dose fluoxetine (40–60 mg/day; n = 15), fluoxetine (20 mg/day) augmented by lithium (300–600 mg/day; n = 14), and fluoxetine (20 mg/day) combined with desipramine (25–50 mg/day; n = 12) [14]. The high-dose fluoxetine group had a nonsignificantly higher response rate (53%) than the augmentation (29%) and combination (25%) groups. The authors suggested that partial responders to the preliminary 8-week low-dose fluoxetine treatment, as determined by less than 50% improvement in their HAMD scores, responded better to high-dose fluoxetine, whereas nonresponders to the preliminary treatment preferentially responded to the augmentation and combination treatments. In a subsequent study of similar design, using a larger sample size of 101 out-patients with major depression, no significant difference in response rates was found both across the three treatment groups and among partial and nonresponders to the preliminary low-dose fluoxetine treatment [15]. A third controlled trial using the combination of fluoxetine and desipramine compared its efficacy with fluoxetine and desipramine monotherapies [16]. In the sample of 39 in-patients with nonpsychotic unipolar major depression, assigned to 6 weeks of treatment with fluoxetine (20 mg/day; n = 14), desipramine (dose adjusted to a plasma level of 160 ng/ml; n = 12), and the combination (dosages as per monotherapy arms; n = 13), no statistical difference was found among the three groups in terms of HAMD and Montgomery-Åsberg Depression Rating Scale (MADRS) scores. However, when the groups were analyzed for categorical levels of response on the MADRS, significantly more patients reached remission in the combination group than in the monotherapy groups. Combination treatment was not associated with a more rapid response.

Three studies were identified that investigated the combination of fluoxetine and mianserin, a tetracyclic agent with 5-hyrdoxytryptamine $(5\text{-HT})_{2A/C}$, presynaptic α_2-adrenergic and postsynaptic α_1-adrenergic antagonistic properties [17–19]. It was theorized that the concomitant use of both antidepressants could minimize the side effects of each [18]. In the Maes and colleagues study, 31 hospitalized patients with major depression were randomized to 5-week treatment arms of fluoxetine (20 mg/day; n = 11), fluoxetine plus pindolol (20 and 7.5 mg/day, respectively; n = 10), and fluoxetine plus mianserin (20 and 30 mg/day, respectively; n = 10) [17]. Measured in terms of change in HAMD scores, fluoxetine plus mianserin was equivalent to fluoxetine plus pindolol and both were significantly more effective than fluoxetine alone. Furthermore, in the treatment-resistant subset, significantly more patients responded to fluoxetine plus pindolol or mianserin (eight out of 14) than fluoxetine monotherapy (0 out of eight). It was also noted that HAMD score improvement 1 week after starting fluoxetine plus mianserin was significantly greater than that in the other two groups, thus, suggesting that combination fluoxetine and mianserin may significantly shorten the latency period of antidepressant effect. Side effects were not specifically addressed. Ferreri and colleagues conducted a 6-week, double-blind study comparing the efficacy and tolerability of fluoxetine plus mianserin with each drug used alone [18]. A sample of 104 patients with major depression, who had not responded to at least 6 weeks of 20 mg/day of fluoxetine, were assigned to continuing fluoxetine monotherapy (20 mg/day; n = 38), mianserin monotherapy (60 mg/day; n = 34) and fluoxetine plus mianserin combination (20 mg/day and 60 mg/day, respectively; n = 32). Reduction in HAMD score was significantly greater in the combination group than the monotherapy groups, and side effects were reported to be more frequent in the mianserin group than the fluoxetine or combination groups, leading to conclusions that this combination therapy was effective and well tolerated. Dam and colleagues, in their 6-week randomized trial of 34 patients with major depression where treatment consisted either of fluoxetine (20 mg/day) and mianserin (30 mg/day; n = 16) or fluoxetine (20 mg/day) and placebo (n = 18), found the combination therapy to be superior to fluoxetine in the efficacy analysis [19]. However, results became insignificant on intention-to-treat analysis (drop-out rates of 31% in the combination group and 39% in the placebo group).

Building on the evidence from these SSRI–mianserin studies, Licht and Qvitzau examined the effect of adding mianserin to sertraline in a population of patients with major

depression who had not responded (<50% reduction in HAMD score) to 6 weeks of treatment with 100 mg/day of sertraline [20]. A total of 295 patients were randomized to 5 weeks of sertraline (100 mg/day) plus placebo (n = 99), sertraline (200 mg/day) plus placebo (n = 98) and sertraline (100 mg/day) plus mianserin (30 mg/day; n = 98). Response rates for sertraline (100 mg/day; 70%) and sertraline plus mianserin (67%) were similar, but were significantly higher than sertraline (200 mg/day; 56%). The authors commented that this discrepancy from the fluoxetine–mianserin trials could reflect a different study design that included prospective follow-up of the open-label monotherapy phase prior to randomization, differences in mianserin dose and SSRI choice [20].

Mirtazapine, a pharmacodynamically unique antidepressant, has noradrenergic and specific 5-HT_{1A} properties through α_2-adrenergic blockade, which have led to its hypothesized synergism with SSRIs. Carpenter and colleagues randomized 26 treatment-resistant patients with major depression to 4 weeks of mirtazapine (15–30 mg/day; n = 11) or placebo (n = 15) in addition to their pre-existing antidepressants, which were SSRIs (n = 22), venlafaxine (n = 3) and bupropion (n = 1) [21]. Mirtazapine was found to be significantly superior to placebo in terms of response rates (64 vs 20%), remission rates (45.5 vs 13.3%), overall functioning and quality of life. There were no significant differences in side effects.

Open-label trials, case series & case reports

The bulk of the antidepressant combination therapy literature was constituted by open-label trials, case series and case reports. The interpretation of the open-label trial results [26–42] is hindered by the lack of controls, usually small sample sizes and the variety of combinations studied.

Almost all open-label studies combined antidepressants from different classes, with the exception of the study by Bondolfi and colleagues, which examined the efficacy of two SSRIs. In a group of seven patients with major depression who had not responded to 3 weeks of citalopram (40 mg/day), the addition of fluvoxamine (100 mg/day) for a further 3 weeks was well-tolerated and resulted in improvement in all but one subject [26]. The main finding of this study was the stereoselective increase in the more potent S-citalopram following addition of fluvoxamine, but the clinical applicability of this result may have since been superseded by the availability of escitalopram on the market.

The remaining open-label trials studied seven combination strategies using different classes of antidepressants. These consisted of MAOI–TCA [27,28], moclobemide–TCA [29], moclobemide–SSRI [30,31], SSRI–TCA [27,32,33], bupropion–SSRI or venlafaxine [34–37], mirtazapine-SSRI [38], and reboxetine–SSRI or venlafaxine or mirtazapine [39–42].

The MAOI–TCA studies reported modest response rates. Amsterdam and colleagues added clomipramine to the treatment of 20 patients who had previously not responded to a MAOI or fluoxetine [27]. The clomipramine–MAOI (n = 9) and clomipramine–fluoxetine (n = 11) groups were compared with a third group of MAOI-resistant patients on TCA augmentation (n = 7). The response rates after 4 weeks were two out of nine clomipramine–MAOI patients, four out of 11 clomipramine–fluoxetine patients and three out of seven MAOI–TCA patients. This gave a combined response rate of 31% for the two MAOI–TCA groups. However, balanced against this was the emergence of serotonin syndrome in a large proportion (56%) of the clomipramine–MAOI group, which necessitated treatment discontinuation. The authors cautioned the use of combination clomipramine and MAOI in view of such findings, thus echoing previously published warnings of potentially lethal outcomes from MAOI–TCA combination therapy [43]. In the Berlanga and Ortega-Soto study, 17 out of 25 stringently defined treatment-resistant depressed patients responded to the combination of isocarboxazide and amitriptyline at 6 weeks, but five of these responders dropped out within 2 months owing to manic switches and weight gain [28]. The distinguishing aspect of this study was the long follow-up period of 3 years, at the end of which six of the 12 responders still required maintenance on the combination, four were maintained on the TCA alone and two had relapsed. Interestingly, no serious adverse effects were reported after the initial 2 months.

Moclobemide, a reversible inhibitor of monoamine oxidase A (RIMA), received some interest in the pursuit of a safer alternative to MAOIs, especially when combined with other antidepressants. In a study combining moclobemide with TCA and tetracyclic antidepressants in patients with treatment-refractory depression, 13 of the 23 patients responded and low rates of side effects were observed [29]. With regards to combination moclobemide and SSRIs, Hawley and colleagues reported that 11 out of 50 treatment-resistant depressed patients were in remission after 6 weeks of combination moclobemide and paroxetine or fluoxetine and an additional five partially responded [30]. A higher response rate of eight out of 11 was reported by Joffe and Bakish in their study using a combination of moclobemide and sertraline or fluvoxamine, although their subjects had more diverse diagnoses to include dysthymic disorder, panic disorder and obsessive–compulsive disorder, in addition to major depression [31]. Both studies reported insomnia to be a common side effect, and a high rate of 188 adverse events was encountered in the Hawley and colleagues study.

Three studies involving SSRI–TCA combinations in treatment-resistant depression reported response rates of four out of 11 subjects (36%) treated with fluoxetine and clomipramine [27], four out of 13 (31%) with fluoxetine and desipramine or imipramine [32], and 12 out of 25 (48%) with fluoxetine and tricyclics or trazadone [33]. Other than one case of seizure during treatment with fluoxetine and maprotiline [33], serious adverse effects were not observed [27] or not mentioned [32].

Bupropion, a noradrenaline and dopamine reuptake inhibitor commonly prescribed in the USA for the indication of depression, has garnered a reputation for counteracting SSRI-induced

sexual dysfunction [34,35,44], although this effect remains in contention [45]. Nevertheless, this possible advantage has encouraged the exploration of bupropion–SSRI combination therapies. The four identified open-label trials of bupropion combined with SSRIs or venlafaxine all reported positive response and tolerance [34–37] and only one reported improvement in sexual dysfunction [35]. Spier designed a two-pronged study to firstly investigate the effectiveness of bupropion and SSRI/venlafaxine combinations in a depressed population not fully responsive to monotherapy with these agents, and secondly, to test the effectiveness of bupropion in counteracting SSRI side effects in patients who had fully responded to SSRI monotherapy but who were experiencing side effects. In the depressed group, a response rate of 12 out of 15 subjects (80%) was obtained with combination therapy, but in the side-effect treatment group, only two out of ten (20%) subjects improved, both in nonsexual side effects [34]. Kennedy and colleagues found that 14 of their 18 (78%) depressed subjects responded to 8 weeks of bupropion combined with venlafaxine, paroxetine and fluoxetine, when they had previously not responded or had only partially responded to 6-week monotherapy with the latter three antidepressants [35]. Of the responders, six (33%) had fully remitted. Statistically significant improvements were noted for orgasm in women and for global sexual functioning in men, but whether such improvements were attributable to amelioration of depression or to the neutralization of SSRI side effects could not be differentiated. DeBattista and colleagues similarly reported a notable response in 15 out of 28 (54%) depressed patients when bupropion was added to their index SSRIs or venlafaxine, which had previously failed to induce an adequate response [36]. Further support for bupropion–SSRIs were provided by Lam and colleagues, who reported a 28% remission rate for their combination bupropion–citalopram group compared with 7% for their monotherapy switching group over a period of 6 weeks [37].

Mirtazapine has received less attention in the combination therapy literature. As a prelude to their randomized controlled trial, Carpenter and colleagues conducted a naturalistic study, in which mirtazapine was added to the pharmacotherapeutic regimen of 20 patients diagnosed with major depression or dysthymia [38]. Their index treatments consisted of fluoxetine, sertraline, paroxetine, venlafaxine, desipramine plus venlafaxine, desipramine plus sertraline, venlafaxine plus fluoxetine and sertraline plus bupropion. After 4 weeks, 11 patients (55%) had responded, as measured by the Clinical Global Impression (CGI) scores and three (15%) had discontinued treatment due to side effects.

The first available selective noradrenaline reuptake inhibitor, reboxetine, has also received some interest as a combination therapy candidate. Lucca and colleagues conducted a prospective open-label study on 14 patients with major depression who had not responded to SSRI monotherapy or SSRI and pindolol augmentation over 4 weeks [39]. Three of these patients were psychotic. Low-dose reboxetine (2–4 mg/day) was added and the patients were monitored over a further 2 weeks, at the end of which five patients (36%) had improved, four (29%) had remitted, three (21%) remained unchanged and two (14%) had dropped out owing to lack of effect. It was of interest that none of the three patients with psychotic symptoms had improved. Addition of low-dose reboxetine was found to be well tolerated on the whole. Hawley and colleagues combined high-dose reboxetine with SSRIs for 24 patients who had not responded to the SSRIs on their own [40]. Remission was achieved in nine (38%) patients after 6 weeks of the combination treatment, but four patients could not continue owing to intolerable side effects and a further four required reduction in reboxetine dose due to side effects. Rubio and colleagues reported that 19 of their 34 depressed patients (56%) had responded to a 6-week trial of reboxetine added to a SSRI and 16 (47%) were in remission [41]. In their subsequent study of similar design, with a larger sample size and expanded to include venlafaxine and mirtazapine, in addition to SSRIs, combination with reboxetine produced a response rate of 33 out of 61 (54%) patients and a remission rate of 28 out of 61 (46%) [42]. No serious adverse effects were reported in either study [41,42].

Finally, a multitude of retrospective chart reviews, case series and case reports were found. However, no additional combinations were reported that were not already addressed by either a randomized controlled trial or an open-label study. Of greater relevance were isolated case reports of serious adverse events from antidepressant combinations, such as a case of serotonin syndrome reported to have occurred during cross-tapering from mirtazapine to venlafaxine [46].

Antidepressant: atypical antipsychotic combinations

Despite early evidence suggesting comparable efficacy of phenothiazine antipsychotics and antidepressants in the treatment of depression, widespread utilization of antipsychotics in nonpsychotic disorders has been checked by the risk of extrapyramidal side effects, in particular, tardive dyskinesia [47]. As such risks are understood to be minimal with atypical antipsychotics, clinical interest in their utility in the treatment of depression has been awoken.

In depressive disorders, the role of antipsychotics has predominantly been confined to the treatment of psychotic depression, in conjunction with antidepressants, as illustrated by recommendations of clinical guidelines [48–50]. However, there have been few studies of the efficacy of antidepressant-atypical antipsychotic combinations in psychotic depression and these have yielded ambiguous results.

Case reports have suggested effectiveness of olanzapine in combination with SSRIs in treatment-resistant psychotic depression [51]. Rothschild and colleagues conducted a retrospective, blinded chart review of hospitalized patients with psychotic depression, and compared 15 patients treated with olanzapine with 15 treated with other (unspecified) neuroleptics, with 80% of both groups also receiving concomitant antidepressants [52]. They found that ten of those taking olanzapine (67%) were much or very much improved on discharge, compared

with four (27%) of those taking other antipsychotics. There was no differential response between bipolar and unipolar psychotic depression. In a 6-week open-label trial of a combination of olanzapine and fluoxetine in 27 patients with psychotic major depression, intent-to-treat analysis generated response rates of 55.6% (n = 18) for depression, 59.3% (n = 16) for psychosis, and 55.6% (n = 15) for psychotic depression and a remission rate of 40.7% (n = 11) for psychotic depression [53].

Several double-blinded controlled trials were identified. Anton and colleagues found similar improvement in depression and psychosis for psychotically depressed patients treated with amoxapine (n = 17) or amitriptyline plus perphenazine (n = 12) [54]. Mulsant and colleagues, in their study of older patients with psychotic depression, found the combination of perphenazine and nortriptyline (n = 14) to be well tolerated, but no more efficacious than nortriptyline alone (n = 16) [55]. Spiker and colleagues found that the combination of amitriptyline and perphenazine (n = 14) was superior to amitriptyline alone (n = 17), for the treatment of delusional depression [56]. Olanzapine plus fluoxetine, olanzapine alone and placebo were compared over 8 weeks in two separate trials (n = 124 and n = 125) of patients with psychotic depression [57]. In the first trial, the response rate for the combination group (63.6%), as measured by greater than 50% reduction in HAMD-24 scores, was significantly higher than 34.9% for olanzapine monotherapy and 28% for placebo. In the second trial there were no significant differences amongst the treatment groups.

In recent years, atypical agents have received some attention in the literature as an augmentation strategy in treatment-resistant, nonpsychotic, unipolar depression. Risperidone, olanzapine, quetiapine, ziprasidone and aripiprazole have all been implicated as promising augmentation candidates [58,59], but support for their efficacy has largely been limited to low-leveled evidence case reports and studies. In fact, only one meta-analysis [60] and two randomized, controlled trials have been published [61,62], all of which pertained to the olanzapine–fluoxetine combination, which has been marketed as a combined formulation in the USA.

Olanzapine

In the often-quoted study by Shelton and colleagues, patients with unipolar, recurrent, nonpsychotic, treatment-resistant depression were first treated with fluoxetine (20–60 mg/day) in the 6-week open-label screening phase [61]. The 28 patients remaining after screening were then randomly allocated in a 1:1:1 ratio to three treatment groups in an 8-week, double-blind trial. The treatment groups consisted of olanzapine (5–20 mg/day) plus fluoxetine (20–60 mg/day; n = 10), olanzapine plus placebo (5–20 mg/day; n = 8) and fluoxetine plus placebo (20–60 mg/day; n = 10). No significant differences between the treatment groups were found in terms of baseline depression ratings or demographics. Those who completed the double-blind trial were then eligible to enter an 8-week open-labeled extension of olanzapine plus fluoxetine therapy. Results from the double-blind phase revealed that the combination group had significantly greater improvement in MADRS scores than either of the monotherapy groups, and significantly greater improvement in HAMD and the Severity subscale of the CGI (CGI-S) scores than the olanzapine, but not the fluoxetine, group. The proportion of responders, as defined by a greater than 50% improvement on the MADRS, was 60% for the combination group, compared with 0% for olanzapine monotherapy and 10% for fluoxetine monotherapy. Furthermore, a significant difference between the combination and fluoxetine groups was detected by week 1 of the trial. Improvement on all three rating scales was maintained in the open-label extension phase for the combination group, but those in the monotherapy groups did not improve during the open-label combination treatment. The medications, alone or in combination, were well tolerated, but weight gain was greater in the olanzapine groups (mean 6.67 and 6.07 kg in the combination and olanzapine monotherapy groups, respectively) than the fluoxetine monotherapy group (mean: 0.88 kg).

A criticism of this study design was the use of fluoxetine, given its long half-life and that of its active metabolite, norfluoxetine. Since the olanzapine monotherapy group had continued fluoxetine up until the day of randomization, the superior results observed in the combination group over the olanzapine monotherapy group seemed to defy logical reason. Whether such unexpected results arose by chance, reflected a decline in fluoxetine and norfluoxetine levels beyond a critical threshold necessary for clinical effect, or were mediated by a separate mechanism, remained possibilities and replication using larger samples and SSRIs with shorter half-lives was advocated [63].

A subsequent meta-analysis was performed on one 8-week and one 12-week double-blind trial (n = 797) comparing the efficacy of the olanzapine–fluoxetine combination with that of olanzapine and fluoxetine alone in treatment-resistant, nonpsychotic, unipolar depression. The combination therapy demonstrated significantly greater improvement in MADRS after 1 week than the monotherapies, an effect that was maintained over 8 weeks. The combination group also demonstrated significantly greater response rates than the olanzapine group (37.3 vs 21.1%), and a significantly greater remission rate than the olanzapine and fluoxetine groups (24.9 vs 13.1 vs 15.2%, respectively) [60].

A large-scaled, double-blinded, randomized trial was undertaken to replicate these results with the olanzapine–fluoxetine combination in treatment-resistant unipolar depression. Depressed patients who had not responded to a SSRI were first treated with nortriptyline in a 7-week, open-label, lead-in phase. Nonresponders (n = 500) were randomized into four treatment groups, which included an olanzapine–fluoxetine combination, olanzapine monotherapy, fluoxetine monotherapy and nortriptyline monotherapy. At the end of the 8-week study period, no significant differences were found among the four groups, as measured by the change in MADRS scores. The olanzapine–fluoxetine combination was associated

with greater improvement in MADRS scores than each of the monotherapy groups in the early weeks (at weeks 2, 4, 6 and 7 as compared with olanzapine; at weeks 2–5 for fluoxetine; and at weeks 1–4 for nortriptyline) [62].

The long-term efficacy, safety and tolerability of the olanzapine–fluoxetine combination were studied by Corya and colleagues in their 76-week open-label study [64]. A total of 560 patients diagnosed with major depressive disorder, 145 (26%) of whom were also determined to have treatment resistance as defined by previous failure to respond to antidepressants from two different classes, were treated with the combination of olanzapine (6–18 mg/day) and fluoxetine (25–75 mg/day). Early MADRS improvement was again observed within the first week (mean total scores decreased by 7 points after half a week and 11 points after 1 week), and improvement was maintained throughout the study period with a mean reduction by 22 points after 76 weeks. Respective response, remission and relapse rates were 62, 56 and 15% for the sample and 53, 44 and 25% for the treatment-resistant subset. The most frequently reported side effects were somnolence, weight gain (mean 5.6 kg over 76 weeks), dry mouth, increased appetite and headache. Other adverse effects included a mean increase by 6.2 mg/dl in nonfasting glucose, development of treatment-emergent hyperglycemia in 2.9% (n = 14) and hypercholesterolemia in 1.5% at end point. There was a statistically significant increase in the QTc interval on electrocardiography, although none became clinically symptomatic and there was no measurable increase in extrapyramidal symptoms.

Parker and colleagues were unable to replicate the early response observed with olanzapine–fluoxetine combination therapy, a finding that the authors queried could be due to their underpowered study (n = 20) [65]. However, augmentation with olanzapine after 2 weeks of antidepressant treatment was associated with remission in four patients, which raised the possibility of an advantage in initial priming with an antidepressant before augmentation with olanzapine.

Case reports have suggested efficacy of olanzapine combined with other antidepressants, including venlafaxine [66], paroxetine and bupropion [67], in treatment-resistant depression, as well as a possible role of olanzapine plus mirtazapine in the treatment of major depression in association with anorexia nervosa [68].

Risperidone

Early case series reported the effectiveness of augmenting SSRIs with risperidone in major depression [69,70]. In the four cases reported by O'Connor and Silver [69], low-dose (0.5–2 mg/day) risperidone appeared to effect a response within 1–2 weeks, especially for symptoms of anxiety and agitation and was well tolerated. Ostroff and Nelson published a larger case series of eight patients with nonpsychotic major depressive disorder, all of whom remitted within 1 week of adding low-dose risperidone (0.5–1 mg/day) to their SSRIs (either fluoxetine or paroxetine) [70]. Building on this empirical evidence, Hirose and Ashby postulated that the use of a SSRI and risperidone combination from the outset of treatment could enhance the response rate compared with SSRI monotherapy. They conducted a 6-week open-label trial of fluvoxamine (100–150 mg/day) and risperidone (0.5–1 mg/day) in 36 patients with major depressive disorder, and although not designed to compare the combination therapy response rates with SSRI monotherapy, their study nevertheless provided promising results. A total of 30 patients completed the trial, giving an intent-to-treat outcome of 26 (72%) remissions, six (17%) responders and four (11%) nonresponders. The combination was again reported to be well tolerated [71].

In a study designed to evaluate citalopram and risperidone combination as maintenance therapy in depression, 502 patients with major depression previously nonresponsive to at least one SSRI, were first processed through an open-label treatment augmentation phase. This involved initial treatment with citalopram (40–60 mg/day), and augmentation with risperidone (0.5–1 mg/day) in those with less than 20% improvement in MADRS scores after 4 weeks. Those who achieved remission from the augmentation therapy were randomly assigned to receive citalopram plus placebo or citalopram plus risperidone for 24 weeks. The time to relapse in patients treated with the combination was significantly longer than that in the citalopram plus placebo group [58].

Other case series reported good outcomes with risperidone added to tranylcypromine [72], and to various antidepressants (SSRIs, bupropion, mirtazapine, trazodone) alone, in combination with one another and with sodium valproate or lithium [73].

Ziprasidone & aripiprazole

A small open-label study (n = 20) of ziprasidone augmentation of SSRIs in nonpsychotic major depression over 6 weeks produced intent-to-treat results of ten (50%) responders and five (25%) who remitted [74].

Two open-label studies investigated the effectiveness of aripiprazole as an augmentation agent for antidepressant therapy [75,76]. One used aripiprazole to augment SSRIs, venlafaxine and bupropion in a group of 15 depressed patients who had not responded to monotherapy. Six of the 15 patients remitted after 1 week of aripiprazole augmentation, as defined by a HAMD score of 7 or less and nine of the 15 remitted by 2 weeks. However, only eight patients completed the 8-week open trial period but all achieved remission by the end point. Akathisia necessitated discontinuation in two out of seven patients on the higher dose of aripiprazole (10 mg/day) and in one out of eight patients on the lower dose (2.5 mg/day) [75]. In the second study of 12 SSRI-resistant depressed patients, intent-to-treat analysis generated a response rate of seven patients (58.3%) and a remission rate of five (41.7%). No severe side effects were reported by any of the patients [76].

In a retrospective chart review, Barbee and colleagues suggested that aripiprazole may be an effective augmentation agent in treatment-resistant unipolar depression where a previous trial of augmentation with an atypical antipsychotic had failed [77].

Quetiapine

There were chart reviews suggesting a role for quetiapine as an antidepressant augmentation strategy [59,78]. McIntyre conducted a double-blind, randomized, placebo-controlled study of the efficacy, safety and tolerability of adjunctive quetiapine or placebo in partial responders with residual symptoms and prominent anxiety symptoms following at least 6-weeks of SSRIs and serotonin norepinephrine reuptake inhibitors (SNRIs) treatment [79]. A total of 29 patients were enrolled in each arm of the study, with the quetiapine group receiving a mean dose of 182 mg daily. At the end of the 8-week study period, the mean HAMD scores in the placebo and quetiapine groups had dropped by 5.5 and 11.2 points, respectively ($p = 0.008$). There were significant differences at end point of the CGI-I, CGI-S, HAM-A and Global Assessment Scale (GAS) scales. This study suggested that the combination of quetiapine and either a SSRI or SNRI is more effective than antidepressant monotherapy in unipolar depression.

Discussion

Clinical studies of combination therapy in unipolar depression are limited in quantity, experimental design and range of drug combinations. Many are underpowered and have biases in patient selection and outcome. Comparability of the studies is complicated by the variable population characteristics, such as history of treatment exposure, level of treatment resistance, depression severity, length of treatment and drug dosages. Notably, the definition of treatment-resistant depression is not unified, and can vary from failure to respond to one SSRI to the more commonly cited nonresponse to adequate trials of two antidepressants from different classes. A more precise staging system for treatment resistance has been proposed by Thase and Rush, with a range from single-agent resistance in stage 1 to multi-agent (including a TCA and a MAOI) and ECT resistance in stage 5 [80]. This may prove useful to communicate and control for the level of treatment resistance in future research. Another caution to the interpretation of available data relates to the typical use of response as study outcome, which may not translate into anticipated levels of clinical and personal benefits.

A large, prospective, multistratum randomized trial is currently under way. The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) clinical trial, of out-patients with nonpsychotic major depressive disorder, has an effectiveness-based design that mirrors real-life clinical practice, and reports on both response and remission as outcomes [81]. The STAR*D study design includes investigations of combination therapies to treat residual symptoms, adding augmenting agents when remission is not achieved. In a STAR*D substudy of adult out-patients without remission after a mean of 11.9 weeks of citalopram therapy, patients were randomized to receive adjunctive treatment with bupropion (n = 565) or buspirone (n = 286). Both treatments were shown to be useful combination therapies for residual symptoms with remission (HAMD-17 scores ≤ 7) in 29.7 and 30.1% of citalopram plus bupropion and citalopram plus buspirone treated patients, respectively [82].

One further comment is that, within drug classes, there can be much variability in individual pharmacodynamic profiles, such that generalizations of combination therapy based on drug classes should be formed with caution. Nevertheless, the existing literature still serves as a useful guide in informing clinical practice decisions.

Overall, the antidepressant combination of fluoxetine and mianserin has the most consistent evidence for its effectiveness, based on three randomized controlled trials [17–19]. Interestingly, similar benefits of the sertraline–mianserin combination were not replicated [20]. Mirtazapine demonstrates promise as an augmentation agent where antidepressant monotherapy has been unsuccessful [21,38], although its rudimentary literature base will require replication in larger-scaled, randomized, placebo-controlled trials. There is level III evidence [83] for the addition of bupropion to SSRIs and venlafaxine [34–37], moclobemide to TCAs and SSRIs [29–31], and reboxetine to SSRIs [39–42], although moclobemide and high-dose reboxetine combinations were associated with significant side effects. Neither randomized controlled nor open-label trials have reported great benefits from TCA–MAOI [10–13,27,28] and TCA–SSRI [14–16,27,32,33] combinations and the former has been associated with high reported rates of serotonin syndrome [27].

There is growing evidence for the efficacy of atypical antipsychotics in nonpsychotic treatment-resistant unipolar depression, although the current small pool of levels II and III evidence [83] is largely limited to olanzapine, quetiapine and risperidone [61,62,64,65]. The olanzapine–fluoxetine combination has been associated with higher response and remission rates than antidepressant or olanzapine monotherapies [60,61], but such advantages were not found in another study [62]. Additionally, the long-term tolerability of olanzapine is of concern, especially with regard to metabolic adverse effects that can increase morbidity and mortality [64]. There is possibly a role for atypical antipsychotics in depressive relapse prevention [58], but further research is again required to clarify this. A noteworthy finding from the atypical antipsychotic–antidepressant combination literature has been the rapid onset of improvement, often within a week, that has been reported with olanzapine, quetiapine, risperidone and aripiprazole [60–62,64,69,70,75,79], and may be largely attributable to improvements in symptoms of anxiety and agitation.

In clinical practice, antidepressant monotherapy should remain the first-line treatment for unipolar major depression. Psychotic depression is an exception, for which combination antidepressant and atypical antipsychotic or ECT would be the preferable first-line treatments. Where the patient has not

responded or has only partially responded to trials of monotherapy, however, the emerging evidence indicates that combination therapy could be a useful and potentially well-tolerated option. Naturally, this should be preceded by the exclusion of causes of apparent treatment resistance, such as noncompliance, misdiagnosis and untreated comorbidities.

It seems intuitively reasonable that the choice of combination treatments should be guided by neuropharmacological mechanisms. The prevailing model of the neurobiology of depression has evolved from the monoamine hypothesis of depression, which attributed depressive symptomatology to deficiency of central noradrenergic, serotonergic and dopaminergic transmission. It was first proposed over 30 years ago, and has since expanded to incorporate notions of monoamine receptor selectivity and adaptivity [84]. Although still an incomplete explanatory model, the refined monoamine hypothesis provides an instructive framework for the pharmacotherapeutic intervention of depression.

In combination strategies, the usual intention is to broaden the monoamine neurotransmitter targets and manipulate the mixture of autoreceptors, heteroreceptors, presynaptic and postsynaptic receptors to optimize antidepressant effects and minimize side effects. As an illustration, the addition of reboxetine to SSRIs is anticipated to produce dual actions on the serotonin and noradrenaline systems. Similarly, mianserin can add on noradrenergic effects when combined with SSRIs through its α_2-adrenergic antagonism. Furthermore, mianserin, mirtazapine and the atypical antipsychotics all have 5-HT$_{2A/C}$ antagonistic properties. These are believed to result in selective enhancement of 5-HT transmission, thus partly accounting for the observed synergism of these agents with SSRIs, which produce an increase in synaptic serotonin concentrations. In addition, as 2-HT$_{2A/C}$ receptors are thought to mediate SSRI side effects, such as anxiety, agitation, insomnia and sexual dysfunction, these agents may increase the tolerability of SSRIs. The beneficial effects of 5-HT$_{2A/C}$ antagonism on sleep architecture may also help to explain their value in the treatment of depression [80]. Bupropion, with its dopaminergic effects, would also seem to be a logical choice in combination treatments. In animal models, atypical antipsychotics have been demonstrated to increase dopamine and noradrenaline in the prefrontal cortex, which could be important mediating mechanisms in the treatment of depression. The pharmacodynamic interplay of these pharmacological agents is known to be complex and involve multiple feedback loops and neurotransmitter systems. Discussion of such mechanisms in greater depth can be found in other sources [80,85].

In their review of augmentation and combination treatments for major depressive disorder, Fava and Rush have also highlighted the thin evidence base for antidepressant–antidepressant and antidepressant–atypical combinations [86]. Nevertheless, they have controversially argued for a novel approach entailing the use of augmented or combined antidepressant treatment as first-line therapy, with the rationale that this may induce remission in a higher proportion of patients and reduce drop-out rates owing to treatment ineffectiveness. This strategy may attract criticisms relating to the use of unnecessary medications in the proportion of patients who would remit on monotherapy and to risks of adverse effects, but this interesting proposal warrants further evaluation. Another novel approach is that of sequential treatment of mood and anxiety disorders. It is distinct from augmentation or combination therapy, and refers to the sequential employment of pharmacological and psychological treatments in an attempt to manage the complexities of these psychiatric conditions at different stages of their course [87]. These examples of novel treatment ideas may signal further innovative developments and a paradigm shift in psychiatric clinical practice.

Conclusions

The published literature contains an increasing database on the efficacy and tolerability of combination therapies in the treatment of unipolar depression. In particular, there is support for the strategic combination of agents targeting different neurotransmitters and their receptors. The widening therapeutic application of atypical antipsychotics is further consolidated by emerging evidence suggesting their augmentative role in antidepressant therapy. As most studies are small and uncontrolled, replication of their results will be required in larger-scaled, randomized, controlled trials.

Expert commentary

Combination treatments are potentially effective in unipolar depression that has not remitted on antidepressant monotherapy. The fluoxetine–mianserin and SSRI–low dose reboxetine combinations, and augmentation with mirtazapine, bupropion and atypical antipsychotics are possible options. Atypical antipsychotics appear to be particularly appropriate in the depressive subgroup that is associated with high levels of agitation and anxiety, and probe the boundaries between agitated depression and mixed states. The utility of atypical antipsychotics and lithium in treatment resistance may serve as a proxy marker of the fact that high proportions of individuals with treatment resistance may be in the soft bipolar spectrum.

Five-year view

It is anticipated that the understanding of the neurobiology of depression will continue to deepen, and will be associated with a parallel increase in sophistication in the selection, or design, of psychopharmacological agents. The classification and common conceptualization of psychotropics will likely evolve to one dominated by their pharmacodynamic actions rather than their main syndromal indications, and the role of atypical antipsychotics, in particular, is expected to expand. The use of agents traditionally associated with other indications will reinforce the spectral nature of mood disorders and challenge established diagnostic boundaries. Developments in pharmacogenetics and pharmacogenomics will possibly start to impact on clinical practice, which may be steered towards more precise drug selection that may ultimately prove more cost-effective.

Key issues

- Unipolar depression is associated with the highest level of disease burden as measured in terms of years lived with disability, but most patients will not achieve remission on antidepressant monotherapy.
- Combination therapy in unipolar depression has an encouraging but restricted evidence base, and further research is needed to clarify the safety and efficacy of various combination strategies.
- Of the antidepressant combinations, the fluoxetine–mianserin and selective serotonin reuptake inhibitor–low dose reboxetine combinations seem well tolerated and efficacious. Augmentation with bupropion and mirtazapine are also promising strategies.
- Atypical antipsychotics seem to have a unique role in combination therapy with antidepressants, and may be particularly useful in those with prominent anxiety and agitation.
- It is necessary to reconfirm diagnosis in treatment resistant cohorts. Medical disorders, substance use and personality disorders play a role in treatment resistance. There are also high rates of undiagnosed bipolar disorder in treatment refractory cohorts.

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