

Potential strategies for treatment-resistant depression

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Munksgaard.

Objective: To review the pharmacological basis of antidepressant potentiation in combination therapy and the clinical evidence for its efficacy.

Method: Literature searches were undertaken and the results reviewed.

Results: Treatment-resistant depression is common (15–30%). Various strategies exist for dealing with resistant depression, including pharmacological potentiation, i.e. adding a treatment that itself does not have antidepressant actions but that enhances the efficacy of the original treatment. Lithium, triiodothyronine (T3) and bupirone are the best studied potentiating drugs, although other options include pindolol, dopaminergic agents, second-generation antipsychotics, psychostimulants, hormones and anticonvulsants.

Conclusion: Several pharmacological potentiation strategies exist.

Whilst good evidence exists for lithium combined with antidepressants, although good results have also been reported with augmentation strategies involving T3 or bupirone.

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Key words: antidepressants; drug combinations; depression; resistant depression; lithium; triiodothyronine; bupirone

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Introduction

The concept of treatment-resistant depression originated in the late 1960s with the conclusion of controlled studies on imipramine and tricyclic derivatives. A number of authors (1–4) reported cases of depressed patients who did not respond to imipramine, but who occasionally responded to treatment with intravenous clomipramine or oral combinations of a range of antidepressants. Satisfactory results, although of short duration, were also obtained with combined treatment using reserpine (5). The term 'potentiation' of antidepressants prescribed to treatment-resistant patients was suggested by Coppen (6) in relation to the enhancing effects of tryptophan on monoamine oxidase inhibitor (MAOI) treatment.

Aims of the study

To review the literature on treatment-resistant depression and identify the available strategies to deal with it.

Material and methods

Searches of the medical literature were undertaken for publications on treatment strategies which have been employed in the management of treatment-resistant depression. The literature so identified was reviewed.

Results

Most authors consider resistance to treatment to be the absence of a therapeutic response to average doses of 150 mg imipramine. However, the first resistance criteria were proposed by Quitkin (7):

- Non-response to imipramine (300 mg/day orally) or to an equivalent tricyclic antidepressant (TCA);
- Non-response to phenelzine;
- Non-response to electroconvulsive therapy (ECT).

Subsequent revisions (8, 9) established the basic criteria for classifying treatment-resistant depression:

- Primary unipolar depression;

This supplement was derived from GEAA meetings. Organon Española S.A. supported GEAA meetings.

- Non-response to imipramine (or equivalent TCA) or to an MAOI;
- Minimum time for response evaluation of 6 weeks;
- Good compliance with treatment regime (determination of plasma levels recommended).

Nowadays there is a tendency to grade the degree of treatment-resistance in terms of the number of antidepressant trials that have produced no conclusive results. The degree of resistance ranges from a single failure to the failure of three or more trials. Trials of antidepressants should be carried out using suitable doses (equivalent to 150–300 mg imipramine), over a suitable period of time (6–8 weeks), and bearing in mind the specific subtype of depression identified, whether psychogenic (reactive) or endogenous (10).

In a review by Paykel (11), it was concluded that the incidence of refractory depression is difficult to quantify given the absence of controlled trials and accepted operational criteria. It is generally acknowledged that 15% of patients with unipolar depression remain clinically symptomatic years after being treated with specific psychopharmacological agents. A possible rate for resistant depression would range from 15% to 30% of all depressed patients.

Predictors of treatment-resistant depression include advanced age, female gender, the presence of concomitant illnesses, a high degree of neurosis, thyroid dysfunction, poor social support and inadequate treatment. A particularly malign association in terms of treatment-resistant depression is a high degree of neurosis combined with symptoms of endogenous depression (12).

Pharmacological therapies for resistant depression

Genuine resistant depression need to be clearly distinguished from other cases of depression that may be erroneously classified as such. In the first place, any possible errors or deficiencies in the existing treatment programme should be assessed, as these may constitute the underlying reasons for a failure to respond to treatment. Secondly, if first-choice treatments are seen to fail, a range of strategies are available, which tend to vary considerably from one care setting to another.

The different treatment options for resistant depression include (not in priority order):

- Re-evaluation of the diagnosis;
- Treatment optimisation;

- Verification of dosage level, treatment duration, compliance with treatment, plasma levels, etc.;
- Verification that treatment indication is correct;
- Pharmacological potentiation strategies;
- Combination strategies using two or more antidepressants;
- Switching to another pharmacological class;
- Experimental pharmacological treatments.

Diagnosis re-evaluation and treatment optimization

The initial diagnosis should be reassessed prior to classifying a patient as having resistant depression. Several weeks after this evaluation, and on the basis of the greater clinical knowledge acquired, the possibility of any comorbid psychiatric disorders should be eliminated, as should the existence of any medical conditions (mood disorder secondary to medical illness) that would explain why improvement was insufficient or failed to occur.

Level of compliance with the treatment programme also needs to be determined. According to some studies, 70% of psychiatric patients fail to comply with their treatment programme. In depressed patients, factors such as a negative attitude to the results of the treatment, side-effects, or the existence of other problems that had not previously been detected – such as alcohol dependence or personality disorders – predict poor compliance with treatment (13).

Dosage should be confirmed as correct. Many depressed patients who fail to respond to treatment receive insufficient doses and/or treatment lasting only 4–6 weeks, which is the absolute minimum period necessary to evaluate the results. Once they experience an improvement, patients may occasionally reduce their medication without informing their doctor.

Plasma levels of antidepressants should be assessed to check that they are appropriate. For example, plasma levels of imipramine and desipramine should be over 220 µg/ml. Plasma concentrations of an antidepressant depend on the unconjugated fraction and vary not only according to dosage, but also according to genetic factors. Variation between individuals, irrespective of dose, ranges between 5% and 23%. The concomitant use of other drugs may also alter plasma levels of antidepressants.

The indication should also be reassessed to ensure that it is appropriate. The following treatments are generally considered effective:

- Heterocyclic antidepressants as first-choice treatment for endogenous depression;
- MAOI antidepressants as first-choice treatment for atypical depression;
- ECT plus heterocyclic antidepressants as first-choice treatment for psychotic depression;
- Compliance with initial treatment should be ensured;
- The maximum recommended doses should be administered;
- Longer duration of initial treatment (with no therapeutic changes) should be considered (up to 8–10 weeks).

In certain circumstances it may be advisable to increase the antidepressant dose above the recommended level. For the TCAs, monitoring of plasma levels is necessary 5 days after each dosage modification. Patients should also be monitored for potentially adverse cardiovascular effects, the risk of seizures and even the risk of death. The efficacy and safety of high doses of tranylcypromine (90–200 mg/day) for treatment-resistant depression have been demonstrated (14–16). There is less widespread agreement on increasing dosage levels of selective serotonin reuptake inhibitors (SSRIs). Some authors recommend waiting longer (e.g. 8 weeks) before increasing above recommended doses (up to 60 mg/day fluoxetine, for example) (17, 18). Some open-label studies, however, advise against increasing the dosage (19). The dose–response rate seen with venlafaxine, which increases noradrenaline and dopamine reuptake at doses of up to 225 and 500 mg/day, respectively, may indicate that the dose should be increased in patients who fail to respond to lower doses. One study reported a 40% rate of response to high doses of venlafaxine (300–450 mg/day) in patients resistant to other treatment strategies (enhancement with lithium or triiodothyronine, and ECT) (20). Blood pressure should be monitored regularly.

Strategies for pharmacological potentiation

There are about two dozen antidepressants available that act in eight different ways. Nonetheless, some patients fail to respond to initial monotherapy with one or another. In this case, there is the possibility of combining two or more antidepressants or of implementing a strategy of pharmacological potentiation so as to obtain neurochemical synergy that may improve the therapeutic prospects for patients with resistant depression.

Pharmacological potentiation consists of adding a substance that itself does not have any

antidepressant actions but which enhances or augments the efficacy of the prescribed antidepressant. The three potentiating agents that have been most frequently studied are lithium, thyroid hormone and buspirone. Other enhancers that have gradually been added to the arsenal include dopaminergic agents, second-generation antipsychotics, psychostimulants, hormones and anticonvulsants.

Lithium. Lithium has, in general, proved to be effective in the treatment of depression. It is hypothesized that this is due either to an increase in the sensitivity of postsynaptic serotonergic receptors or possible synergistic actions on the system of secondary receptors. Practical use of lithium dates back to the 1980s, when studies revealed that the addition of 600 mg/day, divided into various doses and with appropriate plasma levels, increased the therapeutic response in patients who had failed to respond to TCAs, MAOIs or SSRIs (21–25). Response latency has been reported to range from 24–28 h (26) to 3–6 weeks (27). There is no known reason for this wide variation in onset, although a previous lengthy and intensive antidepressant treatment programme is likely to lower the chances of a rapid response to lithium augmentation. Of the 11 double-blind studies on lithium potentiation published to date, 10 (representing a total sample of 135 patients) reported a favourable response to combinations with lithium in 52% of cases (28–37). The other study found a response rate to lithium enhancement of between 56% and 95% (38).

Predictive capacity has not been demonstrated for variables such as age, gender, number of depressive episodes, the seriousness of the depression or the occurrence of delusions, nor by biological variables. Possible predictors for a positive response to lithium augmentation, however, include significant weight loss, psychomotor retardation, hypothalamic–adrenal axis dysfunction and general endogenous depression symptoms (39, 40).

Accurate data are not available on the association between response to lithium potentiation and plasma levels of lithium. Plasma levels of between 0.4 and 0.6 mEq/l may be appropriate, although blood concentrations of 0.1–0.2 mEq/l may be suitable for elderly patients (41). Blood lithium levels should be monitored at frequent intervals from the week after starting treatment and after any modification in dose levels.

Although it would appear that lithium is effective in patients who do not respond to

other antidepressant treatments, recent studies have brought this combination into serious question. A 6-week, double-blind, placebo-controlled study did not find significant differences between lithium and placebo when each was combined with nortriptyline (42). Other controlled studies with fluoxetine and clomipramine obtained similar negative results (30, 43, 44). Questions about the use of lithium combination with SSRIs was also influenced by the toxic risks of lithium and the high incidence of side-effects in patients with a good tolerance to SSRIs. The need for blood monitoring, as well as risks of hypothyroidism, weight gain and neurotoxicity, have all proved to be additional negative aspects of the use of lithium as a potentiator.

Triiodothyronine (T3). Thyroid disorders, particularly in women, are frequently associated with depression; thyroid-based treatments may therefore be effective. Augmentation effects have been observed when supplementary thyroid hormones were prescribed to patients who failed to respond to specific first-choice treatments, even when the patient presented no clear signs of hypothyroidism.

In six of eight controlled double-blind studies involving over 200 patients, T3 proved more effective than placebo (45). This effect was more pronounced in women than in men. Controlled studies on imipramine/thyroid hormone vs. imipramine/placebo in patients with depression resistant to imipramine and amitriptyline showed a clear improvement in response and a faster onset of therapeutic effect (46, 47). These effects were again more evident in women than in men. A meta-analysis of 292 patients confirmed that T3 augmentation of antidepressant treatment may be effective in subgroups of patients with treatment-resistant depression (48).

Little data exists in relation to the possible therapeutic effects of thyroxine (49). It is not widely used in clinical care settings, probably due to the fact that its handling is complex compared with T3.

There are, in general, relatively few genuinely reliable studies on T3 used as augmentation treatment for refractory depression, as samples tend to be small and almost all the studies refer to TCAs; studies with SSRIs are few and uncontrolled (50, 51). Recommended doses range between 25 and 50 µg/day and response can be evaluated at 3 weeks. Treatment beyond 8–12 weeks is not indicated, given the possible risk of hyperthyroidism on withdrawal. The most frequent side-effects associated with this augmentation strategy are nervousness and insomnia.

Buspirone. Buspirone is a partial 5HT_{1A} receptor agonist, principally indicated for generalized anxiety disorder, although it has also been used to augment serotonergic activity in patients with refractory depression. Buspirone acts synergistically with the SSRIs; moreover, as an agonist that partially blocks 5HT_{1A} auto-receptors, it may act more rapidly than the SSRIs.

In a prospective study, a potentiating strategy consisting of 25–50 mg/day buspirone administered for 3 weeks to patients who had failed to respond to 5 weeks of treatment with an SSRI (fluoxetine or fluvoxamine) resulted in positive results (68% response rate) (52). Other studies of variable consistency tend to endorse the potentiating effects of buspirone (53–55). There have been only two controlled trials with buspirone as an enhancer of SSRI antidepressant activity (56, 57). In both studies, buspirone had similar overall effects to placebo; although in one study buspirone resulted in a significantly faster onset of action (57).

A possible advantage of buspirone is that it is more effective than placebo in alleviating the sexual dysfunction that can result from treatment with SSRIs (58). To sum up, buspirone is well tolerated and efficacious as a treatment enhancer for refractory depression. It has, moreover, a useful anxiolytic effect, which is an important benefit as anxiety is frequently a feature of depressive pathologies.

Pindolol. Pindolol is frequently used as an enhancer of antidepressant effects in Europe and Canada, but is far less common in the USA. It is a beta-adrenergic blocker and presynaptic 5HT_{1A} auto-receptor antagonist. Preclinical studies suggest that it may very rapidly activate serotonergic neurones (which are thought to be associated with rapid antidepressant effects), accelerate the onset of action of SSRIs and augment an inadequate response to SSRIs.

Doses of 2.5 mg three times daily have been combined with SSRIs, resulting in an overall improved antidepressant effect in most studies (59–63). Another study, however, reported no response in 10 patients with treatment-resistant depression (64), whilst another found no difference from placebo in a study limited to 10 days of potentiation in refractory depression patients (65). Low doses were generally used. In some cases, an increase in irritability was reported. In summary, pindolol accelerated the antidepressant response of the SSRIs in four of five double-blind studies.

Serotonin precursors. Both tryptophan (L-TP) and 5-hydroxytryptophan (5-HTP) have been used to

treat depression, with controversial results. Pharmacological augmentation effects have been reported in combinations with MAOIs, clomipramine and fluvoxamine (66–68). Satisfactory results were reported with a triple combination of clomipramine, L-TP and lithium in seven patients suffering from refractory depression (69). However, in a review of six studies on 5-HTP as an enhancer, it was concluded that the methodologies were not sufficiently rigorous and that the results were contradictory (70).

Dopaminergic agents. Trials have been conducted to assess the effects of dopaminergic agents in the treatment of refractory depression. Promising findings were obtained with bromocriptine as an enhancer (71, 72). Open-label studies with 0.5–2.0 mg/day pergolide (73, 74) or 100–200 mg/twice daily amantadine (75) also proved successful. Both these drugs have anti-Parkinson effects. Pramipexole (0.125–0.25 mg three times daily) has also been recommended (76). A prospective, open study with pramipexole administered in average doses of 0.84 mg/day and combined with a TCA or SSRI produced a favourable response in 55% in 31 unipolar or bipolar patients resistant to the first-choice antidepressant (77). Unfortunately, as no controlled trials have been carried out to date, and as sample sizes in the above-mentioned studies were small, the effectiveness of dopaminergic agents remains unconfirmed.

An interesting benefit of this pharmacological combination is the possibility of dopaminergic-induced sexual stimulation (reported in animal models), which means that dopaminergic agents may have a potential role to play in alleviating sexual dysfunction caused by the SSRIs (75).

Conventional antipsychotic agents. Some authors have proposed the administration of neuroleptics, particularly reserpine, a few days prior to starting antidepressant treatment. The idea is to sensitize postsynaptic receptors and thereby improve the prospects of an antidepressant response (68, 78). Antidepressant enhancement using reserpine for refractory depression has been endorsed by open-label studies (79), although results from controlled studies have been somewhat less conclusive (80, 81). In clinical care settings, combinations of perphenazine + amitriptyline, perphenazine + nortriptyline and melitracen + flupentixol, among others, have been used empirically, with apparently promising results, for a particularly resistant subtype of anxious depression.

Second-generation antipsychotics. Satisfactory results were obtained with clozapine in the treatment of refractory psychotic depression (82), and a response to augmentation has been seen with both risperidone (83, 84) and olanzapine (85) (0.5–2.0 mg) combined with fluoxetine (5–20 mg). The fluoxetine + olanzapine combination resulted in a marked increase in dopamine, serotonin and noradrenaline levels in the prefrontal cortex in rats (86). The fact that this combination brings both anxiety and irritability rapidly under control would indicate its potential for treating agitation and insomnia in refractory depressive subjects. Recent studies would suggest, moreover, that 40–80 mg twice daily of ziprasidone and aripiprazole effectively enhances the antidepressant effects of the SSRIs (87, 88).

Psychostimulants. Psychostimulants that have a significant impact on dopaminergic neurotransmission have been used in augmentation strategies involving TCAs, MAOIs, SSRIs and selective noradrenaline reuptake inhibitors (89–93). Only a few studies involving only small samples have evaluated the efficacy of these combinations. Drugs that have been evaluated include dextroamphetamine (5–20 mg/day), methylphenidate (5–40 mg/day) and modafinil (up to 400 mg/day).

In 16 treatment-resistant depressive patients, combinations of MAOIs, TCAs and psychostimulants resulted in an improvement in depression symptoms in most cases (94). Modafinil, a new psychostimulant with pharmacological actions that differ somewhat from those of the amphetamines, has shown good results in refractory depression (95). In 14 patients resistant to treatment with SSRIs or venlafaxine, inclusion of modafinil (up to 400 mg/day) in the original antidepressant treatment programme resulted in a 57% positive response (96). Good results with modafinil have also been described in other studies (97, 98). In a double-blind placebo-controlled study, favourable results were reported with modafinil in patients who had only responded partially to SSRIs and who had been suffering from persistent asthenia and somnolence (99).

Side-effects associated with this kind of combination include hypertension, anxiety, irritability and insomnia. Occasional manic episodes have also been described and there is a potential risk of abuse by patients with a history of dependence on psychotropes. One important drawback to the use of psychostimulants is their relatively short half-life. This has led to the development of

slow-release methylphenidate, which ensures rapid onset of the antidepressant action.

Anticonvulsants. Many of the anticonvulsants used to treat bipolar disorder (e.g. valproic acid, valproamide and carbamazepine) have been tested in refractory depression (100–102), although there are no studies that endorse this strategy. Some recent studies, however, have pointed to lamotrigine (103, 104), and gabapentin (105) as potentially effective pharmacological enhancement drugs. In a double-blind study of 15 unipolar patients plus eight bipolar patients in a depressive phase, no statistically significant differences were seen between lamotrigine + fluoxetine and fluoxetine + placebo in either pathology group (106). The doses administered in these studies were 200–400 mg/day of carbamazepine, 100–300 mg/day of lamotrigine and 300–1800 mg/day of gabapentin. These combinations may enhance the side-effects associated with anticonvulsants (sedation, weight gain) and, in some cases, will require plasma concentration monitoring.

Folates and S-adenosylmethionine. Certain folates that play an important role in cerebral methylation processes, in particular methyltetrahydrofolate and S-adenosylmethionine (SAME), have been reported as having antidepressant properties (107, 108). A placebo-controlled study that compared 0.50 mg/day of folic acid + fluoxetine to fluoxetine + placebo found that depression symptoms improved significantly in women, although not in men (109). Recent open-label studies report potentiation effects for 15–30 mg/day methylfolate (110) and 800–1600 mg/day SAME (111). An earlier onset of antidepressant effects has been seen with SAME + imipramine than with imipramine + placebo (112).

Oestrogens. Oestrogens play an important role in behaviour due to their interaction with neuronal receptors. The relatively high incidence of depression in women, the influence of the menstrual cycle on mood, the possible association between lowered hormone levels and mood changes following childbirth, and mood changes associated with the administration of oestrogens to postmenopausal women, have all pointed to lowered hormone levels as implicated in the pathogenesis and resistance to treatment of certain depressions, particularly in the case of postmenopausal women (39).

Anecdotal evidence from clinical care settings would indicate that some women who respond to oestrogens fail to respond to antidepressants, whereas other women who respond to combinations

of oestrogens and antidepressants fail to respond to monotherapy with oestrogens. A reduction in symptoms has been described in depressed women treated exclusively with oestrogens (113). SSRIs have been combined with oestrogen replacement therapies for peri- or postmenopausal women who failed to respond to antidepressant monotherapy. Given that oestrogen is itself a transcription activator, it is possible that, at the genome level, it acts synergistically with SSRI-activated transcription, thereby producing a greater overall effect than the SSRIs acting alone. Nonetheless, all the studies performed to date report only occasional efficacy (114).

A faster onset of action was observed when 25–50 µg ethinyl oestradiol was included in a programme of treatment with 150 mg imipramine; an increase in plasma levels and side-effects were also reported (115). However, these results were not confirmed in a subsequent study (116).

Other augmentation approaches have included the addition of testosterone or dihydroepiandrosterone (DHEA), and the avoidance of cyclical oestrogen/progestagen therapies. Although DHEA is the most important circulating corticoid in humans, little is known about its physiological function. It is a partial precursor for testosterone and oestrogens, and its metabolite (DHEA-S) is implicated in mood regulation. A small, preliminary double-blind study indicated that it may be useful as an antidepressant enhancer for refractory depression patients at doses of up to 90 mg/day (117).

Anti-glucocorticoids. Depression has frequently been associated with activation of the hypothalamic-hypophyseal-adrenal (HPA) axis. Some authors have reported alterations in the HPA-axis (hyperactivity) in anxious depressed patients with poor prognoses and resistant to a wide range of antidepressant treatment strategies.

Since 1991, several authors have proposed the use of anti-glucocorticoid agents – ketoconazole, aminoglutethimide and metyrapone – for the treatment of depression (118–122). In only some of these studies were antidepressant effects reported for patients resistant to treatment with antidepressant medications or ECT. In a double-blind, placebo-controlled study in depressed patients (eight with hypercortisolaemia), an antidepressant response was reported for 48% of subjects taking 400–800 mg ketoconazole compared with 6.6% of those taking placebo (123). Other studies have used ketoconazole as an enhancer for tranlycypromine (15) and for lithium and phenelzine (124). The daily doses of ketoconazole ranged between 300

and 1000 mg. There are, however, side-effects associated with its use, such as hepatotoxicity and hypoadrenalism.

Inositol. One suggested cause of treatment-resistant depression is a deficiency in inositol, which, acting as a second messenger, may not be correctly transmitting presynaptic signals. Preclinical studies would indicate that postsynaptic modulation of the second-messenger system (phosphatidylinositol and cyclic AMP) may be useful in treating depression.

Despite early, anecdotal reports in relation to the efficacy of 6 g/day inositol in reducing the severity of depressive conditions (125), a recent double-blind placebo-controlled study based on doses of 12 g/day inositol combined with an SSRI did not demonstrate the efficacy of this approach in treating refractory depression (126).

Opiates. The little evidence that would support opiates as antidepressant enhancers is based on small-scale studies, such as those with oxycodone, oxymorphone and buprenorphine (127, 128). This lack of validation, added to the possibility for abuse, effectively restricts the use of these substances.

Other potentiation strategies. They include the following:

- *Iron:* It is an essential enzyme for the synthesis of cerebral monoamines. Favourable responses have been observed in some refractory depressive patients when iron was added to the primary antidepressant treatment (78).
- *Thyroid releasing hormone:* It is a hypothalamic hormone that has provoked widespread interest, as has the role played by the entire HPA-axis in depression. It has been used as a mood regulator and as an enhancer of antidepressant therapies for refractory depressive patients (129, 130).
- *Testosterone:* A double-blind study of male refractory depressive patients reported poor results with 10 g/day testosterone 1% gel (131).
- *Dexamethasone:* Although some authors have reported antidepressant effects with high doses of dexamethasone (132), a controlled study failed to confirm this claim (133).
- *Omega-3 fatty acids:* The widespread interest in the possible effects of omega-3 fatty acids for treating bipolar disorder (134) pointed to its potential as an antidepressant enhancer in refractory depressive patients. However, no

studies have been published that endorse this view.

- *Eicosapentaenoic acid:* One study provides anecdotal evidence of eicosapentaenoic acid as a possible antidepressant enhancer (135).

Discussion

A wide range of potentiation strategies are available for dealing with treatment-resistant depression. Perhaps the best evidence is available for the addition of lithium to an antidepressant, although good results have also been reported with augmentation strategies involving T3 or buspirone.

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