Medicating with one antidepressant should always be the first-line treatment of choice. However, in some cases, a combination of two antidepressants, and very rarely three, may be necessary to get an acceptable antidepressant effect with tolerable side effects. This should be limited to failure of attempt at monotherapy with antidepressants from different groups, either because they were not effective enough or because the side effects were not tolerable. When combining antidepressants, an understanding of their biological types of action and of the clinical effects of a particular combination helps to make better informed choices, thereby lowering the risks and increasing the benefits of antidepressant medication to the patient.

Keywords: combination, medication, antidepressant, psychiatry
Contents

Introduction ........................................................................................................................................... 4
Non-Responders ................................................................................................................................... 4
STAR*D .................................................................................................................................................. 5
Selective serotonin reuptake inhibitor (SSRI) combinations .............................................................. 6
SSRI with SSRI ..................................................................................................................................... 6
SSRI with tricyclic antidepressant (TCA) ............................................................................................. 6
SSRI with irreversible monoamine oxidase inhibitor (MAOI) ............................................................. 7
SSRI with reversible MAOI .................................................................................................................. 7
SSRI with NaSSA or trazodone ............................................................................................................... 8
SSRI with NaSSAs ............................................................................................................................... 8
  Mirtazapine ...................................................................................................................................... 8
  Mianserin ......................................................................................................................................... 9
SSRI with SNRI ................................................................................................................................... 9
  Venlafaxine ...................................................................................................................................... 9
  Duloxetine ....................................................................................................................................... 10
SSRI with trazodone ............................................................................................................................. 10
SSRI with reboxetine ........................................................................................................................... 10
Tricyclic antidepressant combinations ................................................................................................. 11
TCA with MAOI ................................................................................................................................... 11
  Moclobemide .................................................................................................................................. 13
  Side-effects ..................................................................................................................................... 13
TCA with NaSSA .................................................................................................................................. 13
  Mianserin ....................................................................................................................................... 13
TCA with SNRI ................................................................................................................................... 14
SNRI combinations ............................................................................................................................... 14
  Venlafaxine with mirtazapine (‘California rocket fuel’) ................................................................. 14
  SNRI with trazodone ....................................................................................................................... 15
  Venlafaxine with reboxetine ........................................................................................................... 16
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAOI combinations</td>
<td>16</td>
</tr>
<tr>
<td>MAOI with trazodone</td>
<td>16</td>
</tr>
<tr>
<td>The Informed Patient and Monitoring</td>
<td>17</td>
</tr>
<tr>
<td>Conclusion</td>
<td>17</td>
</tr>
<tr>
<td>References</td>
<td>18</td>
</tr>
</tbody>
</table>
Introduction

Antidepressants have proven their effectiveness for depression, but are also used many other symptoms and conditions, such as insomnia, OCD, eating disorders and addictions.(1) While monotherapy, the use of only one agent, is the preferred default position, the variations in symptom constellations or the side effect profile of a drug may necessitate the use of two pharmaceutical agents. Only in the rarest cases should a combination of three antidepressants ever be considered. Usually, there is a combination of two which works quite as well or even better.

Psychotherapy and other therapeutic approaches, such as occupational therapy, mindfulness meditation and physical exercise, should always be considered with medication as components of a comprehensive treatment plan. Psychotherapy in particular may be able to achieve results which medication does not, and vice versa.

Non-Responders
At least a third of patients make an inadequate response to their first antidepressant monotherapy. First-line strategies are

- using a higher dose
- switching to another antidepressant of the same or different class.

With the group of selective serotonin reuptake inhibitors (SSRIs), often a switch to another SSRI is perfectly reasonable. However, if even the second SSRI fails, one should consider an antidepressant with a different type of action. Psychotherapy should in any case be considered from the start.

If two or three attempts at monotherapy failed, the following approaches can be explored:

- combining with another antidepressant, or
- augmenting the antidepressant with medication which is not an antidepressant (such as lithium or antipsychotics)

In some cases, one may offer a combination earlier to reduce extreme anxiety or symptoms of OCD with an antipsychotic, for example, and then later see if a monotherapy might work.

Meta-analyses have shown stronger data for switching to a drug in a different class (Papakostas 2008) or augmentation of antidepressants with psychotherapy (Pampallona 2004), lithium (Bauer 1999) or atypical
antipsychotics (Papakostas 2007), suggesting that these strategies should be logical next steps in the management of treatment-resistant depression before employing a combination strategy.

STAR*D

STAR*D was a multisite, prospective, randomized, multistep clinical trial of outpatients with nonpsychotic major depressive disorder. The study compares various treatment options for those who do not attain a satisfactory response with citalopram, a selective serotonin reuptake inhibitor antidepressant.

After receiving citalopram (level 1), participants without sufficient symptomatic benefit are eligible for randomization to level 2 treatments, which entail four switch options (sertraline, bupropion, venlafaxine, cognitive therapy) and three citalopram augment options (bupropion, buspirone, cognitive therapy). Those who receive cognitive therapy (switch or augment options) at level 2 without sufficient improvement are eligible for randomization to one of two level 2A switch options (venlafaxine or bupropion). Level 2 and 2A participants without sufficient improvement are eligible for random assignment to two switch options (mirtazapine or nortriptyline) and to two augment options (lithium or thyroid hormone) added to the primary antidepressant (citalopram, bupropion, sertraline, or venlafaxine) (level 3). Those without sufficient improvement at level 3 are eligible for level 4 random assignment to one of two switch options (tranylcypromine or the combination of mirtazapine and venlafaxine). The primary outcome is the clinician-rated, 17-item Hamilton Rating Scale for Depression, administered at entry and exit from each treatment level through telephone interviews by assessors masked to treatment assignments. Secondary outcomes include self-reported depressive symptoms, physical and mental function, side-effect burden, client satisfaction, and health care utilization and cost. Participants with an adequate symptomatic response may enter the 12-month naturalistic follow-up phase with brief monthly and more complete quarterly assessments. (2)

The STAR*D (Sequenced Treatment Alternatives to Relieve Depression) study provides evidence for a variety of options for up to four failed treatment trials.(3) It reported on antidepressant combinations, but did not show any single combination to be superior.
Selective serotonin reuptake inhibitor (SSRI) combinations

SSRI with SSRI

SSRIs differ to some extent in their receptor profile and exhibit significantly different pharmacokinetics. The clinical effect in some instances, like OCD and bulimia, seems to depend on higher doses of an SSRI. Also, in cases of anxiety higher doses of escitalopram may be required. Still, the empirical data suggest a relatively flat dose–response relationship for SSRIs when used as monotherapy(4).

Two open-label studies have tried combinations of one SSRI with another.(5) In both instances either fluvoxamine (50–100mg; n=7) or fluoxetine (20mg; n=6) was combined with citalopram, with apparent good clinical improvement in patients who did not respond to SSRI monotherapy. It has been proposed that addition of another SSRI increases the active S-enantiomer of citalopram compared with its R-enantiomer, leading to greater reuptake inhibition.(6) There is some evidence that the clinical effect may be due to an increase in the total SSRI dose.(7)

Nausea and tremor are common with the citalopram–fluvoxamine combination but no serious side-effects were noted from either reported series.

Serotonin syndrome is a potential serious adverse reaction with this combination. Also, one should have an eye on the possibility of a prolongation of the QTc interval in the ECG, especially if citalopram is used, which is probably the SSRI with the potential to lengthen the QTc interval the most.

SSRI with tricyclic antidepressant (TCA)

The combination of a predominantly noradrenergic TCA such as nortriptyline and an SSRI may overcome the ceiling effect of SNRIs, such as venlafaxine and duloxetine, and produce a different norepinephrine-serotonin reuptake blockade ratio. However, the combination of tricyclic antidepressants with SSRIs is less effective than raising SSRI dose alone.(8) A double-blind study did not show any difference between monotherapy and fluoxetine–desipramine combination.(9) Furthermore, drug interactions are likely, as some SSRIs inhibit tricyclic metabolism through the cytochrome P450 system, increasing the risk of cardiotoxicity, seizures and delirium.

Another potentially positive effect may be, that the cytochrome P450 (CYP450) inhibition of SSRIs can increase plasma levels of TCAs. It was suggested that the efficacy of the combination is largely due to
increased TCA levels in patients who failed monotherapy with either an SSRI or a TCA. (Levitt et al 1999) The extent of this inhibition varies between SSRIs us, however.

It has been argued that with monotherapy, combination treatment of depression using noradrenaline and serotonin reuptake inhibitors might ameliorate a greater number of symptoms in individual patients and be better at achieving remission. (9) However, using an SSRI and a pure norepinephrine reuptake inhibitor (NRI), such as reboxetine, or just a serotonin norepinephrine reuptake inhibitor (SNRI), such as a venlafaxine, may be a cleaner way than using the less predictable combination of an SSRI and a TCA.

**Side-effects**

Tricyclic toxicity can occur as a result of raised plasma levels. This is a particular risk for the 7% of White people who lack sufficient CYP2D6 to metabolise TCAs. Resultant cardiovascular problems can be life-threatening, especially in the elderly or the predisposed or if there is an overdose of the SSRI TCA combination.

Paroxetine can increase the anticholinergic side-effects of TCAs. Dry mouth and gastrointestinal distress are the most common problems in combining fluoxetine with desipramine (Dodd 2005).

Fluoxetine can prolong the elimination of TCAs, but blood levels are not closely correlated with dosage and are unpredictable (Westermeyer 1991). Fava and colleagues recommend using small doses of TCAs and plasma-level monitoring in such combinations (Fava 2002).

Citalopram inhibits CYP much less.

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**SSRI with irreversible monoamine oxidase inhibitor (MAOI)**

Irreversible MAOIs such as phenelzine and tranylcypromine are dangerous when combined with SSRIs, a combination that should never be used in clinical practice. Deaths have been reported even after an SSRI has been stopped before an MAOI was started. One should consult the current literature for the minimum wash-out times that should be allowed between the two kinds of medication.

**SSRI with reversible MAOI**

Moclobemide selectively and reversibly blocks the monoamine oxidase A enzyme. Three small open-label trials (total n=46) found moclobemide to be effective in combination with SSRIs (5). Both SSRI and
moclobemide were started at lower than usual doses and titrated slowly up. At therapeutic levels, the combination has been viewed as relatively safe. However, given the real risk of the serotonin syndrome when combining MAO inhibitors with serotonergic substances and the range of more modern combinations available, one can hardly think of a situation where the combination of an SSRI with any MAO inhibitor, irreversible or reversible, could ever be reasonable clinically.

**SSRI with NaSSA or trazodone**

The best evidence is for the combination of an SSRI with an NaSSA or trazodone – this combination received some support in the NICE guidelines (National Institute for Health and Clinical Excellence 2004). There is evidence that this combination shows greater efficacy than either drug alone, is well tolerated and carries a low risk of serious interactions. Nonetheless, it is mandatory to carefully monitor such combinations and avoid the routine use of high doses of both drugs.

**SSRI with NaSSAs**

Besides being used frequently in clinical practice, there are a number of reasons why this combination could make sense from a theoretical perspective:

- additive effects are possible because of different mechanisms of action
- rapid onset of effect is possible, owing to the receptor profile of NaSSAs
- side-effects of the SSRI may be nullified by the NaSSA and vice versa
- SSRIs can increase plasma levels of NaSSAs through CYP450 enzyme inhibition

Administered acutely, SSRIs initially suppress 5-HT reuptake at somatodendritic (presynaptic) sites facilitating autoreceptor activation and reduced serotonin transmission. In due course, desensitisation of these autoreceptors enhances serotonin neurotransmission.

**Mirtazapine**

Mirtazapine, being an α2-adrenergic antagonist, reduces autoreceptor (heteroreceptor) feedback at the somatodendritic site directly. This potentially enhances serotonin transmission at a quicker pace. A combination of both medications could thus induce a more rapid and robust antidepressant effect than each medication administered alone.

Paroxetine in combination with mirtazapine showed both, better tolerance and better response compared with either agent alone.(10)
Mianserin

In at least two RCTs (total n=135) mianserin was combined with fluoxetine. The combination was better tolerated than the individual agents alone, with a significantly more rapid onset of action than with fluoxetine alone.(5)

In another RCT (n = 295), the combination of sertraline and mianserin was only as efficacious as 100mg sertraline alone in patients previously unresponsive to 6 weeks of sertraline alone. An open-label study (n=20) followed by a small RCT (n = 26) of mirtazapine 15–30 mg in combination with other antidepressants (including SSRIs) at near-maximum doses revealed a significant response and good tolerance.(11)

Side-effects

Sedation, weight gain and headache are the most commonly reported side-effects of this combination. Restless legs syndrome has been reported in three patients from an RCT sample receiving fluoxetine 20mg/day in combination with mirtazapine 15mg/ day (Prospero-Garcia 2006). Although mirtazapine monotherapy is a possible treatment for some symptoms of serotonin syndrome (e.g. insomnia and agitation), there are case reports of new-onset serotonin syndrome with the combination (Benazzi 1998).

SSRI with SNRI

Venlafaxine

This does not make for rational polypharmacy as venlafaxine has predominant SSRI activity, particularly at low doses. Gonul et al report on four patients who only partially responded to high-dose venlafaxine but fully responded to SSRI–venlafaxine combination.(12) To reduce the risk of serotonin toxicity, the SSRIs were added to lower than the maximum dose of venlafaxine.

Side-effects

Low doses of venlafaxine combined with fluoxetine can cause urinary retention, constipation, dry mouth and blurred vision. This might be due to adrenergic stimulation mimicking anticholinergic effects. There is a potential risk of serotonin toxicity with this combination.
Duloxetine

The situation on a combination of duloxetine with an SSRI is unclear. Duloxetine can inhibit CYP2D6 and this may need to be considered if such a combination is attempted.

SSRI with trazodone

Trazodone is a dual 5-HT2A antagonist and serotonin reuptake inhibitor. Its 5-HT2A blockade is believed to reduce the side-effects associated with the stimulation of 5-HT2A, including sexual dysfunction, insomnia and anxiety. Trazodone has been largely used more for its sedative than its antidepressant properties. It may be one of the most commonly combined antidepressant with SSRIs for this reason.

It has been suggested that the mechanism of any additional antidepressant activity may be through SSRI-induced inhibition of the breakdown of both trazodone and its active metabolite m-chlorophenylpiperazine. Good response to the combination has been demonstrated in a small (n=26) double-blind RCT involving a treatment-resistant sample. In a case series involving eight consecutive patients taking fluoxetine as monotherapy, three reported reduced insomnia and depression when trazodone 100 mg per day was added. (13) This sample was heterogeneous for both severity of depression and response to previous medications.

Side-effects

Despite being 5-HT2 antagonists, trazodone and nefazodone can produce serotonin syndrome in combination with either SSRIs or SNRIs. This may be mediated through increased 5-HT1A transmission. Higher levels of trazodone can produce marked side-effects, including priapism. Citalopram and fluoxetine do not seem to increase trazodone levels significantly, at least in lower doses (Prapotnik 2004).

SSRI with reboxetine

Reboxetine is a noradrenaline reuptake inhibitor. Its combination with SSRIs can produce pharmacological effects similar to TCAs but with a more favorable side-effect profile due to a lower affinity for other receptors. The SSRI–reboxetine combination is now being increasingly used. It is proposed to have quicker onset of effects, at least experimentally. However, the combination mirrors the pharmacological profile of an SNRI and in the absence of compelling data it seems illogical to use two drugs rather than one.
Various open-label trials have been reported, involving reboxetine in doses of up to 8 mg per day (Rubio 2004). Interestingly, the combination appears to work better for non-psychotic than psychotic depression.

Results are less favorable for dysthymia. An open-label series of 141 patients who were partial responders or non-responders to SSRIs showed 50.4% response and 35% remission at 12 weeks when reboxetine was added (López-Muñoz 2007). In another case series, involving patients who had failed to respond to SSRIs (n=43), venlafaxine (n = 12) or mirtazapine (n = 6), the addition of reboxetine to the current drug was effective (Rubio 2004).

**Side-effects**

The combination of an SSRI with reboxetine is generally well tolerated and side-effects are largely related to effects of individual drugs. Nausea, headaches, nervousness with insomnia, urinary retention and periorbital edema were reported, especially in combination with fluoxetine.

**Tricyclic antidepressant combinations**

**TCA with MAOI**

The amount of serotonin and noradrenaline available in synaptic junctions can increase significantly if they are neither taken back (reuptake) nor destroyed (by a monoamine oxidase enzyme). This provides the basis for combining TCAs with MAOIs. The combination of TCAs with MAOIs has been reported on in three double-blind controlled trials, two open-label trials, a controlled trial of the combination against electroconvulsive therapy, and many case series. Despite the positive reports of efficacy in case series (White 1982), the controlled trials are largely negative. In a double-blind controlled trial of 135 outpatients with mild to moderate depression, most of whom had been previously treated with a TCA, trimipramine alone proved to be superior to the combination of an MAOI (phenelzine or isocarboxazid) with trimipramine or an MAOI alone (Young 1979). The combination was, however, found more likely to benefit women with severe depression lacking energy.

Another double-blind controlled trial (n = 79), which excluded treatment-resistant depression, found that the combination of amitriptyline and tranylcypromine had no advantage over either drug alone, although patients on the combination improved more according to their self-ratings after 6 weeks. A substantial proportion did not complete the study (23%) and the combined treatment was less well tolerated than single treatments (O’Brien 1993).
In the third double-blind controlled trial of patients with depression, the combination of amitriptyline and tranylcypromine was not superior to either drug alone (Razani 1983). This trial had been preceded by an open-label study by the same team, involving 30 newly admitted randomly assigned patients with depression, who were not necessarily treatment refractory. In this sample, the combination of amitriptyline and tranylcypromine was not superior to either drug alone and was associated with a slight increase in side-effects (White 1982).

The second open-label trial, of isocarboxazid and amitriptyline (n=25), involved patients with major depression who had failed to respond to at least four previous antidepressants. Follow-up for 3 years of the 12 who responded to combination drugs showed that treatment efficacy diminished after 2 years (Berlanga 1995).

In a controlled trial, electroconvulsive therapy proved superior to amitriptyline with phenelzine in 19 randomly allocated patients with depression previously treated ‘unsuccessfully with conventional psychotropic drugs at adequate doses’ (Davidson 1978).

Side-effects

Most serious adverse events have occurred when a TCA has been added to an established MAOI treatment compared with the reverse sequence. It has been suggested that the safest option is to start MAOI and TCA simultaneously at low doses increasing slowly to a maximum of half that used with single-drug treatment (White 1982).

The most serious adverse reaction is serotonin syndrome (Table 1), which usually occurs very rapidly. Combination of TCAs with MAOIs was not advised owing to severe adverse reactions and fatalities (Otte 2003). Imipramine and clomipramine appear to be particularly dangerous, with reports of serious adverse reactions, including serotonin syndrome. Oefele (1986) reported a fivefold increase in adverse reactions when clomipramine was combined with tranylcypromine compared with either drug alone or other TCA–MAOI combinations.

Animal experiments suggest that trimipramine is the safest of the TCAs in combination with MAOIs. It is suggested that TCAs with weaker serotonergic properties might be safer with respect to serotonin toxicity.

The combination of an MAOI with a TCA might, at least theoretically, protect against the ‘cheese’ reaction. Tyramine uses the presynaptic noradrenaline transporter to enter the neuron, where it induces depolarisation-independent noradrenaline release. Antidepressants with noradrenergic reuptake inhibition properties will prevent tyramine entry and will therefore attenuate the response.
Other side-effects are due to the synergism of the two drugs and include orthostatic hypotension, dizziness, headache, urinary retention, weight gain and nausea, all of which can be caused by either drug alone.

**Moclobemide**

There is a potential for synergism with the combination of dual reuptake inhibition from a TCA and monoamine oxidase inhibition from a monoamine oxidase A enzyme reversible inhibitor. One small RCT (n=58) (Tanghe 1997), one open-label trial (n = 14) (König 1997) and a short report (n = 18) have published on this combination (Steinberg 1994). The RCT showed a non-specific trend towards faster onset of action in the combination group (amitriptyline and moclobemide), but also reported increased agitation. In the open-label trial, more than 50% of the sample responded to the combination when a dose of 300mg/day of moclobemide was added to a TCA stabilised at an average dose of 180mg/day trimipramine equivalents (König 1997).

**Side-effects**

Moclobemide is relatively free of any CYP inhibition effect. Agitation and inner restlessness were the most commonly described adverse events when combining TCAs and moclobemide. Hypomanic switches were reported in the RCT group of inpatients with treatment-resistant major depression (Tanghe 1997). Hypertensive crises may occur, especially in patients with pre-existing hypertension (König 1997).

**TCA with NaSSA**

**Mianserin**

Mianserin predominantly blocks a2-autoreceptors, leading to increased noradrenergic transmission. Its effect on a2-heteroreceptors present in serotonin neurons is mitigated by its direct a1 -blocking effect. This reduces the serotonergic effect expected from such heteroreceptor blockade. Therefore, combining mianserin with TCAs that have a serotonergic profile might provide additive antidepressant efficacy. There are two double-blind controlled studies of TCAs used in combination with mianserin (Lauritzen 1992; Medhus 1994). These reported encouraging results, although the numbers were small (total n=57) and the treatment period was brief. In the first of the two (Lauritzen 1992), imipramine was started at a low dose (25–50mg/day depending on age), aiming for a plasma level of >200nmol/l, and mianserin was given at a dose of 30mg/day.
As far as we are aware, there are no studies that investigate the combination of TCAs with mirtazapine, although the principles behind the combination would be similar to those for mianserin.

**Side-effects**

No additional safety issues of the combination compared with a TCA alone were reported.

**TCA with SNRI**

Both TCAs and SNRIs act through noradrenaline and serotonin reuptake inhibition and therefore it is illogical to combine them. Venlafaxine might be useful in achieving an antidepressant ‘top-up’ effect for patients who require a higher TCA dose than they could tolerate, but there is no direct clinical evidence for this. Desipramine and venlafaxine may act via different noradrenergic reuptake mechanisms and systematic trials of this combination have been encouraged (Gómez Gómez 2000). There is one small (n = 11) open-label trial of venlafaxine combined with a TCA (clomipramine or imipramine) in patients with depression, who had a partial response to TCAs but failed to respond to heterogeneous augmentation strategies. Of the sample, 82% responded, with 64% achieving full remission which in the majority was maintained at 2 years. A stable dose of around 200 mg/day of clomipramine or imipramine was used, to which venlafaxine was added and titrated from 75 to 300mg in divided doses (Gómez Gómez 2000).

**Side-effects**

Reported side-effects with the combination include mild hypersomnia, sexual dysfunction after dose increases, constipation and weight gain. No significant changes in blood pressure, heart rate, blood analyses or electrocardiogram were described. Venlafaxine has little effect on CYP2D6 and therefore should not have a significant impact on TCA levels; dose adjustments in combinations may not be necessary. Venlafaxine may produce a modest increase in the desmethyl metabolite of imipramine, although the clinical significance of this is unclear.

**SNRI combinations**

Venlafaxine with mirtazapine (‘California rocket fuel’)

Venlafaxine and mirtazapine act synergistically to boost noradrenergic, serotonergic and dopaminergic transmission through monoamine reuptake inhibition and a2-blockade. Theoretically, this offers one of
the most potent mechanisms of manipulating the monoamine system, leading to its nickname of ‘California rocket fuel’.

Three studies report on the combination of venlafaxine and mirtazapine, including a 12-week randomized controlled trial (STAR*D, n = 51), a 6-week open-label trial (n=35) and a retrospective chart review (n=32).

In the STAR*D study (McGrath 2006), high dose extended-release venlafaxine was combined with mirtazapine and compared with the MAOI tranylcypromine in adult out-patients with nonpsychotic depression. Overall, 13.7% achieved remission (as defined by a score ≤7 on the Hamilton Rating Scale for Depression (HRSD)); these patients had previously failed to respond to three medication trials. Venlafaxine (extended release) was started at a low dose, built up to a mean dose of 210.3mg/day in combination with mirtazapine gradually titrated to a mean of 35.7mg/day.

In the open-label trial of out- and in-patients with depression who had not responded to adequate monotherapy with two antidepressants, the addition of mirtazapine (15–30 mg/day) to either an SSRI (n=23) or venlafaxine (n=12) led to remission in half of the patients. The decrease in HRSD scores in patients on venlafaxine was higher than in patients on SSRIs (P=0.013) (Aydemir 2005). In the retrospective chart review, 32 patients with recurrent depressive disorder who had previous treatment trials (1–6 trials) received the combination of venlafaxine and mirtazapine: 50% showed improvement at 8 weeks (Hannan 2007).

The combination of mirtazapine and venlafaxine (n = 4) was also included in the Carpenter et al (2002) study discussed earlier. Serotonin syndrome has been reported even during a cross-taper. It is important to be aware of the potential for serotonin syndrome despite reports that mirtazapine may be less likely to cause serotonergic toxicity. Weight gain and sedation may be prominent and related to mirtazapine. In the STAR*D sample, 22.4% had a mild, 24.5% moderate and 6.1% severe to intolerable side-effect burden (McGrath 2006).

SNRI with trazodone

This combination has been tried with a similar rationale to the SSRI–trazodone combination. A prospective 4-week semi-naturalistic study (n=50) in in-patients with depression reported that although clinicians expected improvement of both insomnia and inner agitation with the addition of trazodone to venlafaxine, only insomnia improved (Bertschy 2005). Evidence is too scarce to comment further on this combination.
Venlafaxine with reboxetine

Employing the same rationale as SSRI–reboxetine combination, reboxetine has been added for patients not responding to venlafaxine alone in an open label series – reasonable response rates have been reported (Alamo 2007). Any synergism of such a combination is doubtful, as both drugs act via the same mechanism; the same effects could be achieved by a higher dose of venlafaxine alone, with more predictable pharmacokinetics. No serious adverse effects were reported in this series.

MAOI combinations

Combinations of SSRI–MAOI and TCA–MAOI have been considered in the previous sections. No studies were found for the MAOI–SNRI combination.

MAOI with trazodone

This combination has been tried with a similar rationale to the SSRI–trazodone combination. Two studies have reported on the use of trazodone for the treatment of insomnia in patients established on an MAOI. Both included a heterogeneous diagnostic sample. The first was an open pilot study (n=48) and reported a sustained hypnotic effect in a large majority of the patients (Jacobsen 1990). The second was a case series (n=13) in which 69% of patients experienced a sustained benefit when a mean dose of trazodone 85 mg/day was added to an established mean dose of phenelzine 50mg/day (Nierenberg 1989).

Side-effects

Side-effects included orthostatic hypotension, daytime sedation and mania in one patient with bipolar disorder. One patient experienced nocturnal myoclonus, which may have reflected a hyperserotonergic state. Serotonin syndrome can occur with this combination.
The Informed Patient and Monitoring

Patients should be informed about the state of the evidence base and enter into a trial of these combinations with this information fully explained and shared. Both the practitioner and the patient need to be aware of the potential risks of using a combination strategy as opposed to an alternative strategy and should set up an active monitoring system.

Conclusion

There are very few RCTs and an even greater scarcity of those with adequate size and study designs that are able to determine the efficacy of combinations v. monotherapy with the individual drugs alone. It also highlights a number of combinations with established risks and toxicity and indicates that some combinations are either illogical from a psychopharmacological perspective or unpredictable. Several combinations have a low benefit-risk ratio and should be avoided, and most should only be used with a second opinion and/or specialist advice and support.

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