Continuing Professional Development

MODULE 11: DEC 2011

Antidepressant augmentation and combination in unipolar depression: strong guidance, weak foundations

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Depression will be the second leading contributor to the global burden of disease by 2020.[1] In Ireland, in 2009, 6061 people were hospitalised with depressive disorders.[2] This represents a significant economic and social burden. There is growing awareness of the difficulty in treating depression with medications alone. The likelihood that a patient will achieve remission with the first antidepressant tried is around 30%, and the rates are similar for the second antidepressant tried. This falls to around 15% after three trials.[3] Many patients are exposed to pharmacotherapy for extended periods of time with little beneficial effect, but often with side-effects. Patients are therefore in great need of clear information with regard to their chance of success. Clinicians are in need of clear guidance on prescribing strategies which have proven efficacy. However, this guidance often discusses treatment strategies based on varying levels of evidence. Guiding bodies may approach the problem from varying perspectives. The UK National Institute for Health and Clinical Excellence (NICE) has a clear government mandate with regard to provision of not only effective but cost-effective treatments. The British Association of Psychopharmacology (BAP) is an independent body of interested researchers and therefore may discuss prescribing options from the point of view of tertiary care institutions, and university centres. The South London and Maudsley NHS Foundation Trust publish the popular Maudsley guidelines. These are perhaps more pragmatic in nature, but include very low levels of evidence, including case series.

The American Psychiatric Association (APA) is an independent member association which also publishes guidelines. These are published in the *American Journal of Psychiatry* and the latest guidelines were published in October 2010.

All these bodies attempt to weigh their advice according to the level of evidence available and aim to provide clinical guidance in difficult situations. The burden on guiding organisations is to provide some direction and clarity in areas that are often unclear or controversial. Clinical guidelines are one method of providing support and guidance to busy clinicians. However, this clinician-centered approach has limitations. The onus is on the authors of the guidance to provide ever-more treatment options. This may mean that conclusions about the efficacy of medications is overstated or the limitations of the literature not fully explored in explanatory notes.

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Method

The aim of this paper is to examine the basis of recommendations for pharmacological combination and augmentation therapies in treatment resistant depression (TRD) and the levels of evidence supporting their use.

We performed a search of PubMed and the Cochrane Library using key terms "antidepressant augmentation", "antidepressant combination" and "treatment resistant depression" from inception to May 2011. Inclusion criteria were human trials investigating psychopharmacological approaches to treatment resistant depression in adults and other papers reviewing this issue in English. Exclusion criteria included other physical therapies or psychotherapies, studies in children or adolescents and studies specifically looking at other axis I disorders. We found 808 papers, which was reduced to 238 papers following removal of duplicates and papers not meeting criteria.

Although there are no specific guidelines in Ireland, we commonly refer to UK or US guidelines and we therefore reviewed NICE, BAP, Maudsley and APA prescribing guidelines. The NICE, BAP and APA guidelines include a detailed methodology of how their reviews and recommendations were derived. The Maudsley guidelines do not provide these details.

Our review of the literature assessed studies using the principles laid out by the Oxford Centre for Evidence-based Medicine (CEBM)[4] *(see Table 1)*. The studies with the highest level of evidence were given the most credence.

Background

Depression rarely responds to a 'one size fits all' approach. Combination and augmentation treatment for depression is common in clinical practice.

A survey from the Royal Australian and New Zealand College of Psychiatrists found that 79% of Australian psychiatrists prescribe combination antidepressants and 89% felt that general practitioners should be given more advice on this.[5] A study by Valenstein et al found that 22% of patients in a large sample (n=220,502) of veterans in the United States received either

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Table 1: CEBM Levels of evidence

Level of evidence	Description
1a	Systematic review of RCT's with homogeneity
1b	Individual RCT with narrow Confidence Interval
1c	All or none study
2a	Systematic review of cohort studies with homogeneity
2b	Individual cohort study and low quality RCT's.
2c	"Outcomes" Research; Ecological studies
3a	Systematic review of case-control studies with homogeneity
3b	Individual case control study
4	Case series (and poor quality cohort or case-control studies)
5	Expert opinion without explicit critical appraisal OR based on physiology, bench research or "first principles".

combination or augmentation antidepressant therapy.[6] Despite its common occurrence, there is a lack of consensus in clinical guidelines on how to proceed if initial antidepressant treatment proves unsuccessful.

Pharmacotherapy remains a cornerstone in the treatment of moderate to severe depression. Other evidence-based treatments that have an important role include psychological interventions and physical treatments such as electroconvulsive therapy (ECT).[7] Although low-intensity psychosocial interventions may be sufficient in mild to moderate depression, higher intensity interventions are required to treat moderate to severe depression. The NICE and APA guidelines provide a thorough review of the evidence for the various psychotherapies, with strong support for Cognitive Behavioural Therapy[8] and Interpersonal Psychotherapy[9] in the treatment of depression, both as a stand-alone option or in combination with pharmacotherapy.

If pharmacotherapy is the preferred option, clinical guidelines, such as those provided by NICE[10] suggest initial treatment should be a single Selective Serotonin Reuptake Inhibitor (SSRI) for at least six to eight weeks at an adequate dose. This is based on the NICE Guideline Development Group (GDG) examination of clinical trials, which found that if there was inadequate response to an antidepressant at two weeks, there was still a 40% chance of the patient achieving a response after eight weeks. If there was no response at four weeks, the chance of a response after eight weeks was still 20%. After six to eight weeks of non-response however, only a minority went on to a response over the following weeks.

Although about two-thirds of patients respond to this approach, this leaves about one-third where there is either an incomplete or no response. Treatment resistance refers to an inadequate response to at least one antidepressant given for an adequate duration with adequate compliance. Some insist on two failed trials.[11] Treatment resistance does not refer to medication trials terminated due to side-effects. Unfortunately, there is not a generally agreed exact definition of treatment resistance, which adds to the lack of clarity in this area. The reported prevalence of treatment resistance varies from 20-50% [12,13] and the recent large publicly funded STAR-D trial found decreasing response rates in people who had already required multiple trials of antidepressants.[14]

In drug trials an adequate response is typically defined as a 50% reduction in symptoms on a symptom rating scale such as the Hamilton Depression Rating Scale (HAM-D). A partial response to treatment is usually defined as a 25-50% reduction. There are however some cases where even a 'full' response is inadequate. If an initial HAM-D score is 30, a 50% reduction would still leave a HAM-D score of 15, indicating a significant level of depression.

Combination antidepressant therapy strictly means the use of two separate antidepressants in combination, the rationale being that the agents have differing modes of action. Augmentation strategies on the other hand, involve adding another compound to an antidepressant to boost the antidepressant effect of the initial drug. This compound may not be a first-line antidepressant or suitable in isolation, but have shown some efficacy in combination.

There are several issues to consider before considering combination or augmentation of antidepressant therapy in treatment resistant depression.[15]

First one should ask whether the diagnosis is correct. Some people with personality disorders are likely to score highly on rating scales for depression but the associated distress is unlikely to respond to medication.[16] It is also important to consider undiagnosed bipolar affective disorder. One should also assess for comorbid conditions that may influence treatment, such as substance abuse and anxiety disorders, as well as underlying medical conditions *(see Table 2)*.

Substance misuse disorders are more common in the psychiatric than the general population. Substance misuse can lead to a worsening of depressive symptoms and treatment resistance, but depression can also lead to a worsening of substance misuse.[17] It is important in instances where there is comorbidity to assess whether one or both of the disorders are currently active.

This underlines the necessity of a thorough re-assessment, including chart review and extensive collateral history in patients who have treatment resistant episodes as some causes of treatment resistance could be eliminated.[18]

An adequate period of time and an optimal dose should be used. If patients cannot tolerate the highest dose of a medication due to side effects this does not have the same prognostic implications as the failure to respond.

A population survey by Broly[19] revealed that up to 10% of the Caucasian population may be either extensive or poor CYP2D6 metabolisers which means there can be wide variations in blood medication levels and dosage requirements. Other pharmacokinetic issues which may hinder drug efficacy include p-glycoprotein. P-glycoprotein is a basement membrane transport pump active in the blood brain barrier which inhibits drug entry. Recent studies have shown this may account for a significant variation in response to drugs.[20]

The metabolising status of the individual patient becomes irrelevant if they are not taking the medication so adherence should be assessed, and social factors that may be maintaining the depression should be addressed, again highlighting the necessity of thorough re-evaluation.

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Table 2: When one antidepressant is not enough

Checklist	√
1. Confirm diagnosis	
Collateral history	
Old notes/chart review	
Mood diaries	
2. Rule out co-morbid conditions	
Substance misuse disorders	
Anxiety disorders	
Medication related	
Medical illness	
Thyroid (subclinical)	
Steroids	
Inflammatory disorders	
3. Adequate dose	
4. Adequate trial period	
5. Adherence	
6. Address social factors maintaining depression	

There may also be gender-specific issues such as mood disorders in the menopausal period[21] that should be taken into account. If these factors do not shed any light on the inadequate response, options include switching to another antidepressant, adding another antidepressant, adding an augmenting agent, physical treatments such as ECT or a psychological therapy such as CBT or IPT if not used already.[22] In treatment resistant depression, the psychotherapy with the strongest evidence is CBT,[23] with the STAR*D trial also finding it to be generally as effective as second-step pharmacological therapy.[24]

There are several arguments in favour of combination or augmentation strategies:

- It is postulated that the added compound can act via a different neurotransmitter, through a synergistic effect or through modulation of second messenger systems.[25]
- With substitution, the patient may lose all the gains they may have made when the first antidepressant is stopped. This is especially the case in partial responders, where the loss of even limited gains may be a serious and dangerous setback.
- It can be demoralising for patients after several weeks on one agent to have to start all over again with a new agent.
- When one switches an antidepressant it may involve several weeks of a washout period or time spent titrating dosages up and down.

Theoretically, combination strategies can therefore offer a quicker response than monotherapy[26] due to time saved in washout and titration. However, only limited evidence exists for faster response with certain combinations and these have not necessarily, included treatment resistant patients.[27] Potential drawbacks of a combination or augmentation approach include:

- Increased number of potential drug interactions
- Increased risk of side-effects with the possibility of reduced compliance.
- Increased economic cost
- Lack of clarity as to which pharmacological agent is causing a clinical improvement.[28]

Combining two agents may increase toxicity so the risk of adverse effects would be expected to be higher,[29] but the evidence base suggests that this approach is generally well tolerated, and that the second agent does not substantially alter the side effect profile of the initial antidepressant.[30,31] In some cases the second agent may even reduce side-effects induced by the first drug, such as the use of buspirone to ameliorate sexual side-effects of SSRIs.[32]

There are important differences within the SSRI group in terms of pharmacokinetics and drug interactions despite their similar clinical efficacy, therefore a knowledge of the individual pharmacokinetic properties of the agents used in combination is essential. Fluoxetine, for example, has a much longer half-life than the other SSRIs.

Review of the evidence

The STAR*D trial

The American STAR*D trial (Sequenced Treatment Alternatives to Relieve Depression) was a large, publicly funded, open-label effectiveness trial divided into several levels. The aim was to test the effectiveness of various approaches to the treatment of depression in a clinical setting. The mean HRDS17 score at baseline was 19 indicating a moderate level of depression. Patients not responding to the first level of treatment (citalopram only) would go on to a series of options in the second level. If this was not successful they would go on to the third level and so on. It is an important study, but there are some limitations to bear in mind when reviewing the results. No placebo was used in the trial, and randomisation was often limited by patient choice. Caution should be used in comparing treatments offered at different levels. Patients who previously had not responded to the treatments offered in STAR-D were excluded from the trial which may have inflated the remission rates.[33] The STAR-D trial found that comorbid axis I and III conditions as well as anxious features were associated with higher rates of treatment resistance.[34] These patients may also have a slower response to treatment and can be more susceptible to side-effects.[35]

Augmentation strategies

1. Lithium

Lithium is one of the most widely used and best-studied augmentation strategies, and is one of the few combinations supported by NICE as a next-step treatment in those who do not respond to first-line treatment. It is also supported by the BAP and the Maudsley Guidelines as a first choice treatment for refractory depression. [36] It is recommended with moderate confidence by the APA.

The exact mechanism of action is unknown, however it is thought to enhance serotonin release, possibly by reducing the negative feedback on serotonergic neurons[37], and also up-regulated dopamine second messenger signaling[38]. It has been used with various monoamine reuptake inhibitors, at doses between 600 to 1200 mg. A meta-analysis by Crossley and Bauer[39] in 2007 found that there was a relationship between dose and efficacy, suggesting doses above 800mg may be required to be of benefit. This relationship is important as lithium is often used as an augmenting agent in lower doses than in lithium monotherapy. If low doses are used, the evidence suggests that there are still drawbacks in terms of side-effects and monitoring, but

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Table 3: Features of serotonin syndrome

Features of serotonin syndrome
1. Agitation or restlessness
2. Confusion or delirium
3. Autonomic instability (changes in blood pressure and heart rate)
4. Hyperthermia
5. Nausea
6. Diarrhoea
7. Myoclonus

little clinical benefit.

The Crossley and Bauer meta-analysis showed convincing evidence for lithium as an effective augmentation strategy, but not for its use to accelerate antidepressant response. The study found lithium was three times more effective than placebo as an augmenting agent, with a Number Needed to Treat (NNT) of five to achieve remission.[40] It is worth noting however, that most of the studies augmented lithium with tricyclic antidepressants (TCAs) rather than SSRI's, and the numbers were small (a total of 269 patients from a total of 10 RCTs). Some of the trials also included both bipolar and unipolar depressed patients and there were large differences in dosages.

Regarding the combination of lithium and a SSRI, there are case reports of serotonin syndrome, as well as instances of hypomania and mania, absence seizures and delirium.[41] This risk appears to be higher with fluoxetine, whereas citalopram appears safe.[42]

One arm of the STAR-D trial compared lithium augmentation with tri-iodothyronine (T3) augmentation of citalopram. Patients at this level had already failed two treatments for depression. 15.9% of patients on lithium achieved remission and there were frequent reports of side-effects.[43] Although this study reported a favourable response for T3 over lithium, this was not statistically significant. Also, the mean dose of lithium given was 859mg. Given the findings from the Crossley meta-analysis, this may reflect insufficient dosing for many patients in the STAR-D trial.

2. Tri-iodothyronine (T3)

T3 has been used to augment monoamine oxidase inhibitors (MAOIs), TCAs and SSRIs in non-hypothyroid patients.

The use of T3 is not recommended by the NICE guidelines as only one paper met their stringent criteria (it appeared to show only a subgroup of responders), but it is supported by the BAP, the APA, and the Maudsley guidelines. Small doses (25-50 mcg/day) are used, but due to possible interference with thyroid function, should be discontinued if there is no response within three weeks. The mechanism of its effect is complex but there is evidence that thyroid hormone has substantial effects on brain neurochemistry, neuronal plasticity and gene expression.[44]

The STAR-D trial, discussed above, found remission rates of 24.7% when T3 was added as a third-step option. This was higher than for lithium augmentation (but not statistically significantly)[45] and had fewer side-effects.

A meta-analysis by Aronson et al[46] including 292 patients, showed moderately large improvements with T3 augmentation, mostly of TCAs.[47] There was a large degree of statistical heterogeneity between the studies, and only four of the eight included studies in this meta-analysis were randomised controlled trials (RCTs). When the non-RCT's were excluded, a sub-analysis failed to find any significant advantage for T3.

A more recent meta-analysis in 2009 by Papakostas et al examined T3 augmentation of SSRIs only.[48] Four trials, with 444 patients were included. Again, there was a large degree of heterogeneity between studies. The pooled results failed to find a significant difference between SSRI alone and SSRI with T3 augmentation.

Studies examining doses above 50mcg of T3 are rare. The evidence is limited to an open trial using dose of 100 mcg[49] and a case series with doses up to 150mcg[50], both with 17 patients. Although they showed some promise, there are marked methodological issues due to the nature of the study design.

Together, these results indicate the need for further evidence to clarify the role of T3 as an augmenting agent.

3. Atypical antipsychotics

Antipsychotics are effective in psychotic depression but there is also gathering evidence for the use of atypical antipsychotics in non-psychotic depression. In the 2009 NICE guidelines, aripiprazole, olanzapine, quetiapine and risperidone were recommended as augmenting agents for the first time. Along with the NICE guidelines, the BAP, APA and Maudsley guidelines also support the use of these antipsychotics, with the BAP guidelines reporting stronger evidence for olanzapine and quetiapine. The Maudsley guidelines limit their recommendation of olanzapine for augmenting fluoxetine only.

Aripiprazole was the first of these agents to receive a US Food and Drug Administration (FDA) approval as an augmenting agent in treatment-resistant depression in 2007, followed by olanzapine and quetiapine. Their approval was based on large, drug-company funded trials that have yet to be replicated. The combination of olanzapine and fluoxetine is for sale as Symbyax in the US. In 2010, quetiapine was given a licence in the UK as an augmenting agent. This was followed at the start of 2011 in Ireland. To date, quetiapine remains the only antipsychotic licenced as an augmentation agent in depression in Ireland.

The exact mechanism by which they exert an antidepressant effect is unclear, but it is thought that blockade of 5HT2A receptors plays a key part,[51] and they also have 5HT2C and dopaminergic activity. As yet there is no proven independent antidepressant effect.

A meta-analysis by Nelson et al in 2009 [52] found that olanzapine, risperidone, quetiapine and aripiprazole were an effective adjunct in treatment resistant depression, with an overall number needed to treat of nine to achieve remission acording to indivdual trial criteria. The largest effect-size was for Risperidone (OR =2.63) followed by Aripirazole, with Quetiapine and Olanzapine equally effective. This meta-analysis included a large number of patients (3480) and there was a low level of heterogeneity between the studies.

The meta-analysis points out that the rates of discontinuation specifically attributable to side effects were significant for

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olanzapine, quetiapine, and aripiprazole. The use of antipsychotics are associated with serious adverse events, such as tardive dyskinesia as well as the more common side-effects such as sedation and weight gain. The odds of discontinuation due to side-effects for any reason were non-significant for risperidone, olanzapine and aripirazole, but raised for quetiapine.

A pooled analysis[53] of the two main RCTs supporting the use of quetiapine in depression found that 35% and 44% (300 mg XR and 150mg XR respectively) of the improvement in the HAM-D scores was due to improvement in sleep.

There was also a suggestion of publication bias, with a surplus of small trials showing a large effect, however, when these were removed the outcomes were unchanged. Keitner commented that there are still a number of unanswered questions regarding the use of atypical antipsychotics, such as optimum dosage, necessary duration of treatment and importantly, the long-term effects of antipsychotic use.[54]

It therefore appears atypical antipsychotic augmentation may be helpful in the short-term, but the risk-reward balance for longer use remains unknown.

4. Lamotrigine

Lamotrigine is an anti-epileptic that works by inhibiting glutamate and is used in bipolar affective disorder. The NICE guidelines report that there is insufficient evidence to recommend its use as an augmenting agent in unipolar depression. The BAP and APA guidelines give it some limited support. The Maudsley guidelines recommend it as a second-line augmenting agent. It was not included in the STAR-D trials.

The evidence for its use in unipolar depression is based on retrospective chart reviews and small open trials, only some of which were randomised[55]. Actual randomised controlled trials, have been completely underpowered to detect an effect of lamotrigine, with numbers ranging from 15-40, the larger trials showing some effect on secondary outcomes.[5657] There is very limited evidence for the use of lamotrigine in this group of patients. It requires slow titration and carries a risk of Stevens-Johnson syndrome.

5. Pindolol

Pindolol is a beta-adrenergic antagonist which selectively blocks pre-synaptic 5HT1A receptors. It is not supported by NICE, APA or BAP guidelines and is only recommended as a second-line augmenting agent in the Maudsley guidelines.

Its mechanism of action is thought to be through inhibition of the negative feedback from increased serotonin levels that occurs with the use of SSRI's. [58] It has been thought to accelerate the antidepressant response to SSRI's. [59]

Its role as an augmenting agent remains unclear with a large degree of heterogeneity in studies of its potential benefit. One recent systematic review of pindolol augmentation with SSRI's only, concluded it had an overall beneficial clinical effect, most notably in the first four weeks of treatment. [60] This study included 889 subjects, but was limited by a high degree of heterogeneity. Both unipolar and bipolar, treatment resistant and treatment naive in-patients and outpatients were included. Although there appeared to be a benefit over placebo at 4 weeks, by 6 weeks there was no statistically significant benefit to pindolol augmentation suggesting that if it is effective it is in speeding response, rather than enhancing overall response rates..

Combination strategies

1. Mirtazapine and SSRI/SNRI

One of the more common true combination strategies is the use of Mirtazapine and a SSRI or SNRI. Mirtazapine, a tetracyclic antidepressant is a noradrenergic and specific serotonergic antidepressant (NaSSA) and is recommended as a first choice combination agent by the NICE and Maudsley Guidelines. It is also supported by the BAP and APA guidelines. In the STAR-D trials the combination of venlafaxine and mirtazapine only achieved a 13.7% remission rate, but was used as a fourth-line treatment and so only in the most resistant of cases.[61] It compared favourably with the use of tranylcypromine (a MAOI), especially in terms of side-effect burden and ease of use.

Mirtazapine is thought to increase noradrenaline (NA) transmission through antagonism of $\alpha 2$ adrenoreceptors as well as action on serotonin reuptake. The combination of mirtazapine and high-dose venlafaxine was dubbed "California Rocket Fuel" by Stahl in Essential Psychopharmacology[62], due to its theoretical synergy. Mirtazapine has also been used with high dose venlafaxine to block 5HT2 and 5HT3 receptors with the aim of reducing sexual and anxiety side-effects[63]. The use of duloxetine, another SNRI, with Mirtazapine was reported by Meagher et al who dubbed this combination "Limerick Rocket Fuel"[64]. As with the use of any two serotonergic agents there is a risk of serotonin syndrome.

The evidence-base is chiefly from randomised controlled trials. The NICE guidelines identified one RCT comparing mirtazapine augmentation with placebo by Carpenter et al from 2002[65], which found mirtazapine augmentation resulted in a statistically significant improvement in mean end-point in depression scores and response, but not for remission. This study had small numbers (26 patients), the duration of the study was short, (four weeks) and there was heterogeneity in terms of diagnosis, antidepressants used and dosages used.

Since the NICE guidelines were published a new RCT examining the role of mirtazapine as an augmenting agent has been published by Blier et al.[66] They concluded that combining mirtazapine with either fluoxetine, venlafaxine or bupropion was more clinically effective than fluoxetine alone, with the strongest results for a mirtazapine and venlafaxine combination. There was a statistically significant difference in favour of combination treatment for mean HAM-D scores and remission rates, with a NNT for remission of between 3-5 versus fluoxetine alone. This study had a relatively large sample of 105 patients split into four groups. The randomisation process is somewhat unclear, but the groups were largely similar in terms of demographics and drop-out rates. The dose of fluoxetine may have been sub-optimal favouring the combination treatment arms, and there was a lack of estimate of the precision of the findings.

In both the Carpenter and Blier trial weight gain was associated with mirtazapine vs placebo. This was statistically significant in the larger Blier trial, despite their choice of "weight-neutral" agents to combine with mirtazapine. There was a mean increase of 2.7 kg over a six-week period in those groups a mirtazapine combination.

2. Bupropion and SSRI

Bupropion is a dopamine and noradrenaline reuptake inhibitor licenced for smoking cessation in Ireland and the UK. It is licenced as an antidepressant in the United States and the

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Table 4: Overview of augmentation strategies

Augmentation agent	Proposed mode of action	Used with	Dose	Potential issues
Lithium	Enhances serotonin release. Action on GSK3Beta/Akt signalling complex,	TCA, SSRI, MAOI	0.6-1.2g*	1. Careful monitoring required. Special attention to TFT/U&E 2. Serotonin Syndrome 3. Tolerance to side-effects can be an issue
T3	Exact mode of action unclear	TCA, SSRI, MAOI	25-50 mcg*	1. Monitor thyroid function.
Olanzapine	5HTa2 receptor activity	SSRI (fluoxetine)	12.5mg*	1. Metabolic syndrome 2. Sedation
Quetiapine	5HTa2 receptor activity	SSRI, SNRI	300-600mg*	1. Weight gain 2. Sedation 3. Hypotension
Risperidone	5HTa2 receptor activity	SSRI, SNRI, TCA	0.5-2mg*	1. Hyperprolactinaemia 2. Weight gain 3. Hypotension
Aripiprazole	5HTa2 receptor activity. Partial agonist 5HT1a	SSRI, SNRI	5-20mg*	1. Akathisia, restlessness
Lamotrigine	Glutamate inhibition ?5HT1a activity	SSRI	200mg*	Steven-Johnson syndrome
Pindolol	Blocks pre-synaptic 5HT1a receptor	SSRI, SNRI	7.5-15mg*	May only affect speed of response
Omega-3 triglycerides	Anti-inflammatory effect	SSRI, SNRI TCA, MAOI	1-2g*	Appears safe
Folate	Increased levels of 5HT, DA, NA	SSRI, TCA	2-5mg*	Dosage trials underway

**Indicative doses only. Not to be used as a prescribing guideline. Please review relevant literature.*

combination with an SSRI is supported by the APA. The Maudsley guidelines recommend it as a first-line augmenting agent due to the findings from the STAR-D trial, which found a remission rate of 29.7% when bupropion was combined with citalopram. The limitations of the open-label STAR-D trial have been discussed previously, and it should be noted that bupropion was offered as an early step in the STAR-D algorithm. The remaining evidence base for bupropion and SSRI combination is from small open trials or case reports and as such is not supported by the NICE or BAP guidelines.

It is also thought to be helpful in ameliorating sexual side-effects from SSRIs.[67]

3. Buspirone and SSRI

Buspirone, a pre- and post-synaptic 5HT agonist is sometimes combined with antidepressants, but the evidence is mixed. It is not recommended by the BAP or NICE guidelines. The NICE guidelines specifically state that there is insufficient evidence for its use.[68] The Maudsley guidelines recommend buspirone augmenation as a second-line augmenting agent on the basis

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Table 5: Overview of combination strategies

Combination agents	Proposed mode of action	Used with	Dose*	Potential issues
Mirtazapine	α2 adrenoreceptor antagonism 5HT2, 5HT3 antagonism	SSRI, SNRI	30-45mg*	1. Serotonin syndrome 2. Sedation
Bupropion	NA and DA reuptake inhibition	SSRI	up to 400 mg*	Not licenced for depression in Ireland
Buspirone	5HT1 agonist	SSRI	up to 60mg*	May not be as well tolerated as bupropion. (based on STAR*D)
TCA	5HT and NA increase CYP2D6 inhibtion leading to elevated TCA levels	SSRI	Lower dose than if used alone*	1. Serotonin syndrome 2. Monitor plasma concentrations 3. ECG monitoring recommended
MAOI	Synergy of NA and 5HT increase	TCA	Lower dose than if used alone*	1.Serotonin syndrome 2. Avoid highly serotonergic TCA's like clomipramine, imipramine 3. High-risk combination

**Indicative doses only. Not to be used as a prescribing guideline. Please review relevant literature.*

of the STAR-D trials. The STAR-D trials showed similar remission rates to buproprion (30.1%) but with a higher burden of side-effects. The APA supports its use where anxiety is a prominent feature.[69]

There are some positive case reports and open label trials[70], but two randomised controlled trials failed to find a significant advantage over placebo.[71,72] The first of these trials had an unusually large placebo response of 46.7% and outcomes were only measured on the Clinical Global Impressions-Improvement (CGI-I) scale. The trial also became open-label after only four weeks.

4. TCA and MAOI

The combination of two of the 'older' classes of antidepressant has been used since the 1960's. Its use was limited as the agents either had very similar mechanism of action or the combination was potentially dangerous. One of the first combinations was the use of a MAOI and TCA. This had limited efficacy and frequent occurrence of serotonin syndrome,[73] and is generally not recommended, though the Maudsley guidelines give it some cautious support. Gillmann argues that it is only the TCAs with potent serotonergic action (imipramine and clomipramine) that carry this risk.[74]

5. TCA and SSRI

The combination of a TCA and a SSRI is also generally considered potentially hazardous due to the risk of serotonin syndrome but is used sporadically. The Maudsley and APA guidelines give it some support. Open trials have been encouraging, but the only double-blind trial found that high dose SSRI monotherapy was as good as a SSRI and TCA or SSRI and lithium combination.[75] Mean serum lithium and desipramine levels were low however, indicating these groups may have been under-treated. There was also no placebo group in this study.

As SSRIs can inhibit the cytochrome P450 system (CYP) it is argued that the benefits from this combination is chiefly derived from raised TCA levels due to inhibition of its metabolising enzyme, however, this is just as likely to contribute to toxicity as response.

The SSRIs differ greatly in terms of their inhibitory action on the cytochrome P450 system. Fluvoxamine has a strong inhibitory action on a range of CYP enzymes. Fluoxetine and paroxetine have strong inhibitory action on CYP2D6. Reports of toxicity due to combinations using fluvoxamine, fluoxetine and paroxetine and TCAs are therefore predictable. Sertraline, citalopram and escitalopram have fewer drug interactions and would therefore be preferable agents in a combination strategy.[76]

The combination of an SSRI with another SSRI cannot be recommended due to the risk of serotonin syndrome (*see Table 3*).

Other strategies

There are a number of other augmenting agents that have been suggested to have a potential benefit in treatment resistant depression. These are not supported by the NICE guidelines, which are more conservative than the other guidelines. The NICE guidelines, after its review of the evidence, specifically recommend against the routine use of anticonvulsants (including carbamazepine and valproate) and benzodiazepines beyond two weeks.

The BAP guidelines include more candidates in their recommendations with the caveat that they only be "considered

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in specialist centres with careful monitoring".[77] Their list of candidates include tryptophan, modafinil and other stimulants, oestrogen in perimenopausal women and antiglucocorticoids (metyrapone).

BAP also give some support to the use of omega-3 fatty acids and there is also some evidence that folate may be beneficial. A meta-analysis of folate augmentation by Taylor et al[78] included two RCTs. The trials were relatively homogenous, however, there were only 124 patients included in the meta-analysis and confidence intervals were wide. Due to the small number of trials, the use of funnel plots to establish a publication bias is of limited value. A new randomised controlled trial (FolATED)[79] is under way and may shed more light on the role of folate augmentation in depression.

The APA give some limited support to omega-3 fatty acids, folate, stimulants and anticonvulsants in "individual circumstances".[80] They also give some support to the use of anxiolytics and sedatives in the short-term where anxiety is a prominent comorbid complication.

The Maudsley guidelines have an even more extensive list of agents that are listed as third-line agents, but stress that the evidence-base is limited and "prescribers must familiarise themselves with the primary literature before using these strategies".[81] The evidence base for these include small randomised trials, open trials, case series, case reports and animal studies. These may be useful in specific circumstances.

The Maudsley list include amantadine, cabergoline (dopamine agonist), clonazepam, mecamylamine (nicotinic antagonist), metyrapone, tryptophan, yohimbine (pre-synaptic alpha 2-adrenergic antagonist), zinc, ziprasidone (atypical antipsychotic) and modafinil.

Conclusions

Treatment resistance is a common phenomenon and psychiatrists should familiarise themselves with the available options. The strategies discussed in this paper should not be viewed as the only option when antidepressants fail, but rather as alternatives in the therapeutic arsenal. There are a number of guidelines in use, and there are differences between them. The current evidence-base treatment strategies varies from solid to weak. The best evidence for augmenting or combining treatments remains for the use of lithium with TCAs.

There will be circumstances when one might choose agents outside the general recommendations, or using a medication off-licence, but this should ideally be done by specialists who are familiar with their use and have adequate clinical facilities to monitor their effects. One should also bear in mind that the treatment that has been proven to be the most acutely effective treatment for severe treatment-resistant depression remains ECT.

It is important that the patient is informed of the rationale and evidence for the proposed treatment, especially if one is using a strategy that has a limited or no evidence-base. Nonetheless, given the burden of depression on individuals and society, every effort should be taken to treat it.

Clinicians must remember that treatment guidance is often created from less than systematic reviews of the literature and may use a very subjective evaluation of varying levels of evidence. This must be further criticised and interpreted by the treating clinician. Often, the best available evidence is less than gold standard. In fact, it may be unpersuasive. However, its very discussion in the guidance of supervising and leading bodies encourages the use of treatments with meagre evidence. We must recognise the difficulty in generating good quality research on resistant depression, and should not deprive our patients of treatment options because the research evidence does not meet criteria of certainty. Patients so treated should be informed that their regimen is based on more tentative evidence, as otherwise failure to respond is likely to jeopardise their relationship with their treating clinician and their expectations for the future. It also keeps us honest, because while as clinicians we feel obliged to offer more and more treatment alternatives, we must appreciate that the best evidence does not always support doing "something different".

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Multiple Choice Questions: Module 11

1. Regarding treatment resistance:

In drug trials, an adequate response to a medication is typically defined as a 50% reduction in symptom score	T	F
The likelihood that a patient will achieve remission with the first antidepressant tried is around 50%	T	F
Initial treatment with an SSRI should be for at least 6-8 weeks at an adequate dose	T	F
Two trials of medications terminated due to side-effects indicates treatment resistance	T	F
Reported prevalence of treatment resistance is around 10%	T	F

2. Regarding lithium augmentation:

Lithium is an effective augmentation agent at lower doses than those used in lithium monotherapy	T	F
Lithium is contraindicated with SSRIs	T	F
Lithium is thought to inhibit serotonin release	T	F
Lithium augmentation has a NNT of 5 to achieve remission	T	F
The strongest evidence is for lithium augmentation with TCAs	T	F

3. Other augmentation strategies:

T3 augmentation is reserved for hypothyroid patients	T	F
The safety of long-term augmentation with atypical antipsychotics is yet to be established	T	F
Stevens-Johnson syndrome is associated with lamotrigine	T	F
Pindolol augmentation has a benefit over placebo, but only after six weeks of treatment	T	F
The STAR*D trial found Lithium to be superior to T3 augmentation	T	F

4. Combination strategies:

Mirtazapine is a dopamine and noradrenaline reuptake inhibitor	T	F
Bupropion may ameliorate sexual side-effects of SSRIs	T	F
TCA and MAOI combinations have a high risk of serotonin syndrome	T	F
Citalopram, escitalopram and sertraline are drugs of choice in a combination strategy	T	F
SSRIs can be safely combined with other SSRIs	T	F

5. General recommendations:

Guidelines always reflect gold standards of treatment	T	F
Patients should not be advised that their treatment is based on tentative evidence as this may jeopardise the therapeutic relationship with their clinician	T	F
The randomised controlled trial is the highest level of evidence when appraising a treatment	T	F
ECT is the most acutely effective treatment for severe treatment resistant depression	T	F
CBT has proven efficacy in treatment resistant depression	T	F

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