NHS Greater Glasgow & Clyde

Mental Health Services

Prescribing Management Group

Difficult-to-treat depression pathway

Background

This guidance aims to support the care of patients where treatment within primary care has been difficult to treat (add link to guidelines). To provide prescribers with evidence-based treatment for patients under these circumstances. However, the evidence for treating patients with difficult to treat depression is weak, and the advice included below considers clinical experience and limited supporting evidence.

General principles

- Consider if there are any co-morbidities that are affecting the patient's mental state.
- Review diagnosis if no improvement is seen and seek second opinion.
- Offer lifestyle advice such as meaningful day and regular exercise.
- Psychology input should be considered at all stages of treatment.
- Determine compliance with treatment.
- Provide psychoeducation and manage patients' expectations of pharmacological treatment.

Off-licensed treatment

Some of the recommendations below may be out with the product license, refer to MHS guidance for further information regarding consent and documentation. When requesting Primary Care to prescribe a clear rationale for treatment and plan for review must be communicated with the GP.

Treatment options

Optimise monotherapy, increase dose incrementally ensuring an adequate trial at each dose before further increase. Give 8 weeks at maximum tolerated dose before considering switching.

Switch antidepressant to one with a different mode of action and optimise treatment.

Note: Monoamine oxidase inhibitors (MAOIs) should only be initiated by specialist services and dietary restrictions should be communicated to the patient both verbally and in written format.

For those on antidepressants that affect multiple receptors, e.g. venlafaxine, consider using doses above the BNF maximum only if **partial benefit** is seen (unlicensed use). Doses above the BNF maximum have an increased risk of adverse effects such as hypertension with venlafaxine.

Other treatment options

The current evidence has not demonstrated a clear benefit for augmentation except for lithium. However clinical experience indicates that some benefit can be achieved. The options below do not indicate an order of preference and individual patient factors should be considered when making prescribing decisions.

- Combination antidepressants with different modes of action e.g. SSRI & mirtazapine (30-45mg), SNRI & mirtazapine (30-45mg).

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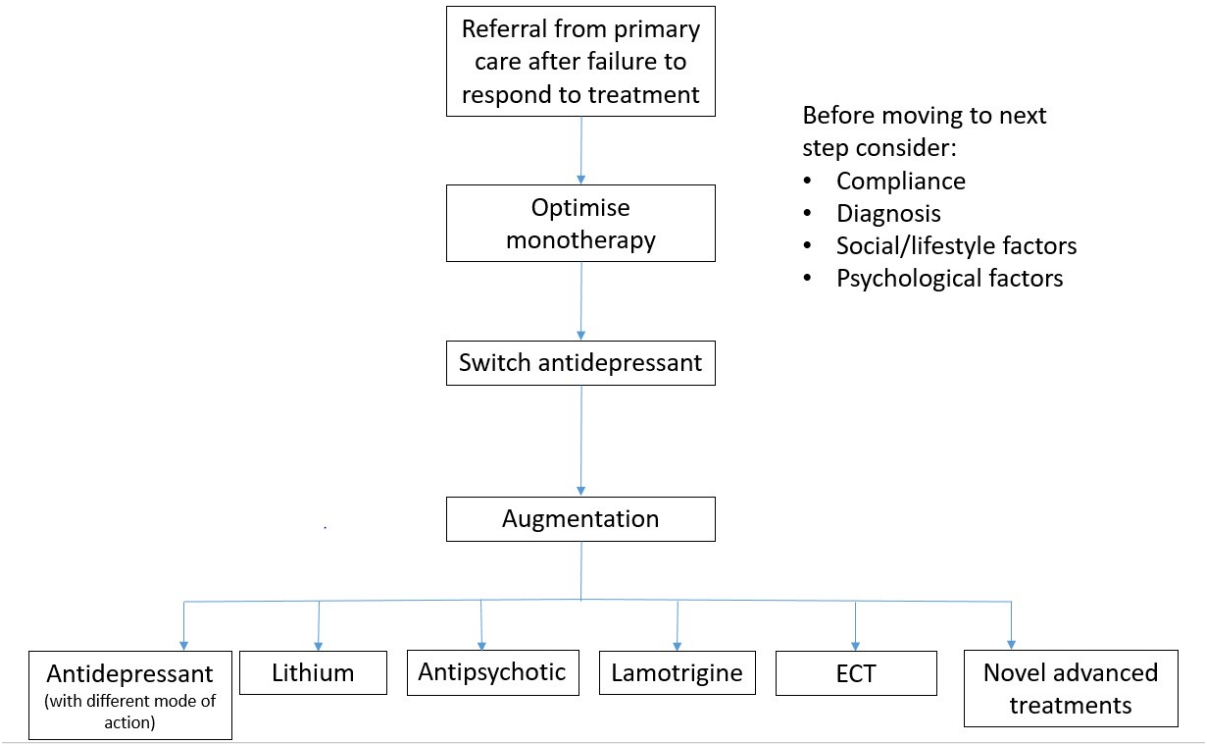
- Augmentation with lithium, has a well-established evidence base for augmentation in depression. As it has a narrow therapeutic window, all monitoring requirements need to be adhered to as set out in the Good Practice Standards- Safe lithium treatment.
- Augmentation with second generation antipsychotic e.g. aripiprazole, olanzapine or quetiapine. Quetiapine is the only 2nd generation antipsychotic licensed as an adjunctive treatment for major depressive disorder. All patients receiving antipsychotics should be monitored for cardiometabolic effects, refer to Primary Care Psychotropic good practice guidance.
- Augmentation with lamotrigine, most evidence is in combination with SSRI/SNRI.
- Electroconvulsive therapy (ECT).
- Low doses of flupentixol (1mg/day) or amisulpride (50mg/day). Limited evidence for monotherapy but could be considered as an augmentation if other treatments are unsuccessful.
- Further novel advanced treatments, such as esketamine or transcranial magnetic stimulation (TMS), will need to be discussed on an individual patient basis.

Flowchart



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Summary of evidence

A huge amount of published evidence is available, but many studies are of lower quality (open-label studies, case series). The 2022 NICE guideline for depression reviewed 125 RCTs for the section on 'further-line treatment', with evidence for 67 different treatment comparisons. (1) In contrast, the 2019 Cochrane review 'Pharmacological interventions for treatment-resistant depression in adults' included only 10 RCTs (due to stricter inclusion criteria). (2)

The most recent high-quality evidence (meta-analyses and systematic reviews, and any subsequently published RCTs) for pharmacological treatments and not any other treatments (e.g. TMS, psychological treatments, ECT) were used for creation of this guidance.

Switching antidepressants

There is no strong evidence to suggest any antidepressant is preferable to switch to in treatment-resistant depression (TRD). Cipriani's 2018 meta-analysis confirmed that most antidepressants have similar efficacy in the treatment of major depressive disorder (although there was a range in efficacy from amitriptyline [most effective] to reboxetine [least effective]). (3) The most significant differences lie in the tolerability of each drug. Agomelatine and fluoxetine were the only two antidepressants which were better tolerated than placebo, with clomipramine the only antidepressant which was significantly worse than placebo. Other antidepressants had a non-significant result. Although not directly applicable to TRD, it seems reasonable to apply it when considering a switch to another antidepressant. The main factors to consider are the relative side effect profile of the drug, any cautions/contraindications with a patient's medical history, and involve the patient in the treatment decision.

Escalating doses

SSRIs

Higher than licensed dosing for SSRIs is not recommended, as most evidence suggests that SSRIs have a flat dose response curve (most likely due to optimal receptor occupancy at the serotonin transporter at standard doses). (4) However, if there is partial benefit at a low dose, it seems reasonable to escalate the dose to maximum licensed doses (provided it is tolerated).

The same is not true of TCAs and venlafaxine, which have effects on multiple receptors, and may be more effective at higher doses.

Venlafaxine

The maximum licensed doses show the best balance between efficacy and tolerability, however, in some cases, if there has been partial response and venlafaxine is well tolerated, it may be reasonable to increase the dose beyond licensed limits. Venlafaxine at lower doses has a predominantly serotonergic effect, additional noradrenergic effect is seen at doses >150 - 225 mg, with additional dopaminergic effect at doses >225 - 375 mg. (5,6) There are many reports of 450 mg/day being effective and well-tolerated (and in some very rare cases up to 600 mg/day). The main dose-limiting adverse effect of high-dose venlafaxine is hypertension.

TCAs

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Higher doses of TCAs are more effective, with doses of ~150 mg/day required for efficacy in depression. (5,7) The usual maximum doses are 250-300 mg/day but any higher is not recommended, primarily because of the risk of seizures. Other dose-related side effects include cardiac effects (arrhythmogenic) and anticholinergic effects which usually limits the tolerable dose. There is also the significant risk of toxicity in overdose.

Other antidepressants

Mirtazapine has been used in doses up to 90 mg/day but there is no good evidence to support any benefit over 45 mg/day in most patients. For MAOIs, it has been suggested that there is a 'flat relationship in the normal to high dose range when MAO-inhibition is the main pharmacological mechanism'. (8) There has long been interest in the use of very high doses of tranylcypromine (e.g. >100 mg per day; usual maximum dose is 30 mg per day in the UK) with the rationale that tranylcypromine has an additional amphetaminergic effect at very high doses. (6)

Augmentation with mood stabilisers or antipsychotics

There are three recent meta-analyses worth discussing:

A 2015 network meta-analysis used a relatively broad criteria of TRD (insufficient response to at least 1 historical antidepressant treatment, and failure to respond to at least 1 first-line antidepressant during the current episode). Forty-eight RCTs were included, with 11 different augmentation agents: aripiprazole, bupropion, buspirone, lamotrigine, lithium, methylphenidate, olanzapine, pindolol, quetiapine, risperidone, and thyroid hormone. In terms of response rates, quetiapine, aripiprazole, thyroid hormone and lithium were significantly more effective than placebo. Most of the other treatments tended towards superiority but this did not reach statistical significance. In terms of remission rates, aripiprazole, buspirone, olanzapine, quetiapine, risperidone and thyroid hormone were significantly better than placebo. Again, the other treatments tended towards superiority but this did not reach statistical significance. No conclusion could be drawn regarding superiority between treatments, as there were few significant differences among the treatments. The authors suggested that quetiapine and aripiprazole are the best-evidence choices for augmentation therapy in patients with TRD, because they considered them to have the best balance of efficacy/tolerability, without the need for biochemical monitoring that lithium and thyroid hormones require. However, the heterogeneous nature of the RCTs is a real limitation to the data. (9)

A later meta-analysis included 25 RCTs investigating pharmacological treatments (and 3 RCTs investigating psychological treatments) for TRD (using a stricter criteria of insufficient response to at least 2 antidepressants before the current episode). All treatments were more effective than placebo, with a large effect size (e.g. pooled antipsychotics and mood stabiliser augmentation had an effect size of 1.12). Ketamine had one of the largest effect sizes (1.47) however, this was based on one trial involving only 47 patients. The authors concluded that their findings suggest that patients with TRD should not be considered as 'lost causes'. They also suggest that the results support the value of aripiprazole and lithium augmentation as first-line treatments for TRD, due to the larger evidence base for these treatments in comparison to others. (10)

A meta-analysis of studies comparing three augmentation strategies (SGAs vs esketamine vs lithium) in major depression, compared the odds ratio of each treatment versus placebo, and calculated

number-needed-to-treat (NNT) and to-harm (NNH) for each treatment. Some, but not all, of the included RCTs involved a TRD population. Twenty-eight trials for SGA augmentation, 14 for lithium and 7 for esketamine were included. All three treatments were significantly superior to placebo, with lithium most effective (OR=2.22 [1.44-3.43], followed by esketamine (OR=1.94 [1.52-2.46] and SGAs (OR=1.59 [1.44-1.75]). However, there was no statistically significant difference between the treatments. NNTs were calculated as lithium = 5, esketamine = 7 and SGAs (pooled) = 11. Of the SGAs, risperidone (NNT = 6) and aripiprazole (NNT = 9) had more favourable results, while cariprazine had one of the least favourable (NNT = 16). NNHs were calculated as lithium = 9, esketamine = 5 and SGAs (pooled) = 5. However, this is harder to interpret because specified adverse events for each drug were used to calculate these values (e.g. tremor for lithium, dizziness for esketamine, sedation for quetiapine and risperidone, and EPS/akathisia for aripiprazole). (11)

Evidence for specific mood stabilisers:

Valproate

A literature search failed to identify any strong evidence to support using valproate augmentation in TRD, although a very small uncontrolled trial (n=14) reported benefit. (12) Considering the risks with valproate and prescribing restrictions this wasn't included as an option in the pathway.

Lamotrigine

A recent meta-analysis of 8 RCTs (total 677 patients) found a significant improvement in HAMD scores in the lamotrigine augmentation group compared with the control group. Most studies used lamotrigine to augment SSRIs or SNRIs. The daily dose of lamotrigine augmentation of the included studies was in the range 25–400 mg/day, with mode (the most common value) 100–150 mg/day. (13)

Lithium

There is a lot of historical evidence for lithium augmentation, with some suggestion that it may be more effective in older adults compared to younger adults. However, a lot of the evidence is older and involved augmentation with tricyclic antidepressants rather than SSRIs/SNRIs.

Evidence for specific antipsychotics

There is no good evidence for first generation antipsychotics, and these are not recommended.

There is no strong evidence to support one antipsychotic over another, although there is most experience with aripiprazole in the literature. The NICE guideline specifically mentions aripiprazole, olanzapine, quetiapine or risperidone as augmentation options (although, surprisingly, it also names low dose amisulpride (50 mg) as an option for monotherapy in patients with chronic depression who have not responded to an SSRI/SNRI). (1) Choice of antipsychotic is best made by considering the individual side effect profiles and preference of the patient.

Amisulpride

There is a dearth of evidence to support augmentation with amisulpride in TRD. A recent case series included a review of the available literature, which consisted of 7 small published studies. (14)

A recent meta-analysis aimed to assess the efficacy of amisulpride in the treatment of acute depressive episodes in individuals with a major mental health disorder. It included 11 RCTs: 8 included patients with dysthymia; 1 included patients with major depressive disorder; 2 included patients with schizophrenia. Meta-analysis was only able to be performed on the studies on dysthymia, where no significant difference in efficacy or tolerability was found when amisulpride monotherapy was compared to SSRI monotherapy (based on the results of 4 studies) or tricyclic monotherapy (based on the results of 3 studies). All studies used a low dose of amisulpride (50 mg/day). (21)

Only one RCT involved patients with a diagnosis of major depressive disorder - these were outpatients attending Italian psychiatric clinics. However, patients with previous lack of response to two or more antidepressants were excluded. Patients were allocated to receive either amisulpride 50 mg/day (n=138) or paroxetine 20 mg/day (n=139) for 8 weeks. The study failed to show that amisulpride is as effective as paroxetine at the end of the 8-week period, although in some secondary outcomes amisulpride performed similarly to paroxetine. (22)

Flupentixol

Early reports from the 1960s that small doses of flupentixol were capable of producing an antidepressant effect of rapid onset (mostly in reducing anxiety symptoms) were largely confirmed by later studies in the 1970s and 1980s comparing the drug with established antidepressant agents (tricyclics, mianserin and fluvoxamine). (23-25) However, these studies were limited almost exclusively to out-patients with mild to moderate depression - patients with severe or treatment-resistant depression were excluded. Furthermore, placebo-controlled trials from the 1970s generally failed to show impressive differences between the treatment groups. (26,27) Consensus in the literature from that time was that 1 mg per day flupentixol is an adequate antidepressant dose.

Augmentation with thyroid hormones

Although a network meta-analysis found antidepressant augmentation with thyroid hormones to be superior to placebo (9), a later 2020 (non-network) meta-analysis investigating thyroid hormones in comparison to lithium or placebo did not. Ten studies were included in this meta-analysis, with varying criteria for TRD. The results indicated that augmentation with thyroid hormones was not superior to placebo or lithium and the authors concluded that there is not sufficient evidence to support the use of adjunctive thyroid hormones in TRD. (15)

Esketamine

A meta-analysis of 7 RCTs found that antidepressant augmentation with intranasal esketamine (most trials used twice weekly dosing) was significantly superior to placebo, with a comparable effect size to that of antipsychotic augmentation. (16) However, long-term data and comparison with other augmentation treatments is still lacking. Interestingly, a recent meta-analysis of trials comparing ketamine with ECT found that ECT had superior response and remission rates. (17)

Combined antidepressants

High quality evidence for antidepressant combinations is lacking and remains partly informed by the STAR*D trial. Combinations with a pharmacological rationale (e.g. a reuptake inhibitor with mirtazapine) are usually preferred. A meta-analysis of 38 studies found that combination

antidepressant treatment was superior to antidepressant monotherapy, with the combination of a reuptake inhibitor with an antagonist of presynaptic alpha2-autoreceptors (mirtazapine, mianserin, trazodone) significantly superior to other combinations. (18) In contrast, a Cochrane review concluded that adding mirtazapine to current antidepressant therapy does not produce a clinically important benefit in reducing depressive symptoms. (2) This conclusion was based on the results of an RCT (n=480) where mirtazapine 30 mg was compared with placebo when added to existing SSRI/SNRI treatment for up to 12 months. Although the mirtazapine group had slightly better improvement compared to placebo, it was not deemed clinically significant. (19)

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