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Managing inadequate antidepressant response in depressive illness

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Abstract

Introduction or background: Depression frequently fails to respond to initial treatment.

Sources of data: Predominantly meta-analyses and RCTs but supplemented where necessary by additional data and the authors' clinical experience.

Areas of agreement: A systematic assessment to identify remedial causes of poor response should be followed by planned sequential treatment trials. Joint decision making by the patient and clinician is essential. Strategies with the strongest support are antidepressant augmentation with lithium or second generation antipsychotics and adding cognitive behavioural treatment. Electroconvulsive therapy is highly effective in resistant depression but there is a high relapse rate when treatment ends.

Areas of controversy: Some pharmacological strategies have inconsistent data (e.g. antidepressant combinations, T3 augmentation) or limited preliminary data (e.g. ketamine, antidepressant augmentation with pramipexole). The efficacy of vagus nerve stimulation, deep brain stimulation and repetitive transcranial magnetic stimulation is unclear.

Growing points: A greater understanding of the causes of depression may assist the development of more effective treatments.

Areas timely for developing research: Role of glutamate antagonists and psychological treatments, other than cognitive behavioural therapy, as adjunctive treatments.

Key words: depression, antidepressants, treatment resistance, lithium, antipsychotics, neurostimulation therapies, ECT

Introduction

Antidepressants are widely used to treat depressive illness and are recommended as first line options for the treatment of moderate and severe episodes of major depression in clinical guidelines.[1,2] However a high proportion of patients fail to show an adequate antidepressant response. In STAR*D (Sequenced Treatment Alternatives to Relieve Depression), the largest randomized trial of the treatment of major depressive disorder (MDD), a representative sample of outpatients with MDD received one to four successive acute treatment steps. Those who did not achieve remission at each treatment step were able to move to the next step. Only 36.8% of patients achieved remission at step 1, namely a first course of antidepressant treatment.[3] The likelihood of remission dropped markedly after the second antidepressant trial with the sequential remission rates being 30.6, 13.7 and 13.0% at steps 2, 3 and 4 of treatment respectively. In this paper we provide a narrative review of the assessment and management of patients with inadequate antidepressant response. We start by considering terminology and the scale of the problem. Assessment is considered in terms of patient-, clinician- and treatment-related factors. Management is dealt with under three headings; pharmacological management, psychosocial management and neurostimulation therapies and neurosurgery. The review is based as far as possible on data from meta-analyses, randomized controlled trials (RCTs) and high quality clinical guidelines. However there are many areas where the evidence base is weak or absent and in such cases our comments inevitably reflect clinical experience.

Terminology

Treatment-resistant depression (TRD) refers to a depressive episode that has not responded to treatment. A widely used definition is failure to improve despite two adequate antidepressant trials[4] but there is no universally accepted definition. The term TRD has inherent drawbacks; it arbitrarily dichotomizes treatment responsiveness and focuses on a 'category of patient', it usually ignores psychological treatments, rarely defines degree of improvement required and neglects the role of illness characteristics, psychosocial factors, treatment intolerance, partial response and treatment response in past episodes. The label of 'TRD' can also be stigmatizing and encourage helplessness in the patient and clinician. The 2009 NICE (National Institute for Health and Care Excellence) depression guideline moved away from using the term TRD, preferring to consider sequenced treatment options for inadequate response.[1] We have followed suit. However TRD remains a widely used term and can be a useful shorthand.

TRD and chronic depression refer to different concepts though the two overlap. 'Chronic' refers to a persistent depressive episode, arbitrarily defined as lasting for ≥2 years, and makes no assumption about the adequacy of treatment. A number of staging systems for treatment non-response have been proposed.[5] Early attempts were based on the number and complexity of antidepressant treatments that had been tried and failed, for example the Thase and Rush 5-stage model. More recently the Maudsley Staging System takes a multidimensional approach considering duration, baseline symptoms and treatment failures to produce a score that represents a continuous spectrum of treatment resistance.[6] Such systems are rarely used in clinical practice. If used in RCTs, they may improve the generalizability of the results but further work is required to assess their reliability and predictive validity.

A range of depressive disorders are recognized in current classification systems. In this paper we

mostly restrict ourselves to MDD. MDD is operationally defined in DSM-5 and the equivalent depressive disorder in ICD-10 with relatively little difference between the two systems. DSM-5 requires five or more symptoms during a 2-week period with at least one of the symptoms being either depressed mood or loss of interest or pleasure.[7] The symptoms must represent a change from previous functioning and result in clinically significant distress or impairment of functioning.

Size and impact of the problem

Studies report wide variation in the 1-year and lifetime prevalence rates for MDD with pooled rates of 4.1 and 6.7% respectively being found in a systematic review.[8] A general population study in the Netherlands found that 50% of cases of MDD recovered within 3 months, 63% within 6 months, 76% within 12 months, though nearly 20% had not recovered at 24 months.[9] Predictors of persistence included greater severity of depression at baseline and comorbid dysthymia. MDD is a recurrent disorder. An international epidemiological study showed that approximately 75% of people who experience an episode of MDD will experience at least one further episode with the mean and median number of lifetime episodes among those with recurrent depression being 4 and 16 respectively.[10] The prevalence of poor antidepressant treatment or treatment resistance is affected by multiple factors but there is a clear consensus that it is a common clinical problem. A UK primary care study found that 55% of patients who had taken antidepressant for ≥6 weeks at an adequate dose fulfilled a broad definition of treatment resistance (≥14 on Beck Depression Inventory, version II).[11] Using failure to respond to at least two antidepressants from different classes as the definition of TRD gave a prevalence of 22% among patients diagnosed with MDD and receiving antidepressant treatment in primary care in Canada.[12]

The economic impact of depression is high and treatment resistance is a greater determining factor than severity.[13] A claims data base study of employees showed that those with TRD, compared with those with non-TRD, were significantly more likely to suffer from comorbid medical psychiatric and physical health problems and had mean direct and indirect costs, assessed over 2-years, that were approximately double those for depression without treatment resistance.[14] Similar findings were reported in an earlier claims database analysis.[15]

Patient assessment

Evaluating a patient with an inadequate antidepressant response requires the clinician to identify contributory factors, particularly those amenable to intervention. These can be divided into patient-, clinician- and treatment-related factors (see Table 1).

Patient-related factors

Diagnosis

The diagnosis of MDD is often straightforward but on occasions it can be extremely challenging. When assessing a person with depression failing to respond to treatment the first step is to consider whether the diagnosis is correct. Bipolar disorder (BD), especially type II, is frequently misdiagnosed as unipolar depression. The distinction is important as antidepressants, although effective in the acute and maintenance treatment of unipolar depression, are relatively ineffective in BD and may worsen the prognosis by contributing to mood instability and rapid cycling. Differentiating BD from unipolar depression rests on identifying a history of mania or hypomania. Low mood, irritability and thoughts of self-harm are common features of ICD-10 emotionally unstable personality disorder (equivalent to borderline personality disorder in DSM-5) and can be misdiagnosed as a MDD leading to inappropriate treatment. The converse diagnostic error is to mistake a depressive illness as a personality disorder with the result that the depression is not thoroughly treated. Points that help differentiate borderline personality disorder and MDD are age of onset, pervasiveness of symptoms and personal history in terms of stability of relationships. The situation is made more complex as people with personality disorders have a high prevalence of comorbid depression and in these cases both disorders require treatment. The only way to avoid diagnostic errors is to take a thorough history from the patient and supplement this with a history from an informant. Assessment may need to take place over several appointments.

Table 1 Factors to consider in the assessment of a patient presenting with depression and inadequate treatment response

Patient-related factors	Ensure correct diagnosis e.g. - Personality disorder - Schizophrenia - Bipolar disorder
	Psychiatric comorbidity, e.g. - Maladaptive personality traits/personality disorder - Anxiety disorders - Psychosis - Drug misuse and dependence - Alcohol misuse and dependence
	Medical comorbidity, e.g. - Chronic pain - Hypothyroidism - Anaemia - Neoplasm
	Social factors, e.g. - Life events - Chronic difficulties - Lack of support
Clinician-related factors	Lack of systematic treatment approach - Partly reflects weak evidence base
	Therapeutic nihilism
Treatment-related factors	Nonadherence - Psychological treatment - Pharmacological treatment
	Inadequate treatment trials - Dose - Duration
	Treatment options not tried - Antidepressant switching - Combination treatments (drugs and psychological treatments) - Antidepressant augmentation strategies

Psychiatric comorbidity

The presence of any comorbid physical or psychiatric disorder is a poor prognostic indicator for MDD. However the outlook of depression can be dramatically improved by successfully treating comorbidities which therefore require identification. Comorbid anxiety disorders are particularly important as they are common and are associated with chronicity, treatment resistance and suicide.[16,17] Alcohol and substance misuse, even at low levels, can lead to poor outcomes in depression.[18] Psychosis is more common in depression than is often recognized. Nihilistic delusions or delusions of guilt may be concealed by the patient due to embarrassment and feelings of worthlessness and hopelessness. In general, psychotic depression has a poorer outcome than non-psychotic depression and usually requires treatment with an antidepressant combined with an antipsychotic, or with ECT.[1,2]

Clinicians should avoid the trap of attributing poor treatment response to a personality disorder and therefore not actively treating the depression. Depressive symptoms can cloud the assessment of personality as shown by a study in which 44% of depressed patients with apparent borderline personality disorder no longer met criteria for the personality disorder after 8 weeks of antidepressant treatment.[19] Personality needs to be assessed using information that relates to behaviour, cognitions and functioning prior to the development of the current depressive episode.

Medical comorbidity

Many medical disorders can cause depressive symptoms including hypothyroidism, Cushing's disease, neoplasm and poorly controlled diabetes. Several drugs may cause depression including corticosteroids, oral contraceptives, L-dopa and beta blockers.[20] Chronic pain, from any cause, is a non-specific risk factor for depression. Painful symptoms occur in around 45% of patients with MDD, approximately three times the rate of the general population.[21] Pain reduces the chances that a physician will recognize and diagnose depression[22] and it reduces the likelihood of a response to antidepressants.[23]

Social factors

Life events and chronic difficulties can precipitate and prolong depression. Social stressors may contribute to treatment resistance by increased activity of the hypothalamic-pituitary-adrenal (HPA) axis given preclinical evidence that elevated cortisol levels militate

against the effects of antidepressant medication.[24] Patients can benefit from verbalizing their social problems and a psychosocial formulation will assist in planning a holistic treatment plan. The clinician may be able to promote effective coping strategies and discourage any that seem counter-therapeutic. Liaison with the patient's general practitioner and involving a social worker can be considered depending on the nature of the issues. If relationship problems appear relevant then involving the partner, with the patient's permission, or recommending joint counselling may be of benefit.

Clinician-related factors

Lack of a systematic treatment approach

Just as patient-related factors can predispose to a sub-optimal response to treatment, so can clinician-related factors, including a lack of a systematic treatment approach. While there is debate in the literature regarding the efficacy of certain treatments, there is consistent evidence that treating MDD by algorithm is superior to treatment as usual (TAU), even when the latter is done by experienced clinicians using published guidelines.[25] It is impossible to define a treatment algorithm appropriate for all patients with treatment resistance as patients entering an algorithm are likely to have very different histories in terms of previous treatments, doses used and response and tolerability experienced. There will also be differences in symptom profile and patient preference for different treatment options. In addition there is a lack of an evidence base for the specific components and order of treatments, and the steps in any algorithm. The general principles are to use better tolerated, and less invasive, treatments earlier in treatment sequencing, and to use treatments with the strongest evidence base first. The data regarding the effectiveness of treatment by algorithm highlight the importance of giving patients timely treatment trials with defined target outcomes at critical decision points in the course of treatment; this requires accurate assessment of symptoms and treatment response which requires the use of standardized assessments, something rarely done in routine clinical practice.

Defining a possible treatment algorithm for an individual patient is hindered by the relatively weak evidence base for managing depression beyond second line treatment, together with difficulty in interpreting what evidence there is. Patients in most RCTs in MDD are not representative of patients seen in routine clinics. RCTs, depending on the strictness of the entry criteria, exclude about 70–90% of patients seen in routine clinics.[26] Patient features leading to exclusion include psychotic features, substance misuse and significant suicidal ideation which are more common in TRD versus non-TRD populations. RCTs also usually exclude patients with milder symptoms and so there are few efficacy studies in people with MDD who are in partial remission, despite this being a common form of sub-optimal response and being associated with increased risk of relapse[27] and continued impairment in psychosocial functioning.[28] Clinical practice frequently requires extrapolation from the evidence base. For example, the second generation antipsychotic (SGA) quetiapine has a license for antidepressant augmentation in patients with sub-optimal response to a single course of a selective serotonin reuptake inhibitor (SSRI) as this reflects the patients recruited into the supporting RCTs. However quetiapine augmentation is not routinely used at this point by most clinicians nor is it recommended at this point by NICE.[1] Whether or not it is possible to extrapolate the trial findings to more refractory patients is not established. Finally, the current evidence base contains conflicting results which are likely to reflect both the heterogeneous nature of patients with non-responsive MDD and the fact that most studies are small and underpowered. The latter highlights the importance of systematic review and meta-analysis where possible, but they cannot make up for a lack of evidence. Despite all these limitations, it is important to be familiar with the existing evidence to guide clinical decisions.

Therapeutic nihilism

There is a decreasing chance of a patient achieving remission with each successive treatment as demonstrated in STAR*D.[3] Consequently, after a patient has failed to achieve optimal response to several treatments, the clinician can easily become pessimistic about the prognosis. This pessimism can be fuelled by identification with similar emotions from the patient who believes the situation is hopeless and that they

will never improve. Coupled with the confusing, and often conflicting evidence base, a nihilistic approach can develop in which further treatment is not even attempted. It is important that clinicians guard against this while being realistic about what is achievable, systematic in their approach and helping patients to manage their illness and minimize disability at each stage.

Treatment-related factors

Nonadherence

Adherence lies on a continuum ranging from those who take no medication, through degrees of partial adherence, to those who are fully adherent. Nonadherence is common in all chronic psychiatric and medical conditions.[29,30] A review, encompassing papers published between 1975 and 1996, reported the mean amount of prescribed medication taken to be 65% for those prescribed antidepressants, 58% for patients prescribed antipsychotics and 76% for those prescribed medication for physical disorders.[31] Nonadherence is often covert and can lead to an incorrect diagnosis of non-response.[32]

Methods to assess adherence include questioning the patient, using pill counts and measuring drug plasma levels, but none is ideal. In clinical practice adherence is usually assessed by asking the patient about their medication taking. Sufficient time is required to explore this in a non-judgemental manner. Two simple screening questions have been suggested.[30]

- 'Most people find it hard to stick perfectly to the treatment plan all the time; do you ever have any problems taking all the medications as prescribed?'
- 'Do you ever try and cope with the illness on your own without taking the medications?'

The second question acknowledges that the patient may not be trying to undermine their recovery though poor adherence. If either screening question reveals nonadherence, the clinician should try to quantify this, for example by asking a question such as: 'How many days' medication do you think you may have missed in the last ten days?' Pill counts can help in assessing medication adherence, especially if a patient is seen at home, but one cannot be certain that 'spent' medication was taken rather than discarded.

The assessment of a depressed person with inadequate response to treatment should involve assessing adherence with all treatments approaches and not just medication. This includes activity scheduling and cognitive behavioural therapy (CBT) sessions or homework. Exploring the underlying reasons, which may include forgetfulness, misperceptions about the treatment, stigma, lack of efficacy or side effects, will help guide approaches to improve adherence and clarify options for future management, both of which need to be approached in a collaborative manner.

Inadequate treatment trials

An apparent poor response to treatment, whether pharmacological or psychosocial, may, on closer examination, be due to an inadequate dose and/or duration of treatment. Assessing past treatment trials in terms of their dose and duration, and associated tolerability and benefit, will help plan a logical sequence of future treatments. Unfortunately it is often impossible to give a precise statement as to what constitutes an adequate trial as the evidence base is insufficient. The dose of drugs recommended in their Summary of Product Characteristics (SPCs) is based on average response and tolerability rates from RCTs conducted by pharmaceutical companies. Lack of early improvement to an antidepressant is an accepted predictor of future non-response. In more detail, only about one in five patients with lack of improvement (usually defined as <20% reduction on a standard depression rating scale score) after 4 weeks of antidepressant treatment will have a response by 8 weeks.[33] This has led to recommendations that a change of treatment should occur if a patient fails to show any response after a 4-week trial of an antidepressant, or only minimal improvement after 6–8 weeks.[2] However this is general guidance based on patients without TRD and some patients will only respond to higher doses of medication and some will show a slower response. As a result, once a patient has failed treatment trials using standard doses and durations, it is important to consider longer trials and potentially higher doses. Nevertheless an antidepressant trial in refractory patients should probably rarely be longer than 10–12 weeks. Some treatment strategies require less time to evaluate. RCTs of SGA as augmentation agents show a

meaningful benefit compared with placebo (on average) after just 1–2 weeks.[34,35] In clinical practice however a trial period of 4–6 weeks of a SGA at adequate dose seems adequate to judge response.

Determining what antidepressant dose constitutes an adequate trial is not straightforward. The first question is *has at least a minimally effective dose been given?* For most SSRIs the minimum effective dose seen in placebo-controlled RCTs is the same as the recommended starting dose given in the SPC e.g. 20 mg of fluoxetine and citalopram or 50 mg of sertraline. However, the minimum therapeutic dose of tricyclic antidepressants (TCAs) is not clear. Many guidelines suggest at least 125 mg/day imipramine/amitriptyline equivalent[2] but some data suggest that lower doses may be as effective.[36] The second question is *should the dose be increased to ensure an adequate dose has been given?* Some antidepressants have little evidence for a dose-response relationship, for example most SSRIs, while others do, examples being escitalopram[37] and venlafaxine.[38] Even in the former case, it is probably worth at least one increase in dose before switching to another antidepressant in a patient who has failed to respond to one or two previous treatments. For drugs with more evidence of a dose–response relationship there is more justification for increasing the dose in incremental steps particularly if there has been some evidence of response. Evidence of incremental response with increasing dose, and tolerability being maintained, may encourage increasing to, or even above, SPC recommended maximum doses. Clinically this is not unreasonable in more refractory patients, but must be appropriately discussed with the patient beforehand and this, and the rationale, recorded in clinical notes whenever a dose exceeding the SPC maximum is employed. It is important to be aware of the particular monitoring needs of individual drugs at higher doses, for example primarily blood pressure for venlafaxine[39] and ECGs to monitor QTc for escitalopram[40] with vigilance being maintained for rarer adverse effects. Failure to improve after higher doses of a drug gives more confidence that the drug is indeed ineffective for that patient. This is important since patients are often reluctant to re-try a previously 'failed' drug. In patients who are struggling to tolerate an effective dose of antidepressant, it may be worth considering using a lower than usual dose and slowly increasing this in the hope that tolerance to adverse effects may develop.

Untried treatment options

As well as determining the adequacy of prior treatment trials it is important to determine obvious treatment gaps. If the patient's treatment history is unclear it can be helpful to review previous records made by the general practitioner or mental health professionals who previously treated the patient.

Pharmacological management

In this section we consider the pharmacological management of MDD, that has not responded adequately to first line antidepressant treatment, under three headings; antidepressant switching, antidepressant combinations and augmentation strategies. The relative efficacy and tolerability of various combination and augmentation strategies are summarized in Table 2. Space does not allow all of these to be discussed, rather we concentrate on those with the best evidence. Combination and augmentation strategies have been investigated with respect to different aims in the treatment of depression including influencing speed of response, and improving efficacy in either initial treatment and after failure to respond to first line treatment. It is only the last of these aims that is relevant to this paper.

Antidepressant switching

Antidepressant switching should be considered if a patient has had an inadequate response to an antidepressant that has been optimized in terms of dose and treatment duration. At what stage and in what situation it occurs depends on the previous history of the patient. For example if they show only partial improvement on their first antidepressant after dose optimization and an adequate duration trial, then it may be worth switching drug. However if a similar situation occurs during a trial of a second, third or subsequent antidepressant, then one would be more likely to continue the antidepressant in question and explore augmentation strategies. It is often recommended to

Table 2 Efficacy* and safety of drug augmentation/combination strategies following inadequate response to an antidepressant

	Efficacy	Adverse interaction
Augmentation strategies		
Lithium + antidepressant (mainly TCAs and SSRIs)	++	–
Aripiprazole or quetiapine + antidepressant (mostly SSRI/SNRI)	++	–
Other SGAs + antidepressant (mostly SSRI/SNRI)	+	–
T3 + antidepressant (mainly TCAs and SSRIs)	(+)	–
Modafinil + antidepressant	+	–
Pramipexole + antidepressant	+	0
Lamotrigine + antidepressant (mostly SSRI)	–	–
l-tryptophan + antidepressant (mostly TCA or MAOI)	(+)	–
Buspirone + antidepressant (SSRIs)	0	–
Combination strategies		
SSRI + mirtazapine	+	–
Venlafaxine + mirtazapine	(+)	–
TCA + MAOI	–	+[†]
SSRI + Bupropion	–	–
SSRI + trazodone	0	–
SSRI + TCA	0	+[‡]
SSRI + reboxetine	0	–

Adapted from Anderson IM. Management of treatment nonresponse (chapter 7). In: Friedman, ES, Anderson, I (eds). *Handbook of Depression*. 2nd edn. London: Springer Healthcare (2014).

Efficacy in TRD: ++ = meta-analysis or replicated RCTs with placebo-controlled evidence; + = some positive data, e.g. small RCT; (+) = inconsistent results from RCTs, non-placebo-controlled RCTs; 0 = no RCT evidence at all. – = evidence it does not work from RCTs.

Adverse interaction: – = no major concerns based on data from RCTs or large studies; 0 = uncertainty due to limited data; + = associated with safety issues.

BOLD, discussed in text.

*Efficacy ratings refer to studies assessing patients with at least one failed antidepressant treatment. Some strategies that are ineffective in this paradigm show superior efficacy to comparators when used as first line treatment.

[†]High risk of serious side effects including serotonin toxicity.

[‡]Depending on drugs used potential for cytochrome interactions leading to elevated TCA levels.

switch when there has been no benefit from an initial drug and augment when there has been partial benefit. In reality the evidence for this is scant though it does receive some support from STAR*D in which there was no difference in rates of remission for patients who were switched or augmented.[41] However, in patients for whom clinicians felt there was a justification to continue initial treatment with citalopram for a full 12 weeks rather than a need to change treatment earlier, and in patients in partial remission, augmentation was better than switching.[41]

A meta-analysis showed that switching to an antidepressant from a different class was only marginally more effective than switching within class.[42] Appropriate guidelines should be followed when switching drugs so as to minimize pharmacodynamic and pharmacokinetic interactions (see Bazire[43]). The switching strategy used will be determined by the clinical situation and the pharmacology of the drugs involved. A complete washout of the previous drug and an intervening drug free period is rarely needed other than for switches involving monoamine oxidase inhibitors (MAOIs) and when switching from fluoxetine to other antidepressants (this reflects the long half-life of fluoxetine). If a drug washout is required, care should be taken because some patients who report no improvement on a drug experience worsening of symptoms on its withdrawal. This may be due to the occurrence of 'withdrawal' or discontinuation symptoms[44] or indicate that the drug was partially effective though this was not fully recognized prior to stoppage.

Many psychiatrists rarely prescribe TCAs and MAOIs reflecting the availability of a wide range of 'newer' antidepressants, predominantly the serotonin noradrenalin reuptake inhibitors (SNRIs) and SSRIs, that are easier to manage in terms of dose adjustment and which have a more favourable tolerability and safety profile including less potential for drug interactions. However we would argue that there is still a role for the use of TCAs and MAOIs in TRD as a high proportion of these patients will have failed trials of SSRIs and SNRIs. In the case of MAOIs it is important that the clinician and patients are fully aware of medications and food stuffs that are contraindicated.

Antidepressant combinations

Over the years, many different antidepressant combinations have been used in patients unresponsive to

antidepressant monotherapy often with little data to support their use.[45] Prior to the advent of the newer second generation antidepressants, a combination that was sometimes used was a TCA combined with a MAOI.[46] Two non-placebo-controlled trials have examined a MAOI plus a TCA in TRD and neither was positive.[46,47] In one, clomipramine plus a MAOI was no more effective than two other antidepressant combinations but was far more likely to cause adverse effects that warranted treatment being stopped.[46] The second trial compared electroconvulsive therapy (ECT) with a phenelzine plus amitriptyline and showed a faster and greater treatment improvement with ECT.[47] The combination of a MAOI plus another antidepressant is associated with a high risk of serious adverse effects including serotonin toxicity which can be fatal. As a result we do not support combining either a SSRI or a TCA with an MAOI (including a reversible selective inhibitor of monoamine oxidase A such as moclobemide) and this is consistent with most other experts[48] although a retrospective study reports using the combination successfully as part of intensive inpatient multimodal treatment.[49]

In recent years interest has focussed on combinations of mirtazapine with SSRIs or SNRIs. These combinations were explored on the basis that the mechanisms of action of the drugs are complimentary with mirtazapine treatment leading to increased release of both noradrenaline and serotonin (5-HT) while SSRIs block 5-HT uptake and SNRIs block both 5-HT and noradrenaline uptake. There has still been only one very small positive placebo-controlled RCT of mirtazapine combination in patients with persistent MDD despite adequate antidepressant monotherapy and the duration was only 4 weeks.[50] Mirtazapine combined with venlafaxine was used in the STAR*D study with tranylcypromine as the comparator but it was no more effective in terms of remission, the primary end point, but did show a greater symptom reduction.[3] Mirtazapine combined with another antidepressant has also been investigated in first-step treatment of depression (i.e. in non-resistant patients) where it has produced conflicting results.[51,52] A small study found a large benefit from mirtazapine augmentation of fluoxetine, venlafaxine and bupropion in comparison with fluoxetine monotherapy but lacked comparison with either mirtazapine or venlafaxine monotherapy.[51] The largest RCT of antidepressant combinations, the CO-MED (Combining Medications to Enhance Depression Outcomes) study, found no difference between combinations of bupropion plus escitalopram (based on the notion that bupropion is blocking noradrenaline and dopamine uptake while escitalopram blocks 5-HT uptake) and venlafaxine plus mirtazapine versus escitalopram monotherapy when used as a first-step treatment in acute depression.[52] CO-MED also reported that the combination of venlafaxine and mirtazapine was associated with a significantly greater side effect burden than escitalopram alone,[52] and that the rates of nonadherence were greater with combination treatment.[53] Therefore, while combining mirtazapine with an SSRI/SNRI is widely used in psychiatric practice for patients with inadequate response, compelling evidence for efficacy is lacking. A large primary care RCT of mirtazapine or placebo augmentation after poor response to at least one SSRI/SNRI is currently underway (http://www.isrctn.com/ISRCTN06653773).

Augmentation

Lithium

A meta-analysis of 10 RCTs showed that lithium augmentation in MDD was effective with an odds ratio of 3.11 which corresponds to a number-needed-to-treat (NNT) of 5.[54] The mean response rate in the lithium group was 41% compared with 14% in the placebo group. Most included studies are small, over two decades old, and involved augmentation of TCAs. Given that SSRIs and other more recently introduced antidepressants dominate the current treatment of depression, and placebo effects have increased, the size of effect needs to be viewed with caution. There is limited evidence from continuation-phase studies regarding the how long lithium augmentation should be continued for after it has led to a response. What data there are suggest it should be continued for a minimum of 1 year to reduce the risk of relapse.[55] Individual studies indicate that a response to lithium augmentation is more likely in those with more severe

depressive symptoms, significant weight loss, psychomotor retardation, more than three major depressive episodes and a family history of major depression. In a meta-analysis lithium was more effective than placebo in reducing the risk of suicide in people with mood disorders and also in a sub-analysis in unipolar depression.[56] This may be mediated through a reduced risk of relapse but it could also reflect lithium reducing aggression and impulsivity. Lithium has a narrow therapeutic index and regular plasma level monitoring is essential. Post-hoc analysis in a study where lithium was compared with quetiapine augmentation found that individuals whose serum lithium concentration was between 0.6 and 1.2 mmol/l did significantly better than those whose concentration was <0.6 mmol/l.[57] Due to an increased risk of toxicity at higher concentrations a target range of 0.6–1.0 mmol/l may be most appropriate. Lithium is associated with hypothyroidism and renal impairment making regular monitoring of renal function and thyroid functions tests necessary.

Triiodothyronine

A meta-analysis of eight studies in people with MDD, refractory to treatment with a TCA, showed that augmentation with triiodothyronine (T3) increased the likelihood of response 2-fold compared with controls.[58] However the relative response was smaller and non-significant when the analysis was restricted to the four randomized double-blind studies. Triiodothyronine augmentation lacks any long-term data and while it remains an option, augmentation strategies with a stronger supporting evidence base, for example lithium and a SGA, should be considered first.

Second generation antipsychotics

A meta-analysis of double-blind RCTs compared the effect of augmentation with a SGA to placebo in patients with MDD that was resistant to antidepressant monotherapy.[59] The analysis included 16 trials ($n = 3480$) with aripiprazole, olanzapine, quetiapine and risperidone being represented. The antidepressants most commonly involved were fluoxetine and venlafaxine. In the pooled analysis augmentation with a SGA was significantly more effective than placebo (odds ratio for response = 1.69) with a NNT of 9. The response rate for the SGA group was 44% versus 30% for placebo. There was no difference in efficacy between individual SGAs. Discontinuation rates for adverse events were higher for SGAs compared with placebo (odds ratio = 3.91). A RCT showed that augmentation with quetiapine 300 mg/day was non-inferior to lithium augmentation.[57]

The only SGA with a UK license to augment antidepressants in MDD is quetiapine though aripirpazole is licensed for this indication in the United States. The antipsychotic dose that is effective for antidepressant augmentation is lower than the antipsychotic dose used in the treatment of mania or psychosis.[59] No RCTs have directly compared individual SGAs in augmentation. Given that current meta-analysis does not show an efficacy difference,[59] the choice of which SGA to use is likely to take account of their different side effect profiles.

Modafinil

Over the years, particularly in North America, there has been interest in the use of psychostimulants as augmentation agents for patients with TRD. There is a lack of quality RCT data to support most approaches. There are however four placebo-controlled RCTs of modafinil augmentation with a meta-analysis demonstrating a significant benefit on depressive symptoms as well as fatigue in unipolar depression.[60] It tends to be well tolerated.

Other augmentation options

Many other augmentation strategies have been tried in TRD, but with weak, mixed or negative data. L-tryptophan, the precursory of 5-HT, has been used for many decades in combination with lithium and either a TCA[61] or MAOI,[62] though there are no RCTs of these combinations. Following some positive open data, there has been one RCT of pramipexole augmentation in TRD that was positive,[63] but more data are required to support its routine clinical use. Similarly, there have been a number of small short-term studies of the anti-inflammatory celecoxib as an augmentation agent with a meta-analysis showing a benefit on remission rates.[64] However the data are from a small number of patients and it is unclear if the strategy should be continued long term

and used only for those with raised inflammatory cytokines. There are three placebo-controlled RCTs examining lamotrigine augmentation in patients who have failed to respond to at least one course of antidepressant monotherapy which are all negative on their primary outcome measures.[65–67]

Another area of research relates to the antidepressant efficacy of the glutamate NMDA receptor antagonist ketamine. Most open-label and RCT studies have reported high response and remission rates (averages 77 and 43%, respectively) from 4 to 72 h after a single sub-anaesthetic dose, usually given as an intravenous infusion.[68] However, not all patients respond and improvement is not generally sustained. Repeated infusions may prolong remission, but relapse remains common after the last infusion. RCTs with an active control are needed and the long-term safety needs to be investigated.[69] At present ketamine remains an experimental procedure.

There has been interest in using folate, vitamin B12 and omega-3 polyunsaturated fatty acids to treat MDD. A meta-analysis showed that omega-3-fatty acids improved depressive symptoms more than placebo in patients with MDD[70] with efficacy associated with their use combined with antidepressants rather than as monotherapy. A second meta-analysis found that no benefit from short-term use of folate and vitamin B12 (days to several weeks) compared with placebo in patients with MDD treated with antidepressants, though there was inconclusive evidence that longer term vitamin use may decrease the risk of relapse and the onset of depressive symptoms in high risk groups.[71] However neither meta-analysis was restricted to people with TRD. Of particular note is a recent large, double-blind, placebo controlled, pragmatic RCT that showed that no clinical benefit for folic acid in augmenting antidepressants in MDD.[72] However, once again patients were not required to have failed an initial treatment. At present there is no evidence from RCTs that dietary supplementation is of benefit in TRD.

Psychosocial management

Psychosocial management of patients with depression covers a wider range of aspects, from good clinical practice, including having a realistic but optimistic attitude and regular assessment and monitoring, to specific psychotherapies. NICE (2009)[1] distinguished between low-intensity and high-intensity interventions; both can offer an alternative or adjunct, to pharmacological treatments for depression. The most studied high-intensity intervention is CBT, with the main alternatives being behavioural activation (BA) and interpersonal psychotherapy (IPT).[1] A network meta-analysis of 198 RCTs using direct and indirect comparisons, found broadly equal efficacy for seven psychotherapies in treating MDD.[73] Psychotherapy and antidepressants are also equally effective, but combined treatment of antidepressants with CBT is more effective than either antidepressants, or probably psychotherapy, alone.[74,75]

There is however a relative lack of evidence for the effectiveness of psychotherapy in TRD. Paykel *et al.* (1999) found that treating patients partially remitted on antidepressants with 16 sessions of CBT doubled the full remission rate after 20 weeks, and reduced the subsequent risk of relapse compared with TAU.[76] In a small study Kennedy *et al.* (2003) found similar efficacy for CBT and lithium augmentation over 8 weeks, although there was an advantage to lithium 4 weeks after the end of treatment.[77] In the STAR*D study, switching to CBT or another antidepressant were equally effective after failed treatment with citalopram, and there was also no difference in overall outcome between CBT augmentation and augmentation with lithium or triiodothyronine, although medication augmentation worked faster.[78] The largest study to date randomized 469 primary care patients to additional CBT or TAU after failure to respond to at least 6 weeks antidepressant treatment. At 6 months the response rate with CBT was over double that with TAU (46 vs 22%) and benefit was sustained to 12 months.[79]

The evidence is therefore consistent, if limited, for the benefit of adding psychotherapy to antidepressants after previous treatment failure, but it has limitations. Evidence for psychotherapies apart from CBT is lacking and it applies to failure with a single antidepressant, rather than multiple, treatments. Extrapolation to a more treatment-resistant population seems

plausible but the size of effect is uncertain. Another problem is equating CBT received by patients in a clinical trial to psychological treatment received in clinical care. NICE (2009)[1] recommends 16–20 sessions of CBT over 3–4 months for the treatment of non-TRD based on the research evidence; from clinical experience patients frequently receive less than this. More experienced therapists achieve better results[80] but the expansion of psychological treatment services has usually emphasized a wider availability of low-intensity therapies delivered by less expert staff. How intensively the therapy is given is also important; although a meta-analysis examining the relationship between 'dose' and outcome in psychological treatment found only a weak relationship between number of sessions and response, twice weekly therapy was considerably more effective than once weekly with an effect size of 0.45.[81] This is an intensity of treatment rarely received in practice. A final issue relates to severity of depression. Evidence for psychological treatments tends to be in the mild-moderate range of depression severity, and there is a lack of evidence for patients encountered in specialist care who are severely depressed (i.e. Hamilton Depression Rating Scale scores above 26).

It is a common clinical experience for patients seen with TRD to have received a previous course of a psychological treatment, usually CBT, either in an earlier episode of depression, or during the current episode. It is important to attempt to assess the adequacy of previous treatment, and response to it, and not make an assumption that past treatment rules out further treatment. An adequate trial of psychotherapy is probably a major missing element from the treatment of many patients with TRD but is often difficult to provide in a timely manner because of the lack of availability of, and pressures on, psychological treatment services. Given the very high relapse rates for patients eventually remitting after a number of failed treatments[3] it is also important to consider psychotherapy at that stage for relapse prevention (e.g. CBT or mindfulness-based cognitive therapy) given the evidence for its efficacy in preventing relapse, which may be better than that seen with antidepressants.[82]

Neurostimulation therapies and neurosurgery

In this section we consider electroconvulsive treatment, repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS) and deep brain stimulation (DBS) (collectively regarded as neurostimulation treatments) plus neurosurgical lesion procedures.

Electroconvulsive therapy

Electroconvulsive therapy is a well-established, safe and widely available treatment option for patients with an inadequate response or poor tolerability to pharmacotherapy. It involves the induction of a therapeutic seizure by the application of electrical current to the brain under general anaesthesia. It is prescribed as a course, typically administered 2 or 3 times per week for 6–12 treatments, although some patients may require more. It is the most effective short-term antidepressant treatment for MDD, including severe and resistant forms, particularly with psychosis or psychomotor retardation. Multiple meta-analyses have shown that it is significantly more effective than pharmacotherapy.[83–85] When used first line in a severe depressive episode remission rates of around 60–80% have been reported, possibly even higher (85–95%) in psychotic depression.[86] Even in more resistant depression a remission rate of 48% has been reported.[87] NICE recommends ECT for consideration for moderate and severe depression when psychological and drug treatments have failed, or severe life-threatening depression when a rapid response is needed.[1]

Despite its effectiveness in the acute episode, without maintenance treatment the relapse rate is extremely high (over 80%) in the 6 months after successful ECT.[88] This can be significantly reduced by either pharmacotherapy, including the combination of nortriptyline and lithium, or continuation ECT.[88,89] However, despite this the overall relapse rate remains 30–50% and more effective strategies for relapse prevention following ECT are urgently needed.[90] Cognitive side effects are the main limitation to the broader application of ECT, particularly acute confusional states, anterograde and retrograde amnesia, word finding

difficulties and deficits in autobiographical memory.[91] Right unilateral electrode placement, compared with the traditional bitemporal placement, may minimize retrograde amnesia.[92]

Repetitive transcranial magnetic stimulation

Repetitive transcranial magnetic stimulation involves the application of repetitive pulses of a high-strength magnetic field through the skull to superficial areas of the cortex from a stimulating coil held above the scalp. It is administered while the patient is awake and reclining in a chair, does not induce an epileptic seizure and does not have significant cognitive side effects. It is well tolerated and side effects are generally mild and transient. For acute treatment of depression, rTMS is usually provided in sessions lasting between 20 and 45 min, 5 days a week, for 3–6 weeks.[93] Meta-analyses and RCTs of high-frequency rTMS to the left dorsolateral prefrontal cortex have concluded that the acute antidepressant effect of active rTMS is significantly superior to sham rTMS and has a moderate effect size,[94] although in TRD the effect size may be small.[95] rTMS is approved for treatment-resistant MDD in several countries including Canada, the United States and the European Union. NICE[1] concluded that although TMS is safe, because of insufficient evidence for its efficacy its use should still be reserved for research studies. Consequently, the availability of rTMS as a clinical option remains low in the UK. When compared with ECT, the largest meta-analysis in more severe and treatment-resistant MDD concluded that ECT is more effective than rTMS, particularly in the short-term and for patients with psychotic depression.[96]

Vagus nerve stimulation

In vagus nerve stimulation, ascending fibres of the left vagus nerve are intermittently stimulated by low-frequency electrical pulses originating from a programmable neurostimulator. The most common side effects are voice alteration, cough, pain, nausea and dyspnoea, although they are generally tolerable[97] and only occur during the intermittent stimulation phases. Although data are limited, there is no evidence that VNS causes cognitive impairment.[98] The use of VNS in depression emerged from the observation of mood improvement in some patients treated with VNS for epilepsy. Early short-term open-label and uncontrolled trials in depression were promising, with approximately 30% response and 15% remission during 10–12 weeks of adjunctive VNS therapy.[91] However, the only randomized, sham-controlled, masked trial in TRD found low rates of remission and no significant benefit of active over sham VNS after 10 weeks.[99] The decision by the US Food and Drug Administration (FDA) in 2005 to approve VNS for patients unresponsive to at least four adequate antidepressant treatments was therefore controversial.[100] A meta-analysis concluded that existing data are insufficient to conclude that VNS is an effective treatment for depression.[101] The efficacy of VNS for depression remains to be definitively established. In the UK, NICE recommend that use of VNS should be limited to TRD and should be used only with special arrangements for clinical governance, consent and audit or research.[102]

Deep brain stimulation

Deep brain stimulation (DBS) involves a reversible neurosurgical procedure to implant stimulating electrode wires into specific brain regions, usually bilaterally.[91] These are connected to a programmable neurostimulator implanted subcutaneously in the anterior chest which typically provides continuous electrical stimulation. Postoperative adjustments are made over time to a variety of stimulation parameters with the aim of achieving optimum outcome. DBS is generally well tolerated, but potential adverse effects associated with the surgery include infection, haemorrhage, perioperative headache, seizure and lead fracture. In the early phase of stimulation anxiety, elation or worsening depression can occur but generally resolve with optimization of the stimulation parameters. Cognitive function is not generally adversely affected and may in fact improve.[98] Because of its invasive nature DBS has been limited to the most treatment-refractory forms of depression.

In open-label studies, response rates of approximately 30–60% have been reported and benefits are generally maintained over several years. However, the only double-blind, randomized, sham-controlled trial found lower rates of response and no statistically significant difference between active and sham DBS after 4 months of treatment.[103] In summary the efficacy of DBS is unproven at present.

Neurosurgical lesion procedures

Several neurosurgical lesion procedures have been used in highly treatment-refractory and functionally impaired patients with MDD (for a review, see Patel *et al.*, 2013[104]). These include anterior cingulotomy (targeting the dorsal anterior cingulate bilaterally), subcaudate tractotomy (substantia innominata bilaterally) and limbic leukotomy (combination of the other two procedures). However the evidence base is far from satisfactory being based on open studies. Despite the availability of the neurostimulation therapies described above, lesion procedures remain an option for appropriately selected patients with severe, refractory MDD. Each year in the UK only a small number of procedures are carried out and the treatment is restricted to the most severe and treatment-resistant cases.

Conclusions

An inadequate response to treatment in MDD is a common clinical problem. It results in suffering for the individual and often family members, disability, increased direct and indirect economic costs and is associated with an increased risk of suicide. In assessing a person presenting with this problem it is important to consider potentially reversible contributory factors (Table 1). Once any underlying factors have been addressed one should progress through a series of treatment trials. The evidence for next-step treatments and for choosing between them are both poor (Table 2). It is not possible to provide a treatment algorithm that will be applicable to all patients. Treatment needs to be individualized and the patient involved as much as possible in treatment decisions.

There is only limited data on using higher than standard doses of antidepressants and no randomized trial of the comparison of increasing dose compared with switching antidepressant. A meta-analysis supports switching between rather than within antidepressant class after failure to respond to first line treatment, but the effect size is very small. The only strategies with clear support from meta-analysis of placebo-controlled RCTs are augmenting antidepressants with lithium or a SGA. In addition several RCTs support the efficacy of CBT in TRD. Clarifying the efficacy of psychological treatments other than CBT is important as positive results would widen treatment choice. A small meta-analysis supports the use of modafinil augmentation. There is inconsistent or weak evidence supporting the use of antidepressant combinations and thyroid hormone augmentation. ECT is an important and effective treatment for depression that has not responded to other treatments or which is life threatening. It is particularly effective when melancholic or psychotic features are present. The efficacy of several other neurostimulation treatments for depression (including repetitive transcranial magnetic stimulation, VNS and DBS) are uncertain and in the UK these treatments are not routinely available but are undergoing further research. A small number of tertiary centres offer lesion treatment but this is seen very much as a last resort for the most severely and chronically ill patients.

It is important to avoid pessimism. In STAR*D the cumulative remission rate after four trials of treatment was 67%.[3] When a person fails to respond to a range of strategies one should consider referral to a tertiary affective disorders service, a practice supported by NICE. Data regarding clinical outcomes following referrals to such services are limited but encouraging.[49,105,106] For example an uncontrolled evaluation of a 225 consecutive patients treated in a national affective disorders unit over 7 years reported a response rate of 69% despite the group being highly treatment resistant.[106]

Conversely, as with any chronic illness, there will be some people with depression who respond poorly despite a systematic and well thought out treatment approach with sequential treatment trials. In such cases one needs to involve the patient in a decision

about whether to continue to pursue active treatment or alternatively to accept the gains that have been made and place the emphasis on support and minimizing disability. When remission is achieved, strategies to reduce the risk of relapse need to be considered. Usually this will involve continuing medication that has been associated with remission though this needs to be balanced against side effects.

Conflict of interest statement

P.M.H.: In the last 3 years P.M.H. has received fees for lecturing and/or consultancy work (including attending advisory boards) from various pharmaceutical companies including Bristol-Myers Squibb, Eli Lilly, Janssen-Cilag, Lundbeck, Otsuka, Quantum Pharmaceutical, Roche, Servier, Sunovion, Takeda and Teva and support to attend conferences from Janssen-Cilag, Otsuka and Sunovion.

I.M.A.: In the last 3 years I.M.A. has received fees for lecturing and/or consultancy work (including attending advisory boards) from various pharmaceutical companies including Servier, Lundbeck/Otsuka, Alkermes and support to attend conferences from Servier.

P.S.T.: In the last year P.S.T. has received fees for attending advisory boards from the pharmaceutical company Sunovion, and MyTomorrows (facilitates early access to drugs in development). P.S.T. undertakes clinical work within a tertiary level specialist affective disorders service.

R.H.M.W.: In the last 2 years R.H.M.W. has received support for research, expenses to attend conferences and fees for lecturing and consultancy work (including attending advisory boards) from various pharmaceutical companies including Astra Zeneca, Eli Lilly, Janssen, Lundbeck, MyTomorrows, Otsuka, Pfizer, Roche, Servier, SPIMACO and Sunovion. R.H.M.W. undertakes clinical work within a tertiary level specialist affective disorders service.

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