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Analysis

Multiple-therapy-resistant major depressive disorder: a clinically important concept

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Summary

Many novel therapeutic options for depression exist that are either not mentioned in clinical guidelines or recommended only for use in highly specialist services. The challenge faced by clinicians is when it might be appropriate to consider such 'non-standard' interventions. This analysis proposes a framework to aid this decision.

Declaration of interest

In the past 3 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, Cyberonics, Eli Lilly, Janssen, LivaNova, Lundbeck, MyTomorrows, Otsuka, Pfizer, Roche, Servier, SPIMACO and Sunovion. D.M.B.C. has received fees from LivaNova for attending an advisory board. In the past 3 years A.J.C. has received fees for lecturing from Astra Zeneca and Lundbeck; fees for consulting from LivaNova, Janssen and Allergan; and research grant support from Lundbeck.

In the past 3 years A.C. has received fees for lecturing from pharmaceutical companies namely Lundbeck and Sunovion. In the past 3 years A.L.M. has received support for attending seminars and fees for consultancy work (including advisory board) from Medtronic Inc and LivaNova. R.M. holds joint research grants with a number of digital companies that investigate devices for depression including Alpha-stim, Big White Wall, P1vital, Intel, Johnson and Johnson and Lundbeck through his mindTech and CLAHRC EM roles. M.S. is an associate at Blueriver Consulting providing intelligence to NHS organisations, pharmaceutical and devices companies. He has received honoraria for presentations and advisory boards with Lundbeck, Eli Lilly, URGO, AstraZeneca, Phillips and Sanofi and holds shares in Johnson and Johnson. In the past 3 years P.R.A.S. has received support for research, expenses to attend conferences and fees for lecturing and consultancy work (including attending an advisory board) from life sciences companies including Corcept Therapeutics, Indivior and LivaNova. In the past 3 years P.S.T. has received consultancy fees as an advisory board member from the following companies: Galen Limited, Sunovion Pharmaceuticals Europe Ltd, myTomorrows and LivaNova. A.H.Y. has undertaken paid lectures and advisory boards for all major pharmaceutical companies with drugs used in affective and related disorders and LivaNova. He has received funding for investigator initiated studies from AstraZeneca, Eli Lilly, Lundbeck and Wyeth.

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There are numerous effective psychological therapies and drug treatments for the management of major depressive disorder (MDD) and guidelines for their use (for example those from the UK's National Institute for Health and Care Excellence (NICE)[1] or British Association for Psychopharmacology (BAP)[2]). However, a major challenge is improving the management of patients with MDD who do not experience full or sustained remission of symptoms with standard, guideline-recommended treatments or who cannot tolerate them. A major issue is that many of the recommended treatments have similar mechanisms of action and in naturalistic studies there appears to be minimal difference in effectiveness between them.[1,2] In addition, duration of depression is associated with worse outcomes,[3] including social breakdown such as loss of job or relationship,[4] which in themselves can become barriers to recovery. Fortunately, many alternative treatments, with potentially different mechanisms of action, exist that are either currently not included in guidelines or are only recommended for use in specialist services – we refer to these as 'non-standard'. These interventions are characterised by having a more limited evidence base to support their use, being associated with greater risks or invasiveness, and/or being more costly than standard treatments. The important clinical question is when to consider them for a particular patient.

Problems and possible solutions

The answer to the question is in some ways simple. If the probability of responding to (or tolerating) a further standard treatment is very low then a case can be made for using a non-standard treatment. However, the evidence base from which to draw such conclusions is far from ideal. Studies vary in their definitions of degree of treatment resistance necessary for inclusion. For example, the data supporting the use of quetiapine augmentation of antidepressants was obtained in studies of patients who had had a suboptimal response to their first, or possibly second, antidepressant.[5] Inclusion in some studies is defined as much by chronicity as lack of treatment response.[6] What studies there are tend to relate to patients who are treatment non-responsive rather than partially responsive, or to patients who have strong preferences for some treatments but not others.[7] Overall, it is also important to note, there is little robust evidence from prospective sequential randomised controlled trials (RCTs) for the efficacy of options beyond third or fourth sequential treatments.[8]

One possible solution is to consider non-standard interventions only when all standard ones have been tried and failed. However, adequate trials of all possible combinations of pharmacotherapy alone would take literally decades. The evidence base does not support this strategy. Naturalistic data suggests that the response rate of patients with chronic treatment- resistant depression to standard interventions is only around 10% over 1 year.[6] Further evidence suggests that the duration of untreated depression has a negative impact on eventual response.[3] It is therefore clinically questionable to cycle endlessly through pharmacologically similar strategies.[9]

An alternative option is to use a 'threshold' approach. Conway and colleagues proposed treatment- resistant depression be divided into 'stage I' defined as failure of two interventions (medication or

psychotherapy) and 'stage II' defined as failure of three interventions.[9] They propose that less invasive non-standard interventions could be considered for stage I treatment- resistant depression and more invasive interventions (such as vagal nerve stimulation (VNS) or deep brain stimulation (DBS)) for stage II treatment-resistant depression.[9] This threshold would allow for DBS for a patient after failure of 20[th]mg of fluoxetine and 20[th]mg of citalopram, both prescribed over 6 weeks, and 8 sessions of cognitive–behavioural therapy (CBT). We believe this is premature. This also illustrates the problem of a simple threshold approach with the challenge being how to find the best balance between timely access to alternative treatments *v.* unnecessary exposure to risky/expensive interventions. The threshold for different interventions is also likely to be different with, for example, the threshold for ablative neurosurgery being substantially higher than for a well-tolerated and safe non-standard medication. There are also a myriad of patient and illness factors that will also influence when a particular treatment might be deemed appropriate. Rather than a simple threshold we suggest a more nuanced approach with a defined reference point, which we refer to as 'multi-therapy-resistant MDD' (MTR-MDD), to help guide clinicians, patients and commissioners.

MTR-MDD

The criteria proposed for MTR-MDD (outlined in the Appendix), for the reasons outlined above, are based more on consensus than clear-cut evidence. They have been developed by clinicians drawn from primary care, secondary care and specialist services (see online supplement DS1, available at https://doi.org/10.1192/bjp.2017.33), including individuals with personal experience of MDD. The intention is that the MTR-MDD criteria can be broken down into its various component parts to help guide discussions between clinicians, patients and commissioners about when it may be reasonable to consider non-standard intervention. In totality, the criteria provide something of a 'back stop' – if a patient meets all of the criteria but has not been considered for non-standard treatment, then the question 'why not?' should be asked. We do not posit that MTR-MDD defines a specific subgroup of patients with MDD that may be characterised, for example, by a specific biology. However, the categorisation is potentially of use in research for stratification in trials of patients with particularly difficult to treat illness.

The term MTR-MDD has been chosen to reflect that: several interventions (more than two) must have failed to produce or maintain a response, or have been intolerable; non-pharmacological interventions should also have been tried and been ineffective or intolerable; and that the criteria are specific to MDD. The full MTR-MDD criteria are met if there has been 'a failure to respond, achieve remission, maintain a response/remission or tolerate' all the treatments listed in the Appendix. For many patients, it can be difficult distinguishing discrete episodes. It is inappropriate to re-trial medications that have failed in previous episodes unless the patient describes previous non-adherence and willingness to retry. As a result, these failures will usually be defined over the lifetime of the patient.

As in any area of medicine, non-response to an intervention should lead to a reappraisal of the diagnosis.[10] Alternative primary diagnoses such as bipolar disorder should be carefully excluded. Comorbidities that may be contributing to the resistant nature of the MDD, such as substance use disorders, personality disorders, anxiety disorder and attention–deficit hyperactivity disorder (ADHD), should be identified and treated vigorously. Similarly, psychosocial factors should be addressed where possible. However, the presence of such comorbidity does not negate a patient meeting the criteria and hence consideration being given to non-standard interventions.

For all medications, an adequate trial is one where the clinician is confident (based on clinical judgement and patient history) that the patient has been adherent to a maximum licensed, or maximum-tolerated, dose for an adequate period of time. In the case of a maximum-tolerated dose, this must be a dose equivalent or higher than the generally regarded minimal therapeutic dose (for example as defined in the drug license). If a patient is not able to tolerate a minimum therapeutic dose, then the trial would be deemed to have failed on the basis of intolerance.

First- and second-line treatment trial durations are recommended to be 4–6 weeks, but for patients with resistant depression longer trials are recommended.[1,2] We recommend that at least one, and ideally two trials of antidepressants have been used for a minimum duration of 8 weeks at maximum or maximum-tolerated doses based on the need to balance 'efficiency' of a trial (shortest reasonable time) with the need to confidently exclude a potential response. The duration of augmentation trials is rarely described in guidelines. RCT data suggests a relatively rapid response to some agents, for example antipsychotic augmentation (such as quetiapine[5]), whereas other strategies may take longer at least in part because of the time needed to reach a therapeutic level (such as lithium). Nevertheless, we would recommend a minimum of 4 weeks, and ideally 8 weeks, at a therapeutic dose, for augmentation trials.

With regards to non-tolerance, in almost all circumstances, clinicians should endeavour to establish that all reasonable efforts have been taken to ensure that the patient can tolerate at least the minimum therapeutic dose. This may require extended dose titration periods, using preparations that allow starting at very low doses, the use of other medications (such as benzodiazepines for example when using an activating drug such as aripiprazole) and frequent review. In many situations, the clinician should recommend at least one other drug from the same drug class to ensure that intolerance is class- rather than drug-specific.

Determining the adequacy of a course of psychotherapy may be more difficult, as factors not always directly related to the patient or their illness have been demonstrated to have an impact on outcome, including therapeutic alliance, therapist adherence to the therapeutic modality and match between patient and therapeutic modality.[11–13] Some patients need several months of preparation by clinicians or psychotherapists to develop the psychological mindedness to benefit from a course of any psychotherapy. These considerations and assessment of past psychotherapy may of itself be a justification for seeking an expert psychotherapy opinion.

The rationale for including electroconvulsive therapy (ECT) as a requirement in the MTR-MDD criteria is that ECT is, for most people, a choice that offers a high chance of improvement[14] and acceptable levels of risk compared with more advanced and/or less evidence-based options. However, a failure of ECT to lead to a maintained response despite antidepressant prophylaxis, or a refusal/inability to undergo a trial of ECT, would be an appropriate prompt to consider alternative interventions with patients, especially if they meet MTR-MDD criteria.

Using the MTR-MDD criteria to guide the use of non-standard treatments

Non-standard interventions can be considered to exist on a spectrum. At one end, there are those that have a relatively strong evidence base to support their use in MDD, are easy to implement, well tolerated, non-invasive and relatively cheap. At the other end, interventions have more limited evidence to support them, their

use is more complex to undertake, they are associated with more risks or invasiveness and/or they are of higher costs than standard interventions. The position of an intervention on the spectrum also depends on its regional and national availability and the expertise of the clinician(s) using it.

Infrequently used interventions are more likely to be appropriate for specialised centres. This, as well as other factors, is prone to change over time as more evidence is acquired. Consideration of these issues can help decisions about the potential position in the treatment algorithm of specific non-standard interventions. Interventions supported by RCT data, well tolerated and of a similar cost to standard treatments are likely to be used early on. It may well be totally inappropriate to wait until a patient has a duration of illness of 2 years and/or has had three episodes of illness. When such interventions are used will be determined primarily by clinician expertise and local availability.

The threshold for some non-standard interventions may be determined by individual elements of the MTR-MDD criteria. For example, transdermal selegiline has been shown to be particularly effective in patients with atypical depression,[15] but in many parts of the world is extremely expensive to acquire. As a result, it is probably reasonable that the MTR-MDD antidepressant criteria are met, including that a standard monoamine oxidase inhibitor (MAOI) that irreversibly blocks monoamine oxidase B (MAO-B) is tried first. Similarly, the complex psychotherapy cognitive–behavioural analysis system of psychotherapy (CBASP), which has data supporting its use in treatment-resistant MDD[16] but which is non-standard primarily because of limited availability, is likely to only be considered if a patient meets the MTR-MDD psychotherapy criteria.

Modafinil is not included in NICE depression guidelines,[1] although it is mentioned as an option for use in specialist centres in BAP guidelines[2] on the basis of four RCTs conducted primarily in patients with non-treatment-resistant MDD.[17] In general it is well tolerated and can be combined with most antidepressants. It is therefore at the more benign end of the non-standard therapy spectra. It would seem reasonable to consider this if the MTR-MDD criteria for pharmacological augmentation are met. Conversely, pramipexole, which is supported by just two conflicting RCTs[18] and is more complex to use (because of the potential for impulse control disorders such as gambling)[19] is likely to be considered only after a range of interventions have been unsuccessful i.e. beyond MTR-MDD augmentation criteria. Further along the spectra, intravenous ketamine, which is supported by a number of studies but which is also associated with risk, invasiveness and limited duration of effect[20] is likely to only be used if broader MTR-MDD criteria are met.

There are an increasing number of non-drug physical treatments for MDD that vary in their degree of invasiveness. Transcranial magnetic stimulation (TMS) is well tolerated and supported by NICE recommendations.[21] Hence by our definitions it is a 'standard' intervention although its use is limited by availability. It may be considered before ECT in the treatment algorithm for some patients at less immediate risk. Conversely, VNS has been reviewed by NICE and recommended for use only 'with special arrangements for clinical governance, consent and audit or research'.[22] It might be appropriate to consider this if ECT has been considered inappropriate, unacceptable or it has led to an inadequate response. Given its cost and limited availability it is also likely that patients will meet the other MTR-MDD criteria. The full MTR-MDD criteria are likely to be the bare minimum for consideration of anterior cingulotomy or other neurosurgical procedures, although the concern is that even for this highly invasive irreversible intervention there is often currently too long a delay before a patient is considered for this.

Clearly an additional factor that influences where an intervention is placed in the algorithm is the patient. For example, a concern about medication may lead to the use of a non-invasive relatively cheap non-drug physical intervention such as TMS early on. Alternatively, the clinical characteristics of a patient may influence choice. With regards to standard interventions an example would be the use of ECT early on for patients with psychotic depression or marked psychomotor retardation. Similarly, VNS might be considered for patients with highly recurrent depression despite ongoing prophylactic medication.[23]

Discussion

With the welcome burgeoning of novel non-standard interventions, the question is where in the treatment algorithm they should be used. The appropriate place will vary between patients and interventions. Clinical decisions regarding this are a complex interplay between various factors such as: the patient's clinical state; research evidence; patient preference and expectations; and the expertise and experience of the clinician. A significant concern is that non-standard interventions are only brought into consideration much later than might be appropriate and that this is to the detriment of the patient, although they may also be used inappropriately early in some situations. We argue that the framework and MTR-MDD criteria described in this paper should complement clinical expertise rather than replace it, to act as a reference point around which to gauge when it is clinically appropriate to use non-standard interventions. We believe that a patient meeting all of the MTR-MDD criteria should be considered for non-standard treatment if this has not already happened. The criteria also act as a prompt for clinicians with regards standard interventions. Whether MTR-MDD criteria are appropriate for all age groups, including adolescents, is an open question. At the very least we hope that this analysis piece prompts debate around these issues.

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Supplementary material

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Appendix

Proposed criteria for MTR-MDD

The patient: diagnosed with MDD (using (DSM-5).[24]
Their depression: MDD of at least moderate severity.
Their treatment

(a) Psychotherapy. At least two trials of structured, evidence-supported psychological therapy.[1] The trials should ideally each be of a different modality and provided by a different therapist. In both cases, the clinician should assure themselves that the patient has received a structured course of therapy delivered by an experienced therapist with whom the patient had a good therapeutic relationship. Ideally, at least one of the trials should have been of at least 16 hours duration and at least one trial should have been given in combination with pharmacotherapy.
(b) Antidepressants. Four adequate trials of antidepressants. There is little consensus with regards how antidepressants should be divided into different 'classes' and how important it is that drugs from different classes are trialed. However, it is recommended that the trials should not all be from the same class of drugs and that at least two trials are using antidepressants that are viewed as being potentially more efficacious in severe depression and/or compared with other antidepressants, for example as listed by BAP guidelines (clomipramine, venlafaxine (≥150[th]mg), escitalopram (20[th]mg), sertraline, amitriptyline or mirtazapine).[2] We would also recommend consideration of a traditional MAOI (for example phenelzine), especially for patients with atypical symptoms.
(c) Pharmacological augmentation. At least two adequate trials of an evidence-based augmentation/combination agent given in combination with an antidepressant. Ideally these should both be agents listed as first-line options in BAP guidelines (lithium (ideally with a plasma level of 0.6–1.0[th]mmol/L), quetiapine and aripiprazole).[2]
(d) ECT. A trial of ECT (at least eight treatments, and ideally bilateral if tolerated).

For all treatments: the requirement for a treatment may be waived if there is a recognised contraindication or the patient has, despite extensive discussions and the provision of information, declined it, or there have been well-documented adverse effects that have limited tolerability. This applies to ECT, psychotherapy and medication.

Given evidence for possible greater efficacy of a structured psychological treatment in combination with medication,[25,26] a period of combined treatment, possibly over a period of 9–15 months, is recommended.

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