Clinical Indications and Patient Selection 5

5.1 Stage of Illness and Treatment Resistance

There are a variety of times during the evolution of depressive illness when patients may potentially present for rTMS treatment. This could include during the initial episode of depression, during depressive relapse, during a period of persistent treatment-resistant depression or possibly when well, in regards to maintenance therapy. There is varying depth in the data that informs the use of rTMS across differing illness stages. It is reasonable to extrapolate potential efficacy across these stages, but sensible decisions about the likelihood of response should be based upon the balanced judgement of the accumulated experience of rTMS treatment in the stage of illness being considered.

There are a variety of established treatment options for patients with depressive disorders. Approximately 40 % of patients with an index episode of depression will respond to a single course of an antidepressant treatment, an additional 30 % to multiple antidepressants and augmentation strategies [1]. Systematic, equivalent data on response rates to psychological treatments is not available. However, it is reasonable to assume that a substantial proportion of individuals will not be suitable for these approaches or will continue to experience depressive symptoms despite adequate therapy. These groups of patients are typically regarded as having treatment-resistant depression (TRD).

Patients with treatment-resistant depression have been the focus of a substantial bulk of the rTMS antidepressant research. However, there is considerable variation in methods used to define TRD [2] and this has affected the consistency and clarity of the definition of patient populations across treatment trials. Some trials have considered treatment-resistant patients as those who have failed as few as two antidepressant medication trials. Stricter definitions expand the number of failed trials and/or require these to have come from at least two separate medication classes. Tools such as the Antidepressant Treatment History Form (ATHF), the Thase and Rush staging model (TRSM) and the Massachusetts General Hospital staging model (MGH-S) have been developed to assist in the characterisation of individuals as treatment resistant but have differing psychometric properties [3]. However, any of

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these are likely to provide assistance in the process of the assessment of patients for rTMS treatment. It is important to gain information on a series of clinical features of past treatment failure as part of this process (see Box 5.1).

Box 5.1. Characteristics of Previous Biological Treatment Trials

1. Number of medication trials in current episode
2. Number of lifetime failed trials
3. Duration of each trial
4. Degree of clinical response (absent/partial/complete)
5. Maximal dose of medication prescribed in relation to therapeutic and maximally recommended doses
6. Number of drug classes covered by medication trials
7. Number of augmentation strategies utilised
8. Characteristics of ECT courses: laterality, stimulation location, pulse parameters, number of treatments, seizure characteristics

Despite a large number of rTMS trials having been conducted in patients who have failed a substantial number of medication trials, registration for rTMS in the USA was based on data from a comparison of antidepressant response between TMS and sham stimulation in patients who had failed to respond to only one antidepressant medication. There is certainly a suggestion in the literature that a lesser number of failed medication trials are a positive predictor of likely antidepressant response (e.g. [4, 5]). However, several large studies have failed to confirm this relationship (e.g. [6]). On the basis of this literature, although it would seem to be favourable to make rTMS treatment available relatively early in the course of a treatment history, patients should not be excluded or dissuaded from treatment when they have failed a greater number of treatment episodes. In our experience, we have seen patients who have failed large numbers of medication trials respond to rTMS. We have also seen patients respond following a failed course of ECT, something that we thought initially was unlikely to be the case. The mechanisms of action of rTMS and ECT are likely to vary significantly, and at this stage, there is no indication of any degree of overlap in the patients likely to respond to either. Therefore, a course of rTMS should still be considered, especially as once patients have failed ECT, they have few other treatment options.

It is also inevitable that as rTMS becomes increasingly available questions will arise as to whether it should be presented as a first-line treatment option. Clearly no comparative data has been obtained as to the relative efficacy, or the efficacy compared to sham, in this early population. rTMS is a more involved, time-consuming and most likely more expensive procedure than antidepressant medication, and as such the market for it as first-line treatment is likely to be limited. However, there is a significant percentage of the population who are resistant to the idea of taking medication for the treatment of depression, and for some of these patients, rTMS

may be an attractive option. In addition, it is possible to speculate that early intervention with a non-medication treatment such as rTMS may avoid medication-related complications and enhance brain plasticity in a way that ultimately improves long-term outcomes for patients with depression.

5.1.1 Clinical Recommendations

It appears reasonable for rTMS to be available as an option to patients with varying degrees of failure to respond to antidepressant strategies. However, response rates are likely to be higher in patients with lesser degrees of treatment resistance. It is possible that earlier intervention with rTMS may enhance longer-term outcomes, but further research, particularly focused on medication naive subjects, is required to establish this.

5.2 Illness Type: Unipolar and Bipolar Depression

Most clinical trials investigating the effectiveness of rTMS have predominately or exclusively enrolled patients with unipolar major depressive disorder. For example, the two largest multisite sham-controlled rTMS studies conducted to date excluded patients with bipolar disorder [7, 8]. Some studies, however, have included both patients in the depressive phase of bipolar disorder and those with unipolar depression. Within these trials, no analyses have suggested that a bipolar diagnosis is a negative predictor of the likelihood of clinical response. In one study of low-frequency stimulation applied to the right prefrontal cortex, patients with bipolar disorder had a substantially higher response rate (almost 70 %) than the overall group (51 %) [6]. However, most studies do not provide this sort of separate analysis to allow sufficient inferences to be made about the relative efficacy of rTMS subtypes in bipolar disorder. There is also a considerable lack of studies that have directly explored the antidepressant efficacy of rTMS in bipolar disorder alone.

In the first of these few studies, 20 patients were randomised to active or sham stimulation provided over 20 treatment sessions [9]. There was a significant improvement in depression with active but not sham stimulation. A second small study enrolled 23 patients and provided 5 Hz stimulation to the left DLPFC but failed to find a significant benefit of active stimulation over sham [10]. A third study, this time open label, provided low-frequency stimulation applied to the right DLPFC [11]. Six of 11 patients responded and four achieved remission. A number of the patients with a greater degree of response remained well over a 12-month follow-up [12]. A more recent study included 19 patients with bipolar disorder who received open-label active rTMS using a novel coil providing deeper brain stimulation [13]. A significant improvement in depression was seen with a response rate greater than 60 %. Of note, one patient experienced a generalised seizure during this trial.

A number of reports have described switching to mania in patients receiving rTMS treatment for bipolar depression (e.g. [14–17]). However, the overall risk of

this appears to be low, and potentially no higher than that seen with sham stimulation [18]. No studies have systematically investigated whether the co-prescription of mood stabilisers reduces the possibility of a manic switch. However, in the absence of evidence that these medications can affect the efficacy of rTMS treatment, provision of mood-stabilising medication would be sensible in any patients who have previously experienced substantial manic symptoms. This would particularly include patients whose past symptoms required hospitalisation or resulted in significant risks to the individual or others. The degree to which the patient can be monitored throughout the treatment course should also be taken into consideration. rTMS treatment should be withheld when manic symptoms are first evident during a course of treatment or when there is a dramatic shift in the level of mood symptoms.

Early research did investigate the possible treatment of mania with rTMS. In a small early study, manic symptoms appeared to be preferentially reduced with the provision of high-frequency rTMS to the right DLPFC compared to the left DLPFC [19]. Two subsequent case series showed promising results with right-sided high-frequency stimulation [20, 21], but when right DLPFC rTMS was compared to sham stimulation, no differences were seen [22]. More recently and in contrast to this earlier research, a larger sham-controlled study of 41 patients has shown a substantial anti-manic effect of right-sided high-frequency stimulation [23].

5.2.1 Clinical Recommendations

The vast majority of rTMS research has focused on the treatment of unipolar major depression. However, there is reasonable support at this stage for the use of rTMS in the treatment of patients with bipolar depression, especially given the clinical challenges with the management of this condition. The use of concurrent mood stabiliser medication should be carefully considered in patients with a history of substantial manic episodes and all patients monitored for the emergence of manic symptoms during treatment. The use of rTMS to treat mania is an area that requires further research before conclusions can be drawn on its clinical utility.

5.3 Elderly Patients with Depression

Depression, and especially treatment resistance, is clearly an important issue in the elderly [24]. Treatment resistance is more common in elderly patients with depression, and there are increasing complications with the use of other antidepressant modalities, including drug-to-drug interactions [25]. However, this importance has not been reflected in rTMS research, with only a minimal body of work investigating the usefulness of rTMS in this patient population. Studies conducted to date consist only of several open case series and several small underpowered and probably ‘underdosed’ clinical trials. In the former category, 49 elderly patients (mean age 69 years) received left- or right-sided rTMS. Treatment dose was quite variable and sometimes low (in some patients at 80 % of the RMT) [26]. However, there was

a significant overall reduction in depression symptoms, and nine patients achieved response criteria. Conversely, a small randomised trial specifically conducted in elderly subjects (mean age 60 years) failed to show differences between active and sham stimulation [27]. However, treatment was only provided for 5 days and, based on pulse number and intensity, at very low dose. A second small trial provided treatment for 10 days but again at relatively low dose and in a small sample of only 24 patients. No differences between active and sham stimulation were found [28].

Based on an initial observation that elderly patients may not respond to rTMS to the same degree, it has been hypothesised that compared with younger patients, the elderly have a greater scalp-to-cortex distance in frontal areas relative to motor cortex. This would result in a lower degree of magnetic stimulus penetration. One approach to address this involves the measurement of scalp-to-cortex distance on MRI scanning in DLPFC and motor cortex. An adjustment of stimulus intensity is then made to take into account differences in motor cortex and frontal cortex scalp-to-cortex distance. Nahas et al. investigated this approach in 18 treatment-resistant elderly subjects (mean age 61 years) [29]. The applied intensities ranged up to 141 % of the RMT. Five of the 18 patients responded to the adjusted treatment, but no comparison was made with non-adjusted rTMS. In an open-label trial, 6 out of 20 patients (mean age 66.8 years) responded to 2 weeks of treatment [30].

Some information about the potential benefit of rTMS treatment in the elderly may come from the analysis of age effects in larger treatment samples. In several large studies we have conducted, there has been no relationship evident between age and a poorer response to rTMS treatment (e.g. [6, 31]). In a recent open-label study of 130 patients treated in a naturalistic setting, there was also no relationship found between clinical response and age [32]. Anecdotally, we have treated patients with depression across the elderly spectrum including patients in their late 80s and early 90s. Treatment has been well tolerated, with no substantial difference in patient experiences or response compared with younger subjects. No adjustment for scalp-to-cortex distance was made in any of these larger studies.

5.3.1 Clinical Recommendations

Treatment-resistant depression in the elderly is common and other treatment alternatives can be frequently difficult to administer. rTMS should be considered as a treatment option in this age group although efficacy is not yet supported by substantial randomised trials. Further research is required to understand whether dose adjustments based on scalp-to-cortex distance enhance clinical outcomes.

5.4 Adolescent Depression

A very limited literature has explored the potential use of rTMS in the treatment of depression in adolescents. The first published paper described the treatment of three adolescent patients and four 18-year-olds with 2 weeks of high-frequency stimulation

applied to the left DLPFC [33]. A relatively low dose of stimulation was used (1,600 pulses per session). Two of the three adolescent patients improved with treatment. A subsequent report evaluated treatment efficacy in two adolescent patients provided with a slightly higher dose of rTMS treatment (2,000 pulses per day) with clinical response seen in both patients [34]. A third case series included five subjects younger than 18 [35]. Each patient received 14 treatment sessions (400 pulses per session). Three of the five patients had a significant reduction in depressive symptoms. No major adverse events were reported in any of the patients described in this case series. However, a recent report described the development of a generalised seizure in a 16-year-old female patient during the first session of a planned course of rTMS treatment [36]. The patient had no predisposing factors for the development of a seizure but was receiving 100 mg of sertraline per day at the time. The authors of this case report do not describe a clear progression of tonic–clonic activity, and it is possible that the event was a syncopal seizure. Notably, the dose of rTMS provided in this case was quite low (4 s 10 Hz trains at 80 % of the motor threshold). It has been proposed that the seizure threshold may be lower in this age group, extrapolating from the situation with ECT [37]. However, this has not been systematically studied. Over 1,000 subjects under 18 have received single- or paired pulse TMS in investigative studies without the report of any seizures [38]. However, two adolescents receiving TMS in a stroke study were reported to have experienced a syncopal event [39], and practitioners should be aware of this possibility, especially where there is a history of syncope with other procedures such as injections.

5.4.1 Clinical Recommendations

Limited systematic research has explored the use of rTMS in the treatment of depression in adolescents. Practitioners should be aware of the possibility of syncope and potentially a lower seizure threshold. rTMS presents as a potentially promising way to avoid the early use of medications treatments but should not be adopted until evaluated adequately.

5.5 Pregnant or Breastfeeding Patients

The presentation of patients with depression in the antenatal or postnatal period often poses significant management challenges. There are frequently concerns about the potential impact of antidepressant medications during these periods, and ECT is often avoided during pregnancy due to concerns about the anaesthetic and the seizure itself. Given that the magnetic field produced with a TMS device is very localised, it is unlikely that a foetus would experience significant exposure to a substantial magnetic field if rTMS was applied during pregnancy. There are clearly no child safety issues with postnatal rTMS provision. As such, rTMS treatment appeals as an alternative option for the treatment of depression presenting in the antenatal and postnatal periods. However, limited research to date has explored the use of rTMS applied at these times, and the rTMS option should be evaluated carefully for each individual.

In regard to pregnancy, a number of case reports have been published since 1999, with no evidence of major adverse events (e.g. [40]). A more recent report described a case series of 10 patients treated during the second or third trimester [41]. These patients received low-frequency right-sided rTMS in up to 20 treatment sessions with seven experiencing clinical response. No adverse maternal or foetal outcomes emerged. One recent study has explored the potential acceptability of rTMS treatment to pregnant women [42]. Researchers surveyed 500 pregnant women and a second sample of 51 women who were exposed to an educational video providing information about rTMS treatment. rTMS was not considered acceptable in the first study but was considered acceptable by 15.7 % of the second sample after provision of the information video.

A similarly narrow range of research has explored the use of rTMS in postpartum depression. One case report described the use of rTMS in the successful postpartum management of a patient with bipolar disorder where rTMS was used for both the treatment of mania and depression [43]. One case series has described the management of nine antidepressant-free women with postpartum depression treated with high-frequency left DLPFC rTMS over 4 weeks [44]. Eight patients achieved remission of depression during acute treatment. Seven of these remained in remission after 6 months without further psychiatric treatment.

Despite these promising initial findings, rTMS treatment in pregnancy or the postpartum period should proceed cautiously. Although it is unlikely that an unborn foetus would be exposed to substantial magnetic fields, it is possible that hormonal changes induced by rTMS could have adverse effects, and this will require systematic research. rTMS could also induce changes in the hormonal profile of breast milk. In addition, provision of rTMS during pregnancy may require the more careful monitoring of motor thresholds and rTMS dose as hormonal fluctuations may affect cortical excitability over time.

5.5.1 Clinical Recommendations

Limited research has evaluated the use of rTMS in pregnancy or the postpartum period to date. However, there are strong reasons to avoid other biological treatments during these times. This is likely to lead to the consideration of the use of rTMS in spite of the limited evidence available for its use. Provision of rTMS under these circumstances should include a careful assessment of the risks and potential benefits of both rTMS and other treatment alternatives. Further research is clearly required in this area.

5.6 Concurrent Illness: Neurological Disease

A small literature has begun to explore whether rTMS is safe and has efficacy in the treatment of patients with depression in the context of substantive comorbid neurological conditions. Depression is a commonly occurring comorbidity in several neurological illnesses. For example, depression is common in the context of the development and persistence of Parkinson's disease [45]. In the first rTMS study to address this clinical

group, Dragasevic et al. provided low-frequency frontal rTMS to ten depressed subjects producing a significant reduction in depression despite a low dose of stimulation. A second open-label study also reported a significant reduction in depression, this time with high-frequency stimulation applied in 14 patients [46]. A small ($n=22$), sham-controlled study of 5 Hz prefrontal DLPFC rTMS also supported the antidepressant effects of rTMS in depression in patients with Parkinson's disease [47].

In a similar manner, open-label data has been collected on the use of rTMS in the treatment of vascular depression or depression that presented following stroke. Jorge et al. randomised 92 patients with depression and substantive vascular disease to active or sham left DLPFC rTMS [48]. Substantial antidepressant effects were seen with active treatment in two dose groups compared to sham. In the first trial in post-stroke depression, antidepressant effects greater than sham were seen in a small group of patients receiving 10 Hz stimulation to the left DLPFC [49]. These findings were confirmed in a subsequent double-blind study, which compared 1 Hz rTMS, 10 Hz rTMS and sham stimulation in patients with post-stroke depression [50]. High-frequency stimulation resulted in improved depression scores although no cognitive improvements were evident.

A third condition that is beginning to be explored is the presentation of depression subsequent to a brain injury. This appears to be a relatively common occurrence, but a history of dramatic head injury has frequently been an exclusion criterion in rTMS treatment trials. No clinical trial data has yet been published in this area, although a case report described promising early results [51].

5.6.1 Clinical Recommendations

The presence of an underlying or comorbid neurological disease such as stroke or Parkinson's disease does not appear to prevent the possibility of successful response to rTMS treatment. The use of rTMS treatment under these circumstances should be balanced against any potential increased risks of seizure induction related to the underlying disease entity with the substantial potential benefits if clinical response is achieved.

5.7 Other Factors

There are a number of other factors that may influence the likelihood of a successful course of rTMS treatment. There are clearly some individuals who for physiological or personality reasons are substantially more sensitive to pain or discomfort and will struggle to tolerate a course of rTMS treatment. Likewise, there are individuals who are more likely to experience headaches resulting from rTMS treatment and have difficulty tolerating this. These issues are probably more likely in patients with a history of significant pain problems and caution should be taken when initiating treatment in individuals with a history of substantial pre-existing headaches. In individuals like this, a slowly increasing stimulus intensity should be considered and low-frequency right-sided rTMS may be a sensible treatment option.

Pre-existing neck pain can also complicate a course of rTMS treatment. Patients are required to sit still for a significant period of time, and unless the neck is adequately supported, this may lead to significant discomfort. Under these circumstances, care should be taken to ensure that the patient is in a comfortable position at all times. The patient may need to have brief breaks during each treatment session to minimise the development of muscle spasm.

The presence of significant psychiatric comorbidity may also limit the likelihood of treatment response although this has not been systematically evaluated in many studies. In our clinical experience, comorbid anxiety symptoms may improve with the successful resolution of depression treated with rTMS, but this is not always the case. When anxiety symptoms persist this is likely to have a long-term negative impact on the patient's mood and contribute to earlier depressive relapse. In our experience, comorbid obsessive-compulsive symptoms are typically not successfully alleviated with standard rTMS depression protocols.

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