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REVIEW ARTICLE

Treatment of difficult-to-treat depression – clinical guideline for selected interventions

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ABSTRACT

Background: Difficult-to-treat-depression (DTD) is a clinical challenge. The interventions that are well-established for DTD are not suitable or effective for all the patients. Therefore, more treatment options are highly warranted. We formulated an evidence-based guideline concerning six interventions not well-established for DTD in Denmark.

Methods: Selected review questions were formulated according to the PICO principle with specific definitions of the patient population (P), the intervention (I), the comparison (C), and the outcomes of interest (O), and systematic literature searches were performed stepwise for each review question to identify relevant systematic reviews/meta-analyses, and randomized controlled trials. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess the methodological quality of the included studies. Clinical recommendations were formulated based on the evidence, the risk-benefit ratio, and perceived patient preferences.

Results: We found sufficient evidence for a weak recommendation of repetitive transcranial magnetic stimulation (rTMS) and cognitive behavioural analysis system of psychotherapy (CBASP). The use of bright light therapy in DTD was not sufficiently supported by the evidence, but should be considered as good clinical practice. The interventions should be considered in addition to ongoing antidepressant treatment. We did not find sufficient evidence to recommend intravenous ketamine/esketamine, rumination-focused psychotherapy, or cognitive remediation to patients with DTD.

Conclusion: The evidence supported two of the six reviewed interventions, however it was generally weak which emphasizes the need for more good quality studies. This guideline does not cover all treatment options and should be regarded as a supplement to relevant DTD-guidelines.

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Introduction

The term difficult-to-treat depression (DTD) arises from heterogenous definitions of 'treatment-resistance' in intervention research; however, there is a lack of an international consensus regarding the DTD definition [1]. Some authors have argued to avoid the term 'treatment-resistance' to reduce stigma. They have suggested using the term 'difficult-to-treat depression,' which also reflects a dimensional approach to accommodate difficulties in describing treatment response [2,3]. In the current clinical guideline, we used a pragmatic DTD definition to make the guideline applicable to patients typically seen in the clinical practice. This definition

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encompassed three patient groups: i) patients without remission despite at least two antidepressants from two different classes given in a sufficient dose and for at least four weeks, or ii) patients with chronic depression, i.e. lasting for two or more years regardless of treatment, or iii) patients assessed as treatment-resistant using an assessment scale such as Maudsley staging method.

The DTD is a substantial clinical problem, as about 30% of depressed patients present with a chronic illness course [4], and only 20–40% achieve remission after the first trial of treatment [2,3].

Patients with DTD have a lower quality of life and a reduced level of functioning compared with other depressed patients [5], and DTD also puts a considerable burden on the patients' relatives [2]. In addition, health service costs related to DTD are 40% higher than the costs spent on non-DTD depression [1, 6].

The empirically supported treatment options for DTD are sparse [7,8], and there is a need to examine whether these patients can benefit from other treatment modalities. The current guideline provides updated evidence for six interventions that have been selected by our expert group according to the following criteria: a) insufficient evidence for the effect of the intervention in DTD, b) the intervention not being established in routine clinical practice, or c) substantial variation in clinical practice regarding the treatment. Our purpose was to extend the range of treatment possibilities for DTD patients. Most treatment modalities selected for evaluation in this guideline are non-pharmacological. This is because many patients with DTD have tried several antidepressants without achieving remission. Some of them may be unwilling to start a new medication trial, but they may be interested in non-pharmacological treatment options, including non-invasive brain stimulation technics, bright light therapy, or specific psychotherapies.

Thus, interventions with well-established effects in DTD, such as electroconvulsive therapy or lithium augmentation, are not included in the review. Neither is this article a comprehensive guideline describing all principles and steps that should be followed in the treatment of DTD. The six interventions selected in this article are briefly described below.

Unilateral high frequency ($\geq$ 5 Hz) repetitive transcranial magnetic stimulation (rTMS) delivered to the left prefrontal cortex (PFC) is a non-invasive antidepressant method that modulates brain activity through a pulsating electromagnetic field. Many studies have investigated the effect of rTMS on depression [9]; however, its effect in DTD has to be determined.

Intravenous ketamine or esketamine in subanesthetic doses have shown a rapid antidepressant effect [10]. However, the long-term effects and potential adverse effects, including the risk of abuse, are not sufficiently documented. Moreover, the treatment is not approved by the Danish authorities and is regarded as off-label use only.

Bright light therapy has shown antidepressant effect in seasonal affective disorder [11] as monotherapy [12] and as an add-on to pharmacotherapy in non-seasonal depression even though the overall quality of evidence is poor [13]. The effect of this treatment in patients with DTD is unknown.

The cognitive behavioral analysis system of psychotherapy (CBASP) was developed to teach chronically depressed patients more adaptive responses to the environment, including interpersonal interactions [14]. Patients with DTD have shown a higher prevalence of comorbid personality disorders as well as inexpedient interpersonal behavior and cognitive styles [15]. Therefore, it is reasonable to assume that CBABS could reduce depressive symptoms in patients with DTD.

Psychotherapy targeting rumination. Rumination is a well-established predictor of the chronicity of depression [16] and increases the risk of relapse [17]. Therefore, a treatment focused on rumination may improve the outcome [18]. The first meta-analysis on the effect of psychotherapy targeting rumination on depression implied that a decrease in rumination is associated with reduction in depressive symptoms [19]. However, whether the treatment improves the clinical outcome in patients with DTD needs to be investigated.

Cognitive remediation is effective in reducing cognitive deficits and improving functional outcomes in patients with schizophrenia [20]. A recent systematic review investigating the influence of cognitive deficits in depression concluded that cognitive deficits are core features of depression and advised that treatment could be enhanced by focusing on amending these deficits [21]. However, the effect of cognitive remediation on the clinical outcome in patients with DTD is unknown.

Aims

We aimed to examine whether six selected interventions are superior for DTD compared with treatment as usual (TAU) or placebo.

Methods

We adhered to the 'Grades of Recommendation, Assessment, Development, and Evaluation' (GRADE) recommendations [22,23] for grading the quality of the evidence and the strength of our recommendations.

Procedure

The National Clinical Guideline adhered to the Danish Health Authority's criteria (www.sst.dk), adopting GRADE as the method. A guideline workgroup comprised 14 professionals in psychiatry, clinical psychology, nursing, general practice, academic experts in psychiatry and psychology, and a patient representative. The members of the guideline workgroup were appointed by relevant organizations to secure a broad and clinical representative perspective in the workgroup. The clinical guideline was developed from January 2019 to June 2020 and published in the full Danish version online (https://www.dpsnet.dk/publikationer/guidelines/).

Before publication, it was reviewed among relevant organizations, stakeholders, including governmental institutions,

Table 1. Outcomes for all six reviews of interventions.

Critical outcomes
Remission at end of treatment (EOT)[a]
Level of functioning at EOT
Hospitalization
Suicide attempts
Important outcomes
Depressive symptoms at EOT
Response at EOT
Quality of life at EOT
Drop out at EOT
Other adverse events at EOT
Remission at longest follow up (6 months)
Depressive symptoms at longest follow up (6 months)

Hospitalization and suicide attempts will be referred to as severe adverse effects (SAE) in the text.
[a]For intravenous ketamine/esketamine 'Remission at end of treatment' was 'Remission at 3–5 days after treatment start' or 'remission at 14–21 days after treatment start'.

regional and local mental health care organizers, and representatives from national service user groups. The guideline was also peer-reviewed by a national and an international reviewer with substantial experience within the field. This article covers the content in a revised and adapted form to fit journal publishing.

Review questions

All members of the working group could propose an intervention based on the criteria mentioned in the introduction section. A total of 20 proposals were discussed, and after voting, six treatments with the largest number of votes were chosen. The selected review questions were formulated according to the PICO principle with specific definitions of the participants (P), the intervention (I), the comparison (C), and the outcomes of interest (O).

For all six review questions, the *participants* were inpatients and outpatients over the age of 18 with a difficult-to-treat moderate to severe episode of Major Depressive Disorder (MDD) according to ICD-10 or DSM-IV or DSM-5 criteria. As described in detail in the introduction, our DTD definition comprised three patient groups.

Interventions were different for all six review questions (see introduction). The detailed definitions of the interventions are available in the supplementary material.

For all six review questions, the *comparisons* were treatment as usual (TAU) or placebo.

Outcomes had to be clinically relevant: Critical outcomes were defined as conclusive in the recommendation for or against an intervention, while Important outcomes were not essential when deciding the recommendation (Table 1). Two of four critical outcomes were severe adverse effects (SAE), including hospitalization and suicidal attempts. Additional intervention-specific outcomes were added to some interventions (see Tables 2 and 3). Detailed information regarding PICO for each review question is available in the supplementary material.

Search and evaluation of literature

For each review question, a systematic literature search and an evaluation of the retrieved literature were performed. The literature search was undertaken in two steps. In the first step, we searched for systematic reviews and meta-analyses published in the last ten years. To evaluate the quality of the systematic reviews, we used the 'A MeaSurement Tool to Assess systematic Reviews' [24]. If a systematic review was included, the search for the randomized controlled trials was conducted from the date where the systematic review ended the literature search. In the second step, we searched for relevant original literature, i.e. randomized controlled trials (RCT). In this search step, we put no limit on publication date unless defined by an included systematic review as mentioned. Additionally, the reference lists of systematic reviews were screened for relevant primary studies. The quality of the trials was assessed using the Cochrane risk-of-bias tool (http://handbook.cochrane.org/).

Literature selection, the risk-of-bias assessment, and the GRADE rating was conducted independently by two reviewers. In case of disagreement, the clinical specialist (KG) or the methods specialist (CH) intervened to resolve the disagreement. The literature search was carried out between June and November 2019 in the following databases: Medline (PubMed), Embase (Ovid), PsycINFO (Ovid), CINAHL (Ebsco), Cochrane Library. All searches were restricted to publications in Danish, English, Norwegian, or Swedish. Detailed search strategies for each review question and each database are available as supplementary material.

Data extraction and synthesis

Data extraction was conducted independently by two reviewers with support from the method- and review specialist. We transferred the extracted data to Review Manager software (version 5.3) for analyses and meta-analyses using pooled data for each of the six review questions. For outcomes where meta-analysis was deemed inappropriate (e.g. if heterogeneity was higher than 70%), results were synthesized narratively. We conducted meta-analyses using the standardized mean difference (SMD) for continuous outcomes and the relative risk (RR) for dichotomous outcomes. Effects were calculated as random effects and with inverse variance weighting. In the case of continuous outcomes, endpoint scores were preferred over 'change from baseline' if both were available. In the results, we included measures of uncertainty such as 95% confidence intervals (CI) and estimates of I^2. The latter measures the percentage of total variation (between-study and within-study), which is due to heterogeneity (between-study variation).

Summary of findings and certainty of the evidence

Certainty of the evidence was assessed using the GRADE. The evaluation was conducted at two levels 1) for each outcome and 2) for each review question. The quality of the evidence was evaluated according to the presence and severity of methodological limitations (risk of bias), inconsistency, indirectness, imprecision, and publication bias [25]. The quality of the evidence was graded as high, moderate, low, or very low. The definitions of each grading level were as

Table 2. Overview of findings for unilateral high-frequency rTMS, intravenous ketamine/esketamine, and bright light therapy.

	Unilateral high-frequency rTMS				Intravenous ketamine/esketamine				Bright light Treatment			
	k/N	Effect estimate	95%CI	GRADE	*k/N*	Effect estimate	95% CI	GRADE	*k/N*	Effect estimate	95%CI	GRADE
Critical outcomes												
Remission at EOT (RR)	11/892	2.33	1.52, 3.58	Moderate	2/82	4.04[b]	1.07, 15.21	Low	1/15	9.17	0.52, 161.48	Very low
Level of functioning at EOT (SMD)												
Hospitalization at EOT (RR)					2/97 3	0.33	0.01, 7.5	Low				
Suicide attempt at EOT (RR)					2/138	2.68	0.12, 61.58	Very low				
Important outcomes												
Depressive Symptoms	18/1113	0.5	0.28, 0.73	Moderate	1/30	−1.18[a]	−2.00, −0.36[c]	Very low	1/20	1.27	0.29, 2.25	Low
at EOT (SMD)		Positive value favors the intervention.			1/71	Negative value favors the intervention. −0.18[a]	−10.68, 0.31[c]			Positive value favors the intervention.		
						Negative value favors the intervention						
					2/76	Inconsistent results		Low				
Response at EOT (RR)	16/1052	2	1.26, 3.19	Moderate	2/101	4.17[a] 2.74[b]	1.49, 11.65	Very low				
					2/82		0.64, 11.68	Low				
Quality of life at EOT (SMD)												
Dropout at EOT (RR)	14/1040	1.11	0.71, 1.76	Moderate	4/194	1.09	0.46, 2.59	Low				
Remission at longes follow up (6 months) (RR)												
Depressive symptoms at longest follow up (6 months) (SMD)												
Other adverse events (RR)					2/138	1.54	1.07, 2.21	Low				
Contractions in the facial	5/457	2.02	1.01, 4.04	Moderat								
muscles at EOT (RR)	8/767	0.34	0.01, 8.13	Moderate								
Seizures at EOT (RR)	3/245	1.33	0.89, 1.97	Moderate								
Headache at EOT (RR)												

Standardized mean difference (SMD) is used with continuous outcomes and risk ratio (RR) with dichotomous outcomes. GRADE 'high quality', further research is very unlikely to change our confidence in the estimate of effect; 'moderate quality', further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; 'low quality', further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality, we are very uncertain about the estimate. [a]3–5 days after treatment start. [b]14–21 days after treatment start. [c]Studies are not meta-analyzed due to high inconsistency and a heterogeneity I^2 of 76%. k/N number of studies/number of participants.

Table 3. Overview of findings for CBASP, psychotherapy targeting rumination, and cognitive remediation.

	CBASP				Psychotherapy targeting rumination				Cognitive remediation			
	k/*N*	Effect estimate	95%CI	GRADE	*k*/*N*	Effect estimate	95% CI	GRADE	*k*/*N*	Effect estimate	95%CI	GRADE
Critical outcomes												
Remission at EOT (RR)	4/302	1.42	1.01, 1.99	Low	1/92	1.58	0.81, 3.11	Very low				
Level of functioning at EOT (SMD)	2/299	0.16	−0.2, 0.52	Low					1/33	−0.12 Negative value favors the intervention.	−0.8, 0.56	Low
Hospitalisation at EOT (RR)												
Suicide attempt at EOT (RR)												
Important outcomes												
Depressive Symptoms at EOT (SMD)	4/750	−0.53 Negativ value favors the intervention.	−0.8, −0.19	Low	1/96	−0.43 Negative value favors the intervention.	−0.83, −0.02	Very low				
Response at EOT (RR)	2/134	1.48	0.75, 2.92	Low								
Quality of life at EOT (SMD)					1/90	0.45 Positive value favors the intervention.	0.03, 0.88	Very low				
Dropout at EOT (RR)	4/944	0.8	0.57, 1.11	Low								
Remission at longest follow up (6 months) (RR)												
Depressive symptoms at longest follow up (6 months) (SMD)												
Rumination at EOT (SMD)					1/90	−0.38 Negative value favors the intervention.	−0.8, 0.05	Very low				
Cognitive Functioning at EOT (Cohen's *d*)									1/33	1.07[a] 0.65[b] ns[c]	na	Very low
Other adverse events at EOT												

[a]Attention and processing speed. [b]Verbal learning and memory. [c]Executive functions. GRADE 'high quality', further research is very unlikely to change our confidence in the estimate of effect; 'moderate quality', further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; 'low quality', further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality, we are very uncertain about the estimate. Cohen's *d* are interpreted as 0.20 = small effect, 0.50 = medium effect, and 0.80 = large effect.

Table 4. Summary of clinical guideline recommendations and practical advice.

Strength and direction of recommendation	Recommendation
Weak recommendation for rTMS	Consider offering unilateral high frequency rTMS, as an add-on to usual antidepressant treatment in patients with DTD.
Practical advice	
• The optimal treatment duration is not defined. The included studies used 10 to 30 sessions of 15–30 minutes duration administered daily. • Be aware of contra-indications such as a cardiac pacemaker, metal devices in the body, organic brain disorder, epilepsy, or epilepsy in the near family. • Due to the risk of seizures, a medical doctor must be present, and access to antiepileptic medication must be ensured. • Follow the updated international guidelines for rTMS.	
Weak recommendation against intravenous ketamine/esketamine	Do not use intravenous ketamine/esketamine in patients with DTD, as benefits are uncertain and short-lived. The adverse effects are considerable, and the long-term effects, including the risk of abuse, unknown.
Good practice recommendation for bright light therapy	It is a good clinical practice to offer bright light therapy to patients with DTD as an add-on to treatment as usual. This recommendation is based on consensus in the guideline working group, as the evidence was insufficient to formulate an evidence-based recommendation.
• The bright light treatment can be executed with a relatively inexpensive lamp for home use. • The treatment should be used daily, in the morning, with a duration of 30–60 minutes, and for at least two weeks. • The recommended light intensity should be at least 10,000 lux measured by the cornea. • The side effects are mild and often short-lived. They include headache, irritability, and nausea. • In the case of rare but severe side effects such as mania or agitation, the treatment should be immediately terminated, and the patient should be referred to a medical doctor. • The treatment is primarily indicated for patient without eye diseases.	
Weak recommendation for CBASP	Consider offering CBASP min. 16 sessions either as individual or group therapy to DTD patients in addition to other antidepressant treatment.
• The treatment should include at least 16 and preferably up to 24 session • Since psychotherapy requires active participation from the patient, it is important to ensure that the patient is well-informed of the treatment model (focused on social skills and interpersonal communication) and the requirements from the patient in participating in therapy • However, motivation cannot be entirely expected from the beginning but is a natural part of the therapy process • It is essential to secure training and supervision of clinicians performing the treatment to ascertain sufficient quality (adherence and competency) of the treatment	
Weak recommendation against psychotherapy targeting rumination	Do not use psychotherapy targeting rumination to DTD as evidence is uncertain and resources invested may subtract from other treatment with certain evidence
Weak recommendation against cognitive remediation	Do not use cognitive remediation to DTD as the benefit is uncertain and resources invested are greater than the benefits.

A good clinical practice is an expert consensus used when evidence cannot support a recommendation, but the expert group agrees on a recommendation based on clinical experience.

follows: 'high quality,' further research is very unlikely to change our confidence in the estimate of effect; 'moderate quality,' further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; 'low quality,' further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; 'very low quality,' we are very uncertain about the estimate.

Development of guideline recommendations

The program Making GRADE the Irresistible Choice (MAGICapp) was used to formulate the recommendations. Four key considerations were taken into account in the formulation: 1) the quality of the evidence [26], 2) the efficacy and tolerability of the interventions, 3) the patient preferences concerning the intervention, and 4) practical issues, for instance, a demand for special training or equipment [27]. Patient preferences were not based on systematic data but were represented by a patient representative appointed by a patient organization. The options for recommendations were as follows: strong recommendation for/or against the intervention, weak recommendation for/or against the intervention or a good clinical practice (in the absence of sufficient relevant evidence) (http://www.gradeworkinggroup.org).

Results

The recommendation for each intervention is followed by a summary of the evidence, including the quality of the evidence, followed by efficacy and tolerability of the interventions. Finally, the rationale for the recommendation is presented. An overview of the findings is presented in Tables 2 and 3. The recommendations with practical advice for all six interventions can be found in Table 4, and detailed summary of evidence for each intervention is available as supplementary material.

Unilateral high-requency rTMS

Recommendation

We established a weak recommendation for the use of unilateral high-frequency rTMS administered to the left prefrontal cortex as add-on to TAU to treat DTD.

Summary of evidence

The evidence was based on a systematic review comprising 19 RCTs with a total of 1113 patients [28]. The overall GRADE rating was 'moderate quality. Many studies were limited by a high risk of bias due to a lack of allocation concealment and insufficient blinding. Other limitations were small sample sizes and a short follow-up time. Finally, 3 out of the 19 RCTs defined treatment resistance as a lack of response to only one treatment trial with antidepressant medicin.

Efficacy and tolerability

The number needed to treat (NNT) was 11 for the remission and 8 for the response. There was a significantly larger reduction in depressive symptoms in the intervention group compared with the control group (Table 2). The studies did not report on the level of functioning and long-term effects. The intervention had no increased dropout. There was no evidence of the increased risk of seizures in the intervention group compared with the control group. However, patients treated with rTMS experienced significantly more contractions in facial muscles (the number needed to harm was 9). The risk of SAE outcomes (i.e. hospitalization and suicidal attempts) was not reported.

Rationale for the recommendation

The risk-benefit ratio was favorable, as the antidepressant effect was moderate, and the side effects were relatively mild and transient. Additionally, the quality of evidence was moderate according to the GRADE. However, only a weak recommendation could be assigned due to two reasons. Three out of four critical outcomes (the level of functioning, hospitalization, and suicide attempts) were not elucidated by the studies. Patient preferences were believed to be heterogeneous as some patients may not want to consent to a treatment that requires daily stimulation at a clinic for at least two consecutive weeks.

Intravenous ketamine or intravenous esketamine

Recommendation

Do not use intravenous ketamine or intravenous esketamine as an add-on to usual antidepressant treatment in patients with DTD.

Summary of evidence

We included four RCTs with a total of 194 patients [29–32]. The overall GRADE rating was 'low quality.' The low quality was because only a few small studies were included. Additionally, there was a lack of blinding of both researchers and participants. Finally, the results were inconsistent between the studies, and the effect estimates were unprecise.

Efficacy and tolerability

Following repeated intravenous ketamine infusions, the chance of remission at 14–21 days from the treatment start was significantly higher in the intervention group compared with the control group (the NNT was 7). The effects of the intervention on depressive symptoms were, however, inconsistent (see Table 2). No studies investigated the long-term effects, and no studies reported on changes in the level of functioning.

More patients in the intervention group experienced side effects compared to the control group. They appeared about 40 min after an infusion and faded within three hours. The most frequent side effects were dissociative symptoms, headache, dizziness, sleepiness, and nausea. No significant differences in dropout or SAEs were found.

Rationale for the recommendation

The intervention benefits were short-lived, and the evidence on the long-term efficacy and side effects, including the risk of abuse, was lacking. Thus, the risk-benefit ratio was not in favor of the intervention. Additionally, the quality of evidence was 'low' to 'very low.' Finally, patients' preferences may vary considerably.

Bright light therapy

Recommendation

No recommendation based on evidence was possible; however, a 'good practice' recommendation for bright light therapy was made (Table 4).

Summary of evidence

A single RCT with 20 patients was included [33]. The GRADE quality rating was 'very low.' In particular, the risk of bias evaluation revealed lacking blinding of both researchers and participants.

Efficacy and tolerability

There was no significant difference in remission rates between bright light therapy and TAU compared to TAU alone. Social functioning was not evaluated. However, the study showed a significantly larger reduction in depressive symptoms in the intervention group compared with the control group (Table 2). The patients in the intervention group did not have significantly more side effects; however, SAEs were not evaluated. Long-term effects were not investigated.

Rationale for the recommendation

The evidence-based recommendation could not be based on a single small study with a high risk of bias. However, we formulated a good clinical practice recommendation due to the following reasons. Firstly, bright light therapy is relatively cheap and easily accessible. Its side effects are usually mild and short-lived, and resource demand is low. Secondly, we assumed that most patients would be interested in the treatment. Thirdly, the treatment has shown promising efficacy in patients with non-DTD depression. Finally, bright light therapy can be used by patients receiving other evidence-based antidepressant interventions.

Cognitive behavioral analysis system of psychotherapy (CBASP)

Recommendation

Evidence supports a weak recommendation of the cognitive behavioral analysis system of psychotherapy (CBASP) for DTD compared to TAU.

Summary of evidence

Four RCTs with a total of 944 patients were included [34–37]. The overall GRADE rating was 'low quality.' The risk of bias evaluation revealed a lack of blinding. Furthermore, the quality was affected by a high inconsistency of the results. There were also marked differences between the populations examined in the included studies and our target population. For instance, one study included 40% of participants with dysthymia, and other studies mainly comprised chronically depressed patients.

Efficacy and tolerability

The intervention significantly increased the chance of remission compared with the control group (NNT was 12). The reduction of depressive symptoms was also significantly larger in the CBASP group (Table 3). However, the level of functioning and the response rate was not different between the groups. The intervention was not associated with increased dropout; however, neither SAEs, other side effects, nor long-term effects were investigated.

Rationale for the recommendation

The risk-benefit ratio was in favor of the treatment. However, the strength of the recommendation was weak for two main reasons. The effect-sizes were small, and the quality of the evidence low. Additionally, substantial recourses are needed to implement CBASP. Finally, even though a majority of patients were anticipated to accept CBASP, some may feel that they do not have the resources required for psychotherapeutic work, focused on social skills and interpersonal communication.

Psychotherapy targeting rumination

Recommendation

The recommendation was not to use psychotherapy targeting rumination to DTD as evidence to support the intervention was uncertain.

Summary of evidence

One RCT using mindfulness-based CBT with 106 patients was included with non-significant or small effects on the outcomes [38]. The GRADE quality rating was 'very low'. The risk of bias evaluation revealed blinding issues and a self-report outcome. Moreover, as the population mainly consisted of chronic depression, the evidence was indirect.

Efficacy and tolerability

No significant effect on remission was found. However, there was a greater reduction in depressive symptoms in the intervention group compared with the control group. The quality of life increased significantly more in the intervention group. Additionally, there was a trend towards a larger reduction in ruminations in patients receiving the mindfulness-based therapy. Neither SAEs, other side effects, nor long term effects were investigated.

Rationale for the recommendation

As the benefits did not outweigh the substantial resources invested from the patients and professionals, the cost-benefit ratio was not in favor of the intervention. We noticed considerable general interest in psychotherapy among patients; however, this does not apply specifically to psychotherapy targeting rumination. The included study examined a mindfulness-based therapy. Some patients with DTD may find the mindfulness approach counter-intuitive and too demanding regarding the time necessary for practicing mindfulness. Other patients, for example, those with high rumination scores, may prefer psychotherapy targeting rumination.

Cognitive remediation

Recommendation

The recommendation was not to use cognitive remediation to DTD as evidence to support the intervention was uncertain.

Summary of evidence

One RCT with 33 patients was included [39]. The GRADE quality rating was 'very low' with a high risk of bias.

Efficacy and tolerability

The study showed that the intervention improved attention and processing speed, and verbal learning and memory, but there was no significant effect on the level of functioning (Table 3). The remission, response, and the change in the depressive symptoms were not investigated. Neither did the study report on side effects, including SAEs, nor long-term effects.

Rationale for the recommendation

The cost-benefit ratio was not in favor of the intervention. Furthermore, some patients may feel too depressed to participate in systematic training, so the treatment preference was expected to be heterogeneous.

The clinical recommendations and practical advice for each intervention are available in Table 4.

Discussion

Sufficient evidence was found for weak recommendations for high-frequency prefrontal rTMS and CBASP as an add-on to

other antidepressant treatment in patients with DTD. Also, bright light therapy was considered by our expert group as good clinical practice in addition to TAU. Insufficient evidence was found to recommend intravenous ketamine or esketamine; psychotherapy focused on rumination or cognitive remediation.

Based on our work, comparisons between the six selected interventions are not possible since each of the included interventions was tested against placebo or TAU. This also means that our work cannot be used to create a hierarchy for the selection of interventions. The present study provides evidence for or against using various interventions in contrast to TAU or placebo.

Our recommendation of rTMS for patients with DTD is in line with both the National Institute for Health and Care Excellence (NICE) [40] and the Royal Australian and New Zealand College of Psychiatrists (RANZCP) guidelines for the treatment of Major Depressive Disorder (MDD) [41]. In contrast, the American Psychiatric Association (APA) lists rTMS as a treatment of MDD but does not mention it as an option for patients with DTD [42]. However, the APA guidelines were conducted in 2009; new evidence for rTMS in DTD has emerged in the past decade.

We do not recommend intravenous ketamine or esketamine for DTD. Even after repeated doses, the effect is transient, and the long-term effect and side effects, including abuse, are unclear. The RANZCP statement concerning the intravenous ketamine for depression agrees with our recommendation. It must be noted that intravenous ketamine in anesthetic doses is not approved for treating depression and should be considered an off-label treatment. In contrast, an intranasal esketamine (Spravato), is easier to administer and has recently been approved for treatment-resistant depression in the European Union. The recommendation for the intranasal esketamine in patients with DTD needs to be established.

Due to insufficient evidence, we could not formulate any evidence-based recommendation for the bright light therapy in DTD. This seems to accord with other guidelines, as neither the RANZCP, APA, nor NICE mentions bright light therapy as a treatment option for DTD. However, due to the reasons listed in the results section, we consider the treatment a good clinical practice in these patients. We underscore that this recommendation is not based on evidence but on the consensus of our expert group.

The most recent guideline [43] on psychotherapeutic interventions in DTD recommended CBASP as the first choice of psychotherapeutic treatment. Moreover, the authors emphasized that psychotherapy combined with pharmacotherapy is superior to either treatment alone and should be considered the first choice. Finally, the guideline recommended a personalized approach, where the treatment selection (e.g. individual/group psychotherapy, pharmacotherapy and/or psychotherapy) is based on the patients' preferences. Recognizing that the effect of psychotherapy on DTD is generally slower than in non-DTD depression, Jobst and co-workers recommend at least 18 sessions to be needed for achieving an optimal effect.

We do not recommend psychotherapy focused specifically on rumination, however in the latest update from the NICE guideline on depression, psychological treatment of DTD was advised to address relevant maintaining processes, for example, avoidance, rumination and interpersonal difficulties [44].

The effect of cognitive remediation for the treatment of DTD is not sufficiently elucidated, and more research should fulfil this gap in knowledge.

Sparse evidence

The evidence for each review question was limited. Only one review question (rTMS) included 19 RCTs, while the evidence for the remaining interventions was based on between one and four studies. In addition, the methodological quality of studies was low, leaving us with limited confidence that the results will robustly reflect the actual effect. The limited body of evidence may be explained by the selection of review questions. In the current guideline, we reviewed interventions where practice seemed less informed by evidence or tended to vary across organizations or countries. As a result, we did not review interventions with well-known evidence in the research and clinical community.

Definition of difficult-to-treat depression

There is a need for consensus on the definition of DTD. Although we applied a pragmatic DTD definition, several studies did not fulfill the criteria and had to be excluded. The main differences were in i) how many treatment trials have been used, ii) whether antidepressants from two different classes have been tried, and iii) whether the dose and duration of the treatment were adequate. Psychotherapeutic interventions were not considered a treatment trial by most of the studies.

Furthermore, the included studies did not report whether possible causes of pseudo-resistance, such as an incorrect diagnosis or insufficient compliance, were ruled out prior to participants' inclusion. Moreover, most of the included studies used a one-dimensional definition of treatment resistance. This definition was exclusively based on the failure of previous medication trials. In contrast, a multidimensional Maudsley staging method of treatment resistance includes two other dimensions 1) the duration and 2) the severity of the current depressive episode [3]. The model has been shown to predict a short-term and long-term risk and duration of a depressive episode [3]. As argued by the authors, the treatment-resistance should be regarded as a continuum under the influence of several dimensions. Furthermore, patients with DTD differ from other patients with depression in a higher frequency of adverse events in childhood [45–49], higher prevalence of comorbid personality disorders, and a greater tendency to rumination [15]. Therefore, we speculate whether the multidimensional model of DTD should also incorporate these patient characteristics [2].

To sum up, our review emphasizes the need for consensus regarding the definition of DTD. The multidimensional

approach proposed by *Fekadu and co-workers* seems to be a reasonable step forward for a better DTD definition.

Evaluation of outcome

As evident from the 'Summary of findings' tables, several outcomes were not covered in the included trials. Cuijpers [50] argued that outcome research tends to focus on symptom reduction (remission and response) at the end of treatment, while research including adverse effects, economic outcomes (cost-effectiveness analyses), and patient-defined outcomes, and to some degree also quality of life and long-term effects (follow up) are limited. Our review substantiates that finding and join the call for the need to achieve a consensus in the research field on what core outcomes randomized trials should include. Also, future research must prioritize outcomes related to the patient perspective, and negative, long-term, and economic outcomes.

From research to clinical practice

Many patients with DTD do not receive optimal evidence-based treatment [51,52]. As clinical practice varies widely across treatment sites and countries, the extent to which these patients are correctly diagnosed and referred to specialized treatment in routine clinical care is unknown and does probably not reflect the true prevalence of DTD. Hopefully, a DTD guideline, such as the present, will aid diagnostic procedures in routine clinical practice to identify these patients. Moreover, such a guideline may expose areas with lacking evidence. The guideline provides evidence-based interventions for the DTD, but as a consequence of the definition, many patients with depression will not respond to treatment. However, they are not covered by this guideline. From a practical perspective, difficult-to-treat depression reflects a failure to a treatment algorithm, or a failure to deliver the treatment optimally. Effective treatment can only work when there are a clear treatment plan and a suitable setting allowing to execute it. Unfortunately, while a clinical guideline helps clinicians, it does not offer tools for dissemination. That responsibility resides with the regional mental health care organizers.

Limitations

Strengths of the current guideline include using the state-of-art methodology to review the literature and conducting the work by researchers and clinicians who are expert within the field. The guideline also includes the patient perspective by a workgroup participant advocating the patients with DTD.

Some limitations are evident. First, as studies varied in DTD definitions, the selection of the literature was challenging. We tried to include studies only if there was a clear indication that the study population fulfilled our inclusion criteria, but a few of the studies had a more heterogeneous sample which we compensated for by downgrading the quality of evidence. Another limitation pertains to the method, where formulating review questions were conducted according to the PICO principle allowing the experimental intervention to be compared with only one control intervention per question. Accordingly, the recommendations in this guideline only represent the selected comparison, and some of the evaluated interventions might have shown different efficacy if another comparator had been chosen. As we reviewed relatively novel interventions for use in daily clinical practice, we systematically used TAU (including placebo) as a comparator. Finally, due to limited recourses, the guideline could only include six interventions. Hence, other potentially relevant treatments cannot be selected. This applies to, for instance, transcutaneous vagus nerve stimulation (tVNS), transcranial direct current stimulation (tDCS), and pulsed electromagnetic field therapy (PEMF). The efficacy of these and other methods for patients with DTD should be evaluated.

Conclusion

We recommend considering rTMS and CBASP in addition to other antidepressant treatments in patients with DTD. Likewise, we recommend bright light therapy as a good clinical practice in this patient group. In contrast, we do not recommend intravenous ketamine or esketamine, psychotherapy targeting rumination, or cognitive remediation for these patients.

We still need more knowledge on patient characteristics predicting DTD and high-quality evidence on effective treatments for DTD. As the evidence was limited on most review questions, an updated version might prove relevant within three to five years.

In treating patients with DTD, the clinician should exclude potential pseudo-resistance causes and consider well-established evidence-based interventions before choosing alternative treatment strategies. This guideline is not an exhaustive review of all possible relevant interventions for these patients. Consequently, the guideline should be used as an addition to clinical knowledge and other available guidelines in providing a balanced approach to treatment.

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