WBC and HBOT in Depression

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Treatment with antidepressants is often insufficiently effective, especially in treatment-resistant depression. In such a situation, it is possible to change the drug, add a second antidepressant, or use pharmacological and non-pharmacological methods of augmenting the effect of pharmacotherapy. New methods that may fall into the scope of multi-module depression treatment as an augmentation of depression treatment are whole body cryotherapy (WBC) and hyperbaric oxygen treatment (HBOT). 545 records were selected and analyzed for these two treatments and finally three clinical trials were selected for analysis.

whole body cryotherapy WBC hyperbaric oxygen treatment HBOT depression pharmacotherapy augmentation treatment resistant depression

1. Introduction

Despite the progress in psychopharmacology and the introduction of new and effective antidepressants [1], the effectiveness of pharmacological treatment of depression is still far from satisfactory. Analyzes of the effectiveness of treating acute depressive episode on large groups of patients have shown that only about 1/3 of patients achieve remission after a 12-week treatment period [2] and most of those treated with even multiple drugs either do not achieve remission or it is not permanent [3][4]. Moreover, despite the efficacy of antidepressants confirmed in clinical trials [1], there is increasing concern about the slight difference between the effect of antidepressants and placebo.

A meta-analysis by Li et al. showed in patients pharmacologically treated for depression not only a high level of placebo response (SMD = 1.22, which indicates a very large therapeutic effect), but also an increase in the placebo effect in recent years [5]. One of the most recent meta-analyzes also indicates the limited efficacy of pharmacological treatment of depression in the elderly, for whom there is no statistically significant difference between treatment with an antidepressant and a placebo [6]. Moreover, the problem of ineffectiveness in treating depression increases with age. It was shown that the effectiveness of treating depression in the elderly population is two times lower than in people in early and middle adulthood, and amounts to 45.3% and 40.5% in the group of people treated with an antidepressant or a placebo, respectively [6].

Ineffective antidepressant treatment of at least two episodes of depression has been shown to lead to treatment-resistant depression (TRD), characterized by more frequent relapses with increasingly severe symptoms of depression, leading to chronic impairment of patients' functioning and increased comorbidity, as well as suicide and

non-suicidal mortality [4]. In the case of ineffective treatment of depression or TRD, treatment augmentation using biological and psychological methods of therapy is indicated.

Strategies to increase the effectiveness of treating depression include changing the antidepressant, adding another antidepressant, or augmenting the treatment by adding another drug like atypical antipsychotic or lithium. There are also non-pharmacological forms of augmentation of depression treatment that have been proven to be effective; they include: cognitive-behavioral psychotherapy, psychoeducation, aerobic exercise, neuromodulatory treatment through vagus nerve stimulation, electroconvulsive therapy (ECT), transcranial direct current stimulation (TDCS), repetitive transcranial magnetic stimulation (rTMS) or deep brain stimulation (DBS) and light therapy [3][4].

2. Current Researches

WBC is a treatment method in which a special cryochamber is used, where the temperature is extremely low (between −110 °C and −160 °C). The patient stays there for a short time between 1–4 min. Exposures to low temperatures are repeated at different time intervals [7]. Scientific studies have shown, that the systematic use of extremely low temperatures reduces the level of IL-1α, and increases the level of cytokines IL-6 and IL-10, and also contributes to the reduction of the level of TAS, having an overall an immune-stimulatory effect [8][9]. So far, the effectiveness of WBC has been proven in the treatment of somatic diseases such as rheumatoid arthritis, multiple sclerosis, fibromyalgia, chronic back pain, and ankylosing spondylitis [7]. One study also showed that in patients with mild cognitive impairment (MCI), cryotherapy reduces the frequency of depressive symptoms measured with Visual Analogue Scales (10 sessions, study group n = 33, temperature from −110 °C to −160 °C) this justifies the attempt to use WBC to treat depression [10].

Our analysis of the publications shows a small number of studies on the effect of WBC on the treatment of endogenous depression. Only two published studies with the use of WBC as an add-on treatment for pharmacological treatment of patients diagnosed with depression were carried out so far, but they indicate that this method can bring about a quick improvement in patients who are already being treated pharmacologically. In both studies, this improvement is significant after 5–6 sessions of WBC. In the study with 10 WBC sessions, the intensity of depressive symptoms decreased by about 35% during this time, and in the study with 15 sessions, even by 69%. This may indicate a rapid and possibly dose-dependent treatment effect.

Conversely, there are some doubts about these results, because however in the study by Rymaszewska et al. patients were assessed psychiatrically with HDRS-17 every week, the depressed group was small (n = 14). In turn, in the next study by Rymaszewska et al. (2020) the group was larger, but the improvement in the following weeks was assessed using the subjective self-assessment scale BDI, and not in an objective psychiatric examining. Therefore, the conclusions regarding the speed of improvement drawn by the authors are only preliminary and require confirmation in studies with mental health assessment performed by a psychiatrist. Unfortunately, no data has yet been published on the follow-up and persistence of improvement due to WBC after the end of treatment. Definitely, the results on the effectiveness of WBC require replication in subsequent studies in much larger study groups—the study by Rymaszewska et al. (2008) included only a very small group of patients with depression. In

both studies by Rymaszewska, women have the advantage in the study group, that raises the question of the effectiveness of WBC in the group of men. It is also worth emphasizing that the results of using HBOT in depression so far come only from one clinical center. Therefore, they need to be verified in a multi-center study of the effectiveness of this method in depression.

The experiences of using WBC in somatic medicine formed the basis for conducting WBC in depressive patients according to a protocol with numerous known contraindications, which limits the possibility of widespread use of this method. A study by Rymaszewska et al. from 2008 indicates 100% tolerance and no drop-outs, while the 2020 study was not completed by 36 people. This may indicate the possibility of a large number of side effects and the need for careful selection of people for treatment. Both studies published so far were outpatient studies. Perhaps conducting WBC in hospital treatment would allow for greater control of the patients' clinical condition and might be associated with a lower risk of side effects.

Despite these doubts and questions, the demonstrated preliminary effectiveness of WBC in the augmentation of the treatment of depression is essential. Therefore, subject to careful patient selection, this method is a promising candidate for an effective method of augmentation of the pharmacological treatment of depression. It will be very interesting to study the effectiveness of WBC in a group of patients diagnosed with treatment-resistant depression. An open question is also the possibility of treating depression with WBC as monotherapy or in a multimodal treatment strategy in combination not only with pharmacotherapy but also with other non-pharmacological treatment methods and psychotherapy.

Research is also needed on the mechanism responsible for the improvement of the mental state of patients suffering from depression and treated with WBC, as it is so far unknown; it is possible that the mechanism of WBC is related to its previously demonstrated immune-modulatory effect [11][8][12]. Interestingly, in one of the studies analyzed, the level of IL-6 and IL-10 as well as TAS was not confirmed for the changes observed in the treatment of somatic patients [13]. Perhaps it is related to the disturbances in the immune system already existing in patients with depression, these results, however, require replication in subsequent studies of the effectiveness of WBC in depression. With regard to the mechanisms of action of WBC, in one of the previous studies, a statistically significant reduction in the brain-derived neurotrophic factor ($p < 0.05$) was observed among the analyzed biochemical parameters, however, this study was conducted not in depressed patients, but in MCI patients with depressive symptoms [10].

The second non-pharmacological augmentation method for depression treatment that we analyzed is HBOT. This method involves the use of 100% pure oxygen at a pressure above atmospheric pressure [12]. HBOT is widely used in patients with foot ulceration resulting from diabetes, with carbon monoxide poisoning, in patients with vascular dementia and after traumatic brain injuries [14][15][16][17]. A 2017 study by Lim et al. suggests that HBOT, in addition to reducing inflammation in the nervous tissue, may also inhibit serotonin reuptake, which may be beneficial in the treatment of depression [18]. This study encourages attempts to use HBOT in the treatment of depression, but as our analysis shows, there are hardly any such studies apart from the Feng et al. study we described [19].

Today it is already known, that HBOT is an effective and safe method of treating post-stroke depression—this topic has been the subject of numerous studies. In a recent meta-analysis of 27 clinical trials (17 randomized) by Liang et al. it was found that the use of HBOT is effective both as add-on treatment as well as in monotherapy and significantly reduces the severity of depression on the HAMD-17 scale (weighted mean difference (WMD) = −4.33; 95% CI (−4 82 to −3.84), p = 0.000) and the HAMD-24 scale (WMD = −4.31; 95% CI (−5.01 to −3.62), p = 0.000) [20]. It was also shown that HBOT caused fewer side effects compared to conventional antidepressant therapy (9.6% versus 16.6%). Based on the research carried out so far, the most common side effect in the group of patients treated with hyperbaric oxygen was ear pain [20].

The antidepressant effectiveness of HBOT was also demonstrated in a case study of a 45-year-old patient with depression in the course of Parkinson's disease [21]. This patient did not agree to pharmacological treatment, because he did not believe that it could bring him any improvement. In addition, the man was burdened with a family history, his mother also suffered from Parkinson's disease, diagnosed at the age of 40. Therefore, he underwent a 30-day HBOT, held in a hyperbaric chamber (the patient inhaled pure oxygen through the mask in 2 sessions of 40 min, separated by a 10-min break, pressure 2.0 ATA). His depressive condition was assessed before and after the intervention using HDRS. After 30-day therapy with hyperbaric oxygen, the intensity of depressive symptoms, measured on HDRS decreased by 20 points. One month after the end of treatment, an observation showed that the improvement in mood was maintained.

Both post-stroke depression and depression in the course of Parkinson's disease are, however, examples of depression on an organic basis and the effectiveness of HBOT in organic mental syndromes is not a direct proof of the effectiveness of HBOT in endogenous depression. In our opinion, the partial evidence for the effectiveness of HBOT in depression may be the study by Feng et al., published 4 years ago, selected for our analysis. This study looks at depression associated with ISCI. Despite the ambiguities or possible methodological flaws, it is so far the only study available in the literature indicating the possibility of HBOT being effective in the treatment of depression that is not directly related to an organic cause.

Patients were qualified for the study after being examined by a psychiatrist and meeting the criteria for depression and/or anxiety disorder. Although the exclusion criterion is the lack of previous episodes of mental disorders, it does not mean that depression in the patients included in the study was associated with ISCI. For this reason, this study was included in the analysis, and was treated as a study of depression with accompanying somatic disease. The study indicates that the patients recruited for the study had depression with anxiety of a similar intensity, so there was no subset of patients with depression and anxiety disorders and the number of patients in the study group seems to be sufficient to draw conclusions from the study. Analysis of the results of this study prove that HBOT treatment can be effective in treating depressed patients, although the conclusion must be repeated in next studies where HBOT is used in depression without comorbidities.

Feng et al. state that HBOT treatment is as effective as psychotherapy, however, based on the methodology of the study it is difficult to define what type of psychotherapy was effective in the psychotherapy group [19]. However, the question remains, would the use of both methods at the same time be more effective and give a greater effect?

The answer to this question requires another study comparing a clearly defined type of psychotherapy with HBOT used jointly and in monotherapy.

Although it may be assumed that since in the study by Feng et al. no side effects were described, they were not present, it seems rather unlikely and tolerance of HBOT treatment should be an element of assessment in subsequent studies. Some help, similarly to WBC, may be the experience with the use of HBOT in somatic indications. It may help rule out patients for whom this procedure is risky, thus reducing the risk of side effects.

3. Conclusions

The results obtained so far from the use of WBC in the augmentation of the treatment of depression are interesting, but require replication in subsequent studies. After confirming the effectiveness of the WBC, its high efficiency and quick treatment effect could make WBC an attractive method of augmentation of the effect of an antidepressant treatment possibly also in TRD. HBOT seems to be effective so far in treating post-stroke depression. The one pilot study conducted so far shows that HBOT may be highly effective in depression, but extensive research is needed to confirm its effectiveness in endogenous depression. Both methods may therefore be effective new ways to improve the effectiveness of treatment of a depressive episode as well as candidates for a treatment of TRD (**Figure 2**), however, it is too early to include them in treatment standards.

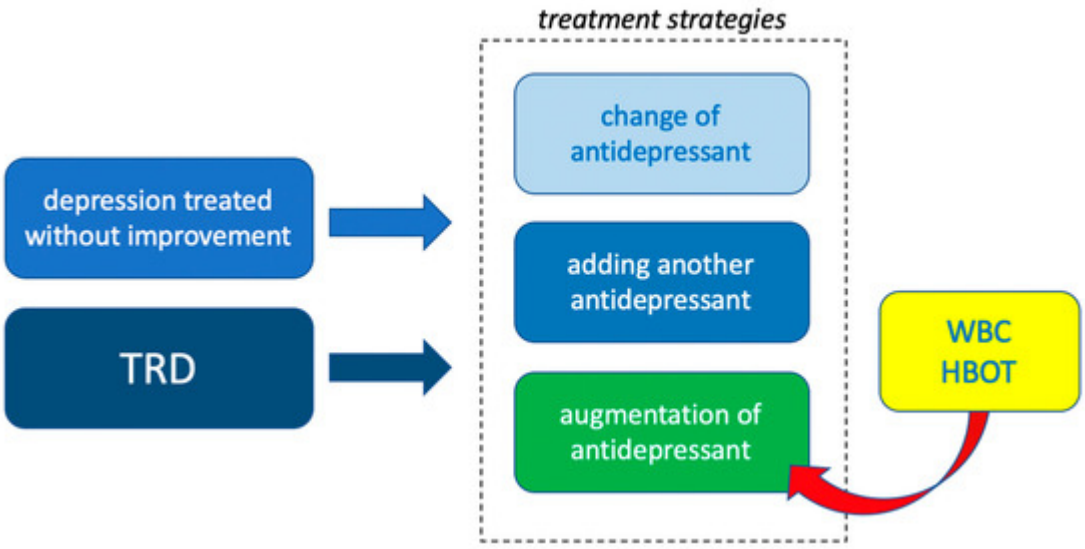

Figure 2. Whole Body Cryotherapy (WBC) and Hyperbaric Treatment (HBOT) could become new methods of antidepressant augmentation, also for treatment resistant depression (TRD).

Both methods, WBC and HBOT, have been used in somatic medicine so far, so the protocols for these forms of therapy are well known and confirmed, which means that their introduction to psychiatry may be burdened with a lower risk of the frequency of drop-outs as well as side effects.

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