Whole-Body Hyperthermia (WBH) in Psychiatry

12

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Abbreviations

5-HT	5-Hydroxytryptamine/serotonin
CES-D	Center for Epidemiologic Studies Depression Scale
FMS	Fibromyalgia syndrome
HAMD	Hamilton Rating Scale for Depression
MDD	Major depressive disorder
MINI	Mini-International Neuropsychiatric Interview
SD	Standard deviation
SE	Standard error
SSRI	Selective serotonin reuptake inhibitor
TRP	Transient receptor potential
TRPA1	Transient receptor potential cation channel subfamily A member 1
TRPV1	Transient receptor potential cation channel subfamily V member 1
WBH	Whole-body hyperthermia

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12.1 Hyperthermia, Fever, and Mental Health

Depressive disorders have significant medical, social, and economic impact [1]. On the one hand, a significant proportion of individuals with mental illness do not have access to specific treatment, and on the other, those who seek help are frequently interested in more natural therapies. A recent critical assessment of conventional pharmacological treatments for depressive episodes has indicated that approximately 30% of patients with depressive episodes do not respond to conventional antidepressant medication or develop side effects [2]. Effective new treatments are therefore urgently needed in psychiatry.

Early written records by Galen of Pergamon (personal physician of Marcus Aurelius, approximately 129–201 B.C.) described the application of therapeutical heat in form of hot baths for the treatment of melancholia. In the early nineteenth century, it was assumed that an impulse to the autonomous nerve system could lead to alterations in the metabolic system, relaxation, and better sleep. In the first half of the twentieth century, "malaria fever cure" was first used by Wagner-Jauregg and Rosenblum for patients with psychiatric symptoms related to syphilis and later for non-syphilitic psychoses. In addition, warm full baths, hot wet packs, and other forms of hydrotherapy have been used to treat agitation, before being replaced by pharmacotherapy [3, 4].

12.2 Whole-Body Hyperthermia (WBH) for Psychiatric Symptoms

Beneficial effects of WBH on mood and quality of life have repeatedly been observed during and after treatment in various fields of medicine, including rheumatology, orthopedics, and oncology. The significant improvement in depressive symptoms induced by WBH in patients with cancer has been correlated with increases in plasma β-endorphin levels [5].

Recently, WBH has received renewed attention in the context of treating mental health issues, with several studies investigating potential effects and clinical applications, especially for patients with depressive symptoms. Most importantly, a randomized, double-blind, and sham-controlled trial delivered by Janssen and colleagues [6] has reported a significant, rapid, and partially lasting reduction of depressive symptoms in non-medicated patients with major depressive disorder (MDD) following a single session of wIRA-WBH using a Heckel-HT3000™ (Hydrosun Medizintechnik, Müllheim, Germany). In 17 out of 34 patients, body core temperature was increased to 38.5 °C (active treatment condition, within 107 min, followed by a heat-retention phase of 60 min, during which the patients achieved a mean maximal body core temperature of 38.9 °C, i.e., a mean increase of 1.9 °C). Depressive symptoms which were assessed 1, 2, 4, and 6 weeks after WBH using the Hamilton Rating Scale for Depression (HAMD) were significantly reduced (4 points on HAMD scale) from week 2 to week 6 after treatment, when compared to sham treatment (see Table 12.1).

Table 12.1 HAMD scores during follow-up after wIRA-WBH vs. Sham intervention (modified from [6])

	HAMD mean score (SD) WBH	HAMD mean score (SD) Sham
Baseline	20.71 (4.87)	22.75 (4.42)
Week 1 (post-intervention)	14.80 (5.40)	20.86 (3.33)
Week 2	12.67 (6.78)	18.71 (3.17)
Week 4	12.93 (4.92)	17.79 (4.06)
Week 6	12.40 (5.45)	17.21 (4.78)

A preceding open clinical trial by the same group [7] was based on findings which demonstrated that WBH and the selective serotonin reuptake inhibitor citalopram independently increased body temperature and acted synergistically to induce antidepressant-like behavioral responses in a rat model of depression [8]. Hanusch et al. [7] have reported that a single session of mild-intensity WBH, using a Heckel-HT2000™ near-infrared WBH device to increase body temperature (average maximum body core temperature 38.4 °C, i.e., an increase of 1.2 °C; mean session time 127 min) resulted in a rapid and sustained reduction in depressive symptoms (CES-D score before treatment: mean = 29.9 [SD 10.6], 5 days after treatment: mean = 19.2 [SD 12.3], t = 5.53, df = 15, $p < 0.001$, effect size = 1.13) in 16 patients with MDD, with WBH-induced reductions in the mean circadian body core temperature correlating with reduced CES-D scores 5 days after treatment. Interestingly, they observed no significant treatment response in patients treated with selective serotonin reuptake inhibitor (SSRI).

A quasi-experimental, observational study of fibromyalgia by Romeyke et al. [9] found that the integration of WBH into a multi-modal inpatient pain therapy regime appeared to improve depressive symptoms ($p = 0.055$, comparing multi-modal therapies with and without WBH; patients in both groups numerically improved from admission to discharge). This study used a Heckel-HT2000™ device targeting a body core temperature of 38.5 °C for 50 min (followed by 60 min rest) with an average of 4.9 sessions per patient. However, it should be noted that the 103 subjects included in this study were suffering from severely progressive forms of fibromyalgia syndrome with a high degree of chronicity and multiple comorbidities and had received multiple therapies including psychotherapy.

Studies have also assessed the effects of WBH using hot baths instead of IR-heating. A communication by Schaper [10] described the antidepressant effects (HAMD-17) of weekly hyperthermic baths ($n = 4$ to 13, depending on the length of their in-patient stay with an average maximum body core temperature of 38.4 °C and an increase of 1.7 °C) in 20 patients with unipolar depression or bipolar disorder. Statistically significant reductions in depression were seen after the second session and during the second week of treatment. Gödl and Glied [11] also reported on results from a study involving weekly WBH treatments of 10 patients in hot tubs for 6–8 weeks with an average maximum body core temperature of 39.3 °C and an average increase of 2.3 °C. At the end of the treatment phase, 50% of all included subjects were below the cutoff for a diagnosis of depression. However, baseline HAMD scores were not obtained, since heart rate variability was chosen as the main

outcome measure. In another study involving 17 patients with confirmed depressive disorder (ICD-10: F32/F33), WBH in hot tubs (twice a week for 4 weeks) significantly reduced depression (HAMD) after four interventions compared with patients in the sham condition. In this study, water was heated to 40.2 °C, and participants spent, on average, 22.6 min in the tub, followed by 33.2 min rest [12].

Taken together, these studies indicate that WBH treatment is generally well tolerated with reported side effects *during* treatment being tachycardia, restlessness, and agitation, as well as emotions such as anger, sadness, or insufficiency. *After* treatment, participants often exhibited short and complete remitting symptoms such as headaches, nausea, ringing in ears, insomnia, vertigo, reduced libido, or areas of hypesthesia in extremities [13].

12.3 Mechanisms of Action of WBH

Depressive disorders are characterized by an altered mineralocorticoid receptor (MR) response, often increased cortisol levels, as well as serotonergic alterations including a down-regulation of 5-HT_{1A} receptors, and increased binding of 5-HT_{2A} receptors in the hippocampus [14, 15]. It is also known that serotonergic (5-HT_{1A}) receptor function and SSRI administration influence temperature and hormone responses [16]. Hyperthermic interventions may modify the release of serotonin in the raphe nuclei via functional transient receptor potential (TRP) channels (see Fig. 12.1). Transient receptor potential ankyrin 1 ($TRPA_1$) and vanilloid 1 ($TRPV_1$) receptors are implicated in the sensation of pain, temperature, inflammation, and cough. $TRPA_1$ is activated by temperatures below 17 °C, $TRPV_1$ (capsaicin receptor) by temperatures above 43 °C. $TRPA_1$ and $TRPV_1$ are often co-expressed in neurons. Consequently, the formation of functional $TRPA_1$-$TRPV_1$ tetramers imparts unique activation profiles, presumably altering the release of serotonin [17].

In summary, WBH may activate warm-sensitive afferent thermosensory pathways and affect mood-regulating neural activity in the midbrain, including nuclei

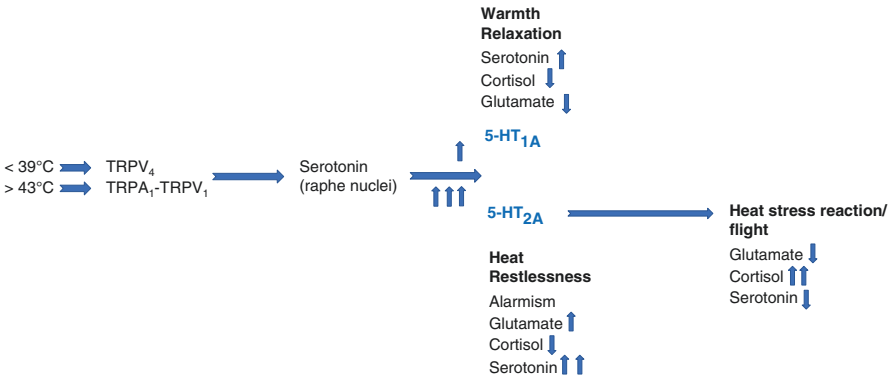

Fig. 12.1 Assumed mechanisms of action of WBH (according to Hanusch, unpublished)

implicated in serotonergic neurotransmission, and thereby elicit antidepressant-like effects as well as thermoregulatory cooling (reduced circadian body temperatures).

The immune hypothesis of depression describes a connection between a chronic subclinical stimulation of the immune system and the development of depression and other mood disorders [18]. There is evidence that at least in subgroups of patients with clinical depression, levels of pro-inflammatory cytokines are elevated during negative mood states and that treatment responses may be related to immune changes, including a decrease in pro-inflammatory markers. Levels of C-Reactive Protein (CRP), IL-1, IL-6, and TNF-α have consistently been reported to be increased in depressed patients [19, 20]. WBH activates or modulates the immune system in a reproducible manner [13], and therapeutic hyperthermia and fever have been associated with a variety of immunological reactions which can be exploited for the treatment of cancer, but which might also have positive therapeutic effects in clinical depression, and the course of at least some forms of depression that are characterized by a chronic subclinical activation of pro-inflammatory cytokines [21].

12.4 Current Research

Three randomized, double-blind, and (sham-) controlled clinical studies are currently being conducted by our groups in Berlin and Essen (Germany). Studies are based on the hypothesis that WBH is a fast-acting non-medical stimulation treatment against depressive symptoms which is well tolerated and improves quality of life. Overall, we are focusing on generating safety and tolerability data and attempting to confirm if WBH improves depressive symptoms and whether antidepressants influence treatment response and possible side effects. We are also monitoring immune parameters in the serum of patients to detect (subclinical) immune activation and possible changes after WBH and their potential correlations to clinical response.

12.4.1 Patients and Methods

In contrast to Janssen et al. [6], our new studies include patients with and without psychopharmacological treatment. The study protocol in Essen compares two different patient groups with depression. The diagnosis of MDD (as an inclusion/exclusion criterion) is undertaken using the MINI interview in version 7.0.2, and the severity of the current state of depression is determined using the Hamilton Depression Scale (HAMD-17). The first group of patients consists of patients with mild or moderate depression (HAMD-17 Score $\geq$17) who are treatment naïve or do not currently receive any antidepressant medication. The other group includes patients with moderate-to-severe depression who are non- or only partial responders to standard pharmacological treatment according to current S3 guidelines for unipolar depression [22]. In each subgroup, patients are randomized to either a treated group receiving two treatments with WBH in 2 weeks, or an untreated group as

controls. For inclusion, patients have to present in a good physical status and have to be free of conditions resulting in an immune-suppressed state at the time of participation. Exclusion criteria are other severe psychiatric comorbidities, relevant somatic disorders, acute suicidality, and prior treatment with WBH. All patients are examined and rated by an experienced psychiatrist who confirms diagnosis and estimates the severity of depression. Response, safety, and efficacy are assessed using expert-rated clinical scales for depression, as well as self-rating instruments (Beck Depression Inventory, Multidimensional Fatigue Inventory, Perceived Stress Scale, Short-Form-Health Survey). To verify the presence of short-term effects of WBH, we distributed a questionnaire that had to be completed within 3 days after treatment. Clinical outcome variables were assessed at weeks 1, 3, and 6 by an experienced psychiatrist who is blinded to the treatment group of the patients. Blood samples were taken at the time of inclusion, at weeks 1, 3, 6, and 12 and stored frozen until the measurement of specific biomarkers (e.g., TNF-α, sICAM-1, hsCRP, IL-6). For the second patient group who have previously received pharmacological treatment, changes in medication or acute pharmaceutical interventions were allowed as clinically required in both the treated and untreated control groups. Any alteration or influence on the participant by medication was recorded in the study protocol. Determining the primary study endpoint after 6 weeks was selected to enable effects to be compared with those reported in the study of Janssen et al. [6].

In contrast to the Janssen study [6], patients received two applications of WBH in the first 2 weeks of the trial. During wIRA-WBH (Heckel HT-3000™ device), the body core temperature was raised to 38.5 °C (peak temperature), followed by 1 h of heat congestion. This process was monitored and vital signs such as blood pressure, heart rate, blood oxyhemoglobin (HbO_2) saturation, and body core temperature were recorded. One treatment of WBH is considered complete when the participant's vital parameters return to a normal state. Control subjects in the control group had the option to receive WBH after their 6-week observation period.

12.4.2 Preliminary Results and Clinical Experience

According to our experience, close support and care is crucial for a successful WBH session in order to provide the patient with a sense of safety and empowerment. For a successful implementation of the procedure, it was also necessary to inform participants of the opportunity to interrupt the process of hyperthermia at any stage. We especially recognized that some patients require mental or emotional support when approaching a core temperature of 38.5 °C. Finally, because thirst was often experienced by participants undergoing WBH, drinking water at room temperature should be offered. Treatment responses regarding negative mood and further symptoms of depression are currently being examined.

Preliminary results regarding safety and tolerability are currently available for 34 participants treated in Essen (16 participants were treatment naïve, 18 participants were non- or partly-responders). WBH was well tolerated (physically and psychologically) in most psychiatric patients with or without antidepressant treatment. To

Table 12.2 Differences in reaching the body core temperature of 38.5 °C between patients with and without antidepressants (*SD* standard deviation, *SE* standard error)

	Treatment group	No. of treatments	Average time (min)	SD	SE
Time to reach 38.5 °C	Not medicated	16	67.1	22.9	5.7
	+ antidepressants	12	83.2	20.5	5.9

date, the dropout rate, independent of treatment group, has been approximately 20%. In patients who received an antidepressant treatment (moderate-to-severe depression), the overall dropout rate was 22% compared with 19% in the group of treatment naïve patients (mild-to-moderate depression). For individuals with moderate-to-severe depression, the dropout rate for the treated and control groups has been 11%. The dropout rate for treatment naïve patients with mild-to-moderate depression has been 12% in the control group and 6% in the group treated with WBH. We have also analyzed the average time necessary to reach a body core temperature of 38.5 °C. Overall, a slight difference was observed between the two treatment groups. Medication prolonged time to reach the core temperature of 38.5 °C (see Table 12.2).

Risk factors for discontinuation of WBH sessions have also been analyzed. Of the patients with moderate-to-severe depression receiving antidepressant treatment, 33% discontinued WBH treatment, compared with only 11% of the patients with mild and moderate depression.

No serious side effects of wIRA-WBH that would have required further treatment have been observed. Side effects that have been noted are related to the physiological body cooling mechanisms and the activation of the sympathetic stress system. For example, almost all patients experienced a drop in systolic and diastolic blood pressure resulting in an increase in heart rate which continued until the end of the warm-up period. Some participants described cardiac palpitations, headache, increase in respiratory rate, or restlessness. Overall, the risk for adverse effects during WBH was increased in individuals having somatic comorbidities (e.g., bronchial asthma).

12.5 Outlook to Future Research

In summary, accumulating evidence from new, randomized, and controlled clinical trials using water-filtered Infrared A (wIRA-) heating shows this to be a well-tolerated and effective approach for treating depressive symptoms, with even a single session being able to improve depressive symptoms [6, 7]. Due to small sample sizes and a lack of suitable control groups in some studies, more randomized, controlled studies with higher numbers of patients are necessary. As implemented in our current studies in Essen and Berlin, well-designed sham conditions should allow participants to experience heat without increasing body core temperature above 38.0 °C. To reflect a realistic clinical population and allow transfer of study results to clinical practice, it is necessary to allow and control for antidepressant medication, since most patients in the psychiatric setting receive multi-modal

therapies due to the severity and chronicity of symptoms. Evidence, albeit limited, indicates that a gradual increase in ambient temperature aimed at delivering a body core temperature between 38 °C and 39 °C followed by 60 min rest while maintaining the temperature is the most effective [13]. Treatment can be repeated in defined time intervals. Defining subtypes of depressive disorders that are most responsive to WBH may be important for better predicting who should be offered a hyperthermia treatment. In this context, examining underlying mechanisms of action is of prime importance. Since endocrine alterations are a frequent finding in major depressive disorder [23–26], future research to investigate whether hormones, such as cortisol, oxytocin, and triiodothyronine/thyroxine (T3/T4), can serve as predictors and indicators of treatment outcomes is warranted. Similarly, as immune effects may play an important role in major depressive disorder, there is a need for studies investigating inflammatory markers such as TNF-α, interleukins, or cell adhesion molecules before and after hyperthermia treatments [27, 28]. Finally, the molecular underpinnings of major depressive disorders are only beginning to be understood, and it would be highly important to unravel which (epi-)genetic signatures are linked with better treatment outcomes and whether at least some of these could be changed by WBH.

In conclusion, wIRA-WBH holds great promise as a treatment for depressive disorders given the findings listed above, especially given its good tolerability. Hopefully, further studies will help to establish recommended applications of WBH, e.g., for patients declining antidepressant medication, as a complimentary treatment for patients that do not, or insufficiently respond to standard therapies, or as a "door opener" enabling patients to engage in other therapies such as psychotherapy, exercising, or medication. At this point, WBH may be considered for individual patients unresponsive to standard therapies providing fully informed consent ("single patient use"). It may be particularly helpful for patients with high psychological strain and unresponsiveness to well-established therapies or those suffering from comorbidities known to respond to hyperthermia, after careful consideration of possible risks.

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