Supplementary Online Content

Janssen CW, Lowry CA, Mehl MR, et al. Whole-body hyperthermia for the treatment of major depressive disorder: a randomized clinical trial. *JAMA Psychiatry*. Published online May 12, 2016. doi:10.1001/jamapsychiatry.2016.1031.

This supplementary material has been provided by the authors to give readers additional information about their work.

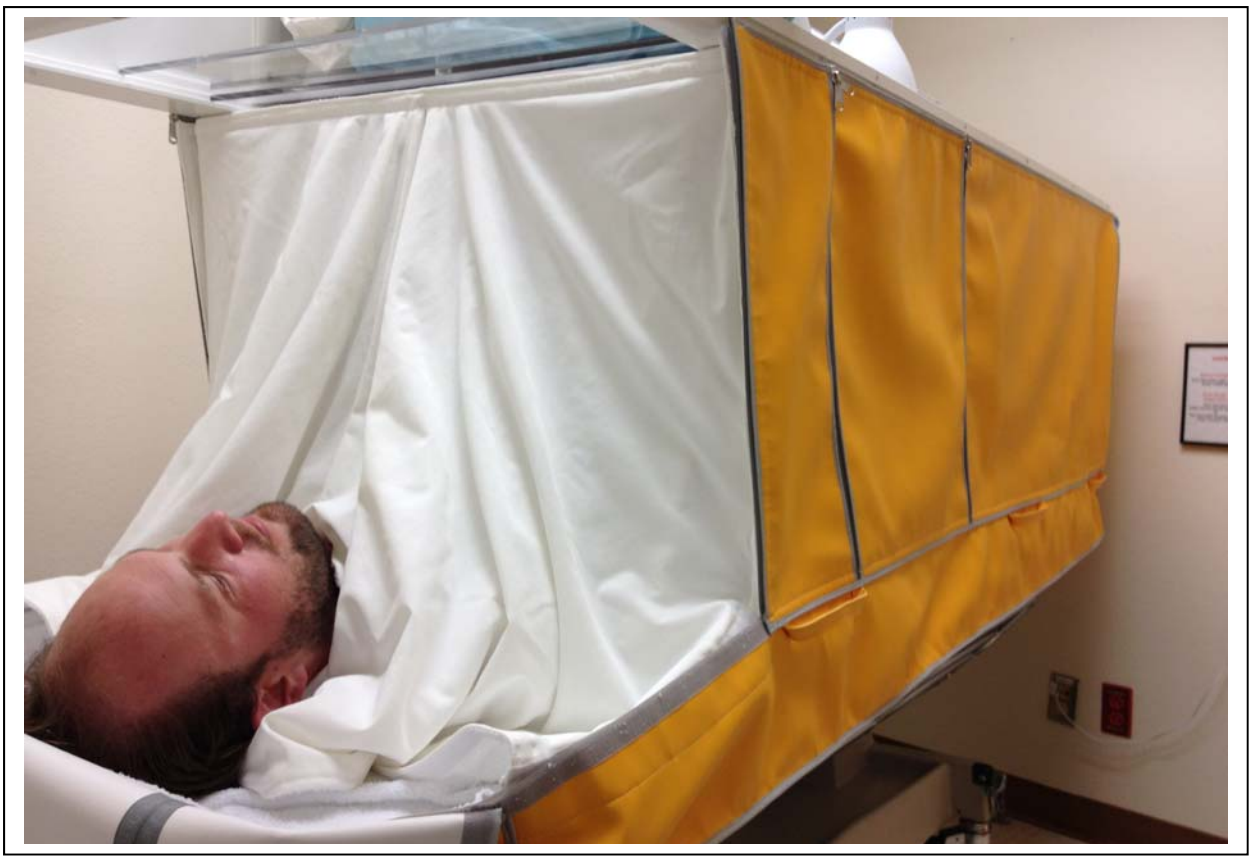
eAppendix. Description of Study Blinding Procedures

All study personnel were blinded to randomization status, except for technicians who administered the study interventions. These individuals directed treatment sessions from a remote room and had minimal contact with participants, all of which occurred during the interventions. An attendant was present in the room with participants during study interventions. Attendants were assigned to only one of the two conditions (i.e., only to attend WBH or sham) and had no exposure to—or knowledge of—the other condition. Attendants were instructed not to initiate conversation during the sessions and to respond to participant comments only by reflecting the comment back to the participant. Compliance with this approach was assessed in real time by the technician who monitored the participant physiology from an adjoining room but who could hear all activities in the treatment room via a microphone. In turn, the technician could communicate in real time with the attendant in the room via a computer-based messaging system to interrupt any problematic behavior. No occasions of unblinding were identified using this approach.

Clinician-based screening and outcome assessments were conducted by personnel blinded to group assignment who had no other interactions with participants. Raters were instructed to stop any post-intervention assessment in which a participant inadvertently provided information about the treatment they received that would potentially unblind the rater. In such instances another blinded rater would complete the current and future assessments, however this did not occur during the study. When a participant was ready for intervention scheduling, the administrator who kept the randomization list contacted the intervention technician and provided the intervention to be delivered. The technician

then provided personnel who scheduled the intervention with the name of an appropriate attendant (i.e. one who only attended either WBH or sham). To maintain the blind, scheduling personnel had no knowledge of which condition any given attendant was assigned to. Adverse events were collected by personnel who obtained no other outcome measures.

eFigure. Heckel HT3000 Hyperthermia Device With Study Personnel Inside



eTable 1. Inclusion and Exclusion Criteria

INCLUSION CRITERIA
Male or female outpatients aged 18-65, no exclusions for race or ethnicity
Able to understand the nature of the study and able to provide written informed consent prior to conduct of any study procedures.
Has met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for Major Depressive Disorder (MDD) for at least 4 weeks prior to signing consent, single or recurrent episode, without psychotic features, as the subject's primary psychiatric disorder, with diagnosis based on the M.I.N.I. International Neuropsychiatric Interview (MINI)
Able to communicate in English with study personnel
Study commenced with requirement for a Hamilton Depression Rating Scale (HDRS) score ≥18 at screening, this was lowered to ≥16 following recruitment of 11 participants. Participants were required to have a HDRS score ≥14 on intervention day
For women of child-bearing potential (i.e., one who is biologically capable of becoming pregnant), must be willing to use a medically acceptable form of birth control or practice abstinence for the duration of her participation in the trial
EXCLUSION CRITERIA
Symptoms of depression which, in the investigator's opinion, are better accounted for by a diagnosis other than MDD.
A current DSM-IV-TR Axis I diagnosis of Dementia
A lifetime history of Schizophrenia, Schizoaffective Disorder, or Bipolar Disorder Type 1
Any current DSM-IV-TR Axis II diagnosis (i.e. antisocial personality disorder) that would suggest potential noncompliance with the protocol
A diagnosis of claustrophobia severe enough that it would impair ability to be in the Heckel HT3000 hyperthermia device
A current (or within 6 months prior to the Screening visit) diagnosis of Anorexia Nervosa or Bulimia Nervosa
Subject has met DSM-IV-TR criteria for Substance Abuse in the 3 months prior to screening visit, or non-remitted Substance Dependence in the 6 months prior to screening visit
A diagnosis of an anxiety disorder that is considered by the investigator to be of greater source of distress or functional impairment than the patient's depressive symptoms. Subjects with comorbid anxiety disorders not excluded above and considered to be of secondary importance will be permitted in the study
Presence of clinically significant suicide risk, based on the investigator's opinion, or a Columbia Suicide Severity Risk Scale (C-SSRS) suicidal ideation score of 4 or 5, or any suicide attempt within 3 months of the Screening visit
Use of any psychotropic medications for 2 weeks (8 weeks for fluoxetine) prior to initiation of the study, with the exception of hypnotic medications (zolpidem, zaleplon, eszopiclone)

Need for any non-protocol psychotropic medication during the trial, with the exception of hypnotics used up to four nights per week
Participation in concurrent formal psychotherapy during the trial, or in the 2 weeks prior to the screening visit
Use of any psychoactive dietary or herbal products in the 2 weeks prior to screening visit or at any time during the trial
Any of the following medical conditions: • cardiovascular conditions or problems (uncontrolled hypertension, congestive heart failure, or documented evidence of coronary artery disease) • chronic conditions/diseases associated with a reduced ability initiate thermoregulatory cooling, including Parkinson's, multiple sclerosis, central nervous system tumors, and diabetes with neuropathy • history of peripheral circulatory disease, i.e. peripheral vascular disease, deep vein thrombosis (DVT), or lymphedema. • history of a cerebral vascular accident • history of epilepsy or cerebral aneurisms • Cancer in the last five years, except for resected non-melanoma skin cancer. • diabetes mellitus types I or II • any clinically significant autoimmune disease (compensated hypothyroidism allowed) • hemophilia or proneness to bleeding • fever the day of study intervention, • hypersensitivity to heat, • recent acute joint injury, • enclosed infections, be they dental, in joints, or in any other tissues, • any other medical condition or disorder that Is unstable and clinically significant, or that could interfere with the accurate assessment of safety or efficacy of treatment
Use of prescription drugs that may impair thermoregulatory cooling, including diuretics, barbiturates, and beta-blockers, or antihistamines
Clinically significant, in the investigator’s opinion, abnormal findings on screening laboratory tests or electrocardiogram.
Individuals with silicone or saline breast implants
Pregnant at screening or planning to become pregnant during the study period
Obesity and overall size of subject. It will be up to the PI’s discretion to determine whether an individual can be safely treated based on his/her size
Current participation in any other clinical trial
Reasonable likelihood for non-compliance with the protocol for any other reason, in the opinion of the Investigator, prohibits enrollment of subject into the study

eTable 2. Means and Standard Deviations (SD) for Secondary Outcome Measures in Participants Randomized to Whole-Body Hyperthermia (WBH) Versus Sham Treatment

Measure	Week	Participants per Group (n)		Means (*SD*)	
		WBH	**SHAM**	**WBH**	**SHAM**
IDS-SR	0	16	14	40.20 (*10.30*)	39.93 (*10.61*)
	1	15	14	24.87 (*12.08*)	35.29 (*13.81*)
	2	15	12	24.33 (*13.68*)	32.86 (*12.45*)
	4	15	11	23.73 (*9.95*)	32.50 (*14.32*)
	6	15	11	23.87 (*10.16*)	32.50 (*14.87*)
SDS	0	16	14	18.71 (*5.53*)	19.07 (*5.02*)
	1	15	14	11.57 (*8.21*)	16.07 (*6.10*)
	2	15	12	8.00 (*6.52*)	16.14 (*6.10*)
	4	15	11	10.00 (*7.36*)	16.00(*6.59*)
	6	15	11	11.86 (*7.91*)	15.57 (*7.31*)
Q-LES-Q	0	16	14	34.67 (*8.09*)	36.93 (*6.72*)
	1	15	14	44.07 (*9.69*)	37.29 (*6.55*)
	2	15	12	47.07 (*11.89*)	38.93 (*8.63*)
	4	15	11	43.73 (*9.48*)	38.86 (*10.13*)
	6	15	11	43.73 (*10.64*)	40.43 (*9.15*)

n = number; (SD) = standard deviation; IDS-SR = Inventory of Depressive Symptomatology--Self Report; SDS = Sheehan Disability Scale; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire

eTable 3. Adverse Events in Participants Randomized to Whole-Body Hyperthermia (WBH) Versus Sham Treatment (Ranked by Frequency)

Rank	WBH | Total AE (n=76)		WBH | Post-RX AE (n=16)		WBH | Week 1 AE (n=15)		WBH | Week 2 AE (n=15)		WBH | Week 4 AE (n=15)		WBH | Week 6 AE (n=15)	
1	Difficulty Sleeping	43	Headache	10	Difficulty Sleeping	11	Difficulty Sleeping	11	Difficulty Sleeping	10	Anxiety	8
2	Headache	38	Fatigue	8	Fatigue	9	Anxiety	7	Headache	8	Headache	7
3	Fatigue	35	Decreased Energy	7	Headache	8	Restlessness	7	Fatigue	8	Difficulty Sleeping	7
4	Anxiety	34	Dry Mouth	6	Anxiety	8	Decreased Energy	6	Anxiety	7	Decreased Energy	6
5	Decreased Energy	27	Difficulty Sleeping	4	Dry Mouth	6	Dry Skin	5	Poor Concentration	6	Dry Skin	5
6	Restlessness	24	Anxiety	4	Dry Skin	6	Headache	5	Restlessness	6	Ringing in Ears	5
7	Dry Mouth	23	Increased Perspiration	3	Restlessness	6	Fatigue	5	Decreased Energy	6	Loss of Sexual Desire	5
8	Dry Skin	22	Dry Skin	3	Itching	5	Ringing in Ears	4	Dry Mouth	5	Poor Concentration	5
9	Loss of Sexual Desire	21	Loss of Sexual Desire	3	Loss of Sexual Desire	4	Loss of Sexual Desire	4	Loss of Sexual Desire	5	Fatigue	5
10	Poor Concentration	21	Poor Concentration	3	Diarrhea	3	Poor Concentration	4	Rash	3	Rash	4
11	Rash	14	General Malaise	3	Rash	3	Diarrhea	3	Dry Skin	3	Blurred Vision	4
12	Ringing in Ears	14	Other	3	Blurred Vision	3	Dry Mouth	3	Blurred Vision	3	Dry Mouth	3
13	Blurred Vision	13	Nausea/Vomiting	2	Ringing in Ears	3	Rash	3	General Malaise	3	Frequent Urination	3
14	Itching	11	Dizziness on Standing	2	Frequent Urination	3	Constipation	2	Other	3	General Malaise	3
15	General Malaise	10	Dizziness	2	Poor Concentration	3	Palpitations	2	Palpitations	2	Restlessness	3
16	Diarrhea	9	Restlessness	2	Constipation	2	Itching	2	Frequent Urination	2	Constipation	2
17	Frequent Urination	9	Diarrhea	1	Decreased Energy	2	Blurred Vision	2	Diarrhea	1	Palpitations	2
18	Other	9	Palpitations	1	Nausea/Vomiting	1	Nausea/Vomiting	1	Constipation	1	Dizziness on Standing	2
19	Palpitations	8	Rash	1	Palpitations	1	Tremors	1	Nausea/Vomiting	1	Itching	2
20	Constipation	7	Itching	1	Dizziness on Standing	1	Dizziness	1	Dizziness on Standing	1	Dizziness	2
21	Nausea/Vomiting	6	Tremors	1	Chest Pain	1	Frequent Urination	1	Chest Pain	1	Diarrhea	1
22	Dizziness on Standing	6	Blurred Vision	1	Tremors	1	Menstrual Irregularity	1	Increased Perspiration	1	Nausea/Vomiting	1
23	Dizziness	6	Ringing in Ears	1	Dizziness	1	General Malaise	1	Itching	1	Chest Pain	1
24	Increased Perspiration	5	Sleeping Too Much	1	Sleeping Too Much	1	Other	1	Ringing in Ears	1	Increased Perspiration	1
25	Chest Pain	3	Constipation	0	Trouble Achieving Orgasm	1	Dizziness on Standing	0	Trouble Achieving Orgasm	1	Trouble Achieving Orgasm	1
26	Tremors	3	Chest Pain	0	Trouble with Erections	1	Chest Pain	0	Tremors	0	Other	1
27	Trouble Achieving	3	Poor Coordination	0	Other	1	Increased Perspiration	0	Poor Coordination	0	Tremors	0
28	Sleeping Too Much	2	Difficulty Urinating	0	Increased Perspiration	0	Poor Coordination	0	Dizziness	0	Poor Coordination	0
29	Menstrual Irregularity	1	Painful Urination	0	Poor Coordination	0	Difficulty Urinating	0	Difficulty Urinating	0	Difficulty Urinating	0
30	Trouble with Erections	1	Frequent Urination	0	Difficulty Urinating	0	Painful Urination	0	Painful Urination	0	Painful Urination	0
31	Poor Coordination	0	Menstrual Irregularity	0	Painful Urination	0	Sleeping Too Much	0	Menstrual Irregularity	0	Menstrual Irregularity	0
32	Difficulty Urinating	0	Trouble Achieving Orgasm	0	Menstrual Irregularity	0	Trouble Achieving Orgasm	0	Sleeping Too Much	0	Sleeping Too Much	0
33	Painful Urination	0	Trouble with Erections	0	General Malaise	0	Trouble with Erections	0	Trouble with Erections	0	Trouble with Erections	0

Rank	SHAM | Total AE (n=62)		SHAM | Post-RX AE (n=14)		SHAM | Week 1 AE (n=14)		SHAM | Week 2 AE (n=12)		SHAM | Week 4 AE (n+11)		SHAM | Week 6 AE (n=11)	
1	Fatigue	40	Fatigue	7	Fatigue	11	Difficulty Sleeping	9	Anxiety	8	Fatigue	8
2	Decreased Energy	33	Decreased Energy	7	Poor Concentration	9	Loss of Sexual Desire	7	Poor Concentration	7	Decreased Energy	7
3	Headache	31	Headache	6	Difficulty Sleeping	8	Poor Concentration	7	Fatigue	7	Headache	6
4	Poor Concentration	31	Restlessness	6	Headache	7	Restlessness	7	Headache	6	Sleeping Too Much	6
5	Difficulty Sleeping	29	Loss of Sexual Desire	5	Anxiety	7	Fatigue	7	General Malaise	6	Anxiety	5
6	Anxiety	29	Difficulty Sleeping	4	Restlessness	7	Decreased Energy	7	Frequent Urination	5	Poor Concentration	5
7	Restlessness	28	Sleeping Too Much	4	Decreased Energy	7	Headache	6	Sleeping Too Much	5	Diarrhea	4
8	Loss of Sexual Desire	24	Anxiety	4	Dry Mouth	6	Frequent Urination	5	Restlessness	5	Difficulty Sleeping	4
9	General Malaise	24	Dry Mouth	3	General Malaise	6	Anxiety	5	Decreased Energy	5	Loss of Sexual Desire	4
10	Sleeping Too Much	22	Dizziness on Standing	3	Loss of Sexual Desire	5	General Malaise	5	Difficulty Sleeping	4	General Malaise	4
11	Dry Mouth	17	Poor Concentration	3	Diarrhea	4	Dry Mouth	4	Diarrhea	3	Restlessness	3
12	Frequent Urination	16	General Malaise	3	Frequent Urination	4	Diarrhea	3	Dry Mouth	3	Constipation	2
13	Diarrhea	15	Other	3	Sleeping Too Much	4	Constipation	3	Loss of Sexual Desire	3	Nausea/Vomiting	2
14	Nausea/Vomiting	10	Nausea/Vomiting	2	Rash	3	Dry Skin	3	Constipation	2	Poor Coordination	2
15	Dizziness on Standing	10	Ringing in Ears	2	Itching	3	Dizziness	3	Nausea/Vomiting	2	Ringing in Ears	2
16	Dry Skin	9	Diarrhea	1	Dry Skin	3	Sleeping Too Much	3	Dizziness on Standing	2	Frequent Urination	2
17	Ringing in Ears	9	Itching	1	Poor Coordination	3	Nausea/Vomiting	2	Dizziness	2	Dry Mouth	1
18	Constipation	8	Dry Skin	1	Ringing in Ears	3	Dizziness on Standing	2	Palpitations	1	Palpitations	1
19	Itching	8	Blurred Vision	1	Nausea/Vomiting	2	Itching	2	Chest Pain	1	Dizziness on Standing	1
20	Dizziness	8	Constipation	0	Palpitations	2	Rash	1	Increased Perspiration	1	Chest Pain	1
21	Poor Coordination	7	Palpitations	0	Dizziness on Standing	2	Increased Perspiration	1	Itching	1	Increased Perspiration	1
22	Palpitations	4	Chest Pain	0	Chest Pain	2	Poor Coordination	1	Dry Skin	1	Itching	1
23	Chest Pain	4	Rash	0	Dizziness	2	Blurred Vision	1	Poor Coordination	1	Dry Skin	1
24	Rash	4	Increased Perspiration	0	Menstrual Irregularity	2	Ringing in Ears	1	Ringing in Ears	1	Dizziness	1
25	Painful Urination	4	Tremors	0	Constipation	1	Painful Urination	1	Painful Urination	1	Painful Urination	1
26	Other	4	Poor Coordination	0	Tremors	1	Menstrual Irregularity	1	Other	1	Rash	0
27	Increased Perspiration	3	Dizziness	0	Painful Urination	1	Palpitations	0	Rash	0	Tremors	0
28	Menstrual Irregularity	3	Difficulty Urinating	0	Trouble Achieving Orgasm	1	Chest Pain	0	Tremors	0	Blurred Vision	0
29	Blurred Vision	2	Painful Urination	0	Increased Perspiration	0	Tremors	0	Blurred Vision	0	Difficulty Urinating	0
30	Tremors	1	Frequent Urination	0	Blurred Vision	0	Difficulty Urinating	0	Difficulty Urinating	0	Menstrual Irregularity	0
31	Trouble Achieving Orgasm	1	Menstrual Irregularity	0	Difficulty Urinating	0	Trouble Achieving Orgasm	0	Menstrual Irregularity	0	Trouble Achieving Orgasm	0
32	Difficulty Urinating	0	Trouble Achieving Orgasm	0	Trouble with Erections	0	Trouble with Erections	0	Trouble Achieving Orgasm	0	Trouble with Erections	0
33	Trouble with Erections	0	Trouble with Erections	0	Other	0	Other	0	Trouble with Erections	0	Other	0

Abbreviations: AE = adverse event; Post-RX = posttreatment

eTable 4. Rates of Response and Remission by Week in Participants Randomized to Whole-Body Hyperthermia (WBH) Versus Sham Treatment

	Week 1		Week 2		Week 4		Week 6		Total	
	WBH (n=15)	**SHAM (n=14)**	**WBH (n=15)**	**SHAM (n=12)**	**WBH (n=15)**	**SHAM (n=11)**	**WBH (n=15)**	**SHAM (n=11)**	**WBH (n=15)**	**SHAM (n=14)**
Response *n* (%)	3 (20%)	0 (0%)	7 (46.67%)	0 (0%)	4 (26.67%)	0 (0%)	5 (33.33%)	1 (9.09%)	9 (60%)	1 (7.14%)
Remission *n* (%)	0 (0%)	0 (0%)	4 (26.67%)	0 (0%)	2 (13.33%)	0 (0%)	2 (13.33%)	0 (0%)	6 (40%)	0 (0%)

Response defined as ≥ 50% decrease from baseline 17-item Hamilton Depression Rating Scale (HDRS) score

Remission defined as HRDS score = ≤ 7