Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Whole body cryotherapy (WBC)

Evidence Summary

Whole body cryotherapy (WBC) may provide short-term benefits for recovery from sports injury, though the quality of the research is poor for other indications.

Neuroprotective Benefit: Little evidence suggests it would be beneficial for neurodegenerative disorders, though it may provide short-term symptomatic relief for MS and depression subjects.

Aging and related health concerns: There is some evidence that WBC may provide short-term benefit for elite athletes, though it is not clear it would benefit a normal individual or impact age-related disorders.

Safety: There are some potential safety issues (e.g. frostbite), but few studies include side effects in their publications.

Availability: Widely available for use in stores that specialize in whole body cryotherapy	**Dose**: Multiple sessions of 1-3 minutes at -100°C to -190°C	**Molecular Formula:** N/A **Molecular weight:** N/A
Half life: N/A	**BBB**: N/A	
Clinical trials: 0 ongoing	**Observational studies**: 0	

What is it?

Whole body cryotherapy (WBC) was invented in 1978 by Toshima Yamauchi, a Japanese doctor who used it to treat rheumatoid arthritis. It involves standing in a chamber that fills with a gas (usually liquid nitrogen) that maintains temperatures between -100°C to -190°C for 2-5 minutes. Before going into the chamber individuals cover all extremities (hands, feet, ears, etc.). It has many reported uses including rheumatoid arthritis, fibromyalgia, ankylosing spondylitis, multiple sclerosis, chronic lower back pain, depression and anxiety, inflammation, and muscle damage recovery. Websites promoting whole body cryotherapy will often make more claims, though these are not validated by any evidence. In WBC, individuals stand inside a chamber. Partial body cryotherapy (PBC) is another form where the head is outside of a chamber, but the body is inside.

Unfortunately, several issues weaken the evidence for WBC. First, there is no way to run a placebo-controlled trial. Some investigators attempt to use a comparator therapy. Others have conducted cross-over studies. However, many studies are open label. In addition, most studies include few participants.

Neuroprotective Benefit: Little evidence suggests it would be beneficial for neurodegenerative disorders, though it may provide short-term symptomatic relief for MS and depression subjects.

Types of evidence:

- One open-label pilot study in MCI patients
- Four studies in multiple sclerosis
- Four studies in depression

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function?

One open-label study investigated the effects of WBC in patients with mild cognitive impairment (MCI) (n=unknown). After 10 sessions, cognitive function improved ($p<0.05$), especially memory, plasma nitric oxide (NO) increased ($p<0.05$), BDNF increased ($p<0.05$), and IL-6 decreased ($p<0.05$) (Inaccessible - Rymaszewska et al, 2018).

Human research to suggest benefits to patients with dementia

None.

Mechanisms of action for neuroprotection identified from laboratory and clinical research

In a medical hypothesis paper, Misiak and Kiejna (2012) suggest that WBC could be beneficial for Alzheimer's patients by increasing antioxidant capacity, reducing inflammation, and affecting lipid metabolism.

APOE4 Effects

None reported

Other neurological disorders

Multiple Sclerosis (MS)

Sixty patients with MS were randomized to WBC, physical exercise (PE), or WBC followed by physical exercise (WBCPE). WBC consisted of 10 sessions over 2 weeks. Physical exercise consisted of a 60-minute session using resistance bands. General well-being improved for the PE and WBCPE groups, depression was reduced for the WBC and WBCPE groups, anxiety was reduced for the WBCPE group, and mobility improved for the WBC group (Pawik et al, 2019). Similarly, an open-label study of 24 MS patients showed that 10 sessions of WBC improved functional status and feelings of fatigue (Miller et al, 2016). Ten sessions of WBC also improved functional status and reduced levels of uric acid in secondary

progressive MS patients in an open-label study, an effect that lasted 3 months later (Miller et al, 2013), and increased total antioxidant status in secondary progressive MS patients (Miller et al, 2011).

Depression

In an open-label study of 21 patients diagnosed with depressive symptoms, 10 sessions of WBC over two weeks improved measures of depression, physical health, and psychological health two weeks after the final session. There were no changes in inflammatory cytokines (Rymaszewska et al, 2019). In another study, patients with anxiety and depression (n=60) were treated with either standard psychopharmacotherapy or WBC + standard psychopharmacotherapy for 15 daily sessions over three weeks. Patients achieving a decrease of at least 50% on a depression scale were greater in the WBC group (34.6% vs. 2.9%), and patients achieving a decrease of at least 50% on an anxiety scale were greater in the WBC group (46.2% vs. 0%). Note that patients in the WBC group had greater anxiety and depression at baseline (Rymaszewska et al, 2008).

Similar results were reported in two other open-label studies showing benefits on quality of life in patients with spinal pain or peripheral joint pain and depressive symptoms in depression patients after 10 WBC treatments over two weeks (Rymaszewska et al, 2003; Szczepanska-Gieracha et al, 2014).

Aging and related health concerns: There is some evidence that WBC may provide short-term benefit for elite athletes, though it is not clear it would benefit a normal individual or impact age-related disorders.

Types of evidence:

- One systematic review on recovery after sports injury
- Five studies in rheumatoid arthritis
- Three studies for pain
- Three studies on heart rate variability
- Two studies on sleep after elite athlete exercise

Recovery after sports injury

Potential short-term benefit: Rose et al (2017) conducted a systematic review of the effects of WBC after damaging exercise-induced muscle injury in healthy, physically active subjects (not a specific injury, rather the normal muscle injury that occurs with heavy exercise). The review found 16 papers on the topic. All participants were exposed to WBC for 2-3 minutes with varying repeated exposures of 1-30

sessions over 1-10 days. The articles were separated into "Laboratory controlled studies" (a single exercise session) or "Applied studies" (those where WBC was part of routine training).

Laboratory controlled studies (10)
The four studies that used multiple WBC exposures found a significant decrease in muscle pain and an increase in muscle function.

- *Muscle function: Improvement, though* most of the studies that used one WBC treatment did not see an increase in muscle function.
- *Pain:* Of the studies that examined pain, only those where WBC was administered immediately after exercise showed a reduction in pain.
- *Muscle damage:* Muscle damage was measured by levels circulating creatine kinase. There was a dose-response relationship, where more WBC treatments were associated with less muscle damage.
- *Inflammation:* All studies showed a decrease in inflammation (measured by plasma cytokines) after with WBC.

Applied studies (6)
All "Applied studies" used multiple WBC treatments, with 15 exposures the average.

- *Muscle function:* Improvement
- *Pain*: No information
- *Muscle damage*: Improvement
- *Inflammation*: Mixed results, most were positive, though some showed no change and other an increase in inflammation

Rheumatoid Arthritis (RA)
Potential short-term benefit (possibly not better than standard of care): Forty-four postmenopausal women with RA were randomized to WBC (3 min) or a traditional rehabilitation program with other physical agents (magnetotherapy, electrotherapy, ultrasound therapy, and laser therapy) for two weeks. Procedures were carried out each weekday along with a kinesitherapy program. All clinical measures (pain, fatigue, inflammation, etc.) were improved in each group though WBC was not better than traditional rehabilitation programs (Gizinska et al, 2015). In another study, 40 patients with RA were randomized to WBC (-110°C) or WBC (-60°C). After seven days (3 treatments per day for six days with 2 on the last) there were decreases in disease score activity (DAS) and pain in both groups, with pain being significantly more reduced in the WBC -100°C group (Hirvonen et al, 2006; Bouzigon et al, 2016). Forty patients with RA also received either WBC (-160°C) or cold air flow (-30°C) over 10 days. Both groups

showed improvements in clinical outcomes and a reduction in TNFα levels (though no change in IL-6), with no difference between groups (Jastrzabek et al, 2013). Finally, 20 patients with RA underwent daily WBC or conventional therapy for four weeks. There were reductions of histamine in the WBC group with no reductions in measures of neutrophil activation or markers of cartilage metabolism in either group (Wojtecka-Lukasik et al, 2009).

Pain

Potential short-term benefit: In an open-label study in 50 patients with osteoarthritis, 10 daily WBC treatments reduced the intensity of pain, the incidence of pain, the limitation of physical activity, and reduced the number of patients on pain killers (Chrusciak, 2016). Ninety-six elderly male patients suffering from chronic lower back pain were randomized to physical activity or WBC + physical activity. Over 3 weeks, those who underwent WBC prior to physical activity had a greater range of lumbar spine motility (Giemza et al, 2014). Another study from the same group compared WBC twice a week to WBC daily for 3 weeks in elderly men with lower back pain and found that only daily treatment improved lumbar spine mobility (Giemza et al, 2015).

Autonomic nervous system

Potential short-term benefit: Eleven elite synchronized swimmers performed two water ballets separated by 70 minutes with either WBC, contrast-water therapy (CWT), active recovery (ACT), or passive recovery (PAS). After the first ballet, heart rate variability (HRV) was decreased and went back to baseline after CWT, ACT, and PAS. WBC increased HRV 2- to 4-fold (Schaal et al, 2012). Forty healthy men underwent either WBC, PBC or no treatment. HRV increased after PBC (effect size = 0.60) and WBC (ES = 0.52) (Hausswirth et al, 2013). Similar results were found in a follow-up study from the same group with PBC increasing the Root Mean Square of the Successive Differences (RMSSD – a measure of HRV) by 49.1% and WBC increasing RMSSD by 38.8% (Louis et al, 2015).

Sleep

Reverses negative impact of extreme training: In a cross-over trial, 10 elite swimmers underwent two 2-week high intensity training sessions, one of which was followed by WBC. Sleep latency in the control session increased by 11 minutes, sleep duration decreased by 21 minutes, and sleep efficiency decreased by 1.9%. In the WBC session, there were no significant differences in sleep latency or sleep duration, though sleep efficiency decreased by 1.6% (Schaal et al, 2014). In another study in 27 elite basketball players, a single session of PBC increased perceived sleep quality by 15% (Bouzigon et al, 2016).

Safety: There are some potential safety issues (e.g. frostbite), but few studies include side effects in their publications.

Types of evidence:

- One case report
- Information from websites

Carrad et al (2017) suggested that although there are some reports of local side effects such as burns and hives, the quality of reporting of systemic risks (e.g. increased blood pressure, nausea, infection) are rarely described in the literature. They describe a case report of a subject who was experiencing transient global amnesia which resolved after a couple of days. The subject did not remember anything for the 3-4 hours surrounding WBC, and the amnesia surrounding the WBC session persisted one year later (though there were no other long-term effects).

Unfortunately, WBC studies tend not to report potential side effects. After searching several websites, there are several reports of frostbite, and it is suggested that individuals with cardiac conditions (e.g. high blood pressure) not do WBC. The Cryobar (thecryobar.com), a company that provides WBC, suggests the following contraindications: pregnancy, severe hypertension, acute or recent myocardial infarction, unstable angina pectoris, arrhythmia, symptomatic cardiovascular disease, cardiac pacemaker, peripheral arterial occlusive disease, venous thrombosis, acute or recent cerebrovascular accident, uncontrolled seizures, severe Raynaud's Syndrome, fever, tumor disease, symptomatic lung disorders, bleeding disorders, severe anemia, infections, cold-allergy, acute kidney disease, and urinary tract diseases.

Drug interactions:
There are no known drug interactions. However, see the Safety section for potential contraindications.

Sources and dosing:
WBC is widely available as a consumer health product. Usually sessions last 1-3 minutes and can be purchased for ~$90. Multiple sessions are necessary for some effects. However, specific treatment schedules have not been elucidated.

Research underway:
There are no reported studies ongoing for WBC on clinicaltrials.gov.

Search terms:
whole body cryotherapy + alzheimer, memory, rheumatoid arthritis, osteoarthritis, depression, multiple sclerosis, lifespan, neuropathy, pain

Websites:

- Pubmed
- Clinicaltrials.gov
- Google