



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.

Oxygen nanobubbles (RNS6o)

Evidence Summary

Unclear biological rationale but may have anti-inflammatory properties, and warrants further study.

Neuroprotective Benefit: Very little data is available (e.g. published data on 2 animal models from 1 lab) but it may be anti-inflammatory.

Aging and related health concerns: No direct data. In young adults, the water might help exercise recovery and blunt CRP induction.

Safety: A couple of unpublished safety trials have been done. Theoretically, this treatment isn't expected to have any effect (benefit or harm), but the data suggests it might be beneficial. Therefore, studies are needed to confirm that it doesn't also cause harm.

What is it? RNS6o is saline with charged oxygenated nanobubbles, created by mixing saline with pressurized oxygen in a technique called Taylor-Couette-Poiseuille (TCP). The technology and products are owned by [Revalesio](#). The production method is detailed by [Choi 2014](#).

RNS6o appears to be Revalesio's only clinical candidate, but another product, Reliant Recovery Water, is sold by a subsidiary company and marketed to promote recovery from sports. It received media attention recently when an NFL player, Russell Wilson, credited it for his recovery from a head-impact. While RNS6o is 0.9% saline, Reliant Recovery Water is water processed with the TCP method with added minerals (magnesium, calcium, and potassium) and a higher oxygen concentration. It is uncertain if the two products would have similar effects, particularly because the water is drunk whereas RNS6o is either inhaled or infused IV. It is possible that the lack of saline ions may also influence the capacity to retain the charged nanobubbles, unless the added minerals compensate.

Neuroprotective Benefit: Very little data is available (e.g. published data on 2 animal models from 1 lab) but it may be anti-inflammatory.

Types of evidence:

- 0 meta-analyses/systematic reviews
- 0 published clinical trials or observational data; 5 trials completed but none published
- 7 laboratory studies in Pubmed from 2 laboratories
- 1 self-report of use in ALS

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function? None

Human research to suggest benefits to patients with dementia or cognitive aging: None

Mechanisms of action for neuroprotection identified from laboratory and clinical research

Putative neuroprotective properties of RNS6o have been published by only one lab – K Pahan at Rush University, although unpublished confidential reports from a second lab at Harvard appear to confirm some details. Using transgenic mouse models for Alzheimer's (5xFAD) or Parkinson's (MPTP injection), daily 300 ul IP injection was reported to reduce neuronal cell death and inflammation ([Modi 2014](#), [Roy 2014](#), [Khasnavis 2014](#)). The purported mechanism of action is activation of the PI3K-Akt-BAD pathway, leading to a variety of effects like reduced inflammation measured through glial activation or p65/phospho-p65 and reduced GSK3 β activity leading to reduced tau phosphorylation.



How RNS6o might influence these cellular pathways is unknown. The oxygen content is up to 8 times that of normal water but there's no evidence that the bubbles are stable until they reach cells to deliver the oxygen. One lab (RR Llinas, NYU) has reported some effects in test tube preparations (e.g. giant squid axon, xenopus oocytes). For example, they've reported increased ATP production, increased mitochondrial length, and increased membrane potential ([Choi 2014](#), [Choi 2015](#)). Whether these effects will occur in mammals at feasible doses is unclear. The concentration of RNS6o used in these studies was essentially 100%, with the RNS6o used in place of saline.

Another possibility is that RNS6o contains unexpected contaminants that have biological properties. According to comments in a medicinal chemistry [blog by Derek Lowe](#), this has happened with past examples of "medicinal" water. Except for the Llinas studies, all experiments have used RNS6o and controls supplied by Revalesio.

APOE4 interactions: No data

Aging and related health concerns: No direct data. In young adults, the water might help exercise recovery and blunt CRP induction.

Types of evidence:

- *o meta-analyses/systematic reviews*
- *o published clinical trials or observational data; 5 trials completed but none published*
- *o laboratory studies in Pubmed*
- *o indirect data from 2 trials Reliant Recovery Water in healthy fit adults*

There is no relevant data published on aging overall and non-CNS age-related diseases. 2 clinical protocols for sports injuries were withdrawn prior to enrollment, with no explanation provided.

A related product, Reliant Recovery Water, was reported to help young adults recover from exercise in 3 clinical trials funded by the company. One of these trials was never published ([Cooper 2011](#)) and a second trial has questionable analyses ([Borsa 2014](#)). The third trial, however, reported an intriguing reduction in markers of muscle damage (hsCRP and creatine kinase) in the days following a biceps exercise along with less self-reported arm disability, less pain with elbow extension, and less range of motion impairment ([Borsa 2013](#)).

Safety: A couple of unpublished safety trials have been done. Theoretically, this treatment isn't expected to have any effect (benefit or harm), but the data suggests it might be beneficial. Therefore, studies are needed to confirm that it doesn't also cause harm.

Types of evidence:

- *o meta-analyses/systematic reviews*
- *o published clinical trials or observational data; 5 trials completed but none published*
- *o laboratory studies in Pubmed from 2 laboratories*

There are no published reports of RNS60 in humans. Reportedly, 5 clinical trials have been completed, 3 of which were completed before 2014, but none have been published. Even the Longevity forum has no personal accounts of use although the inventor has reportedly been using it for his ALS (AlzForum) under a compassionate use protocol approved by the FDA, which suggests that at least one of the trials (the Phase I safety study) did not show warning signs.

Reliant Recovery Water has been reported in 3 clinical trials on exercise physiology. None reported (positively or negatively) on adverse outcomes or side effects. All the studies were 2-3 weeks in duration in healthy, active adults. ([Cooper 2011](#), [Borsa 2014](#), [Borsa 2013](#)).

Sources and dosing: RNS60 itself is not on the market but it is in use in clinical trials either through IV infusion (125-250 ml once per week) or nebulized (inhaled) formulations (e.g. 4 ml per day). For the ALS trial, each patient receives a weekly IV infusion of 375 ml over 40 minutes and, on the remaining 6 days per week, a nebulized 4ml/day. How these doses were selected and whether they will have any effects is unclear. Although 5 clinical trials have been completed on RNS60, none of the results have been published.

Reliant Recovery Water in trials has been consumed 1000-3000 ml per day, tailored to the weight of each participant. The bubbles are reportedly unstable and recommended to be kept refrigerated.

Research underway:

Sabrina Paganoni at Mass General Hospital is leading a clinical trial on the use of RNS60 in ALS ([NCT02525471](#)). Another clinical trial is supposedly underway for [multiple sclerosis](#) but the study was begun in 2012 and has yet to begin recruiting patients.

A major problem in the clinical development of RNS60 is dosing. RNS60 cannot be measured from patient blood and whether adequate dosing will require inhalation, injection, or even oral intake as



occurs with Reliant Recovery Water. The mechanism of action, if any, is also uncertain. PI3K activation has been suggested to be a requisite biological pathway by one lab's studies. Perhaps clinical trials could evaluate PI3K activation in white blood cells to help guide dosing. Biomarkers of neuroinflammation, perhaps TSPO PET imaging, could also be helpful.

Search terms:

Pubmed: RNS6o, Reliant recovery water, recovery water, electrokinetically modified water

Google: reliant recovery water, reliant water, electrokinetically modified water, RNS6o

Clinicaltrials.gov: RNS6o, Reliant recovery water, recovery water

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