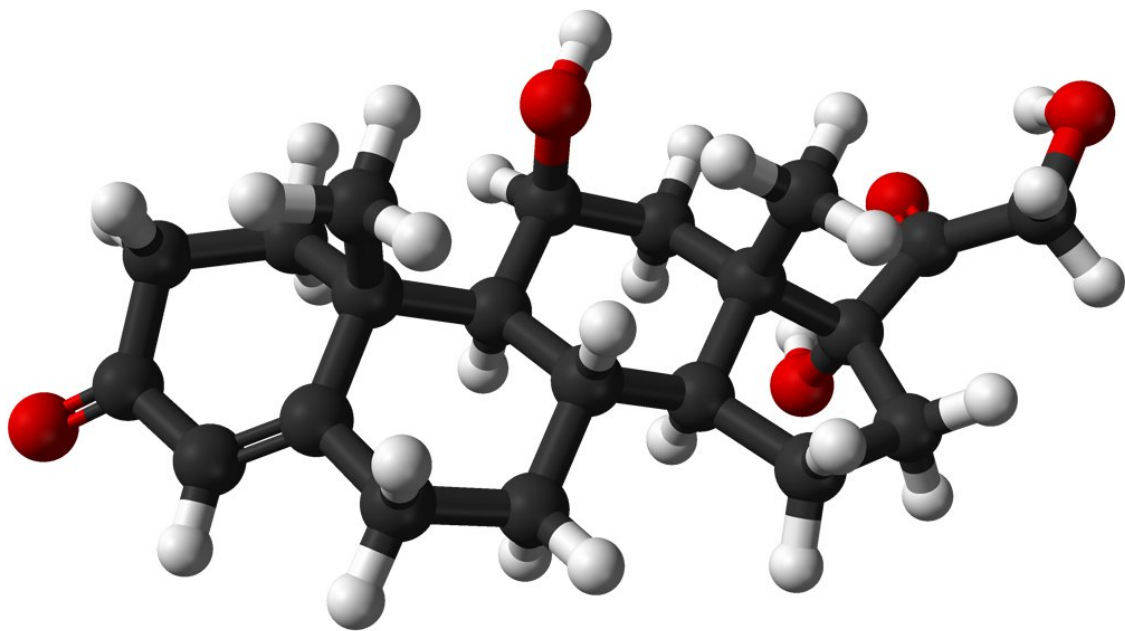


First-of-its kind hormone replacement treatment shows promise in patient trials

October 19 2023



Ball-and-stick model of the cortisol (hydrocortisone) molecule. Credit: Public Domain

A first-of-its kind hormone replacement therapy that more closely replicates the natural circadian and ultradian rhythms of our hormones has shown to improve symptoms in patients with adrenal conditions. Results from the University of Bristol-led clinical trial are published

today in the *Journal of Internal Medicine*.

Low levels of a key hormone called cortisol is typically a result of conditions such as Addison's and congenital adrenal hyperplasia. The hormone regulates a range of vital processes, from cognitive processes such as memory formation, metabolism and immune responses, through to [blood pressure](#) and blood sugar levels. When low, it can trigger symptoms of debilitating fatigue, nausea, [muscle weakness](#), dangerously [low blood pressure](#) and depression. Although rare, these adrenal conditions require lifelong daily hydrocortisone replacement therapy.

Although existing oral hormone replacement treatment can restore [cortisol levels](#), it is still associated with an impaired quality of life for patients. Scientists believe this is because the current treatment does not mimic the body's normal physiological timing, missing cortisol's anticipatory rise and lacking its underlying ultradian and [circadian rhythms](#).

The new "pulsatility" therapy, the culmination of ten years' research by the Bristol team, is designed to deliver standard hydrocortisone replacement to patients via a pump which replicates more closely cortisol's natural rhythmic secretion pattern. The pulsatile subcutaneous pump has now revealed promising results in its first clinical trial.

Twenty participants aged 18 to 64 years with adrenal insufficiency conditions were assessed during the double-blinded PULSES six-week trial and treated with usual dose hydrocortisone replacement therapy administered either via the pump or the standard three times daily oral treatment.

While only psychological and metabolic symptoms were assessed during the trial, results revealed the pump therapy decreased fatigue by approximately 10%, improved mood and increased patient energy levels

by 30% first thing in the morning—a key time frame when many patients struggle. Patient MRI scans also revealed alteration in the way that the brain processes emotional information.

Dr. Georgina Russell, Honorary Lecturer at the University's Bristol Medical School, and the lead author, explained, "Patients on cortisol replacement therapy often have side effects which makes it difficult for them to lead normal lives. We hope this [new therapy](#) will offer greater hope for the thousands of people living with hormone insufficiency conditions."

Stafford Lightman, a neuroendocrinology expert and Professor of Medicine at Bristol Medical School: Translational Health Sciences (THS), and the study's joint lead author, added, "Besides reduction in dosage, cortisol replacement has remained unchanged for many decades. It is widely recognized that current replacement therapy is unphysiological due to its lack of pre-awakening surge, ultradian rhythmicity, and post dose supraphysiological peaks. The new therapy clearly shows that the timing of cortisol delivery- in line with the body's own rhythmic pattern of cortisol secretion—is important for normal cognition and behavior.

"Our findings support the administration of hormone [therapy](#) that mimics natural physiology, and is one of the first major advances in adrenal insufficiency treatment to date."

Joe Miles, a participant on the PULSES trial, explained, "The Crono P pump has been life-changing. I noticed a very quick improvement compared to tablets when I was on the PULSES study. I went from feeling tired all the time to having sudden energy.

"When the PULSES study ended and I had to return the pump, I simply couldn't cope with going back to how I used to be, so I made it my

mission to write to as many doctors to have it prescribed privately.

"I've now been on it for six years and have introduced a number of other people with Addison's disease to the pump, and all of them have said it's life changing. Some have gone from being seriously ill to feeling better than they have done for years."

Dr. Russell said, "Approximately 1% of the UK population is taking steroids at any moment in time; these individuals can experience debilitating psychological side effects. This trial has shown that even at physiological levels, brain functioning is disrupted and that we need to explore not only the dose but the pattern of steroids delivery when considering any type of steroid treatment."

More information: Ultradian hydrocortisone replacement alters neuronal processing, emotional ambiguity, affect and fatigue in adrenal insufficiency: The PULSES trial, *Journal of Internal Medicine* (2023). [DOI: 10.1111/joim.13721](https://doi.org/10.1111/joim.13721)

Provided by University of Bristol

Citation: First-of-its kind hormone replacement treatment shows promise in patient trials (2023, October 19) retrieved 29 April 2024 from <https://medicalxpress.com/news/2023-10-first-of-its-kind-hormone-treatment-patient.html>

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