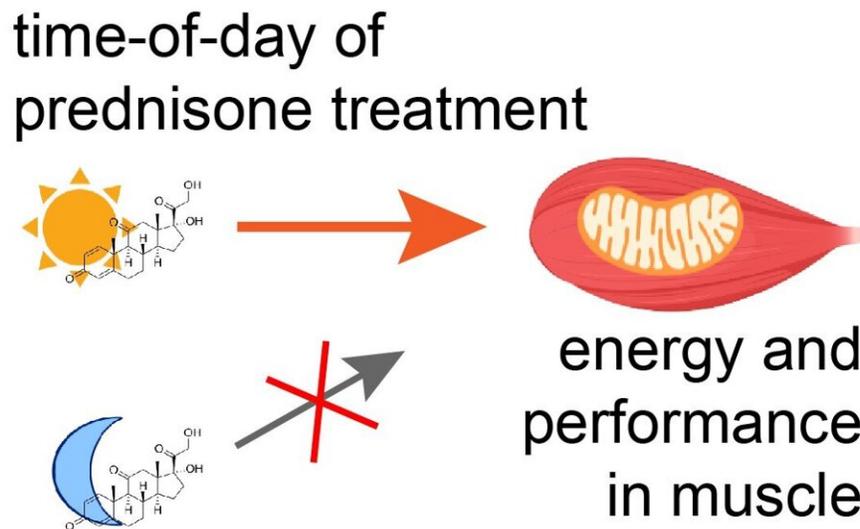


Steroid treatments for Duchenne muscular dystrophy may depend on the clock

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In mice, prednisone enhances muscle activities when once-weekly doses are given at the beginning of the day but not at the beginning of the night cycle.
Credit: Cincinnati Children's

Each year, about 20,000 children are diagnosed with Duchenne muscular dystrophy, a rare genetic condition that causes progressive muscle weakness and other systemic damage.

Duchenne primarily affects males and is usually diagnosed by age 4. While a variety of therapies can slow progression and extend life

expectancy, the disease has no cure yet. Those born with Duchenne seldom live beyond their mid-20s.

In 2017, researchers learned that weekly doses of prednisone, a widely prescribed steroid, appear to provide better support for weakening muscles compared to daily doses while also reducing the significant side effects induced by daily intake. Now, a new study reports that the time of day for providing the [drug](#) may be crucial to the effectiveness of such treatments.

Detailed findings, based on mouse models, were published online Feb. 18, 2022, in *Science Advances*. Mattia Quattrocchi, Ph.D., a researcher with the Heart Institute at Cincinnati Children's, is the study's corresponding author. Co-authors included lab team members Michelle Wintzinger and Karen Miz of Cincinnati Children's and Northwestern University researchers Daniel Levine, Ph.D., Clara Peek, Ph.D., Joseph Bass, MD, Ph.D., and Elizabeth McNally, MD.

The findings represent another advance in the growing field of chronopharmacology, which examines how medications work in sync—or in conflict—with the circadian rhythms of our bodies. A number of important findings in this field have been led by experts at Cincinnati Children's, which recently launched the country's only clinic dedicated to childhood circadian sleep disorders.

Confirming a clear time-based influence for the use of prednisone among Duchenne patients very likely will help improve outcomes for affected children, but it also raises questions about the time of day for other uses of the steroid. More than 2.5 million Americans use prednisone and similar drugs to manage inflammation for conditions ranging from allergy treatment to preventing organ transplant rejection.

"Our internal clock system is quite complex. Not only do we have our

central circadian rhythm dictated by a special region in our brain, but all our tissues—for instance, muscle—have their own internal molecular clock constantly ticking," Quattrocelli says. "We are beginning to learn much more about the importance of the timing of drug administrations for their effects in our tissues."

"In this study, we have focused on the interaction between the muscle clock and drug-activated molecules. But it will require considerably more research to determine how these findings may extend beyond the specific use of prednisone that we studied," he says.

Potential tool for precision dosing

In mice, the researchers found that once-weekly prednisone doses administered at the start of the light period (approximately 7 am) promoted muscle function. The team observed that the treatment boosted nutrient utilization and strengthened mitochondrial bioenergetics in muscle. It also increased endurance and improved muscle mass and muscle force. However, these responses were lost when dosing occurred in the dark period.

With mice being primarily nocturnal, their circadian clocks vary considerably from humans, so the specific time of day that achieves the most beneficial effect would be different for humans than for mice. However, Quattrocelli and colleagues report that many of the time-based mechanisms involving muscle cell activity are conserved between mice and humans, which suggests that timing also will matter for treating people with muscle diseases.

If confirmed in future human studies, the findings suggest that precision drug timing may maximize the drug benefits while avoiding side effects that may be more likely when a drug is given at the wrong [time of day](#). That might help improve efficacy of treatment and possibly quality of

life for a range of muscle conditions, from muscular dystrophy to aging to metabolic stress.

More study needed to explore implications

This study focused exclusively on prednisone and muscle tissue. The time-based effectiveness of other synthetic glucocorticoids, such as dexamethasone and vamorolone (currently in trial for Duchenne muscular dystrophy (NCT03439670)) remain to be determined.

Another pilot clinical trial with once-weekly prednisone in non-Duchenne forms of [muscular dystrophy](#) is ongoing at Northwestern University (NCT04054375). This trial is adapting the time of drug intake based on the new findings reported here.

Patients were instructed to take the drug in the evening after their last meal (between 7-9 pm) in a first attempt to mirror the positive findings found in mice. "Results from the trial are still pending and hopefully will inform our refinement of chronopharmacology approaches for muscular dystrophies and other conditions," Quattrocelli says.

Aside from differing drug characteristics, various tissues have their own internal clocks. So more research will be needed to determine if the day vs. night effects of prednisone also apply when treating conditions affecting other organ tissues. Notably, most uses of prednisone are related to controlling inflammation, often in immune conditions rather than muscle diseases. Time of day studies for treating immune conditions have only just begun.

"Every tissue of our body has an internal clock and this work reports on the fact that we can exploit the internal clock of [muscle](#) to interact with time-specific drug dosing to boost the positive effects of the drug on energy and function. However, more studies are required to precisely

translate these findings to humans," Quattrocelli says. "Besides the obvious difference that mice are nocturnal animals while humans are mainly diurnal, we must consider many factors that will inevitably affect chronopharmacology in our population. For instance, people have far more complex patterns of eating, working, playing and sleeping compared to mice. All these differences would need further exploration to translate mouse-based learning to human medical care."

More information: Mattia Quattrocelli, Muscle mitochondrial remodeling by intermittent glucocorticoid drugs requires an intact circadian clock and muscle PGC1 β , *Science Advances* (2022). [DOI: 10.1126/sciadv.abm1189](https://doi.org/10.1126/sciadv.abm1189).
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Provided by Cincinnati Children's Hospital Medical Center

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