



Chronotherapy — the specific timing of drug delivery — has shown promise in clinical trials. But that may not be enough to overcome the practical challenges.

TIME TRIALS

BY LYNNE PEEPLES

Carole Godain remembers a lot of the little details from the clinical trial she took part in nine years ago. There was the blue button she pushed to get her chemotherapy drugs, and the green light that came on to confirm that the medication was dripping into her veins. Then, of course, there was the hour — 10:00 p.m. without fail, for every treatment.

By all accounts, Godain's own time was running short. The first treatment for her colon cancer had failed, and her last body scan had revealed 27 tumours growing inside her liver. So the psychologist from Tours, France, jumped at the opportunity to take part in a trial at Paul Brousse hospital in Villejuif, which aimed to test whether delivering drugs at a specific time of day might make them more effective or reduce their toxic side effects. Ideally, it would accomplish both. "I was interested in increasing my chances of being cured," says Godain.

Today, at the age of 43, she is cancer-free. And Francis Lévi, the oncologist who treated Godain, says that

although such an amazing result is anomalous, emerging evidence should encourage more interest in the concept of chronotherapy — scheduling treatments so that they provide the most help and do the least harm.

More than four decades of studies describe how accounting for the body's cycle of daily rhythms — its circadian clock — can influence responses to medications and procedures for everything from asthma to epileptic seizures. Research suggests that the majority of today's best-selling drugs, including heartburn medications and treatments for erectile dysfunction, work better when taken at specific times of day. "When you give a medication, you always know the dose," says Lévi, who also now works at Warwick Medical School in Coventry, UK, where he leads a team associated with INSERM, the French national biomedical research agency. "We have found that the timing is sometimes more important than the dose."

Yet chronotherapy, sometimes called chronomedicine, remains at the fringes of clinical practice and drug-development programmes; the reasons for that are varied. Until about a decade ago, scientists could not explain the

molecular underpinnings for these circadian effects. And clinical data have been inconsistent — although a couple of Lévi's early trials, for example, showed clear benefits for people taking timed treatments, a later, larger trial produced more mixed results. Most patients haven't been as fortunate as Godain.

Axel Grothey, an oncologist at Mayo Clinic in Rochester, Minnesota says that the challenges facing chronotherapy are twofold: "You need more solid data. And you need to show it is feasible." The strategy can be impractical for cancer therapies, he says. Seats in his chemotherapy unit book up in much the same way as those for a movie. "The 4 p.m. showing could be oversold because we have too many patients who need to be started at that time," Grothey says.

Still, Lévi and others are optimistic. Chi Van Dang, the scientific director of the Ludwig Institute for Cancer Research, a global non-profit research organization, has noticed what he calls a "rebirth of interest" in chronotherapy, spurred by the rapidly advancing science of circadian rhythms and a handful of trials and technologies aimed at tailoring the approach to people's individual circadian clocks. These efforts could help to elucidate inconsistencies in clinical trials and make chronotherapy more practicable for doctors and patients alike, Lévi argues. Dang gave a keynote address at a chronotherapy workshop held by the US National Cancer Institute (NCI) last September. As the world's largest funder of cancer research, the NCI had put out a call a few months earlier for studies looking into how circadian processes influence disease progression and response to treatment. "I would argue that the evidence shows there is a benefit and we can't ignore it," says Dang. "We just need to be more clever on how to approach the challenges."

CLOCK WATCHERS

Chronotherapy enjoyed a publicity boost of sorts last year. Just a week after the NCI workshop, the Nobel Prize in Physiology or Medicine was awarded to a trio of scientists for elucidating the cellular mechanisms that control circadian rhythms. The circadian clock is a remarkable system. A central timekeeper in the hypothalamus orchestrates a network of peripheral clocks in nearly every organ and tissue of the body, turning on and off a bevy of genes, including some that encode the molecular targets for drugs and the enzymes that break drugs down. These clock genes are particularly important in cancer because they govern cell cycles, cell proliferation, cell death and DNA damage repair — all processes that can go haywire in cancer.

Some, but not all, cancers live by the clock as well, and researchers are trying to exploit their daily rhythms. When Joshua Rubin, a neuro-oncologist at Washington University School of Medicine in St. Louis, and his colleagues wanted to launch a chronotherapy clinical trial on a common and deadly form of brain tumour known as glioblastoma, they needed to check how the cancer behaved over time. So his team engineered cells from patient tumours to express luciferase — the protein that makes fireflies glow — every time core clock genes switched on. Then they watched. "It was so dynamic," says Rubin. "Lights go on, lights go off. Lights go on, lights go off." The team started treating the tumour cells with drugs at different times in the cells' cycle and found that they were most sensitive to an oral drug, temozolomide, near the daily peak in expression of the core clock gene *Bmal1* (ref. 1). If patients could be directed to take this pill — part of the standard glioblastoma treatment — at the time of peak *Bmal1* expression, the drug might be more effective, Rubin reasoned. His team is now testing that hypothesis in mouse models, and in more than

two dozen humans being treated at different times of day.

The trial is the first to apply chronotherapy in glioblastoma, and the only current trial in the United States that accounts for the circadian clock in cancer. A few previous US trials hinted that chronotherapy could be beneficial in treating ovarian², breast³ and non-small-cell lung⁴ cancers. Yet today, of the tens of thousands of ongoing clinical trials around the world, only a small fraction of 1% incorporate time-of-day considerations, according to a 2016 survey⁵.

The prospect nevertheless has some people excited, in part because of its simplicity. "If we can help people live longer and live better with fewer side effects, just by changing our scheduling, that would be tremendous," says Jeremy Rich, a neuro-oncologist at the University of California, San Diego. And the findings have intuitive appeal. Steroid levels, for example, naturally cycle with the circadian clock. In the late 1960s, scientists found that the synthetic corticosteroid methylprednisolone is safer for treating arthritis and asthma if taken in the morning rather than at other times of the day. This is because the feedback loop in the hypothalamus, which controls the release of cortisol, is least vulnerable to inhibition in the morning. These rhythms might affect responses to radiation treatment, too, says Eric Holland, a neurosurgeon at the Fred Hutchinson Cancer Research Center. Holland has shown that corticosteroids can reduce the effectiveness of radiation therapy in humans⁶ and that there are optimal times to administer radiation in mice⁷.

In one of the most cited cancer chronotherapy studies so far, Lévi and his team randomly assigned 186 people to either chronotherapy or standard treatment for colon cancer⁸. Slightly more than half of the people who, like Godain, had their chemotherapy infusion synchronized with their circadian rhythms responded to the treatment, compared with 29% of individuals on a standard schedule. And in a study published in January⁹, researchers found that for 298 patients randomly assigned to cardiac surgery in the afternoon, the subsequent risk of sustaining major heart damage was half what it was for 298 patients who underwent the same surgery in the morning. To avoid the possibility that the choice of surgeon was responsible for this difference, the study had the same doctors performing operations both in the morning and the afternoon.

The optimal time for various procedures seems to vary. Akhilesh Reddy, a physician-scientist at the Francis Crick Institute in London, suggests the cardiac surgery findings may translate to other surgeries — with prime times dependent on the peak expression levels of particular enzymes in respective tissues. For radiation treatment, Dang and other researchers have found mornings to be preferable to afternoons¹⁰. But as with the administration of chemotherapy, different types of tumours — and different people — may respond differently, says Dang. Lévi and others think that this might explain why many trials trying to reap the benefits of timed drug delivery have had more equivocal findings. The largest cancer chronotherapy trial so far — also led by Lévi — tested chronotherapy or conventional chemotherapy delivery in 564 people with metastatic colorectal cancer¹¹. Overall, it found that survival times were similar in both groups. But when results were broken down by sex, the risk of an earlier death dropped by 25% for men whereas it increased by 38% for women.

The reason behind those sex-related differences is not yet clear, although Lévi is starting to make some sense of them. His team presented findings in September 2017 suggesting that men best tolerate one type of cancer drug between four and seven hours earlier in the day than women do. Lévi also suggests that women experience more toxic effects, in

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general, than do men from cancer treatment.

Age is another factor that can affect an individual's rhythms. People's body clocks tend to shift in adolescence¹² — hence teens' preference for late nights and sleeping in — and back again as they age¹³. Overall, Lévi has found that about half of patients have similar circadian patterns. One-quarter have cycles that begin earlier, and the remaining quarter have ones that begin later — these two groups perhaps corresponding to the 'morning larks' and 'night owls' of the world. The bottom line is that there's no one-time-fits-all for chronotherapy.

CHALLENGING TIMES

Phyllis Zee, chief of sleep medicine at Northwestern University Feinberg School of Medicine in Chicago, says that chronotherapy has great potential, but that practical biomarkers are needed to help clinicians identify optimal times for treatment. "Those are the legs required for chronotherapy really to be translated," she says. "It may not be ready for prime time."

Lévi has been working on trying to track individual rhythms better. Before Godain started her home chronotherapy regimen, she strapped on a watch-like device that logged her daily rhythms, says Lévi. Godain had very regular sleep-wake cycles, which Lévi thinks probably contributed to her successful treatment. He and other researchers are now wielding even more sophisticated tools to discern circadian timing, including temperature sensors worn on the chest or ingested, blood samples and saliva tests. One research team at the University of Pennsylvania in Philadelphia is integrating data from wearable devices, smart phone apps and physiological samples in an effort to define each person's 'chronobiome' and pinpoint the best predictors for optimizing chronotherapy.

In some ways, chronotherapy could represent another arm in the effort to individualize treatments. "In the field of personalized medicine, adding this dimension of time could make a tremendous difference," says Carla Finkielstein, a molecular biologist at Virginia Tech in Blacksburg. "We now have a really good molecular foundation. Hopefully, this is the beginning."

Other practical challenges remain. Costs and convenience are at the heart of most scheduling decisions in a hospital. Bart Staels, a molecular pharmacologist at the University of Lille in France, and senior author of the cardiac surgery paper⁹, acknowledges that limiting heart surgeries to a certain time of day is not realistic. But doctors could identify patients at high risk of complications and prioritize them for afternoon surgery. Or perhaps clinicians could one day deliver a drug that artificially 'jet lags' a patient's heart into thinking a morning surgery is actually happening in the afternoon, says Staels.

Drug companies have been reluctant to take chronotherapy approaches for several reasons, says David Ray, an endocrinologist at the University of Manchester, UK. It can be difficult enough to get patients to take medication, regardless of time. Only about 50% of people with a chronic illness follow their treatment recommendations, according to the World Health Organization. What's more, regulators might insist that marketing a medication optimized for a specific time of day requires extra warnings about the risks of deviating from the schedule. That's not a good selling point for a liability-wary drug maker — nor is the price tag of running studies to show a time-based response. Twice as many study groups would be necessary to show that giving a drug at one time is better than giving it at another, says Ray. And for drugs already making money, companies

lack an incentive to go back and specify a time of day.

Ray and others also say that they are concerned by the trend among pharmaceutical companies to create once-a-day and other long-acting drug formulations. Doing so, they say, could have unintended consequences. Sustaining levels of a drug that targets the inflammatory molecule TNF- α , for example, could leave the immune system impaired throughout the day, says Ray. For conditions such as rheumatoid arthritis, he says, "you only really need to block TNF for a critical 4-to-5-hour window".

John Hogenesch, a circadian biologist at the University of Pennsylvania, says that paying attention to the timing of treatments could eventually cut costs for companies. "I think what will change minds is showing people that when you take time of day into account, you can lower the noise and improve the signal between the controls and your clinical arm," Hogenesch says. That could also mean rescuing some of the 90% of drug candidates that fail in early stages of development, says Ray.

As Rubin and his team look towards the next phase of their trial in the United States, they intend to measure participants' rhythms and give temozolomide accordingly, he says. Meanwhile, in Europe, researchers are using portable devices to track around-the-clock blood pressure in thousands of patients, to build on evidence that conventional hypertension medications are best dosed at night. A study¹⁴ published in February notes a 67% reduction in heart attacks, strokes and other major cardiovascular events among patients taking bedtime doses, compared with those on morning doses. Juan Crespo Sabaris, a physician affiliated with the University of Vigo, Spain, who has been involved with the hypertension work, noted that doctors in his region of Spain are now advising bedtime dosing as a simple, low-cost form of chronotherapy.

For champions of the approach, such as Lévi, the prospects for chronotherapy have never looked better. But given the mixed results from trials, and the practical challenges for implementation, many scientists remain circumspect, especially with regards to cancer treatments. "At some point, we either need to revisit chronotherapy completely and put in some effort to get more data and make this work," says Grothey, "or we say, 'OK, that was just a side note in the history of oncology.'" He recalls fleeting excitement surrounding chronotherapy when he entered the cancer field about 20 years ago. "A lot of us discarded it as something that was too complicated," he says. "We didn't have the technology. That might be different now." ■

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