All sleepless and light

Eight hours' sleep may cure all manner of ills, but, for people who are manic depressive, staying awake all night may well be the answer. A small clinic in Milan is proving that sleep deprivation, supported by light therapy, can significantly – and rapidly – ease depression

By Joe Studwell
Illustration by Jonathan Burton

Mariangela Grassini is trying to give an interview. It is not particularly comfortable for her because when she suffers an acute depressive episode she weeps uncontrollably. Yesterday she cried continually for five hours. With an apologetic smile she wipes away a tear as she explains the background of her illness. Her father was bipolar – or manic depressive – which gave her a genetic predisposition. She suffered her first unipolar attack – that is depression, without the mania – at the age of 31, right after her son was born. "I sat at the table and cried like a madwoman," she recalls. Since that first six-month breakdown in 1996 she has had about 10 episodes.

Yesterday morning, the day before her admission to the San Raffaele university hospital in Milan, Grassini could not manage to wash her hair, which set off the hours of weeping. She was overwhelmed, as she had been in previous episodes, with a sense of inadequacy, which is odd for a woman with a demanding job in international logistics. "I can't find the courage to confront the day," she explains. Yet this morning, sitting in her doctor's office at San Raffaele, she knows that tomorrow she will feel better. She also knows that in a week she will be back at work. She knows all this because it has happened twice before.

Mariangela is not taking a new miracle drug or undergoing some extraordinary alternative healing. Every aspect of her treatment at San Raffaele has been available to doctors for 30 years. What is different about this Milan clinic is that it combines drug and non-drug therapies in creative ways with little regard for orthodoxy or ideology. It simply finds out what works best for each patient, and in depression cases like Grassini's, San Raffaele has had great success combining sleep deprivation, light therapy and follow-up medication to stabilise patients over the long term. The clinical data from San Raffaele, which has been published in a handful of medical journals since the late 1990s, shows that this approach is more effective and less expensive than conventional interventions. So the work of a small group of clinical psychiatrists and theoretical biologists is finally attracting the attention of their medical peers. Major international conferences – traditionally funded and shaped by the multinational pharmaceutical companies – are, for the first time in a generation, adding sleep and light protocols to their agendas. Meanwhile, San Raffaele and its network of corresponding hospitals are beginning to apply these treatments to Alzheimer's and bulimia nervosa with early positive results.

The story is best begun in Tübingen, Germany, in the late 1960s. The first anti-psychotic and anti-depressant drugs had been discovered in the 1950s and had already had a big impact in Europe and America. But it quickly became apparent that pills alone were not going to solve every mental health problem – responses were uneven and side effects often severe. So doctors at the Tübingen hospital were intrigued by a somewhat eccentric patient who insisted that she could cure her own acute depression by going out cycling all night. The woman's claim – that the less she slept the better she felt the next day – was entirely counterintuitive. Depressives usually struggle with insomnia and strive desperately to go to sleep in order to feel better.

In 1968 a young Tübingen doctor named Burkhard Pflug decided to explore the woman's claims in his doctoral thesis. He >>

>> began systematically depriving depressives of sleep, and the results – subsequently verified in several thousand patients in different experiments around the world – were astonishing. Three-fifths of acutely depressed patients showed a stark decrease in symptoms after a single night without sleep.

There was, however, one big problem. The great majority of patients who responded positively relapsed as soon as they slept as little as 15 minutes. Fewer than 20 per cent of these patients experienced any long-term benefit. For his work, Pflug received a prize from the Anna-Monika foundation – the Nobel of depression – but after a brief period of excitement in psychiatric circles most clinicians wrote off sleep deprivation as a paradoxical curiosity. It simply was not practical to keep 100 acute depressive patients awake all night in order to create a long-term benefit for 15 or 20 of them.

This point becomes quite clear in the middle of the night at San Raffaele. At check-in time, severely depressed people – often with suicidal impulses – will agree to do whatever the doctors tell them. But when the doctors go home at 6pm the real work begins for the nursing staff. By 3am the patients who have never undergone this therapy before begin to have doubts about the treatment, particularly if they, like many bipolar people, are prone to see conspiracies all around them.

"It's normal during the night," says Francesco Benedetti, one of the senior doctors, "for patients to want to get out because they think the doctors have gone mad." They will not start to feel better until at least 6am, and the nurses must work hard to persuade exhausted, frightened people to remain awake, talking to them, walking them around the hospital gardens, making them snacks and dosing them with espresso. San Raffaele is a purely voluntary hospital with no powers of restraint, but the nurses have become adept at convincing patients to stick it out.

Back in the 1970s, there was little appetite for putting doctors, nurses and – most of all – patients through the rigours of sleep-deprivation therapy. Nonetheless, a few research biologists refused to let go of the Tübingen conundrum.

"When you see this 80-year-old woman dancing around you say, 'What has happened?'" explains Anna Wirz-Justice, a Basel University research scientist who became one of the key "chronobiologists" – as they are now known. "It was a model to understand the mechanism of depression." The anecdotal evidence that sleep and light affect emotional states was too plentiful to ignore. Psychiatrists had long noted that disrupted sleep was the "common final pathway" to different forms of mental breakdown. Modern hospital records also showed seasonal variations such as an increased intake of depressives in the winter months.

To make sense of all this, the chronobiologists left hamsters in perpetual darkness to plot their activities and biological rhythms in the absence of light. They devised similar experiments for humans kept in bunkers underground. They lesioned mouse and hamster brains until they identified the suprachiasmatic nucleus (SCN) – a couple of clusters of nerve fibres on either side of the brain – that is every mammal's central timepiece. Interestingly, they found the SCN in humans to have the highest concentration in the body of serotonin – the very chemical that had captured the attention of the psychopharmaceutical industry in the 1970s and would soon bring the world Prozac, Zoloft, Paxil and all the other Selective Serotonin Reuptake Inhibitors (SSRIs).

By 1980, what Wirz-Justice calls "the basic canon" of time biology was in place. In crude outline, this shows that humans have an internal clock that resets itself roughly every 24 hours. It was named the circadian clock, from the Latin *circa* and *diem*, meaning "about once a day". In recent years, about a dozen specific genes have been identified that control the main SCN clock and subsidiary clocks in other organs of the body. The circadian clock is synchronised, or "entrained", each day by external stimuli such as light, food, and the sleep-wake cycle.

A light therapy session at the San Raffaele university hospital in Milan

A study of bipolar patients at San Raffaele showed that those with east-facing rooms checked out earlier than those with west-facing rooms

Scientists in the late 1970s were able to show that it is not simply the loss of sleep that affects mood, but rather the timing of the sleep deprivation. Only loss of sleep in the second half of the night relieves depression, and this occurs through what they term Sleep Phase Advance (SPA). By putting people to bed in the middle of the afternoon and waking them in the middle of the night – then gradually shifting their sleep times back to normal over several days – doctors achieved the same anti-depressant effect as total sleep deprivation. Several studies of long-haul airline passengers have also confirmed this thesis: people travelling from west to east suffer a depressive effect due to sleep phase delay, while those going from east to west experience a mood lift thanks to sleep phase advance.

Just as science was getting to grips with sleep deprivation, however, a second momentous breakthrough occurred that precipitated widespread confusion. Again, it began with an eccentric, self-helping patient. Herbert Kern, a materials scientist at AT&T's Bell Laboratories in the US, had suffered from what appeared to be a severe bipolar disorder since his forties. Being a scientist and something of a pedant, he kept careful notes on his depressive and manic episodes. By his early sixties Kern had enough data to define a clear seasonal variation in his condition. He made graphs of day length and sunlight hours and then plotted against these the best proxy he had for his mood

JACOB LANGVAD

states: the number of pages he wrote in his notebooks each month. In 1980, armed with 14 years of statistics, graphs and notes, he presented himself to the National Institute of Mental Health (NIMH) in Bethesda, outside Washington DC.

There, a team of researchers including Tom Wehr, who had worked with Anna Wirz-Justice on sleep deprivation, were entranced by their new guinea pig. The appearance of Kern "was the key event", says Wehr, whose team had already demonstrated that light can turn on and off the brain's production of melatonin – a hormone that regulates sleep. Wehr and his colleagues also suspected that light could be employed therapeutically to adjust the circadian clock. Kern and his notebooks arrived like a gift from the gods. "Every doctor in the place wanted to get his hands on me and get a sample of whatever he was studying, from spinal fluid on," Kern recalls. "I was full of holes."

Kern became the first clinical research patient in light therapy – as well as co-author of the subsequent, seminal scientific paper. The timing of the experiment was set for the nadir of his seasonal depression, in December. When the moment arrived, Kern was so depressed he tried to back out. It was only with difficulty that he was persuaded to travel to Bethesda. In what today would be considered an incredibly crude treatment, he was placed in a room with 40 powerful fluorescent lights for six hours a day.

"After four days I couldn't believe it," he says. "I was starting to smile, talking to people, joking – my brain was starting to function again." Kern, Wehr and the rest of the NIMH team had cured what is now called Seasonal Affective Disorder (SAD), something that has been alluded to for millennia in its mild incarnations with terms like "winter blues". Since then, light-box therapy has become a multi-million-dollar industry in Northern Europe and North America.

For the acutely mentally ill, however, the discovery of light therapy was counterproductive because it sent many chronobiologists off into a research cul-de-sac. The researchers assumed that it was the light itself that relieved SAD, and concluded that the condition was caused simply by the deprivation of light. Therefore the same treatment wasn't likely to be of much help to patients whose depression has other root causes. This remained received opinion for almost two decades. Only in the last few years have new trials shown that what benefits a SAD patient is not light, per se, but the use of light to re-entrain the circadian clock – and that being out of phase, not just light-deprived, is what triggers SAD.

Michael Terman, a chronobiologist at the Columbia University Medical Center in New York, did the groundbreaking work. He developed a questionnaire and algorithm to calculate the time of day at which half an hour of light therapy would be most effective. Only morning light, he discovered, which causes phase advance, had a therapeutic effect. "Circadian theory is right," says Terman. "Evening light is irrelevant." When he completed his research in 2002 he posted the algorithm on the internet (www.cet.org). In the US, Terman says, the use of combination therapy is limited to a scattering of individual practitioners. It has not been adopted by any major healthcare institutions.

There is little doubt among key researchers that sleep deprivation, light therapy and the action of SSRI drugs are synergistically linked in some unknown but fundamental way. For both political and financial reasons, however, the breakthrough research on these connections has been done at small private clinics such as San Raffaele rather than in the big US teaching hospitals or in Europe's massive public health systems. Since the 1970s, well-meaning but short-sighted reforms in Italy have shut down the vast majority of psychiatric in-patient facilities. Consequently, San Raffaele and a couple of other specialist hospitals have one of the purest supplies of untreated, acutely mentally ill patients in any developed country, as well as a financial incentive to treat them as efficiently as possible. The government pays San Raffaele roughly €2,300 for each "acute intervention", and the fee is the same whether that patient remains at the hospital for a few days or several weeks.

The head of the psychiatric unit at San Raffaele, Professor Enrico Smeraldi, is elegantly patrician but also ruthlessly pragmatic. He has created an environment in which a team of senior psychiatrists can do whatever they want so long as it works and patients are happy. Smeraldi himself began experimenting with sleep deprivation while working at another Milan hospital, San Paolo, in the 1980s. There, he had no in-patient beds available and relied on families and friends to keep patients awake and bring them back and forth to hospital. At San Raffaele, with 148 beds, Smeraldi and his team have been able to amass and publish a wealth of important clinical data. In 1999 they completed a retrospective analysis of 602 former patients from the main depression wing, where all rooms face either due east or due west. It showed that bipolar patients – those most susceptible to early-morning light therapy – checked out an average of three-and-a-half days earlier from east-facing rooms than from west-facing ones. In other words, natural light therapy – though less targeted than the artificial kind – had been having an effect all along.

Between 1997 and 2003, the San Raffaele team published studies showing how both sleep deprivation and light therapy hasten the anti-depressant effects of SSRI drugs; how sleep deprivation affects unipolar and bipolar depressives differently; and how lithium is the drug of choice in preventing relapse after sleep deprivation in manic depressives. The consistent theme of these studies is that combination therapy reduces the likelihood of suicide, allows patients to resume their lives more quickly, and saves the hospital money. Bipolar patients treated with combination therapy stay in the hospital an average of just over 12 days; without it, the average stay is three weeks. The time difference for unipolar patients is somewhat less but still significant.

These points are easily understood. In depression cases, SSRI drugs take from two to four weeks to have any effect. Psychotherapy typically requires three months to show results. In the meantime, a proportion of patients kill themselves (acute bipolar patients have a lifetime suicide risk of one in five). By contrast, sleep deprivation works for most patients in 24 hours, and the effect can then be sustained with light therapy and drugs. It is too soon to prove beyond statistical doubt that San Raffaele is saving lives because the hospital only made sleep deprivation, light and lithium its first-choice treatment for bipolar patients in 1999, and sleep deprivation, light and SSRIs its first choice for unipolar depressives in 2002. But the doctors have little doubt. Meanwhile, the home and work-life benefits to patients are already indisputable. Mariangela Grassini – despite being an acute case – is being treated on an outpatient basis so that she can continue to work from home. She will not lose her job and will be discharged in a week.

In most circumstances patients are quick to choose combination therapy over the more expensive and slow-acting alternatives. Chiara (she was unwilling to give her surname) is a 29-year-old woman whom Dr Benedetti treated once previously, >>

>> in 1996, before sleep and light therapies were standard at San Raffaele. Now she has returned after several miserable months in which she was unable to face work, lost her job at Hewlett-Packard, and then spent long periods in bed, contemplating death. In Benedetti's view, she has acute bipolar depression and suicidal impulses. But Chiara resists this diagnosis. In the early 1990s, she was told by a doctor in a general hospital that she suffers from a panic disorder, and she prefers this view. She tells Benedetti that she had long since stopped taking the lithium he prescribed for her last episode.

Benedetti gave Chiara a choice. If she thought she was suffering from panic, he would prescribe an anti-depressant for the long term. If she thought, as he did, there were bipolar features to her condition, she could try the new sleep deprivation, light therapy and lithium salts combination. She opted, as he was sure she would, for the latter. At 4.30am on the first night of sleep deprivation she wanted to call Benedetti to tell him the treatment wasn't working. The nurses advise patients that they can tell the doctors directly when they come in to work in the morning, knowing that, by then, change will have kicked in.

"I started to feel better after breakfast," says Chiara. After a second session of sleep deprivation she felt transformed. San Raffaele no longer offers the sleep phase advance system of gradually changing sleeping and waking times, preferring instead three cycles of 36 hours of total sleep deprivation interspersed with as much rest as patients want. Each morning Chiara underwent a half-hour session of light therapy, using a green light that appears to be effective at low luminosity; the timing was dictated by Terman's algorithm.

On the eighth day of treatment, Chiara appears happy and normal – what the doctors call "euthymic". The day before, she left the hospital and travelled to the busiest part of town to buy a new pullover, which she is wearing. On day nine she will be checked out with a maintenance prescription for inexpensive lithium salts. "She'll go home, she'll get her life back," says Benedetti. If, instead, Chiara had chosen to be treated with drugs only, her symptoms would have indicated long-term use of olanzapine (Zyprexa), the latest blockbuster from Eli Lilly, which costs more than €150 for a one-month supply.

Benedetti, the most relentlessly enthusiastic member of the Smeraldi group, is the one who corresponds with like-minded researchers around the world. He is gratified that the research done at San Raffaele has finally caught the attention of the broader psychiatric community. "In the 10 years that I've been working on this I've never seen so much interest," he says. Of particular significance to him is the fact that the first controlled trial of sleep, light and drug combination therapy is under way in the US – the world's drug fortress – at the University of California.

Outlining the preliminary results (the trials will not be completed until 2005), the California research co-ordinator Joe Wu says: "It does seem to be efficacious and it does seem to be a major facilitator of drug response." Wu has been somewhat surprised that the US's "managed care" providers, in their relentless drive to control costs, have not taken more notice of the new combination therapies. "This has been a tragically ignored and neglected area that can have a real impact in clinical management," he says. One possible explanation, according to Wu, is that "the inundation of marketing [by the giant pharmaceutical companies] drowns out ideas that don't have that

kind of massive advertising". But "overall, it's a mystery", he admits. "I don't think the culture will change quickly."

Institutional acceptance may come more quickly in the UK. Professor Chris Thompson, director of healthcare services at the Priory Group – best known in the tabloids for detoxing rock stars at its flagship facility – wants to introduce the Italian protocols in the Priory's 50 mental health and affective disorder clinics across Britain. Thompson, a former member of the General Medical Council and vice-president of the Royal College of Psychiatry, has impeccable mainstream credentials. In the process of reviewing San Raffaele's research and consulting with its doctors, he has passed from being "quite suspicious" of combination therapies to being "an enthusiast".

"I do think the literature is beginning to show that sleep deprivation and bright light therapy in addition to medication lead to faster treatment," Thompson says. "If I can show at Priory that there is a reduction in length of stay, I'll be going to talk to Bupa and the rest."

Meanwhile, the science presses forward into areas other than depression. In 1998 and 1999 Tom Wehr and Anna Wirz-Justice demonstrated for the first time that they could invert the sleep-phase advance effect to calm "rapid-cycling" bipolar patients in the manic phase – a group with one of the highest suicide rates among the mentally ill. They kept two patients in the dark, supported by nursing staff, for periods of 10 to 14 hours and saw that this extended rest-sleep ended the mania cycles.

In depression cases, SSRI drugs take from two to four weeks to show any effect. Psychotherapy typically requires three months. Sleep deprivation works for most patients in 24 hours

Researchers at McLean hospital in Boston and others in the Netherlands are running light-therapy trials with Alzheimer's patients, who often sleep by day and wander about in the middle of the night because the disease has damaged their suprachiasmatic nucleus. Light therapy is being used to re-entrain their biological clocks. In Canada, doctors are using light therapy to treat eating disorders such as bulimia nervosa, which often become more severe in winter.

Back at San Rafaele, Mariangela is knitting a bag at 5.45am and waiting for the appointed hour for her light therapy. She went home yesterday morning starting to feel a little better. She cried for only half an hour, had lunch with a friend, washed her hair, and spent the afternoon dealing with clients by phone. During the night she did some yoga and wandered around her garden. Now she's been awake for 26 hours and feels transformed. "Can you see the difference?" she asks. It would be hard not to. She knows the therapy works because she has done it twice before; she is more concerned about future relapse. This time she will try a low dose of venlafaxine hydrochloride (Effexor), an SSRI, to try to prevent this. Her attacks – more than one a year – are taking their toll. Still, she says, it is Friday today and her treatment will finish on Tuesday. "I'll be back at the office on Wednesday." FT

Joe Studwell is a freelance writer living in Italy. jstudwell@libero.it