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## FAKING IT

### Why Nothing Works

Until a few months after his second birthday, Parker Beck from Bedford, New Hampshire, seemed to be a happy, healthy little boy. Then he began to withdraw from the world. Parker stopped smiling, speaking or responding to his parents. He woke frequently during the night, made odd, high-pitched screams and developed repetitive habits such as spinning around and banging his head with his hands. After seeking medical advice, his parents Victoria and Gary heard the words they dreaded: their son was showing classic signs of autism. Despite their efforts to gain the best treatment for their son, Parker continued to deteriorate. Until April 1996, that is, when Parker was three. Then something amazing happened.

As is common in children with autism, Parker also had gastrointestinal problems, including chronic diarrhoea. So Victoria took him to see Karoly Horvath, a gut specialist at the University of Maryland. At Horvath's suggestion, Parker underwent a routine diagnostic test called an endoscopy, in which a camera on the end of a flexible tube is inserted into the intestinal tract. The test itself didn't reveal anything useful. But almost overnight, Parker began to make a dramatic recovery. His gut function improved, and he started sleeping soundly. And he began to

communicate again – smiling, making eye contact, and from being almost completely mute, he was suddenly naming flashcards and saying ‘Mommy’ and ‘Daddy’ for the first time in over a year.

The label of autism covers a wide spectrum of disorders characterised by problems with language and social interaction, and it affects around half a million children in the United States. Although some children show impaired development from birth, others like Parker appear normal but then regress. Some of the individual symptoms can be treated with drugs. Educational and behavioural therapies (for children and parents) can make a huge difference. But there is no effective treatment or cure. For Victoria, Parker’s sudden transformation seemed like a miracle.

She persuaded the hospital to tell her every detail of the endoscopy procedure that Parker had received, right down to the dose of anaesthetic they used. After a process of elimination, she became convinced that the change in her son’s symptoms was due to a dose of a gut hormone called secretin. This hormone stimulates the pancreas into producing digestive juices, and was given to Parker as part of a test to make sure that his pancreas was working properly. Victoria believed that there was a connection between her son’s gut problems and his symptoms of autism, and concluded that the hormone must have triggered his dramatic improvement.

Desperate to get another dose of secretin for Parker, Victoria called and wrote to the physicians at the University of Maryland to tell them about her theory, but they showed no interest. She also contacted autism researchers and doctors around the country, sending home videos that documented Parker’s progress. Finally, in November 1996, her story reached an assistant professor of psychopharmacology at the University of California in Irvine, Kenneth Sokolski, whose son Aaron had autism. Sokolski persuaded a local gastroenterologist to give Aaron the same diagnostic test. He, too, started making eye contact and repeating words.

This was enough to persuade Horvath at the University of Maryland to infuse a third boy with secretin – and he showed the same response. Horvath also gave a second dose to Parker, and Victoria noted another surge in her son's progress. In 1998, Horvath published a report in a medical journal of the three boys' secretin treatment, claiming a 'dramatic improvement in their behavior, manifested by improved eye contact, alertness and expansion of expressive language'.<sup>1</sup>

Horvath refused to give Parker any more doses after that, citing concern that secretin was not licensed for use as a treatment. Victoria eventually found another doctor who was willing to treat Parker, however, and on 7 October 1998, his story was broadcast to an audience of millions on the NBC *Dateline* show. The programme showed the videos of Parker becoming a playful, connected little boy, and featured testimony from other parents who had tried the hormone after hearing of Parker's progress. 'After that secretin, no more diarrhoea, potty trained, looking in the eyes, talking, saying, "Look how pretty outside!"' enthused one mother. 'He was staring right in my face, looking at my eyes, looking like, "Mom, I haven't seen you in a year,"' said another.<sup>2</sup> The *Dateline* programme claimed that of 200 children with autism who had been given the hormone, more than half showed a positive response.

It took just two weeks for Ferring Pharmaceuticals, the only US company licensed to produce secretin, to sell out. Doses of secretin exchanged hands for thousands of dollars on the internet. There were stories of families mortgaging houses to afford it, or buying black-market batches from Mexico and Japan. In the following months, more than 2,500 children were given secretin, and success stories continued to flood in.

'There was tremendous excitement,' recalls paediatrician Adrian Sandler at the Olsen Huff Center for Child Development in Asheville, North Carolina. 'Our phones were ringing off the hook, because parents of kids with autism who we were following wanted

to have them treated with secretin.<sup>3</sup> But medical professionals were concerned about a potential public health crisis. With no hard data on whether secretin was safe to use in repeated doses, let alone whether it worked, more than a dozen clinical trials were urgently commissioned at medical centres across the country. Sandler led the first controlled trial to be published, of 60 autistic children.

As is the gold standard in such trials, Sandler's participants were randomly divided into two groups. One group received the hormone, the other a fake treatment or placebo (in this case, an injection of saline). To be judged an effective drug, secretin would have to do better than placebo. The children's symptoms were assessed before and after the injection by clinicians, parents and teachers who had no idea which treatment each child had received.

Sandler's report appeared in the prestigious *New England Journal of Medicine* in December 1999, and the results were as surprising as they were damning.<sup>4</sup> There was no significant difference between the two groups. The results from the other trials were the same: secretin showed absolutely no benefit when compared to the fake treatment. As a drug for autism, it was useless. The entire promise of secretin was apparently an illusion, invented by parents so desperate to see an improvement in their kids that they had literally imagined it. The secretin story was over.

Or was it? The conclusion in Sandler's paper is one line long: 'A single dose of synthetic human secretin is not an effective treatment for autism.' But what he didn't write in that paper was how struck he was by the fact that *both* groups significantly improved. 'The interesting thing for me was that kids in both groups got better,' he tells me. 'There was a significant treatment response in the group that received secretin and in the group that received saline.'

Was it a lucky coincidence? As with many chronic conditions, symptoms in autism can fluctuate over time. One reason why it is so important to test new treatments against placebo is that any

apparent change in symptoms after taking a medicine might be down to chance. But Sandler was surprised by how big the improvement was.

The children in his trial were assessed on an official scale called the Autism Behavior Checklist, which covers a wide range of symptoms from whether they respond to a painful cut or bruise to whether they return a hug. The scale runs from 0 to 158, with higher numbers denoting more severe symptoms. The kids in Sandler's placebo group started the trial with an average score of 63. A month after receiving an injection of the fake hormone (saline solution), they averaged just 45.<sup>5</sup> That's an almost 30% improvement within a few weeks – something that to many parents of kids with autism would seem like a miracle. What's more, the effect was not evenly distributed. Although some children showed no response, others responded dramatically.

This pattern suggested to Sandler that the Becks and other parents convinced of the treatment's benefits had not imagined the changes in their children. Their kids' symptoms really did improve. But it had nothing to do with secretin.

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Bonnie Anderson didn't notice the water on her kitchen floor until it was too late. One summer evening in 2005, the 75-year-old had fallen asleep on her Davenport sofa while watching TV.<sup>6</sup> She doesn't remember what programme was on, a decorating show, maybe, or an old movie (she doesn't like the bad-language ones, or the bloody kind). When she woke it was dark, and she walked barefoot into the kitchen for a glass of water, without bothering to switch on the lights. But the water purifier had been leaking and she slipped on the wet tiles, landing flat on her back.

Unable to move, Bonnie felt an excruciating pain in her spine. 'It was scary,' she says. 'I thought, "My God, I broke my back."' Her partner, Don, dragged her down the hall and put a blanket

over her, and a couple of hours later she was able to get up onto the sofa. Thankfully she wasn't paralysed, but she had fractured her spine – an injury common in elderly people whose bones have been weakened by osteoporosis.

Bonnie lives with Don in a small, white bungalow in Austin, Minnesota. She worked for 40 years as a telephone operator for the town's main employer, Hormel Foods (makers of Spam) and has stayed active into her retirement. She has orange make-up, big white hair and a busy social life, and loves nothing more than an 18-hole round of golf; a sport she has played all her life. But the accident left her devastated. She was in constant pain and couldn't even stand up to do the dishes. 'I couldn't sleep at night,' she says. 'I couldn't play the golf I wanted to play. I'd go and sit in the den with a heating pad.'

A few months later, Bonnie took part in a trial of a promising surgical procedure called vertebroplasty, which injects medical cement into the fractured bone to strengthen it. Don drove Bonnie to the hospital – the Mayo Clinic in Rochester, Minnesota – just before dawn on a cold October morning. She walked out of the hospital after the procedure, and felt better immediately. 'It was wonderful,' she says. 'It really took care of the pain. I was able to go back to my golfing, and everything I wanted to do.'

Almost a decade on, Bonnie is still delighted with the outcome. 'It was a miracle how well it turned out,' she says. Although breathing problems are now starting to slow her down, she isn't limited by her back. 'I have a birthday coming up, I'll be 84,' she chuckles. 'But I still plan on playing a little golf this summer.'

The vertebroplasty apparently healed the effects of Bonnie's fractured spine. Except there's something Bonnie didn't know when she took part in that trial: she wasn't in the vertebroplasty group. The surgery she received was fake.

In 2005, when Bonnie slipped on her wet floor, the technique of vertebroplasty was rapidly gaining popularity. 'Orthopaedic surgeons were doing it. Physiatrists [rehabilitation physicians] were

doing it, anaesthesiologists were doing it,' says Jerry Jarvik, a radiologist from the University of Washington in Seattle. 'Anecdotally there were lots and lots of reports as to how effective this procedure was. You'd get them on the procedure table, inject the cement, and they'd effectively jump off cured.'<sup>7</sup>

Bonnie's surgeon at the Mayo Clinic, David Kallmes, says he too had seen 'positive' results from the procedure, with around 80% of his patients getting substantial benefit from it.<sup>8</sup> But nonetheless he was starting to have doubts. The amount of cement that surgeons injected didn't seem to matter much. And Kallmes knew of several cases in which cement was accidentally injected into the wrong part of the spine, and yet the patients still improved. 'There were clues that maybe there was a lot more going on than just the cement,' he says.

To find out what, Kallmes teamed up with Jarvik to do something groundbreaking – at least in the field of surgery. They planned to test the effectiveness of vertebroplasty against a group of patients who would unknowingly receive a pretend operation. Although such placebo-controlled trials are routinely used to test new drugs like secretin, they are not generally required for new surgical procedures, partly because it often isn't seen as ethical to give patients fake surgery. Kallmes points out, however, that with surgery just as with drugs, untested therapies risk harming millions of patients. 'There's nothing unethical about a sham trial or a placebo trial,' he says. 'What is unethical is not doing the trial.'

Kallmes and Jarvik enrolled 131 patients with spinal fractures, including Bonnie, at 11 different medical centres worldwide. Half of them received vertebroplasty and half received a fake procedure. The patients knew that they only had a 50% chance of receiving the cement, but Kallmes went to great lengths to make sure that the sham surgery was as realistic as possible, so that the trial participants wouldn't guess which group they were in. Each patient was taken into the operating room, and a short-acting local anaesthetic was injected into his or her spine. Only then did the surgeon

open an envelope to discover whether the patient would receive the real vertebroplasty or not. Either way, the operating team acted out the same predetermined script, saying the same words, opening a tube of the cement so that its characteristic smell of nail polish remover filled the room, and pressing on the patient's back to simulate the placement of the vertebroplasty needles. The only difference was whether or not the surgeon actually injected the cement.

Afterwards, all of the patients were followed for a month, and asked to rate their pain and disability using questionnaires. The study was published in 2009.<sup>9</sup> And even though Kallmes had harboured some doubts about the procedure, he was shocked by the results. Despite all of the apparent benefits of vertebroplasty, there was no significant difference between it and the fake operation.

Both groups substantially improved, however. On average, their pain scores were reduced by almost half, from 7/10 to just 4/10. The disability score was based on a series of questions such as: can you walk a block, or climb stairs without holding a handrail? At the beginning of the trial, the patients answered no to an average of 17 out of 23 questions, a score that is categorised as 'severe disability'. A month after the surgery, they scored on average just 11. Although some were still in pain after the procedure, others, like Bonnie, were practically cured. A second trial of vertebroplasty carried out in Australia was published around the same time, with very similar results.

The patients' improvement was probably due to a range of factors. Pain symptoms can fluctuate, and vertebral fractures do heal, slowly, over time. But both Kallmes and Jarvik believe that to produce such a dramatic improvement, there must have been something else going on – something in the patients' minds. Just as with secretin, it appears that the mere belief they had received a potent treatment was enough to ease – and in some cases banish – their symptoms.



The phenomenon in which people seem to recover after they are given a fake treatment is called the placebo effect, and it is well known in medicine. Clinical trials consistently show a strong placebo effect across a wide range of conditions, from asthma, high blood pressure and gut disorders to morning sickness and erectile dysfunction. In general, however, scientists and doctors view it as a mirage or trick: a statistical anomaly where people would have improved whether they received the treatment or not, combined with a morally dubious phenomenon in which desperate or gullible people are fooled into thinking they are better when they really aren't.

Back in 1954, an article in the medical journal *The Lancet* stated that placebos comfort the ego of 'unintelligent or inadequate patients'.<sup>10</sup> Although doctors might not put it so bluntly today, attitudes haven't changed much since then. The placebo-controlled trials introduced at around that time have been one of the most important developments in medicine, allowing us to determine scientifically which medicines work and which don't, saving countless lives in the process. They form the bedrock of modern medical practice, and rightly so. But within this framework, the placebo effect is of no interest beyond being something to guard against in clinical trials. If a promising therapy is shown to be no better than placebo, it is thrown out.

Trial results show that neither secretin nor vertebroplasty has any active effect. So according to the rules of evidence-based medicine, the improvements experienced by patients like Parker and Bonnie are worthless.

Yet when Sandler told the parents in his study of secretin that he had found no benefit for the hormone over placebo, a huge 69% of them still wanted it for their kids.<sup>11</sup> Likewise radiologists have refused to give up on vertebroplasty. After Kallmes and Jarvik's report was published, the pair were attacked in hostile editorials and personal letters, and even screamed at in a meeting. 'People felt extraordinarily strongly that we were taking away

something that was helping their patients,’ says Jarvik. In the US, many insurers still cover the procedure, and even Kallmes still carries out vertebroplasties regardless of his trial results, arguing that for many of his patients there is no other option. ‘I see patients get better,’ he says. ‘So I still do the procedure. You just do what you need to do.’

We see similar cases again and again. In 2012, a popular class of sleeping pills called Z-drugs was shown to be of little value after accounting for the placebo effect.<sup>12</sup> The same year, the sedative ketamine was tested in a double-blind trial for cancer pain; previous studies had described its effects as ‘complete’, ‘dramatic’ and ‘excellent’, yet it too proved to be no better than placebo.<sup>13</sup> In 2014, experts analysed 53 placebo-controlled trials of promising surgical procedures for conditions from angina to arthritic knees, and found that for half of them, sham surgery was just as good.<sup>14</sup>

Perhaps the doctors and patients in all of these cases really were fooled by a combination of random chance and wishful thinking. But by continuing to dismiss the experiences of so many people, I can’t help wondering if we are also throwing out something that could be of real help. So here’s my question. Might the placebo effect, instead of being an illusion that we should puncture, sometimes be of real clinical value – and if it is, can we harness it *without* exposing patients to potentially risky treatments?

Or to put it another way, can a simple belief – that we are about to get better – have the power to heal?

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Rosanna Consonni hunches over the desk, gripping its edge with her left hand. In front of her is a grey, rectangular trackpad, and she tentatively places her right index finger on a green circle at its centre. Every few seconds, a red circle lights up at varying positions around the edge of the pad. When that happens, Rosanna has to trace her finger from green to red as quickly as she can.

It's a task that most people would find easy. But the 74-year-old's brow is furrowed in concentration, and she looks like a child struggling to write. She's willing her hand to move but her finger drags slowly, as if it's not really hers. 'Breathe,' advises a young, white-coated neuroscientist, Elisa Frisaldi. Each time Rosanna arrives successfully on red, her time pops up as a blue bar on a graph on Frisaldi's computer screen.

This is the neuroscience department of the Molinette Hospital in Turin, Italy. It is early in the morning and outside the spring sun is shining. A stone's throw away, joggers and dog walkers pass up and down the towpath by the wide, glossy river Po. Blossoms are falling and there are lizards in the grass. But we're squeezed into a windowless basement room packed with computers, lab equipment and a blue couch.

Frisaldi is part of a team headed by one of the pioneers of placebo research, neuroscientist Fabrizio Benedetti. The problem with clinical trials like those of vertebroplasty and secretin is that they are not designed to measure the placebo effect, only to eliminate it. Any changes seen in a placebo group can be due to a range of causes, including random chance, so it's never certain how much improvement, if any, is a result of the placebo itself. Benedetti and Frisaldi, on the other hand, are using carefully controlled laboratory experiments to probe exactly how and when beliefs can ease our symptoms.

Today's volunteer, Rosanna, was 50 when she first noticed that her right hand was trembling. After two years of denial and uncertainty, she finally received a diagnosis: Parkinson's disease. The condition affects about 1 in 500 people; more than half a million in the United States alone. It's a degenerative disease in which brain cells that make a chemical messenger called dopamine gradually die. As levels of dopamine in the brain drop, patients experience steadily worsening symptoms that include stiff muscles, sluggish movement and tremors.

The condition is generally treated with levodopa, a chemical

building block that the body converts into dopamine. Rosanna hasn't taken her drug since last night, however, so that her Parkinson's is in full flow for Frisaldi's experiment. She arrives clutching her husband's arm, taking shaky, shuffling steps. Even when she sits, she is in constant motion. She sways as she's speaking, her silver earrings wobbling and her hands waving to and fro. Her chin and throat tremble as if she's chewing. She's wearing kneepads under her grey trousers because she so often falls.

But her spirit appears not to match her frail physical appearance. She is fiercely independent and jokingly refers to her husband, Domenico, as *badente*, or nursemaid. After her initial diagnosis, Rosanna tells me, she didn't want to know anything about her disease. She took her pills, but otherwise 'I didn't read about it. I didn't want to know my future.'<sup>15</sup> For 20 years after her diagnosis, that strategy seemed to work. 'I could drive. I was a good mother. My life didn't change so much.' She enjoyed cycling trips, and snorkelling at the beaches of Versilia, about 150 miles south of Turin.

But in 2008, her symptoms started getting worse. Her body stiffened and her limbs resisted her will to move. One day she went to the supermarket alone, against her doctor's advice, and when a woman in the queue bumped into her she was unable to step to regain her balance. She clattered to the ground and broke her arm. 'I was afraid,' she says. 'I felt something changing in my life.'

Rosanna's doctor recommended surgical intervention, and she now wears a black shoulder strap, attached to a pouch that looks like a small camera bag. It contains a portable infusion pump that delivers her drug continuously, through a plastic tube that dives through her abdomen and into her small intestine. She hates the implant – 'It makes me feel as if I have a handicap,' she says – but it allows her to keep some measure of independence.

Now, with the pump switched off, Frisaldi runs Rosanna through a series of tasks to assess the severity of her symptoms

without any drugs. In addition to the track test, she has to circle her arms, walk in a straight line and repeatedly touch her nose. Once the baseline assessment is complete, it's time to open the pouch and activate the pump to begin Rosanna's daily drug infusion. It whirs and beeps; the moment she has been waiting for. 'As soon as I take the drug, I can control my movements better,' she says. 'I feel my hands relaxing, the rigidity in my legs disappearing.' After 45 minutes, I can see what she means. She sits more upright. Her chin is almost still. She moves with more confidence. And her time on the track test is halved.

But how much of this transformation is due to the drug itself, and how much to her expectation of the relief that she is about to feel? This is the type of question that most clinical trials are ill-equipped to address, but that Frisaldi is hoping to answer. Today, Rosanna is getting a full dose of her drug, but on other days she and her fellow volunteers will get a range of different doses, and sometimes they'll know what they're getting and sometimes not (for ethical reasons, Frisaldi isn't allowed to give them no drug at all).

It seems amazing to me that symptoms as severe as Rosanna's – caused by a degenerative neurological disease – might be eased by mere suggestion. But this is what studies of Parkinson's have repeatedly shown. For example, a series of trials carried out by Jon Stoessl, a neurologist at the University of British Columbia in Vancouver, Canada, showed a strong placebo effect when Parkinson's patients were given fake pills.<sup>16</sup> One of them was a keen mountain biker called Paul Pattison. He duly took his capsule and waited for the drug to kick in. 'Boom!' he told the makers of a BBC documentary about the placebo effect.<sup>17</sup> 'My body becomes erect, my shoulders go back.' When he found out he had actually taken a placebo, 'I was in a state of shock. There are physical things that change in me when I take my meds so how could a blank thing, a nothing, create those same feelings?'

Stoessl's experiments answered that question. Using brain scans,

he showed that after taking a placebo, the participants' brains were flooded with dopamine, just as when they take their real drug. And it wasn't a small effect – dopamine levels tripled, equivalent to a dose of amphetamine in a healthy person – all from simply *thinking* they had taken their medication.

That finding was followed up by Benedetti, here in Turin. He was carrying out surgery on Parkinson's patients for a therapy called deep brain stimulation. This involves implanting electrodes deep into the brain, in an area called the subthalamic nucleus, which helps to control movement. The neurons in this region are usually kept in check by dopamine, but in Parkinson's patients these cells fire out of control, causing freezing and tremors. Once implanted, the electrodes stimulate these regions and calm the neurons down.

The surgery is done while patients are awake, and Benedetti saw the perfect opportunity to watch the placebo effect in action. The electrode would allow him to monitor activity deep inside the brain as someone takes a placebo – something that isn't usually possible with human volunteers. So he carried out a series of trials: once the electrode was in place, he gave patients a saline injection, and told them it was a powerful anti-Parkinson's drug called apomorphine.

As we wait for Rosanna's drug to kick in, Frisaldi pulls up a series of slides on her computer screen. First, she shows me brain activity that Benedetti recorded before the saline injection. It's a black-and-white line graph, showing the behaviour of a single neuron from the subthalamic nucleus of one of the patients in the study. Each time the neuron fires, the line jumps in a sharp peak. Overall the graph looks like a barcode, a dense forest of spikes that's almost completely black – this is a neuron firing out of control. Then she shows me the activity of the same neuron just after the placebo injection. There's virtual silence; an overwhelmingly white space broken only by the odd, lone spike.

'It's incredible,' says Frisaldi. 'I think it's one of the most

impressive studies that Benedetti has done.’ Benedetti had chased a belief right down to an individual cell – demonstrating that in Parkinson’s patients, motor neurons fire more slowly after injection of a placebo, exactly as they do in response to a real drug.<sup>18</sup>

Between them, what Stoessl and Benedetti showed was remarkable. Although placebo effects had been noted in Parkinson’s patients, it never occurred to anyone that placebos might actually mimic the biological effect of treatment. But here was proof that patients weren’t imagining their response, or compensating for their symptoms in some other way. The effect was measurable. Real. And physiologically identical to that of the actual drug.

An hour or so later, Rosanna’s drug has worn off and the experiment is over. She tells me that she still plans to swim in Versilia this summer, even with her implant, and that she doesn’t waste time worrying about how her disease might progress. ‘I’m always thinking about the present moment, I don’t want to project into the future,’ she says. ‘That’s how I am generally, and the disease hasn’t changed that.’ She takes out her phone and proudly shows me a picture: 70 kg of lemons from her garden. When she stands to leave, she’s tiny and still swaying; she looks like a frail plant being buffeted by the wind.

After learning about the research with Parkinson’s patients, I’m impressed by the effect that placebos can have, but I’m left with more questions. If a belief can have the same effect as a drug, why do we need drugs at all? Do placebos work for all conditions, or just some? How does a mere suggestion create a biological effect? To find out, I decide to visit Benedetti himself. But although this is his lab, he’s not here. To track him down I have to travel 75 miles north from Turin – and nearly 12,000 feet up.

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I’m standing on the edge of a cliff, looking down on alpine crows swooping black against the blinding white snow, and across a

crinkled blanket of mountain peaks that stretches to the horizon. Sounds are muffled in the thin air, and at  $-10^{\circ}\text{C}$ , it's biting cold. Behind me is a huge expanse of ice: the Plateau Rosa glacier. This is 3,500 metres above sea level, on the border between what scientists describe as 'high altitude' and 'very high altitude'. In the Alps, this is almost as high as you can get. From here, only the iconic peak of the Matterhorn rises another kilometre, cutting its crooked triangle out of the azure blue sky.

It is early in the morning, and the plateau is deserted. Then a huge cable car arrives and tips out its load of brightly clad skiers. They pour past me, heading for the shallow slope of the glacier and barely noticing what looks like a metal shed perched on the mountainside. It's half buried in snow and covered in scaffolding.

Inside the shed is Benedetti. He's tall and welcoming, dressed in black ski trousers and a fleece. This is his high-altitude laboratory, packed with equipment and lined with pine slats like a sauna. He shows me round, pointing out the leaking roof – 'It's terrible in summer,' he says – and letting me peek at a three-metre infrared telescope with which he shares this accommodation.

Telescope aside, Benedetti has kitted this space out himself, arranging for all the supplies to be brought in by helicopter. There's a basic living area and kitchen, as well as two bedrooms with bunks, sleep-monitoring equipment and a breathtaking view. The international border runs right through the hut so we step from the living area, which is in Italy, to the lab, which is in Switzerland.

This turns out to be two adjoining rooms, equipped with a mess of machinery and monitors, blinking lights and switches, and bookcases stuffed with files. Wires run across the ceiling and big, green gas canisters lean against the wall. I'm struck by the noise: hums and buzzes, clicks of different frequencies, a periodic hiss. And the thump-thump-thump of an exercise stepper. Working out on the stepper is Benedetti's guinea pig for the day: a stout, young engineer called Davide.

Benedetti is here because the thin air is perfect for studying



the placebo effect in another ailment: altitude sickness. Instead of working with ill patients, he can induce symptoms in healthy volunteers simply by bringing them here. Then he plays with their beliefs and expectations, and monitors the physiological effects.

Altitude sickness is caused by a lack of oxygen. As we travel higher above sea level, the percentage of oxygen in the air stays the same, but that air becomes less dense, meaning that there's less oxygen in each lungful that we breathe. Here at 3,500 metres, the oxygen density is only two thirds what it would be at sea level. That can cause symptoms including dizziness, nausea and headaches. The advice to skiers travelling to Plateau Rosa is to allow time to acclimatise by staggering the journey here overnight. To maximise the effects of the altitude for Benedetti's experiment, however, Davide has travelled here in just three hours from sea-level Turin.

With ski poles and a focused expression, Davide looks like an explorer. He's wearing a black neoprene cap fitted with wireless electrodes to monitor his brain activity. Meanwhile various sensors attached to a harness around his chest measure nervous system activity, body and skin temperature, heart activity and the oxygen saturation in his blood. The data are beamed wirelessly from a black recorder, the size of a stopwatch. It's the same 15,000-Euro system that the skydiver Felix Baumgartner used on his record-breaking jump from space,<sup>19</sup> says Benedetti. 'Only we're at 4 kilometres rather than 40 kilometres.'

As Davide works out, Benedetti watches the data come in on his iPad. The engineer's heartbeats are translated into green lines rolling across a black screen, while a digital display shows the oxygen saturation in his blood – at sea level it would normally be around 97–98%, but now it has fallen to just 80%. On a nearby computer screen, a rotating head pulsates with waves of yellow, red and blue – Davide's brain activity.

He steps for 15 minutes, then puts on an oxygen mask attached to a small white canister on his chest, which Benedetti explains

will make his activity easier for the remainder of the test. What Benedetti doesn't tell him (or me) is that the mask isn't connected, and the canister is empty. Davide is breathing fake oxygen.

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I first met Benedetti the evening before, over beer and pizza down in the nearest ski resort of Breuil-Cervinia. Dressed in a zigzag woollen jumper, he looked utterly at home in an alpine lodge. Although he's from the Italian coast, he was always bored on the beach, he tells me. He loves the mountains.

Benedetti sees placebo effects in all aspects of life, from music to sex. He explains that if he gives me a glass of wine and tells me how good it is, that will affect how it tastes to me. Or that if I'm given a hospital room that has a pretty view out of the window, I will recover faster. 'We are symbolic animals,' he says. 'The psychological component is important everywhere.'<sup>20</sup>

His interest in how psychological factors affect our physical bodies began in the 1970s, when he was starting his career as a neuroscientist at the University of Turin. He had already noticed that when he ran clinical trials, patients in the placebo group often did as well as or better than those who received the active drugs. Then he saw a paper that changed his life, not to mention the world's understanding of the placebo effect.

Scientists had recently discovered a class of molecules produced in the brain called endorphins, that act as natural painkillers. Endorphins are opiates, meaning that they belong to the same chemical family as morphine and heroin. The effects that these powerful drugs have on the body were well known, but the fact that we might make our own versions of such molecules was a revelation. It was the first hint that the brain was capable of producing its own drugs.

A neuroscientist called Jon Levine, at the University of California in San Francisco, wondered if this might help to explain how

placebos are able to relieve pain. Scientists had generally assumed that gullible patients are somehow tricked into thinking they are in less pain than they actually are. But what if taking a placebo could trigger the release of these natural painkillers? Then the reduction in pain would be real. Levine tested his idea on patients who were in the hospital recovering from oral surgery. Just over a third of them reported significant pain relief after taking a placebo – an intravenous infusion of saline that they thought was a powerful painkiller. Then, without telling them, Levine gave them naloxone, a drug that blocks the effects of endorphins. The patients' pain returned.<sup>21</sup>

It was at this moment, says Benedetti, that 'the biology of placebo was born'. This was the first evidence of biochemical pathways behind the placebo effect. In other words, if someone takes a placebo and feels their pain melt away, it isn't trickery, wishful thinking, or all in the mind. It is a physical mechanism, as concrete as the effects of any drug. Benedetti wondered if this could also explain why the placebo patients in his trials did so well. 'I decided to investigate what was going on in their brains.'

He dedicated his career to lifting the veil of the placebo effect – starting with pain relief. In trials he identified more natural brain chemicals that, triggered by our beliefs, can turn our response to pain up or down. He found that when people take placebo painkillers in place of opioid drugs, these don't just relieve pain, they also slow breathing and heart rate, just as opiates do. And he discovered that some drugs thought to be potent painkillers have no direct effect on pain at all.

Opioid painkillers are supposed to work by binding to endorphin receptors in the brain. This mechanism isn't affected by whether we know we've taken a particular drug. Benedetti showed that in addition to this mode of action, such drugs also work as placebos – they trigger an expectation that our pain will ease, which in turn causes a release of natural endorphins in the brain. This second pathway does depend on us knowing we have taken

a drug (and having a positive expectation for it). Incredibly, Benedetti found that some drugs previously thought to be powerful painkillers *only* work in this second way. If you don't know you've taken them, they are useless.

But this is just one placebo mechanism. Benedetti also found pain-relieving placebo effects that are not mediated by endorphins and can't be blocked by naloxone. Then he moved on to studying placebo effects in Parkinson's, the research I learned about from Frisaldi, which works via yet another mechanism: release of dopamine. Placebo effects have only been studied in a few systems so far, but there are probably many others. Benedetti emphasises that the placebo effect isn't a single phenomenon but a 'melting pot' of responses, each using different ingredients from the brain's natural pharmacy.

Up here in the Alps, Benedetti has just started to study how placebos work for altitude sickness. When we're at altitude, low oxygen levels in the blood trigger the brain to produce chemical messengers called prostaglandins. These neurotransmitters cause a variety of physical changes, such as dilating blood vessels, to help pump more oxygen around the body. They are also thought to induce the headaches, dizziness and nausea of altitude sickness. So can fake oxygen interrupt this pathway and ease the symptoms?

Davide finishes his half-hour exercise stint. The altitude has clearly affected him; he looks woozy, and totters slightly as Benedetti helps him to a chair. But he has put in a solid performance on the stepper, impressive for someone who was at sea level just a few hours ago. Benedetti tells me later, after analysing the results from Davide and other volunteers, that the fake oxygen did indeed create a biological effect in their brains compared to a control group who weren't given the placebo. Even though oxygen levels in the blood stayed the same, prostaglandin levels and vasodilation were reduced. When volunteers experience a placebo effect (and not everyone does) their brains respond as if

they are breathing real oxygen, reducing their symptoms and allowing them to perform better.

This result illustrates two important points about the limitations of the placebo effect. The first is that any effects caused by belief in a treatment are limited to the natural tools that the body has available. Breathing fake oxygen can cause the brain to respond as if there is more oxygen in the air, but it cannot increase the underlying level of oxygen within the blood. This principle applies to medical conditions too. A placebo might help a patient with cystic fibrosis to breathe a little more easily but it won't create the missing protein that their lungs need, any more than an amputee can grow a new leg. For someone with type 1 diabetes, a placebo can't replace their dose of insulin.

The second point, which is becoming clear from a range of placebo studies, is that effects mediated by expectation tend to be limited to symptoms – things that we are consciously aware of, such as pain, itching, rashes or diarrhoea, as well as cognitive function, sleep and the effects of drugs such as caffeine and alcohol. Placebo effects also seem to be particularly strong for psychiatric disorders such as depression, anxiety and addiction.

In fact, they may be the main mode of action for many psychiatric drugs. Irving Kirsch, a psychologist and associate director of the placebo studies programme at Harvard University, has used freedom-of-information legislation to force the US Food and Drug Administration (FDA) to share clinical trial data sent to it by drug companies. This revealed what the companies had been hiding: that in most cases (severely ill patients are an exception), antidepressant drugs such as Prozac have little effect over and above placebo.<sup>22</sup> Meanwhile Benedetti has found that valium, which is widely prescribed for anxiety disorders, has no effect unless patients know they are taking it.<sup>23</sup> 'The more we know about placebos,' he says, 'the more we learn that many positive outcomes of clinical trials are attributable to placebo effects.'

Placebos, then, are very good at influencing how we *feel*. But

there's little evidence that they affect measures we're not consciously aware of, such as cholesterol or blood sugar levels, and they don't seem to address the underlying processes or causes of disease. Bonnie Anderson's fake surgery banished her pain and disability, but it probably didn't mend her spine. One asthma study found that although patients reported that they could breathe more easily after taking a placebo, objective measurements of their lung function did not change.<sup>24</sup> Clinical trials involving cancer patients generally show significant placebo effects for pain and quality of life, but the proportion of patients in placebo groups whose tumours shrink is low (in one analysis of seven trials, it was 2.7%).<sup>25</sup>

These are crucial limitations. Placebos don't create an all-powerful protective magic that can keep us well in every circumstance. We're not going to be able to throw out physical drugs and treatments. But on the other hand, Benedetti's research shows that the effects of placebos are underpinned by measurable, physical changes in the brain and body. And just because the benefits mediated by placebos are mostly subjective, that doesn't mean they have no potential value for medicine.

After all, many of the treatments used in medicine target symptoms rather than underlying disease processes, particularly when the underlying disease is hard to diagnose or treat. Tumour growth and survival time are critical for a cancer patient, but pain control and quality of life are important too. Telling a patient with fibromyalgia or irritable bowel syndrome that there's nothing physically wrong with them will not give them much comfort. A subjective improvement in suicidal thoughts in a patient with depression can mean the difference between life and death.

In lab experiments, placebo effects are often short-lived, but there is evidence that in clinical practice, placebos can keep working for months or years. In a US trial published in 2001, researchers injected neurons from aborted human embryos into the brains of Parkinson's patients, in the hope that they would

thrive there and start producing dopamine.<sup>26</sup> The trial was essentially a failure – there was no significant difference between the treatment group and placebo controls. What did make a difference, however, was which group the patients *thought* that they were in. A year later, those who guessed they had received the transplant were doing significantly better (in terms of their own reported scores, and those of blinded medical staff) than those who believed they had received placebo.

Of course, patients who did better might be more likely to guess that they had received the transplant. But the researchers who analysed the data from this study suggest there was more to the effect than that, concluding that even over the course of a year, ‘the placebo effect was very strong’.<sup>27</sup> Rosanna believes her refusal to see herself as ill might be one reason why her disease was slow to progress for so many years after her initial diagnosis – this study hints that she might be right.

On the face of it, then, placebos might seem to be a magic pill, with wide-ranging benefits, no side effects, and essentially zero cost. But there has always been one huge problem, which causes even doctors who acknowledge the power of placebos to reject their use in medicine. It has always been assumed that you have to lie to patients for placebos to be effective – to fool them into thinking that they’re receiving an active treatment when they are not. No matter what the potential benefit of placebos, critics argue, it is not worth jeopardising the fundamental bond of trust between doctors and patients.

But within the last few years, a handful of scientists have started to suggest that this traditional assumption is wrong. Their results could turn conventional medicine on its head.