Gaboxadol

In 1755 the naturalist Stepan Krasheninnikov observed the *Amanita muscaria* mushroom's effects on Russian soldiers in Siberia ingesting it for the first time. Claiming to have been seized by an invisible power, the men submitted to the mushroom's strange and often violent commands. A servant strangled his master. A soldier found himself ordered to his knees and confessed his sins before God. Krasheninnikov's interpreter drank some mushroom liquor and "went into such a frenzy that he slashed open his abdomen, on the command . . . of mukhomor, the mushroom." One soldier who ate this mukhomor found a certain dose reduced his fatigue while marching, but after eating more of the mushroom he "gripped his testicles and died."

Krasheninnikov's report seems to describe the response drug-naïve users can have to GABAergic deliriants, which act on a neurotransmitter that reduces the transmission of excitatory impulses in about half the brain's neurons.[1] Subsequent centuries of eager reporting on the outré customs he had described culminated in an extermination campaign begun under Stalin and continued by the KGB that is said to have completely eradicated traditional *A. muscaria* use by 1980. While operatives were systematically destroying the ostensibly anticommunist Siberian mushroom traditions via a series of assassinations in which shamans were reportedly thrown from helicopters, plunged into frozen lakes, or simply shot, with their drums kept as trophies, biochemists internationally were recognizing the enormous value of muscimol, a psychoactive alkaloid produced by *A. muscaria,* which, instead of changing the activity of endogenous GABA, actually *replaces* it in the brain.

[1] Comparing the behavior of Krasheninnikov's soldiers with a few recent case reports on the well-known GABA modulator Ambien (zolpidem tartrate) will reveal striking similarities. A 2010 article entitled "Command Hallucinations with Self-Stabbing Associated with Zolpidem Overdose" may be an apposite place to begin.

A team of Danish researchers led by the medicinal chemist and GABA expert Povl Krogsgaard-Larsen began synthesizing and publishing on dozens of muscimol derivatives. One molecule created in 1977 stood out: a derivative that, like muscimol itself, behaved as a direct agonist of the $GABA_A$ receptor and could be ingested orally. Furthermore, it was less toxic than muscimol. This compound would come to be known as gaboxadol.

Until relatively recently, self-experimentation was a vital component of drug discovery, and so when Krogsgaard-Larsen recognized the uniqueness of gaboxadol he ingested the drug in increasing doses to characterize its qualitative effects. "We had blood samples taken continuously," he told me. "Normally I'm scared of blood and I don't like the pain of needles, but this time I was not scared and there was no pain whatsoever. At 10mg the general feeling I had when I was walking around was just as if I had taken two or three beers — it was a very comfortable feeling." Krogsgaard-Larsen filed for a patent for gaboxadol and transferred it to the pharmaceutical company Lundbeck. Then came a surge of human testing.

Given that gaboxadol was the product of investigations into the active principle of a mushroom that has since at least the seventeenth century been recognized for inducing a hallucinogenic delirium — a delirium profound enough that many Siberians used specialized wooden bowls to steal and save the urine of those who had just partaken — its unusual "side effects" should have been predictable. Yet from the very beginning gaboxadol suffered something of an identity crisis. As is often the case in the testing of new drugs, the first trial population was mentally ill. Eighteen patients with tardive dyskinesia, a movement disorder that afflicts long-term users of antipsychotic drugs, were administered daily doses ranging from 10mg to a potently deliriogenic 120mg. There was no change in their repetitive movements, but there *were* side effects: sedation, confusion, and dizziness. One schizophrenic man "remained in a confusional state for three hours, followed by amnesia for the episode." The authors concluded that the doses may have been too low to produce the desired antihyperkinetic effect, suggesting gaboxadol might work better as an antianxiety drug.

Then came fourteen patients with advanced-stage cancer in a trial testing gaboxadol as a non-narcotic, nonaddictive analgesic. Intramuscular gaboxadol injections proved effective against malignant cancer pain without causing the breathing problems that underlie most opiate-related fatalities. Patients reported euphoria, the feeling of having drunk "a couple of beers too much," and a " 'closed' sensation in the head." Two found gaboxadol's hypnotic effect so strong they lost consciousness entirely.

Following the lead suggested by the unsuccessful tardive-dyskinesia study, clinicians at Johns Hopkins tested gaboxadol in eight patients with generalized anxiety disorder. While the drug did to some degree ease their symptoms (though not significantly more than the placebo), once again patients spoke of side effects. Five of the eight reported feelings of unreality; one described "dream-like illusions similar to those she had previously experienced during a high fever." Additionally there were feelings of giddiness, depersonalization, and, of course, sleepiness. Whether gaboxadol truly lacked efficacy or simply confused anxious patients accustomed to Valium's gentle, nonhallucinatory languor is unclear; what is clear is that the drug had yet to find its niche.

Most of the commonly encountered GABAergic drugs — Valium, Ambien, Xanax, alcohol — exert their effect on the $GABA_A$ receptor, thereby increasing the effectiveness of the GABA already circulating naturally in the human brain; but both muscimol and gaboxadol exert their effect independent of endogenous GABA concentrations, replacing native GABA on the neuron. For this reason, Krogsgaard-Larsen suggested, gaboxadol might be a viable treatment for Huntington's disease, in which depressed GABA production and reduced binding sites limit the efficacy of traditional drugs. But even at inadvisably high 120mg doses, gaboxadol failed to reduce the involuntary movements that characterize the disease. One patient reported hallucinations in the moments before sleep, and all five participants experienced somnolence and dissociation. There were further trials employing gaboxadol as an intervention for epilepsy, mania, and spasticity, all of them characterized by the same mixed to negative results on the target disorder and the unavoidable desire to sleep.

Krogsgaard-Larsen published a review in the journal *Neuropharmacology* defending the potential of gaboxadol in the face of the repeated clinical failures of the early '80s, calling for more human trials and dismissing the reported side effects as little more than a new drug's youthful indiscretions — certainly nothing an enteric coating couldn't fix. In no place did he propose that the side effects might be the very properties that defined gaboxadol's potential as a pharmaceutical. And so the drug was shelved. Save for a single unsuccessful trial that employed an unprecedentedly high 160mg dose in Alzheimer's patients, gaboxadol spent the next decade dancing across the $GABA_A$ receptors of rodents and the occasional grivet monkey but neglecting the large, sleep-disorderridden brain of man.

Then, in 1996, Marike Lancel, a somnologist at the Max Planck Institute for Psychiatry in Munich, made the connection that had eluded her predecessors. She noted, in a trial involving rats, that gaboxadol not only induced sleep effectively but also preserved sleep's natural architecture. Traditional benzodiazepine hypnotics (such as the aforementioned Valium and Xanax) suppress the REM cycle, but gaboxadol leaves REM undisturbed while lengthening the duration of slow-wave sleep, a dreamful stage of non-REM sleep considered important for memory consolidation and feelings of restedness. The drug was reintroduced to clinical trials and performed exceptionally in human testing, showing comparable efficacy to the industry standard, Ambien, without causing the rebound insomnia that typically follows Ambien cessation. In rodents, gaboxadol could be administered repeatedly without the development of tolerance, and it did not interact synergistically with alcohol, as virtually all other hypnotics do. Because the average duration of slow-wave sleep decreases with age, the drug was found particularly effective in the elderly. Merck offered to pay Lundbeck $270 million for the rights to sell gaboxadol in the United States and predicted the drug would bring in $350 million in profits by 2009. It was during this frenzy of clinical and Big Pharma interest, with articles flooding the pages of scientific journals such as *SLEEP,* that I heard about gaboxadol and decided I had to try it.

By 2007 gaboxadol had entered phase 3 clinical trials and Lundbeck had established an office in Pennsylvania to oversee U.S. sales of the drug they hoped would usurp some of the $1.5 billion in sales boasted the previous year by Sanofi's Ambien. Then it happened again: Lundbeck announced that development would be discontinued, citing the findings of a study (the details of which have never been published) on a panel of drug abusers who experienced hallucinations and other psychiatric side effects at high doses. Merck's representatives, meanwhile, cited a lack of efficacy. It must be noted that this was a time of great sleep anxiety for the pharmaceutical industry. Starting in 2006, the media was flooded with bizarre reports of Ambien-induced delirium: Patrick Kennedy woke up in his somnambulistically crashed Mustang convertible; people discovered empty food containers in their beds, evidence of uncontrollable bouts of nocturnal binge eating; an Australian woman awoke with brush in hand to find she had repainted her front door; and a teenager reportedly stole his mother's credit card to purchase four alpacas he could neither afford nor care for. Tiger Woods's mistress Rachel Uchitel said he exploited the drug for its disinhibitory, aphrodisiacal properties, proudly declaring, "We have crazy Ambien sex."

Perhaps the seers at Merck predicted a similar fate for gaboxadol. The cardiotoxicity of the arthritis drug Vioxx had resulted, in 2004, in the biggest pharmaceutical recall since fen-phen and wound up costing the company billions in settlements; Merck was suddenly, understandably, less willing to compete against generic Ambien in the race to hypnotize America. The company's choice may have deprived millions of insomnia sufferers access to a safe and nonaddictive treatment, but it's best not to dwell on the counterfactual. Maybe Merck's prognostications were correct; maybe they saved us from a new generation of delirious gaboxadol habitués, wooden urine bowls in hand, ceremonially recycling the waters of life while the company's profits poured down the drain (like muscimol, gaboxadol is excreted almost entirely unchanged in the urine). Maybe insomniacs shrouded in animal skins would have swarmed pharmacies hoping to barter reindeer for prescriptions while beating drums to accelerate the FDA's approval of a generic gaboxadol formulation. No, Merck would not have that.

This is all to say that my hope of trying gaboxadol crumbled like an *Amanita muscaria* in the sun. The synthesis of gaboxadol is not so much difficult as it is tedious: Povl Krogsgaard-Larsen's original process starts with a commercially unavailable precursor and requires at least six synthetic steps before arriving at a product with abysmally low yields — the sort of drug that must be made industrially and with much optimization to be economically feasible. Conversely, Ambien can be prepared in a single-step, one-pot reaction with a 72 percent yield. The combination of practical unattainability and miraculous clinical results elevated gaboxadol to near mythic status among Pharma pipeline–savvy insomniacs and the hypnotic cognoscenti. Gaboxadol seemed exemplary of a pharmaceutical industry that would prefer to sell minimally effective drugs devoid of side effects than medicines which might possess a therapeutic effect but put the maker at risk of litigation.

And then, for all my searching, gaboxadol in the end found me: while looking for supplies in the catalogue of a small Copenhagen laboratory, I found gaboxadol for the astonishingly low price of twenty dollars a gram, a significant improvement over the $1,000 charged by the multinational chemicals supplier Sigma-Aldrich. Within a week I had a bag containing two grams of brilliant white powder, complete with 1H and 13C nuclear magnetic resonance spectra indicating its molecular structure.

I had read and reread the results of almost every published clinical trial and so wasted no time in weighing out a 20mg dose and dropping it into my mouth. Within fifteen minutes I began to feel the effects. There was no euphoria, no psychedelic ideation, and no command hallucinations (except, perhaps, "Lie down and go to sleep"). That night I fell asleep three hours before my usual four a.m. bedtime and enjoyed a profoundly restful, uninterrupted night of slumber, one that could not have been better had Hypnos himself come to tuck me in to his velvet bed in a cave surrounded by murmuring rivers of fermenting soporific herbs. This was not the black, concussed coma-sleep some hypnotics afford; rather, it felt like the effortless sleep experienced after a day of strong physical exertion. It felt like healthy sleep — true sleep.

The next night I increased the dose to 35mg sublingually, and it was then that gaboxadol's relationship to muscimol became manifest. In my darkened bedroom I could hear otherworldly music emanating from the motor of a box fan, the white-noise buzzing slowing, taking on the character of an electric viola, the room's various shadows animated by strange movements, as if cast by a flickering candle — but none of this proved distracting. Once again I fell into an all-consuming slumber. The following days I used it again, and again, and again, and again. And when I stopped taking it I was amazed to find there was indeed no withdrawal or discontinuation-related insomnia. Apparently the rumors were true: gaboxadol was the perfect hypnotic. I decided to send off a sample of the material to a toxicologist friend for gas chromatography–mass spectroscopy (GC–MS) analysis. When the results came back they were not consistent with gaboxadol, rather indicating the chemical ibotenic acid, a brainlesioning agent.

In life there are things that can serve to boost your self-esteem, such as a new romance or an unprompted compliment from a stranger, and there are things that do not boost your self-esteem, such as learning that you have spent the past two weeks repeatedly poisoning yourself with a high-potency brain-lesioning agent. The morning I read the results of the GC–MS analysis I didn't get out of bed, staying motionless for a long time thinking about how I would never be able to think again.

There was the possibility that assuming I had incurred irreversible brain damage was hypochondriacal. Like muscimol, ibotenic acid is an alkaloid present in the *A. muscaria* mushroom, yet none of the numerous *A. muscaria* poisonings in the toxicological literature suggested lasting cognitive dysfunction, and most studies on ibotenic acid–induced brain lesioning involved direct intracerebral injection.[2] Humans have experimentally consumed doses of pure ibotenic acid as high as 100mg without noted neurological aftereffects, but none of this changed the fact that there were more than forty scientific publications with the words "ibotenic acid" and "lesion" in their titles.

[2] Additionally, ibotenic acid has enjoyed some uses outside the arena of brain lesioning, most notably as an experimental seasoning. The scientist Tsunematsu Takemoto found ibotenic acid possesses the ability to enhance food flavor at a threshold one tenth that of MSG, characterizing the agent as having "mild, subtle, delicate taste and a good body, and the taste is a lingering one." Ibotenic acid's extreme umami intensity produced both vegetable and miso soups that were for 90 percent of tasters preferable to ibotenic acid–free control soups.

Perhaps one of the most frightening things about the human mind is how poorly it gauges its own functioning and, more specifically, detects its own deficits. Things quickly become complicated when you attempt to measure the performance of an instrument with the instrument being measured. In 1969, a Dutch psychiatrist named Herman Van Praag conducted a series of experiments on depressed patients with a new drug, 4-chloroamphetamine, which he found exerted a significant therapeutic effect and was tolerated excellently; not a single patient complained of side effects. Though Praag discontinued this work by the mid-'70s, 4-chloroamphetamine is still used widely today, not as an antidepressant but as a neurotoxin for selectively destroying serotonin-producing neurons in experimental animals. The point being that humans cannot necessarily feel changes in their own brains. With many disorders of the brain comes a commensurate inability to notice. The later stages of

Alzheimer's, for example, are in many people characterized by a denial of the disease entirely.

But I *could* feel the deficits: a reduction in working memory, impaired focus, decreased verbal fluency. I spent my subway rides deeply engaged in thoughts about metacognition and thoughts about thinking about metacognition, the Dunning–Kruger effect, anosognosia, and the distant hope of advancements in neural grafting. I became extremely uncomfortable with the word "lesion" and avoided it whenever possible, but whether I liked it or not, lesions were on my mind. It wasn't just that I was plagued by worry; the worry was also keeping me up at night, and I slowly became accustomed to watching the sun rise while internally debating how strong the lesioning capabilities of sublingually administered ibotenic acid could be relative to those observed with intracerebral injection.

That the sample would have been ibotenic acid, though, seemed very strange: most scientific suppliers sell ibotenic acid for a much higher price than gaboxadol; and it's an old saw that lesioning the brains of your customers with glutamatergic excitotoxins is bad for business. I began to wonder whether gaboxadol could behave like the structurally similar ibotenic acid when subjected to the high oven temperatures of GC–MS.[3] I brought the sample back to my friend's lab and we repeated the nuclear magnetic resonance analysis to check against both the vendor's spectra and a reference in the patent literature. Gaboxadol contains two important carbon atoms that distinguish its structure from that of ibotenic acid, and each of them is bound to two hydrogen atoms that produce a unique signal not present in ibotenic acid. When I saw the signal of these hydrogens I was overjoyed, experiencing the spontaneous neuroregeneration that would allow me to do things like write articles about the heartbreak of psychogenic brain damage.

[3] Why the original GC–MS analysis produced a spectrum so strongly aligned with the theoretical mass and fragments of ibotenic acid is still unclear. The low thermostability of ibotenic acid and gaboxadol necessitates derivatization of either compound before it can be subjected to the high temperatures of GC–MS, meaning that, paradoxically, even ibotenic acid would not produce the expected spectrum for ibotenic acid.

Since Merck's 2007 discontinuation, gaboxadol has been unsuccessfully tried as an adjunct to SSRI-based antidepressant therapy, but all subsequent analyses have further supported its efficacy as a hypnotic, particularly in the elderly. Most recently, gaboxadol allowed 101 test subjects to fall asleep and remain asleep while exposed to a recorded stream of continuous road-traffic noise. I keep my small amount of remaining gaboxadol in a vial as an analytic reference and a reminder of the nocebo effect's awesome power, and now make do with some warm chamomile tea, time-release melatonin, and the occasional wooden bowl of muscimol urine.