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ESSAY

How an opioid giant deployed a playbook for moulding doctors' minds

The opioid giant Mallinckrodt, selling more in the US than Purdue Pharma, was forced by the courts to publish more than 1.3 million internal documents. **Sergio Sismondo** and **Maud Bernisson** sift through nearly 900 contracts to reveal the tricks used to shape scientific and medical opinions

Sergio Sismondo,[1,2] Maud Bernisson[2]

Mallinckrodt may be the largest seller of prescription opioids in the US that has garnered the fewest headlines. With $18bn (£14.1bn; €16.6bn) in sales from 2006 to 2012 and nearly 40% of all opioid pills sold on the US market, it was the lead producer of prescription opioids during that time.[1 2] The more notorious Purdue Pharma ranked third. Mallinckrodt, with its baby blue 30 mg oxycodone tablets and various other opioids, paved a "blue highway" along the Appalachians to Florida.[3] These tablets were so popular that counterfeits in the same hue and with Mallinckrodt's "M30" marking—but containing fentanyl—are still sold on the street today.[4]

Mallinckrodt survives as a multimillion dollar corporation, despite settling with the US government for lax handling of its opioid supply and later being ordered to pay $1.7bn over accusations of misleading and deceptive marketing practices to boost opioid sales. It has twice filed for bankruptcy and has largely avoided paying,[5] but it did have to turn over 1.3 million internal documents, mostly from 2009 to 2017, which became public.

Mallinckrodt wasn't the first drug manufacturer forced by litigation into legal discovery, but unlike Purdue it didn't fight tooth and nail to keep its documents out of the public eye.[6] The *Washington Post*, which had an exclusive first look at the Mallinckrodt files in 2022, revealed that the company "cultivated a reliable stable of hundreds of doctors it could count on to write a steady stream of prescriptions for pain pills." A company spokesperson told the *Post* that it disagreed with the allegations despite "negotiating a comprehensive, complete and final settlement." Mallinckrodt didn't respond to our request for comment.

For those of us who study pharma influence, the document trove was an unprecedented window into the inner workings of how a corporation not just directly co-opts physicians to push pills but also seeks to increase sales by influencing medical science and opinion—an extensive marketing playbook that we call the ghost management of medicine.[7] The day after the documents' release, we started exploring them.

The documents outline a smorgasbord of tactics to achieve greater sales—from shaping the language of medicine through designing continuing medical education (CME) courses and recruiting physicians to serve as influencers, to planting articles in scientific journals. And all of this against the backdrop of an epidemic of addiction, in which the company's commercial rival Purdue was made to pay out hundreds of millions for fraudulent marketing.

Contracts to shape pain medicine

Contracts are especially telling because they reflect concrete efforts backed up by payments. We found 876 contracts for the development or circulation of medical information.[8] Together they reveal a carefully coordinated effort to shape medical attitudes to pain medicine: specifically, to frame extended release opioids such as Exalgo and Xartemis as trustworthy innovations, while portraying opioids in general as the right treatment for both acute and chronic pain.

In 2009 the US Food and Drug Administration began requiring opioid producers to develop and implement risk evaluation and mitigation strategies using educational programmes for healthcare providers, pharmacists, nurses, and sometimes patients and others.[9 10] At that time the addiction crisis in the US was raging: prescription opioid overdose deaths had more than quadrupled in the preceding decade.[11] Purdue had just settled charges of "fraudulent" marketing with a payout of $600m in 2007—at the time one of the largest in drug industry history. Headlines such as "Addiction by prescription" ran on covers of national magazines and newspapers and explained how some pain clinics and pharmacies had become "pill mills."[12]

While some doctors were still writing prescription after prescription—and Mallinckrodt was selling more than ever—other doctors were becoming cautious. As one sales representative reported back regarding "flattening" sales, doctors were concerned that Exalgo was "too powerful" and that "patients are experiencing withdrawal and it's being interpreted as an adverse event."

Drug companies have a long history of managing physicians' and public opinion by engineering buy-in from the top down, tapping physicians as key opinion leaders, designing research and ghostwriting medical journal articles, coordinating conference presentations, and even writing CME curriculums. As Mallinckrodt faced growing hesitancy among frontline prescribers, we found that the contracts showed how it employed each of those tactics as it sought to reframe concerns about addiction as a phobia and to muddle the very concept of dependence as "pseudoaddiction." It even went so far as casting opioids as preventive medicine for chronic pain. To many busy physicians, these

messages would have appeared as trustworthy scholarship and evidence based guidance.

We sought the reaction of long time observers of the drug industry. "This behaviour is disturbing but not surprising," says Robert Steinbrook, adjunct professor of internal medicine at Yale University and director of the Health Research Group of the advocacy organisation Public Citizen. "It's like they used every trick in the book."

"Opioid-phobia"

In response to the FDA's requirement that opioid manufacturers educate physicians about the risks and benefits of opioids, Mallinckrodt launched a CME programme named Remedies: Focus on Opioid Tolerance. Mallinckrodt initially spent about $2.5m on the CME, targeting 10 000 physicians, and then expanded and continued the programme to reach 88 316 prescribers by February 2017.

In a summary of the programme, a Mallinckrodt regulatory expert listed among its advantages: "education on higher doses of long acting opioids," "[enhancing] Mallinckrodt's reputation with key opinion leaders, patient advocacy groups, and medical specialty societies," and "[underscoring] Mallinckrodt's credibility with the FDA as a company that cares about . . . safe opioid prescribing." Art Morelli, Mallinckrodt's vice president of medical affairs at the time, said that key opinion leaders (KOLs) needed to be "involved in content to make it credible." One of the company's paid KOLs, Michael Brennan, a pain management physician in Bridgeport, Connecticut, was reported as listing "opioid-phobia" as one of the primary barriers to optimal pain management. The report went on to quote him as saying, "If REMS [risk evaluation and mitigation strategy] is proscriptive, we will see a significant reduction in what are considered optimum meds."

Mallinckrodt had revived the idea of physicians' "irrational and undocumented fear that appropriate use will lead patients to become addicts," as one 1985 journal article had defined "opiophobia."[13] The term was almost always used to downplay or dismiss physicians' and patients' concerns about addiction.

Charles Argoff was programme co-chair of Mallinckrodt's Remedies programme and also served as an educator. He came with an impressive résumé—he had written more than 130 papers and was on the editorial boards of *Pain Medicine News*, the *International Journal of Pain*, and the *Clinical Journal of Pain*. And from 2013 to 2022 he received around $200 000 a year from opioid manufacturers.[14,15] Argoff declined our request to comment.

Pseudoaddiction

Many of Mallinckrodt's key messages were to be found in Argoff's 2010 book *Defeat Chronic Pain Now!*, which the company actively promoted: at some of Mallinckrodt's CMEs, Argoff would do book signings. Among other things, the book discussed pseudoaddiction—the idea that a patient's need for higher doses (traditionally seen as developing tolerance of, or dependence on, a substance) was different from addiction. "Only rarely does opioid medication cause a true addiction when prescribed appropriately to a chronic pain patient who does not have a prior history of addiction," Argoff and his coauthor wrote.[16]

Concepts such as pseudoaddiction are helpful for framing expert opinions. Mallinckrodt arranged for a medical education and communication company called MedLogix to prepare slides for Lynn Webster, one of Mallinckrodt's KOLs, to deliver at a 2013 advisory board meeting. The slides carefully circumscribed and downplayed addiction: tolerance, physical dependence, and pseudoaddiction, they suggested, were easily confused with addiction; misuse, abuse, and overdose were conceptually distinct. This allowed the company to focus on its positive contributions: Mallinckrodt's long acting and extended release formulations, including its new oxycodone, were cast as "abuse-deterrent formulations" that had a "role in filling unmet needs in acute pain management."

Adriane Fugh-Berman, professor of pharmacology and physiology at Georgetown University in Washington, DC, has been researching the marketing tactics of the drug industry for 30 years. She says that "creating the term 'pseudoaddiction' and distorting the terms 'tolerance' and 'dependence' were strategies that distracted physicians from noticing their patients were addicted."

Many roles of KOLs

Key opinion leaders are central to the marketing playbook. They appear in articles, advisory boards, speaker programmes, and CMEs. From 2014 to 2019 Mallinckrodt provided grants of around $1m a year to the American College of Physicians and Pri-Med, a CME provider, to develop more risk evaluation and mitigation strategy initiatives. The grants funded five Mallinckrodt KOLs, including Argoff and another veteran of the Remedies CME, Bill McCarberg, to develop and teach a new programme on safe opioid prescribing.

Mallinckrodt's managers lauded Argoff's performances. In an email Morelli described Argoff as a "top, top KOL." Morelli went on to say, "I have worked with him at three pharma companies on various pain programs. He knows what we are trying to do and supports us."

KOLs would often be brought into the company's fold by invitations to serve on advisory boards. The term "advisory board," or "ad board," suggests that physicians will be in the role of advising pharma executives. More often, however, the guidance flows the other way.

For example, a 2014 advisory board in Orlando, Florida, focused on possible research plans. The organisers' summary of the event paid scant attention to gathering information, recording only one brief scientific or medical comment from each of five of the attendees. However, the summary did record attendees' very high scores for "meeting planning communications, hotel accommodations, travel arrangements, and quality of food and beverages." Mallinckrodt seems to have wanted to communicate information to the attendees and to cement relationships through hospitality.

The most common way that companies such as Mallinckrodt use KOLs is for speaker programmes, in which a KOL gives a presentation to a group of clinicians, assembled by a sales representative, often over a catered meal. In the US the programmes are typically treated by the FDA as marketing events, meaning that KOLs must use the slides and rough script given to them by the company, to avoid risks of off-label marketing.[7]

Speakers need training, of course, and this is often accomplished over long weekends in attractive locations, such as Orlando, Florida (home of the Walt Disney World Resort), where 70 physicians and their families attended a 2011 speaker training event for the newly launched Exalgo. Typically, so called medical education and communication companies develop the slides and run these training events. A 2011 contract with one such company, the Selva Group, involved creating four slide decks on a methadone product that Mallinckrodt was distributing. The contract specified that Selva would provide around 40 slides for each presentation and speaker

notes for all slides, which would be vetted by Mallinckrodt and a small number of KOLs to be chosen by the company.

Drug companies pay KOLs to read the slides, but the physicians understand that part of their responsibility is also to put on a good show. In 2010, after receiving a 71 slide programme for Exalgo, Steven Simon, a physician specialising in pain management and one of Mallinckrodt's KOLs, complained to the speaker bureau coordinator that "it will be difficult to hold the attendees' attention" and suggested that he would improvise with some "creative conversation." In 2012 a Kansas City based district sales manager raved that Simon was "the best Exalgo speaker I have heard" and that he "happens to be one of the largest if not the largest Exalgo [prescription] writer in the nation."

"Pain is a disease"

Another aspect of the ghost management of medicine is strategically charting out medical journal articles and abstracts that must be written so that KOLs have evidence they can point to in professional meetings. "Publication planning is a normal part of medical marketing," says Fugh-Berman, "and is extremely important to the manipulation of physicians' perceptions of both drugs and diseases."

Advisory boards and KOLs are often engaged in publication planning. At a June 2013 meeting in Dallas, Texas, Mallinckrodt convened 14 of its top KOLs for a wide ranging discussion aimed at developing scientific articles about "unmet needs in acute [pain] management." The group would brainstorm at least 12 rough concepts for articles, mostly review articles on subjects ranging from directions in acute pain management to the more controversial "risk factors for pain chronification" to one with the direct title, "The Time has Come: Pain is a Disease."

Alongside "pseudoaddiction," Mallinckrodt used the term "chronification" for the market friendly notion that untreated acute pain develops into chronic pain. That concept showed up in a review article that began as a 2013 contract with MedLogix. The article would look at risk factors for misuse, as well as the twin problem that "acute pain is commonly undertreated in a wide variety of populations." MedLogix would "research, draft, revise, submit, and coordinate authorship"—a classic case of ghostwriting.

The first author of the review article was among Mallinckrodt's most prolific physician KOLs: Lynn Webster, one of the founders of a specialised contract research organisation, Lifetree Clinical Research. There he led many studies of Mallinckrodt products, earning Lifetree millions of dollars in revenue. He also served as an author on manuscripts sponsored by the company and sat on multiple advisory boards. Later, in 2018-19, Webster garnered some $75 000 from Mallinckrodt in "general payments," according to CMS Open Payments, a federal transparency database.

Webster was no stranger to the problem of opioid misuse. A prominent pain specialist, he was coauthor of an "opioid risk tool" to assess patients' chances of misusing the drugs, a 10 item questionnaire widely used and often cited. In 2013 he was president of the American Academy of Pain Medicine. At a personal level, his own son had become addicted in the mid-2000s. In a recent memoir Webster described his deep anguish and the questions that his son's addiction had raised about his own practice. Ultimately, he focused blame on an interior "blueprint" made up of genetics, internal constitution, and perhaps family circumstances—not the availability of prescription drugs.[17] Webster, who didn't respond to our request for comment, continued to treat patients in pain with opioids.

When the review article, first raised in 2013, was published, it suggested that, relative to their immediate release cousins, extended release opioids (such as Exalgo) decreased the risk of misuse and that clinicians and payers should give them preference.[18] Then the idea of chronification neatly turned the tables on the problem: physicians can reduce the use and misuse of opioids by prescribing them promptly and effectively. "Efforts to prevent chronic pain may eliminate extended exposure to opioids, which could, in turn, minimize drug abuse," the article declared.

Stephen Butler, an anaesthesiologist at Uppsala University in Sweden, who has researched opioids and chronic pain, says that there is "almost no evidence from good research to support the claim that there is any preventive strategy in the treatment of acute pain that prevents the evolution to long term pain." However, he notes that "early cessation of opioids . . . will avoid opioid dependence."

Unfortunately, early cessation conflicted with Mallinckrodt's primary goal, captured by a sales manager's exhortation in a 2013 email to the reps under him: "You have only 1 responsibility, SELL BABY SELL!"[19] Despite the judgments against it and bankruptcy filings, Mallinckrodt continues to sell opioids today, with sales of some $262m in 2023, up 25% from the year before.

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1 Armstrong D, Ernsthausen J. Data touted by OxyContin maker to fight lawsuits doesn't tell the whole story. *ProPublica* 2019 Sep 9. https://www.propublica.org/article/data-touted-by-oxycontin-maker-to-fight-lawsuits-doesnt-tell-the-whole-story

2 Higham S, Horwitz S, Rich S. 76 billion opioid pills: newly released federal data unmasks the epidemic. *Washington Post* 2019 Jul 16. https://www.washingtonpost.com/investigations/76-billion-opioid-pills-newly-released-federal-data-unmasks-the-epidemic/2019/07/16/5f29fd62-a73e-11e9-86dd-d7f0e60391e9_story.html (Login needed)

3 Kornfield M, Higham S, Rich S. Inside the sales machine of the "kingpin" of opioid makers. *Washington Post* 2022 May 10. https://www.washingtonpost.com/investigations/interactive/2022/mallinckrodt-documents-doctors-sales/

4 Hayes S. The fatal "blues." *Law Enforcement Bull* 2023 Jun 6. https://leb.fbi.gov/articles/featured-articles/the-fatal-blues

5 State of California Department of Justice, Office of the Attorney General. National opioids settlements—information for California cities and counties. 2021. https://oag.ca.gov/opioids

6 Keefe PR. *Empire of pain: the secret history of the Sackler dynasty*. Knopf Doubleday Publishing Group, 2021. https://play.google.com/store/books/details?id=Qb4IEAAAQBAJ

7 Sismondo S. *Ghost-managed medicine: big pharma's invisible hands*. Mattering Press, 2018. https://play.google.com/store/books/details?id=7yU1zgEACAAJ

8 Bernisson M, Sismondo S. Promoting opioids, a story about how to influence medical science and opinions. *Front Med (Lausanne)* 2024;11:1327939. doi: 10.3389/fmed.2024.1327939. pmid: 38737766

9 US Food and Drug Administration. Timeline of selected FDA activities and significant events addressing substance use and overdose prevention. 2024. https://www.fda.gov/drugs/information-drug-class/timeline-selected-fda-activities-and-significant-events-addressing-substance-use-and-overdose

10 US Food and Drug Administration. What's in a REMS? 2023. https://www.fda.gov/drugs/risk-evaluation-and-mitigation-strategies-rems/whats-rems

11 National Institute on Drug Abuse. Drug overdose death rates. 2024. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates

12 Kluger J. The new drug crisis; addiction by prescription. *Time* 2010 Sep 13. https://time.com/archive/6597559/the-new-drug-crisis-addiction-by-prescription/

13 Morgan JP. American opiophobia: customary underutilization of opioid analgesics. *Adv Alcohol Subst Abuse* 1985;5:-73. doi: 10.1300/J251v05n01_11. pmid: 2870626

14 US Senate Homeland Security & Governmental Affairs Committee. Fueling an epidemic: exposing the financial ties between opioid manufacturers and third party advocacy groups (report 2). 2018. https://bit.ly/4aSIgOu

15 Gac BW, Yakubi H, Apollonio DE. Issues arising from the study design, conduct, and promotion of clinical trials funded by opioid manufacturers: a review of internal pharmaceutical industry documents. *Evid Policy* 2023;19:-53. https://bristoluniversitypressdigital.com/view/journals/evp/19/4/article-p536.xmldoi: 10.1332/174426421X16856230946027

16 Argoff C, Galer B. *Defeat Chronic Pain Now!: groundbreaking strategies for eliminating the pain of arthritis, back and neck conditions, migraines* . Fair Winds Press, 2010. https://play.google.com/store/books/details?id=VcSQGYKXWdYC

17 Webster LR. Two worlds collide: the opioid crisis at work and at home. Independently published, 2023. https://www.amazon.com/Two-Worlds-Collide-Opioid-Crisis/dp/B0CMSGLJ3N

18 Webster LR, Brennan MJ, Kwong LM, Levandowski R, Gudin JA. Opioid abuse-deterrent strategies: role of clinicians in acute pain management. *Postgrad Med* 2016;128:-84. doi: 10.1080/00325481.2016.1113841. pmid: 26631936

19 Klein DE, Mackenzie R, Hawkins B, Koon A. Inside “Operation Change Agent”: Mallinckrodt’s plan for capturing the opioid market. *J Health Polit Policy Law* 2024:11186127. doi: 10.1215/03616878-11186127. pmid: 38324355