Evidence & Policy • vol XX • no XX • 1–18 • © Policy Press 2023
Print ISSN 1744-2648 • Online ISSN 1744-2656 • https://doi.org/10.1332/174426421X16856230946027
Accepted for publication 01 June 2023 • First published online 22 June 2023

research article

Issues arising from the study design, conduct, and promotion of clinical trials funded by opioid manufacturers: a review of internal pharmaceutical industry documents

Brian W. Gac, brian.gac@ucsf.edu
Hanna Yakubi, hanna.yakubi@ucsf.edu
Dorie E. Apollonio, dorie.apollonio@ucsf.edu
University of California, San Francisco, USA

Background: From 1999 to 2021 opioid overdoses caused over one million deaths in the US. The pharmaceutical industry has been held legally responsible in some cases for overstating the benefits and understating the risks of opioid use, leading to overprescribing that contributed to these deaths.
Aims and objectives: In this study we describe issues with research funded by opioid manufacturers that was used to support increased opioid prescribing.
Methods: We analysed 503 internal industry documents from opioid manufacturers released from State of Oklahoma v. Purdue Pharma, LP, et al in January 2020.
Findings: Internal documents identified three research practices of concern – enriched enrollment, ghostwriting, and overstatement of research findings – that resulted in claims that opioids were safe, nonaddictive, and effective in treating pain. These claims were used to promote increased opioid use.
Discussion and conclusions: Research created by opioid manufacturers distorted the addictive potential of opioids using strategies that hid authorship and overstated findings. The claims were used in marketing and promotional materials to promote opioids as being safe and effective.

Key words analgesics • opioid • inappropriate prescribing • authorship • drug industry • policy

To cite this article: Gac, B., Yakubi, H. and Apollonio, D. (2023) Issues arising from the study design, conduct, and promotion of clinical trials funded by opioid manufacturers: a review of internal pharmaceutical industry documents, *Evidence & Policy*, XX(XX): 1–18, DOI: 10.1332/174426421X16856230946027

Background

Between 1999 and 2021 opioid overdoses caused over one million deaths in the United States with more than 80,000 occurring in 2021 alone (Anon, 2021; Spencer et al, 2022). The age-adjusted rate of drug overdose deaths increased almost five-fold from 6.8 per 100,000 standard population in 2001 to 32.4 in 2021 (Spencer et al, 2022).

In 2022 pharmaceutical manufacturer Johnson & Johnson (J&J) finalised $26 billion nationwide settlements along with three major pharmaceutical distributors over their

role in the opioid overdose epidemic in the largest collection of settlements up to that point (Mulvihill, 2022). Prior to this, in 2019, the Cleveland County District Court in Oklahoma ordered the company to pay a fine of $465 million for intentionally overstating the benefits and understating the risks of prescription opioids in the first trial against drug manufacturers for the damage caused by the opioid overdose epidemic in the US, which had claimed about 6,000 lives in Oklahoma from 2000 to the time of the trial (Hoffman, 2019; Dwyer and Fortier, 2019). The settlement was later overturned by the Oklahoma Supreme Court on the grounds that public nuisance law does not provide a remedy for the problem of opioid addiction in the state (Raymond, 2021).

As with other medications, opioid manufacturers like J&J sponsor clinical trials to generate scientific evidence that supports use of their products for approval to prescribe by the Food & Drug Administration (FDA) and in commercial materials to promote drug sales. Previous research has found industry sponsored research may use dubious research practices to generate findings that justify use (Bero, 2005; Bero, 2022). Three examples of such research practices include inappropriate use of enriched enrollment trial design, ghost authorship, and overstatement of research findings.

Enriched enrollment (or enriched enrollment randomised withdrawal) is a study design divided into two phases: an initial open label phase before moving to a second double-blind phase with only the participants who exhibit the desired response (Furlan et al, 2011; Campbell and King, 2017). For example, 1000 participants might be enrolled, of whom 300 report the desired response to the medication. Only those 300 participants would be randomised to treatment or control groups, ensuring that findings demonstrate the intended clinical effect. The stated purpose of the design is to identify and exclude patients who do not respond to or tolerate a medication (Furlan et al, 2011; Campbell and King, 2017). Supporters have argued this method makes it possible to detect drugs that work for only a subset of the population and reduces costs and patient exposure to placebo (Furlan et al, 2011; Campbell and King, 2017). However, this increased internal validity comes at the cost of potential unblinding – meaning that researchers are aware that participants in the second phase are known respondents, which can affect their interpretations – and reduced generalisability, because the participants in the study do not represent the general population (Furlan et al, 2011; Campbell and King, 2017). Although results apply only to known responders, pharmaceutical manufacturers have used them to pursue general approval even when studies showed intolerance or inadequate response (Furlan et al, 2011; Kaplan, 2013; Campbell and King, 2017). A systematic review of enriched and nonenriched trials of opioids found enriched enrollment studies also underestimated adverse effects (Furlan et al, 2011).

Ghostwriting is the practice of omitting someone who has made significant contributions to an article as an author and is typically used to obscure that person's employment by a sponsoring drug company and increase study credibility (Gøtzsche et al, 2007). One study found evidence of ghost authorship in 75% of industry-initiated trials, which increased to 91% when a person qualifying for authorship appeared in an acknowledgement (Gøtzsche et al, 2007). Previous research using internal pharmaceutical documents – which assessed clinical trials that sought to expand citalopram use to children – found that ghost authorship was used as a form of marketing (Jureidini et al, 2016).

Companies may also overstate previous research findings to justify further research, regulatory approval of a product or products, or other efforts to increase prescribing and sales. This may be done by the inappropriate generalisation of study results to a larger population or by the diminution of study limitations (Fihn, 2019). In 2007, Purdue Pharma pleaded guilty for misbranding their opioid product OxyContin by making claims understating the drug's risk of addiction that misrepresented the conclusions the FDA provided upon the product's approval (Meier, 2007).

Misrepresentation of research findings has also been used to justify further trials that lead to a drug's expanded indication, obscuring early studies with poorer study designs and diluting recommendations for caution in prescribing. For example, a clinical trial sponsored by the manufacturer of Celexa overstated research findings to encourage paediatric use of the medication, which resulted in criminal charges filed against the company and a $313 million settlement (Singer, 2010; Jureidini et al, 2016).

The contribution of these research practices to the approval and promotion of medications historically has been difficult to identify (Bero, 2003; Pimentel et al, 2016). Primary data underlying industry studies typically remain the intellectual property of the sponsoring companies and are protected by trade secrets law. However, opportunities for analysis arise when injured plaintiffs sue for damages because settlements may result in the release of confidential documents. Research on other industries has used these resources to identify changes in policy and clinical practice that protect public health (Bero, 2003).

The purpose of this study was to identify research practices used in clinical trials funded by opioid manufacturers that created the perception that opioids were safe, nonaddictive, and effective in treating pain. This research relied on previously confidential documents released in 2020 through an Oklahoma lawsuit against pharmaceutical companies that financially benefited from opioid overprescribing. To our knowledge, there has been no prior use of these documents to assess the research practices of opioid manufacturers. While there are multiple areas in which opioid manufacturers have been challenged regarding their practices (Becker and Fiellin, 2017), including direct to physician marketing (Eisenberg et al, 2020), financial support for patient advocacy groups (McCoy et al, 2018), and efforts to influence the development of clinical practice guidelines (Lin et al, 2017; Marks, 2020; Spithoff et al, 2020), we focused on this relatively novel area given that understanding research practices would be challenging without access to internal industry documents. We sought to characterise research practices used to create the perception that opioids were safe and effective, identifying three areas of concern: enriched enrollment, ghostwriting, and overstatement. Understanding how these practices were used to promote increased opioid prescribing may help better identify the use of comparable practices in the development and marketing of other drugs, particularly those with abuse potential.

Methods

This study relied on a retrospective qualitative review of industry documents released in State of Oklahoma vs. Purdue Pharma, L.P. et al. Since 2005, confidential documents made public in litigation against pharmaceutical companies have been collected in the Opioid Industry Documents Archive (OIDA) at the University of California San Francisco for storage in perpetuity (Department of Justice, 2004; University of

California San Francisco, nd). As of February 2023, OIDA hosted over 2.7 million documents. In January 2020, OIDA made available the first 503 documents that later became part of the larger OIDA, totaling over 62,000 pages, that were released as part of the Oklahoma litigation in a discrete collection named the Oklahoma Opioid Litigation Documents. These documents included clinical trial reports, witness declarations, internal corporate communications, and marketing strategies regarding opioids, and served as the primary data source for the study (University of California San Francisco, nd). The primary dataset was supplemented with the final judgement against defendant J&J written by District Judge Thad Balkman, which was intended to serve as a summary for the case and contextualise the trial for which the documents were submitted by defendants and the State as exhibits (State of Oklahoma vs. Purdue Pharma L.P. et al, 2019). Data analysis occurred before the final ruling for the case was overturned by the Oklahoma Supreme Court.

Key concepts were identified inductively by one author (BG), primarily from Judge Balkman's final judgement for the case and from an exhibit included in the Oklahoma Opioid Litigation Documents: a trial declaration from an industry-funded researcher, Russell K. Portenoy, MD (District Court of Cleveland County, 2010; State of Oklahoma vs. Purdue Pharma L.P. et al, 2019). Two authors (BG, HY) conducted the initial review. Unique identification codes assigned to each document by OIDA ensured every document was reviewed. Documents were excluded from analysis if they did not contain usable information due to redaction within the document prior to release, or when it was impossible to determine whether they were relevant with the available information (for example, logs tracking calls with unnamed providers described only by proprietary identification codes not released with the ruling). Documents identified as relevant were organised in a master file by key concept. The master file and supporting documents were then reviewed by all three authors (the codebook and description of each document's coding have been archived at the Open Science Foundation, DOI 10.17605/OSF.IO/GCKMB). If there was a question of document's relevance to this study or its categorisation, issues were discussed among all authors until consensus was reached. From the final list of documents relevant to the key concepts in this study, one author (BG) selected documents that illustrated the general and specific characteristics of research practices, comprised of legal rulings, government reports, correspondence, witness statements, clinical trial reports, and corporate communications. These documents were reviewed and discussed by the other authors (HY, DA) until a consensus was reached regarding final interpretation.

The authors of this paper have declared that research ethics approval was not required since the paper does not present or draw directly on findings from empirical research and only used publicly available documents as data.

Results

Before State of Oklahoma vs. Purdue Pharma, et al was overturned, Judge Thad Balkman found the defendant corporations overestimated the efficacy and underestimated the safety risks of opioids, leading physicians to prescribe more of these medications even when patients exhibited signs of addiction (State of Oklahoma vs. Purdue Pharma L.P. et al, 2019). We identified three research practices that were used to encourage increased prescribing: enriched enrollment, ghostwriting, and misinterpretation of research findings.

Enriched enrollment

In assigning responsibility to manufacturers, Judge Balkman pointed to three major studies: Simpson (Simpson et al, 1997), Allan (Allan et al, 2001), and Milligan (Milligan et al, 2001), that J&J funded and used 'to support misleading claims that downplay the risk of addiction and overstate the efficacy of opioids' (State of Oklahoma vs. Purdue Pharma L.P. et al, 2019). In 2004, J&J received a warning letter from the FDA Division of Drug Marketing, Advertising, and Communications (DDMAC) stating the effectiveness claims for Duragesic® (fentanyl transdermal system) could not be substantiated based on these studies, criticising their study designs, and indicating the company 'misbrand[ed] Duragesic in violation of the [Federal Food, Drug, and Cosmetic] Act [Section 502(a)] 21 U.S.C. § 352(a)' (Abrams et al, 2004). 'Janssen and [Johnson & Johnson Pharmaceutical Research and Development] respectfully disagree[d]' and 'provide[d] DDMAC with additional information to address the concerns raised in [DDMAC's] letter' (Burrus and Johnson & Johnson Pharmaceutical Research and Development, 2004) However, they discontinued the professional file card (promotional brochure) and all promotional materials containing the same or similar representations, totaling 62 items including the original file card in question (Burrus and Johnson & Johnson Pharmaceutical Research and Development, 2004).

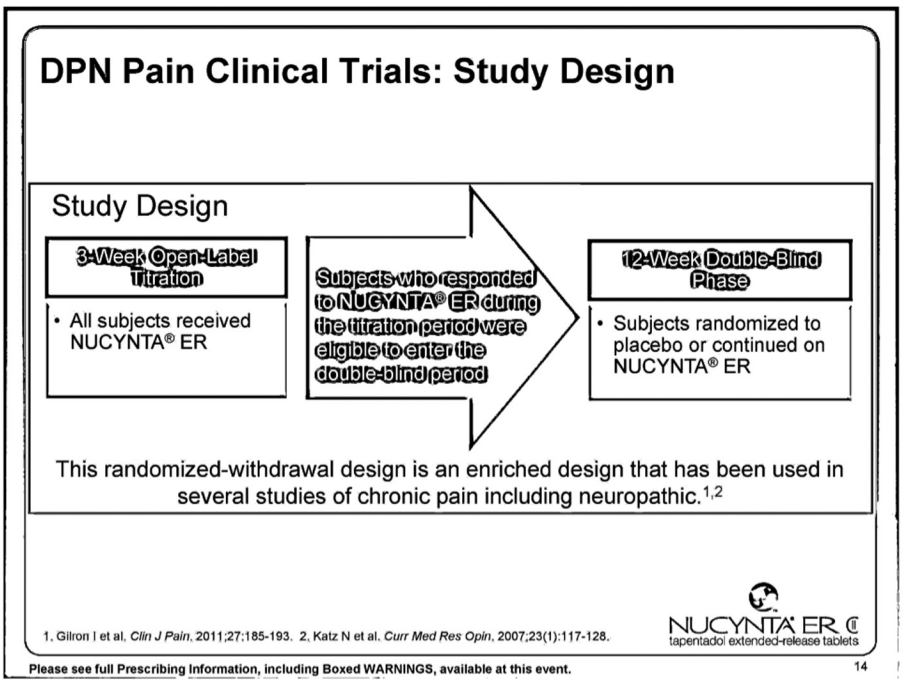
While these studies did not explicitly state that they used enriched enrollment, each incorporated elements intrinsic to the design. All three studies had inclusion criteria that called for continuous use of oral opioids for a minimum of six weeks (Allan et al, 2001; Milligan et al, 2001) or six months (Simpson et al, 1997) before enrollment. Each study excluded subjects with a history of substance abuse and two excluded patients without an adequate response to opioids (Simpson et al, 1997; Allan et al, 2001; Milligan et al, 2001). Patients in the Allan study 'had to have achieved moderate pain control with a stable dose of oral opioid for seven days before the trial. Exclusion criteria included pain not responding to opioids…' (Allan et al, 2001). The Milligan study required prior opioid treatment that 'must have provided at least moderate pain relief in a weekly assessment of pain control, and daily dosing must have been stable for at least 1 week preceding the trial' (Milligan, et al, 2001). While the Allan and Milligan studies claimed to exclude subjects who had recently participated in another clinical trial, the Milligan study included 103 patients from the Allan study (out of 532 total recruited subjects) (Allan et al, 2001; Milligan et al, 2001). Despite these limitations, J&J cited these studies in broad claims of effectiveness that the FDA later deemed had violated federal regulations (Intercontinental Chicago O'Hare Hotel & Interactive Forums Inc, 2019).

Janssen, a pharmaceutical company owned by J&J, explicitly stated it used enriched enrollment studies to market opioids. Following a report from the Institute of Medicine Committee on Advancing Pain Research, Care, and Education, Janssen held a Chronic Pain Advisory Board Meeting in 2011 'to obtain expert feedback and recommendations on current and future opportunities for clinical research… aimed at improving the benefit/risk balance associated with the use of opioid analgesics for chronic pain management' (Intercontinental Chicago O'Hare Hotel & Interactive Forums Inc, 2019). Janssen stated it 'intend[ed] to use this information to support the clinical and commercial development of Nucynta® ER [tapentadol] and its other analgesic drugs in development' with a specific objective to '[i]dentify clinical and educational programs to maximize the benefit

and minimize the risk of opioid therapy' (Intercontinental Chicago O'Hare Hotel & Interactive Forums Inc, 2019). In other words, Janssen sought out advice on how to conduct studies on their opioid products that would provide a clinical justification for efforts to convince prescribers opioids were safe and efficacious. While this practice is not unusual, using study designs like enriched enrollment that should not be generalised to support broad claims of safety and efficacy can lead to inappropriate prescribing of drugs with abuse potential.

In this meeting, discussion of enriched enrollment studies focused on their use to differentiate products from other opioids (Intercontinental Chicago O'Hare Hotel & Interactive Forums Inc, 2019), already a shift from the appropriate use for this study design, which is to identify patients who do not respond to or tolerate a specific medication and to establish dosing levels. By 2013, Janssen was using enriched enrollment studies to compare efficacy and safety of Nucynta to placebo for treatment of diabetic peripheral neuropathy (DPN) (Janssen Pharmaceutical, Inc, 2013). Describing the enriched enrollment design of a study it funded in a promotional educational activity (Figure 1), Janssen stated, 'NUCYNTA® ER Demonstrated Powerful Efficacy in DPN Pain[:] Results From Clinical Trials 1 [Schwartz et al.] and 2 [proprietary data cited]' (Janssen Pharmaceutical Inc, 2013). This statement did not include the study's stated limitations which resulted from the study design: homogeneity of the study population and the potential for unblinding (Schwartz et al, 2011). Additionally, it did not discuss the study's exclusion of patients with a history of alcohol and/or drug abuse (Janssen Pharmaceutical Inc, 2013; Schwartz et al, 2011).

Figure 1: Slide from Janssen promotional lecture for Nucynta® (tapentadol) and Nucynta® ER (tapentadol extended-release tablets) summarising enriched enrollment study design (Janssen Pharmaceutical Inc, 2013)



Ghostwriting

Studies used to support opioid prescribing also showed evidence of ghostwriting. In 2009, Johnson & Johnson's 'Tapentadol Team' detailed the progress of 12 manuscripts it was tracking for publication in academic journals (Anon, 2009). One entry titled 'State of the Art: Multimodal Therapy for Chronic Pain' stated the established author had 'disengaged from [the] project' with a listed 'Current Status' of 'Author confirmation' and 'Next [Step]' of 'Author approval of outline' (Anon, 2009). Seven of the twelve projects in the table indicated the company had designed the study, written the study, or both, before sending them to listed authors for review (Anon, 2009). The 'State of the Art' project illustrates the limited involvement that listed authors could have with projects Johnson & Johnson was tracking: entire outlines or drafts were prepared before the person to be listed as the primary author and most significant contributor to the project had been identified.

Another listed manuscript, labelled as authored by Charles Argoff, Professor of Neurology at Albany Medical College, had been extensively revised for content and sent to him for review (Figure 2) (Anon, 2009). Argoff received over $1.6 million from pharmaceutical manufacturers, a large majority from opioid manufacturers, for consulting fees and travel and lodging reimbursements between 2013 (the first year Center for Medicare Services began publishing industry contributions to physicians) and 2021 (Anon, 2023; US Centers for Medicare & Medicaid Services, 2023a; 2023b). In 2014, Argoff received at least $16,000 from Purdue Pharma, L.P. and at least $127,000 more from other opioid manufacturers (US Centers for Medicare & Medicaid Services, 2023a). That year, he was asked by Purdue representatives to contribute public comment for a press release related to FDA approval of Hysingla® ER (hydrocodone bitartrate) (Figure 3) (Heins and Purdue Pharma, 2014). While asking for 'your opinion, of course', the request also included the company's proposed talking points (Heins and Purdue Pharma, 2014). The final quote attributed to Argoff in the press release was written by James W. Heins, Senior Director of Public Affairs for Purdue Pharma, L.P (Figure 4) (Heins and Purdue Pharma, 2014).

A paper assessing the abuse potential of tapentadol (marketed as Nucynta by Janssen) by Dart et al also showed evidence of ghostwriting (Dart et al, 2012). Richard C. Dart, MD, PhD, was a 'physician specializing in emergency medicine and toxicology', who served as the Director of Rocky Mountain Poison & Drug Safety as of 2023 and received over $330,000 in general payments (which exclude research funding) from

Figure 2: Selections from a June 24, 2009 Janssen research publication project status table for tapentadol (Anon, 2009)

Tapentadol Team Status - 6/24/2009 - Acute Pain Publications

IN PROGRESS - 2008/2009 Acute Pain Publications

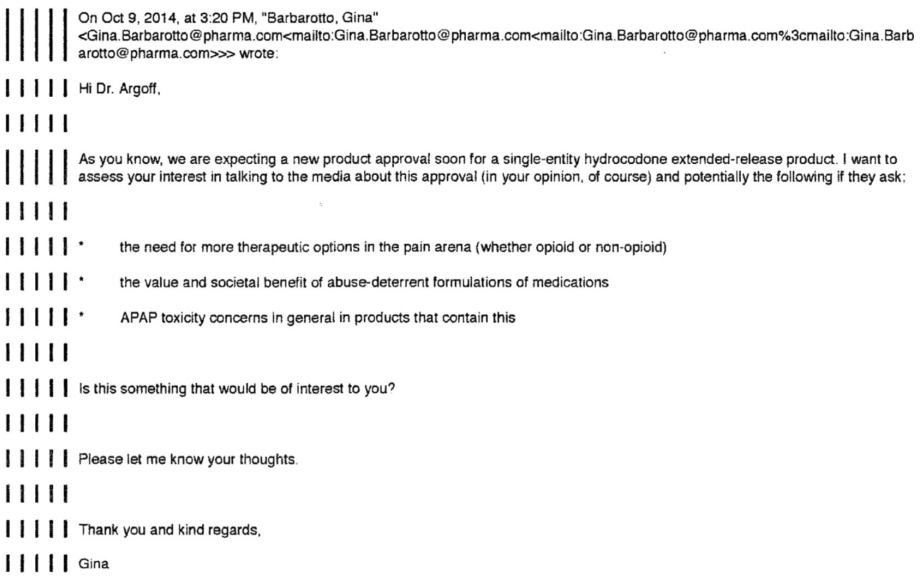
Project Title	Author	Journal	Past Steps	Current Status	Next Steps
Acute Publication #3 (Job # 01ORTPUB-09-03528): Pain pathways and the mechanisms of analgesia	Charles Argoff	*Journal of Family Practice*	• Conference call with Dr. Argoff 12/3 • Outline sent to Dr. Argoff for review 1/30 • Outline approved by Dr. Argoff 2/8 • Follow-up call with Author 2/25 • 1st draft sent to author 4/16 • TC with author 5/5 - approved draft with minor comments	• Revised draft with alternative journal target sent to Dr Argoff 6/19	• Editorial styling for journal

Tapentadol Team Status - 6/24/2009 - Chronic Pain Publications

IN PROGRESS - 2009 Chronic Pain Publications

Project Title	Author	Journal	Past Steps	Current Status	Next Steps
Chronic Publication #5 (01ORTPUB-09-03254): State of the Art: Multi-modal Therapy for Chronic Pain	TBC	*American Journal of Medicine (TBC)*	• Author call 5/13 • Discussion points sent to author 5/19 • Dr Gilron disengaged from project 6/12	• Author confirmation	• Author approval of outline • Begin 1st draft development

Figure 3: Request to Dr Charles Argoff from Purdue Pharma for a quote to include in a Hysingla ER (hydrocodone bitartrate) press release (Heins and Purdue Pharma, 2014)



On Oct 9, 2014, at 3:20 PM, "Barbarotto, Gina" <Gina.Barbarotto@pharma.com<mailto:Gina.Barbarotto@pharma.com<mailto:Gina.Barbarotto@pharma.com%3cmailto:Gina.Barbarotto@pharma.com>>> wrote:

Hi Dr. Argoff,

As you know, we are expecting a new product approval soon for a single-entity hydrocodone extended-release product. I want to assess your interest in talking to the media about this approval (in your opinion, of course) and potentially the following if they ask:

* the need for more therapeutic options in the pain arena (whether opioid or non-opioid)
* the value and societal benefit of abuse-deterrent formulations of medications
* APAP toxicity concerns in general in products that contain this

Is this something that would be of interest to you?

Please let me know your thoughts.

Thank you and kind regards,

Gina

opioid manufacturers between 2013 and 2021 (US Centers for Medicare & Medicaid Services, 2023b; Anon, nd). Second author Theodore Cicero, PhD was a professor of psychiatry at Washington University School of Medicine in St Louis who helped develop post marketing drug abuse surveillance programs and had not received any reported pharmaceutical payments as of 2023 (US Centers for Medicare & Medicaid Services, 2023c). Cicero expressed concern in an email to Ashley O'Dunne, PhD on 6 February, 2012 that began, 'I am having trouble with the manuscript that I think all authors need to be involved in (can you send to them): [sic]' (Dart et al, 2012) He continued:

> I worry about the dual mechanism explanation for dependence as I have for years about its role in tramadol misuse. Specifically you have to argue that tramadol/tapentadol produce euphoria whereas the norepi reuptake acts as an anti-euphoric agent. I don't know of any evidence to support that, but I can live with the people at J&J and Edgar Adams believing this to be true. At least the paper does say it is a hypothesis, but it is weak in my view [sic]. (Dart et al, 2012)

According to her LinkedIn profile, O'Dunne was employed in February 2012 as the Senior Director of Medical Writing for MedErgy HealthGroup, a 'healthcare communications consulting company' owned by Cello Health PLC (Anon, nd; Anon, 2011). O'Dunne was not listed as an author on the publication nor was she acknowledged as a contributor, although another MedErgy employee, Cherie Koch, PhD, was acknowledged for editorial support (Dart et al, 2012). A response from author Dart to all other listed authors on the publication, plus O'Dunne, Felice Sweeney (another MedErgy employee), and three employees of Ortho-McNeil Janssen concurred:

Figure 4: Final quote from Dr Charles Argoff for Hysingla ER (hydrocodone bitartrate) press release drafted by Purdue Pharma Senior Director of Public Affairs James Heins (Heins and Purdue Pharma, 2014)

On Oct 23, 2014, at 6:00 PM, "Charles Argoff" <pargoff@optonline.net<mailto:pargoff@optonline.net>> wrote:

Excellent
Well done
I have no suggested changes

Sent from my iPhone

On Oct 23, 2014, at 4:04 PM, "Heins, James" <James.Heins@pharma.com<mailto:James.Heins@pharma.com>> wrote:

Here is the press release and the note I sent yesterday. I apologize if you didn't receive it. Can you please confirm receipt?

Original message

Dear Dr. Argoff,

Attached and below in this email for your review is a confidential draft press release announcing the anticipated FDA approval of Hysingla ER. As discussed, we are hoping that you would agree to provide a comment for the press release. We have included a suggested comment for you that reflects some of the key points we discussed this morning. Can you please take a look and let us know what you think?

"The burden of chronic pain and the abuse of prescription medications are both pressing societal problems," said Charles E. Argoff, MD, Professor of Neurology at Albany Medical College and Director of the Comprehensive Pain Center at Albany Medical Center in New York. "Opioids are an essential tool in our arsenal of medical treatments options, so greater availability and use of opioid analgesics with abuse-deterrent properties has the potential to help alleviate suffering among people with chronic pain while reducing the abuse of these medications. Furthermore, this product gives treatment providers the option to use hydrocodone without acetaminophen if they are concerned that their patients may be taking too much acetaminophen on a daily basis."

Thank you so much for your time and assistance. We look forward to hearing from you.

James W. Heins

Senior Director, Public Affairs

Purdue Pharma L.P.

Tel: (203) 588-8069

Fax: (203) 588-6223

Cell: (203) 856-2121

www.purduepharma.com<http://www.purduepharma.com>

www.rxsafetymatters.org<http://www.rxsafetymatters.org>



> I don't completely get it either. I can live with it, but I didn't want to expand on the concept because this paper is epidemiological and doesn't really address that question well. The statement is clearly hypothetical and I would suggest we leave as is and see how reviewers react. (Dart et al, 2012)

The published article retained the claim that, 'Tapentadol's inhibition of norepinephrine reuptake has been shown to have an opioid-sparing effect, such that tapentadol produces potent analgesia despite having a lower affinity for the μ-opioid receptor than other analgesics that act primarily on this receptor (e.g., oxycodone and hydrocodone). In addition, studies in animals and humans have shown drugs with noradrenergic mechanisms of action may reduce the addiction-related effects of opioids and other drugs of abuse' (Dart et al, 2012). However the studies cited

to support these claims were limited to investigation of the noradrenergic effects of fluoxetine and venlafaxine (Dart et al, 2012). In other words, Johnson & Johnson included a claim implying their opioid product tapentadol might have a lower risk of causing addiction because of a particular aspect of its mechanism of action, but supported this claim only with studies on medications in a different class that did not carry a risk of dependency or addiction. Despite this claim being unstudied in drugs with abuse potential and, in their own words, weak and hypothetical, Drs Dart and Cicero agreed to include it at the request of the sponsoring company.

Overstatement of research findings

Marketing and promotion using existing research

Russell K. Portenoy MD had been researching pain since the 1980s, including an extensive bibliography assessing opioids for pain management; many of those studies were funded by opioid manufacturers (District Court of Cleveland County, 2010). In exchange for his dismissal as a defendant in the Oklahoma case Portenoy submitted a declaration detailing his relationship with the defendant opioid manufacturers and his professional opinion regarding decisions that he and other relevant parties made that contributed to the opioid epidemic (District Court of Cleveland County, 2010). Until the early 1990s use of opioids in clinical practice had mostly been limited to treating acute pain in inpatient settings or treating chronic malignant or end-of-life pain given concerns about abuse and addiction (District Court of Cleveland County, 2010). Portenoy's work served as part of the foundation of opioid research used to justify expanded use of opioids for non-cancer pain patients.

Portenoy stated, 'it is clear that drug company research grants provided to academicians for studies of approved drugs generally fund studies that aim to identify or confirm benefits that would be helpful in marketing' (District Court of Cleveland County, 2010). He continued:

> [M]y teaching and writing at various times emphasized the potential benefits… and deemphasized the risks that are always present when opioids are administered…. [D]rug companies used my work to provide content and expert support for a strongly positive message about opioids…. The effect was to promote opioid therapy to prescribers. (District Court of Cleveland County, 2010)

Misrepresenting existing research findings to claim opioids were not addictive

Portenoy was an early advocate for expanded use of opioids for pain and authored a paper in 1996 titled 'Opioid Therapy for Chronic Nonmalignant Pain: A Review of the Critical Issues' that concluded:

> The available data do not support doctrinaire pronouncements about the role of opioid therapy for nonmalignant pain…. Controlled clinical trials of long-term opioid therapy are needed, but the lack of these trials should not exclude empirical treatment when medical judgement supports it and therapy is undertaken with appropriate monitoring. If

> treatment is offered, documentation in the medical record of pain, side effects, functional status, and drug-related behaviors must be ongoing and explicit. (Portenoy, 1996)

However, this paper was summarised in the study by Allan et al as, 'A review of retrospective and survey data confirms the efficacy of opioids in the treatment of chronic non-cancer pain and found that fears of addiction were not justified' (Allan et al, 2001). Milligan et al similarly cited a Portenoy review that claimed, 'The available evidence suggests that there is probably a selected subpopulation of patients with chronic nonmalignant pain who may obtain sustained partial analgesia without the development of toxicity or the psychologic and behavioral characteristics of addiction' (Portenoy, 1990), with the summary, 'Persistent, albeit largely unfounded, fears about the risks of addiction, toxicity, physical dependence and tolerance have led to the rejection of opioid analgesia for chronic pain resulting from noncancer disease' (Milligan et al, 2001).

Johnson & Johnson 'distributed visual aids citing the Allan, Simpson and Milligan studies thousands of times', and 'their sales representatives us[ed these]… studies over 1,000 times in sales visits to Oklahoma doctors between 1998 and 2004' (State of Oklahoma vs. Purdue Pharma L.P. et al, 2019). Two physicians testified, 'the multi-faceted marketing misinformation campaign by the opioid industry… influenced their practices and caused them to liberally and aggressively write opioid prescriptions they would never write today', and, 'the increase in opioid overdose deaths and opioid addiction treatment admissions in Oklahoma was caused by the oversupply of opioids through increased opioid sales and overprescribing since the late 1990s' (State of Oklahoma vs. Purdue Pharma L.P. et al, 2019). Oklahoma Department of Mental Health and Substance Abuse Services Commissioner Terri White found, 'The increase in opioid addiction and overdose deaths following the parallel increase in opioid sales in Oklahoma was not a coincidence; these variables were "causally linked"' (State of Oklahoma vs. Purdue Pharma L.P. et al, 2019).

The three clinical trials were cited in guidelines and almost 100 other studies. As of July 2020, Simpson had been cited 15 times, Allan 66 times, and Milligan 15 times in PubMed; Milligan was summarised with overly broad statements of efficacy and/or safety in at least nine of the 15 citations.

Discussion

Previous studies have identified extensive efforts to influence research by pharmaceutical manufacturers, some related to study design, which were being used to increase prescribing and sales (Landefeld and Steinman, 2009; Jureidini et al, 2016). Lawsuits against opioid manufacturers in the US have primarily focused on other areas of concern, including direct to physician marketing, financial support to patient advocacy groups, and attempts to modify clinical practice guidelines (Becker and Fiellin, 2017; Lin et al, 2017; McCoy et al, 2018; Eisenberg et al, 2020; Marks, 2020; Spithoff et al, 2020). The findings in this study extend those from previous studies and examine these subjects in a manner not addressed in litigation. Our access to a unique dataset containing documents released by opioid manufacturers in the course of legal discovery made it possible to focus on a relatively understudied question: efforts to influence the conduct and promotion of clinical trials. These findings indicate

opioid manufacturers used enriched enrollment, ghostwriting, and overstatement of results to generate claims of safety and efficacy that were used as justification for increased prescribing.

These three research practices – enriched enrollment, ghostwriting, and overstatement – made it possible to present increased opioid prescribing as safe and efficacious. Studies using enriched enrollment are limited by reduced generalisability, and prior research has found they underestimate adverse drug effects (Furlan et al, 2011; Campbell and King, 2017). We identified multiple examples of opioid trials that used enriched enrollment, which were leveraged to support clinical use of opioids; in at least one case, this was later found to be in violation of federal misbranding law. Upon receipt of a warning from the FDA about this practice, the company formally challenged the interpretation although it discontinued the promotions nonetheless. Documents released in discovery also indicate efforts to ghostwrite scientific manuscripts, which were discussed in internal communications relating to over half a dozen studies of opioids. It appears the resulting papers were designed and drafted by sponsoring companies and sent to listed authors, identified later, for review. The contributions made by the writers hired by the sponsoring company were not named in the manuscript, even though in at least one case the final listed authors deferred to the judgment of writers hired by the company when they had scientific reservations. Studies based on enriched enrollment and that were initially ghostwritten were later summarised in terms that promoted increased opioid use, despite written findings in the manuscripts themselves that were more cautious. These summaries of research used in advertisements were the crux of the Oklahoma verdict and appear to have been disseminated into practice guidelines and used to justify further clinical research.

Lawsuits against companies and individuals involved in the opioid epidemic remained ongoing as of 2023 with mixed outcomes. At the time of the 2019 ruling in Oklahoma, Johnson & Johnson lawyers stated, 'Janssen did not cause the opioid crisis in Oklahoma, and neither the facts nor the law support this outcome', and that the company has, 'many strong grounds for appeal and we intend to pursue those vigorously' (Hoffman, 2019). In 2021, the Oklahoma Supreme Court overturned the judgement on the grounds that, 'public nuisance claims [are allowed] to address discrete, localized problems, not policy problems' (Mann, 2021). Multiple state and federal opioid cases remain pending in other states and, in 2022, San Francisco received a settlement against opioid manufacturers Allergan and Teva on the grounds that their corporate practices fueled opioid addiction and overdoses, and won a trial against Walgreens for substantially contributing to the opioid crisis by failing to stop fills of suspicious prescriptions (City Attorney of San Francisco, 2022. Some individuals who previously supported expanded opioid use have expressed culpability. A 2012 Wall Street Journal profile of Russell Portenoy reports him as saying, "Clearly, if I had an inkling of what I know now then, I wouldn't have spoken in the way that I spoke. It was clearly the wrong thing to do" (McGreal, 2019). Portenoy made similar statements in the declaration he gave during State of Oklahoma vs. Purdue Pharma L.P., et al.

Our study has limitations. Documents used in the analysis were made available in a judgement by the State of Oklahoma, meaning only documents stipulated in the decision were released. Although this particular case was overturned, that decision does not substantially affect the documents produced in the case. Additional documents relevant to the development, production, marketing, and distribution of opioids from each of the defendant corporations may not have been made public, and non-written

communications were not included. Some documents were presentation aids presented without context; as a result, they may not have been distributed outside the company or potentially not used at all. Finally, the conclusions of this study are only relevant to the companies and opioid products discussed and cannot necessarily be applied to other companies or products. Despite these limitations, the findings are relevant to a large body of academic and clinical research that is still referenced and used in practice, and they suggest caution in consideration of research related to pharmaceuticals created by manufacturers that have comparable incentives.

Conclusions

To our knowledge, this study is the first investigation of efforts to generate research findings that supported increased opioid prescribing, a major contributor to the US opioid epidemic. The findings suggest that companies used specific study designs, ghostwriting, and overstatement of study findings in the conduct and promotion of clinical trials involving opioids. Previous research has identified issues related to study conduct for other medications, including widespread ghostwriting in clinical trials supported by pharmaceutical companies (Jureidini et al, 2016; Fihn, 2019). Although US regulators contemporaneously identified at least one case where a company misrepresented research findings, which resulted in an FDA warning letter, these letters are typically insufficient to change behaviour (Nguyen et al, 2020), and the other issues related to study design, conduct, and promotion identified in this research remained undiscovered prior to litigation. The findings suggest that preventing inappropriate marketing of medications may require increased federal regulation of clinical trials and promotional material supplied to prescribers, and increased transparency requirements by journals regarding the identification of authors and design and reporting of findings from clinical trials. In 1997, the US Congress first began requiring registration of clinical trials, which was implemented in 2000 and reduced the likelihood of suppressing findings from industry-funded studies that did not support use of medications. This type of regulation could be expanded to regulate or increase reporting of study designs. Medical journals might also revisit policies addressing research funded by industry; there is historical precedent for such actions in efforts to limit publication of research funded by the tobacco industry (Rabe et al, 2012; Godlee et al, 2013). Similarly, journals now nearly universally require reporting of ethical approval to conduct research, a practice that has reduced misuse of protected health information. The findings also suggest the importance of continued release of industry documents released through legal discovery to identify potential issues involving pharmaceutical industry research, building on past research related to tobacco and food, and which could in the future extend to other potential substances of abuse such as alcohol and cannabis.

Funding

This work was supported by National Institute on Drug Abuse #046051 (Apollonio) and a UCSF School of Pharmacy Pathway Project Grant (Gac, Yakubi). The funders had no role in the design or conduct of the study.

Acknowledgements

The authors acknowledge Rachel Taketa for her assistance in searching for documents.

Declarations

Ethics approval and consent to participate: the authors of this paper have declared that research ethics approval was not required since the paper does not present or draw directly on data/findings from empirical research.

Availability of data and materials

The publicly available dataset supporting the conclusions of this article is available at https://www.industrydocuments.ucsf.edu/opioids/. Unique persistent identifiers are provided for each cited document in the list of references.The codebook and description of each document's coding have been archived at the Open Science Foundation, DOI 10.17605/OSF.IO/GCKMB.

Authors' contributions

BG and HY searched the documents and completed preliminary coding; additional searches and coding reviews were completed by DA. BG, HY, and DA worked together to design the study, interpret the results, and revise the manuscript. BG drafted the manuscript. All authors have read and approved the manuscript.

Conflict of interest

The authors declare that there is no conflict of interest.

References

Abrams, T.W. and Food and Drug Administration, Department of Health and Human Services (2004) Warning letter regarding NDA #19–813 duragesic (fentanyl transdermal system), s.l., Oklahoma Opioid Litigation Documents. Nix, Patterson and Roach, L.L.P. https://www.industrydocuments.ucsf.edu/docs/hggg0230.

Allan, L., Hays, H., Jensen, N.H., de Waroux, B.L., Bolt, M., Donald, R. and Kalso, E. (2001) Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain, s.l: Oklahoma Opioid Litigation Documents, Nix, Patterson and Roach, L.L.P., *BMJ*, 322(7295): 1154–58, doi: 10.1136/bmj.322.7295.1154.

Anon (2009) Tapentadol team status - 6/24/2009 - acute pain publications, s.l.:Oklahoma Opioid Litigation Documents. Nix, Patterson and Roach, L.L.P. https://www.industrydocuments.ucsf.edu/docs/jlgg0230.

Anon (2011) Acquisition of MedErgy, https://cellohealthplc.com/acquisition-of-medergy.

Anon (2021) *Wide-Ranging Online Data for Epidemiologic Research (WONDER)*, Atlanta, GA: CDC, National Center for Health Statistics.

Anon (2023) Theodore cicero, https://psychiatry.wustl.edu/people/theodore-cicero-phd/.

Anon (nd) Ashley O'Dunne, https://www.linkedin.com/in/ashley-o-dunne-b48a2019/.

Anon (nd) Richard dart, https://www.linkedin.com/in/richard-dart-8854318/.

Becker, W.C. and Fiellin, D.A. (2017) Limited evidence, faulty reasoning, and potential for a global opioid crisis, *BMJ*, 358: j3115, doi: 10.1136/bmj.j3115.

Bero, L. (2003) Implications of the tobacco industry documents for public health and policy, *Annual Review of Public Health*, 24: 267–88, doi: 10.1146/annurev.publhealth.24.100901.140813.

Bero, L.A. (2005) Tobacco industry manipulation of research, *Public Health Reports*, 120(2): 200–08, www.jstor.org/stable/20056773. doi: 10.1177/003335490512000215

Bero, L.A. (2022) Stamp out fake clinical data by working together, *Nature*, 601(7892): 167, doi: 10.1038/d41586-022-00025-6.

Burrus, J.K. and Johnson & Johnson Pharmaceutical Research and Development (2004) *Duragesic Warning Letter Response*, Oklahoma Opioid Litigation Documents, Nix, Patterson and Roach, L.L.P., https://www.industrydocuments.ucsf.edu/docs/tpfg0230.

Campbell, J. and King, N.B. (2017) 'Unsettling circularity': clinical trial enrichment and the evidentiary politics of chronic pain, *BioSocieties*, 12: 191–216, doi: 10.1057/biosoc.2016.7.

City Attorney of San Francisco (2022) City attorney announces $54 Million settlement with opioid defendants Allergan and Teva, https://www.sfcityattorney.org/2022/07/12/city-attorney-announces-54-million-settlement-with-opioid-defendants-allergan-and-teva/.

Dart, R., Vorsanger, G.J. and Cecero, T. (2012) RE: Conference Call Availability FW, 2012 February 11, Oklahoma Opioid Litigation Documents. Nix, Patterson and Roach, L.L.P, https://www.industrydocuments.ucsf.edu/docs/xhhg0230.

Dart, R.C., Cicero, T.J., Surratt, H.L., Rosenblum, A., Bartelson, B.B. and Adams, E.H. (2012) Assessment of the abuse of tapentadol immediate release: the first 24 months, *Journal of Opioid Management*, 8(6): 395–402, doi: 10.5055/jom.2012.0139.

Department of Justice (2004) Warner-Lambert to pay $430 million to resolve criminal & civil health care liability relating to off-label promotion, https://www.justice.gov/archive/opa/pr/2004/May/04_civ_322.htm.

District Court of Cleveland County, State of Oklahoma (2010) Declaration of Russell K Portenoy, MD in State of Oklahoma v Purdue Pharma LP, *et al.*, s.l.:Oklahoma Opioid Litigation Documents. Nix, Patterson and Roach, L.L.P. https://www.industrydocuments.ucsf.edu/docs/nshg0230.

Dwyer, C. and Fortier, J. (2019) Oklahoma judge shaves $107 million off, 15 November, *NPR*, https://www.npr.org/2019/11/15/779439374/oklahoma-judge-shaves-107-million-off-opioid-decision-against-johnson-johnson.

Eisenberg, M.D., Stone, E.M., Pittell, H. and McGinty, E.E. (2020) The impact of academic medical center policies restricting direct-to-physician marketing on opioid prescribing, *Health Affairs (Millwood)*, 39(6): 1002–10, doi: 10.1377/hlthaff.2019.01289.

Fihn, S.D. (2019) Combating misrepresentation of research findings, *JAMA Network Open*, 2(5): e192553, doi: 10.1001/jamanetworkopen.2019.2553.

Furlan, A.D., Chaparro, L.E., Irvin, E. and Mailis-Gagnon, A. (2011) A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain, *Pain Research and Management*, 16(5): 337–51, doi: 10.1155/2011/465281.

Godlee, F., Malone, R., Timmis, A., Otto, C., Bush, A., Pavord, I. et al. (2013) Journal policy on research funded by the tobacco industry, *BMJ*, 347: f5193, doi: 10.1136/bmj.f5193.

Gøtzsche, P.C., Hróbjartsson, A., Johansen, H.K., Haahr, M.T., Altman, D.G. and Chan, A-W. (2007) Ghost authorship in industry-initiated randomised trials, *PLoS Med*, 4(1): e19, doi: 10.1371/journal.pmed.0040019.

Heins, J. and Purdue Pharma (2014) Greetings and Questions, s.l.: Oklahoma Opioid Litigation Documents. Nix, Patterson and Roach, L.L.P. https://www.industrydocuments.ucsf.edu/docs/thgg0230.

Hoffman, J. (2019) Johnson & Johnson ordered to pay $572 million in landmark opioid trial, 26 August, *New York Times*, https://www.nytimes.com/2019/08/26/health/oklahoma-opioids-johnson-and-johnson.html.

Intercontinental Chicago O'Hare Hotel & Interactive Forums Inc (2019) Benefit/risk assessment of opioid therapy for chronic pain advisory board meeting, s.l.: Oklahoma Opioid Litigation Documents. Nix, Patterson and Roach, L.L.P. https://www.industrydocuments.ucsf.edu/docs/thgg0230.

Janssen Pharmaceutical, Inc (2013) Powerful chronic and acute pain management - Nucynta ER, s.l.: Oklahoma Opioid Litigation Documents. Nix, Patterson and Roach, L.L.P. https://www.industrydocuments.ucsf.edu/docs/pnfg0230.

Jureidini, J.N., Amsterdam, J.D. and McHenry, L.B. (2016) The citalopram CIT-MD-18 pediatric depression trial: deconstruction of medical ghostwriting, data mischaracterization and academic malfeasance, *International Journal of Risk & Safety in Medicine*, 28(1): 33–43, doi: 10.3233/JRS-160671.

Kaplan, R. (2013) Reports: emails show alleged pay-to-play between drug companies, FDA, 7 October, *CBS News*, https://www.cbsnews.com/news/reports-emails-show-alleged-pay-to-play-between-drug-companies-fda/.

Landefeld, C.S. and Steinman, M.A. (2009) The neurontin legacy: marketing through misinformation and manipulation, *New England Journal of Medicine*, 360(2): 103–6, doi: 10.1056/NEJMp0808659.

Lin, D.H., Lucas, E., Murimi, I.B., Kolodny, A. and Alexander, G.C. (2017) Financial conflicts of interest and the Center for Disease Control and Prevention's 2016 guideline for prescribing opioids for chronic pain, *JAMA Internal Medicine*, 177(3): 427–28, doi: 10.1001/jamainternmed.2016.8471.

Mann, B. (2021) Oklahoma's supreme court tossed out a landmark $465 million opioid ruling, 9 November, *NPR*, https://www.npr.org/2021/11/09/1054000996/oklahoma-supreme-court-465-million-opioid-ruling.

Marks, J.H. (2020) Lessons from corporate influence in the opioid epidemic: toward a norm of separation, *Journal of Bioethical Inquiry*, 17(2): 173–89, doi: 10.1007/s11673-020-09982-x.

McCoy, M.S., Pagán, O., Donohoe, G., Kanter, G.P. and Litman, R.S. (2018) Conflicts of interest of public speakers at meetings of the Anesthetic and Analgesic Drug Products Advisory Committee, *JAMA Internal Medicine*, 178(7): 996–97, doi: 10.1001/jamainternmed.2018.1325.

McGreal, C. (2019) Doctor who was paid by Purdue to push opioids to testify against drugmaker, 10 April, *Guardian*, https://www.theguardian.com/us-news/2019/apr/10/purdue-opioids-crisis-doctor-testify-against-drugmaker.

Meier, B. (2007) In guilty plea, oxycontin maker to pay $600 Million, 10 May, *New York Times*, https://www.nytimes.com/2007/05/10/business/11drug-web.html.

Milligan, K., Lanteri-Minet, M., Borchert, K., Helmers, H., Donald, R., Kress, H.G., Adriaensen, H., Moulin, D., Järvimäki, V. and Haazen, L. (2001) Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain, s.l.: Oklahoma Opioid Litigation Documents. Nix, Patterson and Roach, L.L.P., *Journal of Pain*, 2*(4):* 197–204, doi: 10.1054/jpai.2001.25352.

Mulvihill, G. (2022) J&J, distributors finalize $26B landmark opioid settlement, https://apnews.com/article/coronavirus-pandemic-business-health-opioids-camden-dec0982c4c40ad08b2b30b725471e000.

Nguyen, H., Dennehy, C.E. and Tsourounis, C. (2020) Violation of US regulations regarding online marketing and sale of e-cigarettes: FDA warnings and retailer responses, *BMJ Tobacco Control*, 29: e4–e9, https://tobaccocontrol.bmj.com/content/29/e1/e4.info.

Pimentel, C.B., Donovan, J.L., Field, T.S., Gurwitz, J.H., Harrold, L.R., Kanaan, A.O., Lemay, C.A., Mazor, K.M., Tjia, J. and Briesacher, B.A. (2016) Use of atypical antipsychotics in nursing homes and pharmaceutical marketing, *Journal of the American Geriatric Society*, 63(2): 297–301, doi: 10.1111/jgs.13180.

Portenoy, R.K. (1990) Chronic opioid therapy in nonmalignant pain, *Journal of Pain and Symptom Management*, 5(Suppl 1): S46-62, https://pubmed.ncbi.nlm.nih.gov/1969892/. doi: 10.1016/0885-3924(90)90047-N

Portenoy, R.K. (1996) Opioid therapy for chronic nonmalignant pain: a review of the critical issues, *Journal of Pain and Symptom Management*, 11(4): 203–17, doi: 10.1016/0885-3924(95)00187-5.

Rabe, K.F., Gratziou, C., Ward, B. and Berteletti, F. (2012) Towards a total ban on links with the tobacco industry: new rules for the ERS, *European Respiratory Journal*, 40(4): 809–10, https://www.ers-education.org/lr/show-details/?idP=123520. doi: 10.1183/09031936.00117012

Raymond, N. (2021) Oklahoma court overturns $465 mln opioid judgement against J&J, 9 November, *Reuters*, https://www.reuters.com/business/oklahoma-court-overturns-465-million-opioid-award-against-johnson-johnson-2021-11-09/.

Schwartz, S., Etropolski, M., Shapiro, D.Y., Okamoto, A., Lange, R., Haeussler, J. and Rauschkolb, C. (2011) Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial, *Current Medical Research and Opinion*, 27(1): 151–62, doi: 10.1185/03007995.2010.537589.

Simpson, R.K. Jr, Edmondson, E.A., Constant, C.F. and Collier, C. (1997) Transdermal fentanyl as treatment for chronic low back pain, s.l.: Oklahoma Opioid Litigation Documents, Nix, Patterson and Roach, L.L.P., *Journal of Pain and Symptom Management*, 14(4): 218–24, doi: 10.1016/s0885-3924(97)00183-8.

Singer, N. (2010) Forest, maker of celexa, settles marketing claims, 15 September, *New York Times*, https://www.nytimes.com/2010/09/16/health/16drug.html.

Spencer, M.R.M., Miniño, A.M.M. and Warner, M.P. (2022) Drug overdose deaths in the United States, 2001–2021, *NCHS Data Brief*, 457, https://www.cdc.gov/nchs/products/databriefs/db457.htm.

Spithoff, S., Leece, P., Sullivan, F., Persaud, N., Belesiotis, P. and Steiner, L. (2020) Drivers of the opioid crisis: an appraisal of financial conflicts of interest in clinical practice guideline panels at the peak of opioid prescribing, *PLoS One*, 15(1): e0227045, doi: 10.1371/journal.pone.0227045.

State of Oklahoma vs. Purdue Pharma, L.P. et al. (2019) https://www.networkforphl.org/resources/state-of-oklahoma-ex-rel-hunter-v-purdue-pharma-l-p-et-al/#:~:text=Aug.,a%20low%20risk%20for%20abuse.

University of California San Francisco (n.d.) Oklahoma opioid litigation documents, s.l.: s.n, https://www.industrydocuments.ucsf.edu/opioids.

University of California San Francisco (n.d.) Opioid industry document archive, s.l.: s.n.. https://www.industrydocuments.ucsf.edu/opioids/
US Centers for Medicare & Medicaid Services (2023a) Open payments data: charles e argoff - entity profile page, https://openpaymentsdata.cms.gov/physician/93628.
US Centers for Medicare & Medicaid Services (2023b) Open payments data: richard c dart - entity profile page, https://openpaymentsdata.cms.gov/physician/204780.
US Centers for Medicare & Medicaid Services (2023c) Open payments, https://www.cms.gov/openpayments.