BMJ Open

Marketing opioids to children and women: A content analysis of internal industry documents

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052636
Article Type:	Original research
Date Submitted by the Author:	21-Apr-2021
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Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PAEDIATRICS, QUALITATIVE RESEARCH, PUBLIC HEALTH, PAIN MANAGEMENT

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Title: Marketing opioids to children and women: A content analysis of internal industry documents

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Word count: 249 abstract/ 4137 manuscript

Number of tables: 0

Number of figures: 3

Number of references: 84

Number of supplementary files: 0

ABSTRACT

Objective: Identify advertising strategies used to market opioids to women and children

Design: Qualitative content analysis of internal pharmaceutical industry documents

Setting: United States

Participants: Women and children targeted by opioid advertising in 1999-2016

Primary and secondary outcome measures: Advertising campaigns, industry executive statements regarding marketing goals

Results: We examined documents released in *State of Oklahoma v. Johnson & Johnson (2019)* to identify marketing strategies and campaigns developed by opioid manufacturers directed at children and women. We also reviewed public records, including websites developed by manufacturers and their allies, to confirm that marketing campaigns proposed and reported in the documents were launched. We found that opioid manufacturers explicitly targeted children and women by recruiting role models including coaches and school nurses, developing unbranded initiatives that encouraged adolescents to reach out to providers for pain care medications, and making emotional appeals to women that suggested that opioid use would reduce health risks from untreated pain.

Conclusions: Our analysis found that despite efforts to limit marketing to populations at risk, including children, through restrictions on direct marketing of addictive medications, opioid manufacturers were able to sidestep these restrictions by development indirect marketing campaigns. These campaigns were promoted as public health initiatives, rather than advertising, despite the fact that they were explicitly designed to increase sales of opioids to children and women. We conclude that existing regulations on pharmaceutical advertising were insufficient to prevent targeted marketing of opioids to children and women, which appear to have contributed to increased use and overdoses.

Keywords: Analgesics, Opioid; Advertising; Drug Industry; Public Policy

ARTICLE SUMMARY

Strengths and limitations of this study

- A major strength of this study is that to our knowledge, it represents one of the first attempts to use internal industry documents drawn from lawsuits against opioid manufacturers to understand industry marketing, and constitutes the first description of opioid industry advertising directed at children, adolescents, and women.
- Our review on internal industry documents demonstrates that pharmaceutical companies explicitly sought to increase the use of opioids by children and women, through indirect marketing to potential users and by promoting opioid use in these groups to policymakers. Over the same time period there were significant increases in opioid use, poisonings, and related mortality in these populations.
- The findings are limited by the fact that documents released during legal discovery are incomplete and may exclude relevant material; in addition, these findings may not be generalizable to other companies not named in the settlement agreement.

INTRODUCTION

Between 2000 and 2017, prescription opioid overdoses were estimated to cause the death of 165,000 people in the United States (1). In 2018 roughly 70% of all drug overdose deaths involved opioids and mortality rates from synthetic opioids increased by 10% (2). A 2013 systematic review reported that between 21% and 29% of opioid users report misuse and 8% to 12% advance to addiction (3). Eighty percent of people who used heroin in the U.S. from 2002-2011 had a previous history of opioid use, further highlighting the danger of widespread opioid prescribing (4). Sixty-five percent of opioid prescriptions are held by women (5) and their use has led to negative health consequences during pregnancy; the incidence of neonatal abstinence syndrome (NAS) increased five-fold from 2004 to 2014 in the United States, with the incidence of maternal opioid use disorder rising by a similar rate (6, 7). Parental opioid prescriptions are strongly associated with overdoses among children ages 0-5 years (8), particularly prescriptions held by mothers (9). However research on the risks of opioids has paid relatively limited attention to children (10-12), despite the fact that by 2015 one-fourth of US high school seniors reported using opioids (13, 14). Younger children also use opioids; in one study of children ages 2-17 enrolled in Medicaid in Tennessee from 1999-2014, 15% had filled an opioid prescription annually (15). Among those prescribed opioids for pain, prescriptions were frequently given for conditions that were not severe, one in every 2611 prescriptions was associated with an emergency department visit, hospitalization, or death, and 89% of those adverse events were related to therapeutic use (15, 16). Pediatric hospitalizations for opioid poisonings doubled between 1997 and 2012 (10), representing over a quarter of all opioid poisonings as of 2018 (17), and mortality rates from pediatric opioid exposures nearly tripled from 1999 and 2016 (11). As with adults, opioid misuse among adolescents typically follows medical use by prescription (13, 16).

On June 30, 2017, the state of Oklahoma brought a lawsuit against Johnson & Johnson, Purdue Pharma, and 11 other pharmaceutical manufacturers, claiming that they overestimated the efficacy and underestimated the safety risks of opioids and encouraged physicians to prescribe more of these medications, even when patients exhibited signs of addiction (18). In 2019 these manufacturers were fined $465 million for intentionally overstating the clinical benefit and minimizing the addictive potential of opioids (19, 20), and since then additional litigation has led to fines of over $355 million (21). The Oklahoma verdict specifically referenced issues with unbranded campaigns, a form of direct-to-consumer marketing that highlights disease awareness and the need to seek medical care. Direct-to-consumer advertising has been found to misinform patients about disease causes and prevalence, overemphasize drug benefits, sensationalize natural or trivial conditions, and lead to inappropriate prescribing (22). These advertisements have a more pronounced effect in people with lower incomes and education levels, and among women (23), who are already prescribed more medications and often experience higher rates of harmful side effects (23). A specific type of direct-to-consumer advertising, unbranded campaigns, is are used to develop positive perceptions about medications, however because unbranded campaigns do not reference a specific brand or medication they are not subject to FDA regulations that require a "fair balance" of both positive and negative information in advertising (24). As a result they can lead to inappropriate medication use, unreasonable patient expectations, and strained patient-doctor relationships (25). By encouraging patients to seek prescriptions, they can also increase sales for manufacturers (26, 27).

Studying industry marketing may be challenging in part due to difficulties in collecting data, however research on other industries has addressed this limitation by reviewing internal documents released in litigation (28, 29). Although industry documents are often first reported on in the popular media, past document-based research has identified ways that industries seek to influence

consumers, clinicians, and researchers to increase sales and profits (28). Studies using internal industry documents have found that other industries, such as tobacco and sugar companies, have marketed directly to vulnerable groups, including children (30-32) and women (33), among others (34-36). Children are particularly susceptible to predatory marketing tactics (37), which in the case of tobacco included tailored slogans and emotional appeals (38), misrepresentation of the potential for addiction (35), and sponsorship of popular brands and events (34). Prior research on opioid industry marketing has primarily focused on efforts by manufacturers to influence physicians (39-41), with little or no study of how the industry efforts to reach patient groups that have been disproportionately affected by the opioid epidemic. The extent of opioid industry marketing is an area of concern given increasing mortality attributed to opioid use. In this study we reviewed and analyzed internal industry documents released in the State of Oklahoma lawsuit to identify strategies used to market opioids to children and women. We hypothesized that like the tobacco and food industries, opioid manufacturers advertised directly to these groups in order to increase opioid use.

METHODS

Our study relied on a retrospective qualitative content analysis of pharmaceutical industry documents. Since 2005, internal documents released during lawsuits against pharmaceutical companies have been stored in the Drug Industry Document Archive (DIDA) at the University of California, San Francisco. In January 2020, DIDA released 503 documents totaling 62,703 pages drawn from the State of Oklahoma lawsuit brought against 13 opioid manufacturers including Purdue Pharma, Johnson & Johnson, Teva, Cephalon, Janssen, Ortho-McNeil-Janssen, Allergan, Watson, and Actavis (18, 42). Documents produced in the lawsuit included reports of relevant clinical trials, witness declarations, internal corporate communications, and marketing strategy

outlines regarding opioids through 2017. The 503 documents constituting the Oklahoma Opioid Litigation Document Collection were the primary database for the study.

Two authors (HY, BG) independently reviewed all 503 documents and created a master file with key quotes, figures, and concepts. To ensure every document was examined, each author who assisted in the initial review (HY, BG) individually checked each of the 503 documents' unique identification codes to ensure it was represented in one or more categories in the master document shared by all authors. The authors then reviewed the master file and used grounded theory, an inductive methodology that uses source material to identify hypotheses and that has previously been used in the analysis of pharmaceutical industry documents (43), to categorize evidence based on general themes related to industry misconduct. When multiple documents made similar claims or presented similar ideas, they were categorized together. If there was question of a document's relevance to the study or its categorization, it was discussed by all three authors until consensus was reached. Documents were excluded if they did not contain information due to redaction prior to release or the inability to identify whether they were relevant (e.g., logs tracking calls with unnamed providers described only by proprietary identification codes not released by the ruling). The industry's targeted marketing to groups that had been disproportionately affected by the opioid epidemic was independently identified by all authors as a unique category for coding.

After this initial review, one investigator (HY) synthesized notes from the master file to create a secondary list of documents related to the industry's targeting of these populations, defined as patients with psychosocial characteristics that may make them more vulnerable to pharmaceutical industry marketing and that include, but are not limited to, populations that were historically exploited by the tobacco industry (35, 36, 44, 45). Targeting was defined as any explicit reference to

business, marketing, outreach, or advertising strategies that focused on increasing opioid sales or creating favorable perceptions of opioid products among these groups.

Finally, the same investigator (HY), conducted a qualitative review of each entry in the secondary list to identify documents that explicitly referred to either children or women. Following this review, all authors generated a list of relevant search terms, including "adolescent", "school", "coaches", "sports", "pregnancy", "RSD", and "fibromyalgia". Two authors (HY, BG) searched these terms against the secondary document list, the master file, and the initial DIDA archive of all 503 documents to ensure all relevant entries were included. From this final list of relevant documents, one author (HY) selected those that illustrated general and specific characteristics of the opioid industry's marketing to children and women, which focused on unbranded campaigns and efforts to influence policymakers. These documents were reviewed and discussed by the other authors (BG and DA) until a consensus was reached regarding final interpretation.

To triangulate and verify these findings, one author (DA) checked the Internet Archive "Wayback Machine" (https://archive.org/web/) to track changes in industry-sponsored websites for unbranded campaigns identified in the documents. Another (HY) searched Dollars for Docs from ProPublica (https://projects.propublica.org/docdollars/) and Open Secrets (https://opensecrets.org) for payments made from pharmaceutical companies to physicians and policymakers named in the documents.

Patient and public involvement: No patient involved.

RESULTS

We reviewed industry strategies to market opioids to two groups: children (including adolescents) and women (including pregnant women). For each of these groups, the following results first review corporate marketing plans, and assess how they were implemented using advocacy to policymakers and unbranded campaigns.

Opioid industry targeting of children

Corporate strategic planning

In 2003, Janssen (the pharmaceutical division of Johnson & Johnson) generated an internal summary of their Duragesic® (fentanyl patch) brand that targeted young patients as a source of franchise expansion. Analysis of the marketplace for Duragesic listed "pediatric exclusivity" as a growth opportunity and indicated that a "pediatric extension request" was submitted to the FDA as part of an initiative to "continue development of products to maximize the pain franchise." (46)

Janssen's focus on young patients was not limited to their Duragesic brand. In an October 2011 meeting of the Imagine the Possibilities Pain Coalition, a group of professionals within Janssen who aimed to "create a broad-based community in the field of Pain Management," repeatedly identified youth as a desired target (47). The Coalition's Media Outreach team was tasked with targeting three separate groups: "youth, military veterans, public" and sought to "destigmatize pain." (47) The team targeted children as young as elementary school in an initiative to "reach early" and designed a "practical message" of "pain is your body telling you something is important" to be delivered "via respected channels, e.g., coaches." (47) A slide from the presentation is shown in Figure 1.

Figure 1 here

In a May 2012 meeting, the Coalition's Public Policy/Advocacy team, with the stated goal of "chang[ing] the conversation about pain," (47) also identified adolescents as a target audience. Like the Media Outreach team, the Public Policy/Advocacy team proposed emphasizing the role of pain in "sports and activities" with the tagline "LESSONS LEARNED – HEALTH MATTERS [emphasis in original]." (48)

Advocacy to policymakers

One of the leaders of the Public Policy/Advocacy team, Bob Twillman, had historically worked closely with pharmaceutical companies to advocate opioid-friendly policy positions. In 2012, Twillman led a task force development a "Pain Care Forum" to create and urge CDC approval of "Clinical guidelines for the use of Chronic Opioid Therapy in Chronic Non-Cancer Pain" (49) and in 2013, Twillman spoke at a FDA public hearing to argue that the reclassification of hydrocodone products from Schedule III to Schedule II would be too costly (50). The Pain Care Forum was a coalition of pharmaceutical companies and advocacy organizations that aimed to be the "voice on pain care issues in Washington," (51) and in 2010, was compromised of 60 organizations including Johnson and Johnson, Cephalon, Purdue, Pfizer, Allergan, American Pain Foundation, American Academy of Pain Management, and American Pharmacists Association (52). The executive committee was compromised of industry leaders from Purdue Pharma and Ligand Pharmaceuticals, as well as leaders from American Pain Foundation and National Hospice and Palliative Care Organization (52, 53). In a 2008 email from Howard R. Udell, Executive Vice President and Chief Legal Officer at Purdue Pharma, to Burt Rosen, Vice President of Government Affairs at Purdue Pharma, Udell noted that "The PCF [Pain Care Forum] has become 'a force' to be courted by members of Congress." (54)

In June 2006, the American Pain Foundation and the Pain Care Forum presented a briefing on the "Epidemic of Pain in America" to members of Congress on Capitol Hill (55). The presentation was in cooperation with Representative Mike Rogers, who had received over $600,000 in contributions from the pharmaceutical industry from 1995 to 2015 (56). Supporting material from the Epidemic of Pain in American briefing showed that the Pain Care Forum advocated for pain treatment in young patients. The Forum emphasized that "pain affects people at all stages of life – including infants, children, young adults, and the elderly." (55)

Research!America, an advocacy organization that promotes medical research, included a flyer in the briefing noting, "as many as 20 percent of children experience chronic pain." (55) Research!America was extensively involved with the pharmaceutical and opioid industry; a November 2008 internal memo from the Pain Care Forum showed that Research!America was actively "looking for industry financial (and planning) support" for a 2009 Pain Summit (49), and an internal email from Jon Sackler of Purdue indicated that Research!America had a long term relationship with the Sackler family and until February 2018 named their national leadership award the "R&BS [Raymond and Beverley Sackler] award." (57)

Unbranded campaigns

The companies named in the Oklahoma lawsuit also created unbranded campaigns to target adolescents. In June 2007, an Ortho-McNeil internal presentation titled "Non-Branded Promotions" indicated that it sought to partner with advocacy groups in unbranded campaigns to "establish instant credibility," "develop good will," and "alleviate regulatory anxiety." (58) A 2008 strategy document for the marketing of Janssen's Nucynta® (tapentadol) showed that the goal of direct-to-patient unbranded campaigns was "to increase patient origination." (59)

A separate 2008 Janssen internal presentation titled "Pain Non-Branded Campaign Market Research" described an unbranded initiative with the outward-facing message of bringing awareness to physicians about undertreated acute pain, but indicated that the expected impact was "PCPs [primary care providers] stat[ing] that they will be more aggressive in their treatment and use more opioids." (60) This unbranded initiative focused on the negative consequences of undertreated acute pain and emphasized multi-pathway pain treatment in order to encourage physicians to adopt a "more aggressive approach to treating (stronger dosing and meds)." (60) The campaign also attempted to address physician concerns about addiction by "refocusing them from addiction to side effect concerns." (60) The marketing research concluded with the identification of "the elderly, younger patients, post-operative and post-trauma patients" as target groups (60).

Two specific unbranded campaigns by Janssen centered on young patients. In 2008, Janssen partnered with the National Association of School Nurses to launch *Smart Moves, Smart Choices*, a program that proposed bringing awareness to prescription drug abuse among teenagers (61). However, internal Janssen documents classified *Smart Moves, Smart Choices* as an unbranded campaign (62). *Smart Moves, Smart Choices* was also included as part of Janssen's "Pain Franchise" public relations program and for their opioid product Nucynta (63), specifically as part of a larger strategic approach to "redirect dialogue from *drug control* to *controlling pain* [emphasis in original]" (64) and to "educate/influence to maintain physician/patient access." (63) At the end of 2020, *Smart Moves, Smart Choices* still existed as an outreach program run by the National Association of School Nurses, but Janssen was no longer listed as a partner or sponsor (65); screenshots from the program website are shown in Figure 2.

Figure 2 here

In December 2011, Janssen partnered with the American Chronic Pain Association (ACPA) to launch a separate unbranded campaign, *Growing Pains*. Robyn Kohn, Director of Medical Education at Janssen, noted this was a "significant contribution to the understanding of pain among the child and adolescent populations." (66) The ACPA described *Growing Pains* as a "a new social networking site for young people with pain" and allowed children as young as 13 years old to become members (67). This unbranded campaign encouraged adolescent patients to seek help for pain and provided information on how to talk to health care providers (68); a screen shot is shown in Figure 3. At the end of 2020 *Growing Pains* was still an active website listing funding by Janssen.

Figure 3 here

Opioid industry targeting of women

Corporate strategic planning

In a presentation to increase its European sales after 2001, Johnson & Johnson emphasized that one of its "major franchises" was "women's health." (69) In 2012, Janssen (its pharmaceutical subsidiary) expanded its marketing to women with a new "Mainstream Media Pitch." (70) In 2013, Teva created an "Advocacy Mapping" plan to "understand potential alliances and detractors… to engage and/or minimize them" which specifically noted potential allies that focused on women's health (71).

Advocacy to policymakers

The Pain Care Forum developed by multiple opioid manufacturers also advocated for opioid use by women. Documents from the Pain Care Forum's June 2006 briefing with lawmakers, described above, indicated it sought to establish a perceived need for painkillers among women. While describing the demographics of pain, the Forum specified "women's pain reports are taken

less seriously than men's" and "women receive less aggressive treatment than men for their pain."(55)

As part of their message that chronic undertreated pain disproportionately affects women, the Pain Care Forum shared stories of women suffering from unresolved chronic pain due to reflex sympathetic dystrophy (RSD), which it spotlighted as a pain condition that affected women more than men (55). Documents used as supporting material from the Pain Care Forum briefing showed a pattern of using personal anecdotes about RSD to warn of the disastrous effects of untreated chronic pain among women. One story focused on Barbara, who suffered from RSD, and warned "when the pain rises up, I think it is not really worth living." (55) The story featured Barbara's female friend who "probably had RSD" and "eventually committed suicide." (55) Another story focused on Alexandra, a sixteen-year-old woman suffering from RSD since the age of ten, who grieved the loss of her childhood due to untreated chronic pain and noted that her senior year had been spent "tak[ing] more medications than my grandparents" and spending time in the hospital "just wishing to walk." (55) Although the Pain Care Forum claimed that pain stories like Alexandra's are "told 50 million times," (55) there was no accompanying context: RSD is a rare disease and likely not representative of how most women experience pain or their resulting levels of disability (72, 73).

The same briefing included a 2006 article from *The Washington Post* which focused on physician Howard Heit. It highlighted his decision to prescribe Oxycontin® to his pregnant daughter-in-law and that her infant did not experience withdrawal symptoms, implying that opioid use could be safe for pregnant women and their newborns (55). The article noted, "she [Heit's daughter-in-law] knew she could never get through the pregnancy without the medication [Oxycontin]." (55) At the time of the article's publication, the risk of neonatal abstinence syndrome in infants exposed *in utero* to opioids was known and characterized (74, 75). The article failed to

mention that in 2004 Dr. Heit had provided consulting services promoting Actiq®, a fentanyl transmucosal lozenge sold by Cephalon.(76) Dr. Heit continued to consult for Cephalon and Johnson & Johnson in 2011 (77, 78).

A separate *New York Times* article titled "When it Comes to Severe Pain, Doctors Still Have Much to Learn" was also included in the supporting material for the briefing and focused on "clueless or unnecessarily cautious" doctors and their reluctance to prescribe opioids (55). The article included a quote from a 1995 entry into *The Journal of the American Medical Association*: "Bringing about significant change may depend on empowering patients to demand adequate pain treatment. This empowerment will not come easily, especially if opioids must be used for pain relief and the pain is of nonmalignant origin." (55)

Unbranded campaigns

In keeping with the theme of patient empowerment, the American Pain Foundation brainstormed techniques to target women for a fibromyalgia disease awareness campaign funded by a $10,000 check from Pfizer in July 2007 (55). The notes claimed that the "empowerment angle can be used with any program [emphasis in original]" and that the disease awareness program aimed to "create patient demand for proper pain diagnosis and treatment." (55) The Foundation planned to use "viral tactics/word of mouth education (sic)" by "let[ting] women educate women in their natural setting (e.g., Tupperware parties, garden groups, e-cards)." (55) The Foundation also proposed to share this outreach message via communication channels such as "women's books" and "the National Women's Health Resource Center." (55)

In 2012, Janssen targeted women as part of their public relation program for their pain franchise and marketing of its opioid product Nucynta in a similar fashion. Janssen's pitch stated,

"Women are feeling the pain, study says—what every woman needs to know," and the message was to be targeted to "women's books" among other advertising venues (63).

DISCUSSION

This study of internal opioid industry documents detailed how opioids were marketed to children and women at the beginning of the 21st century through targeted advocacy directed to policymakers and using unbranded campaigns intended to increase demand for opioids among prospective users. It builds on previous documents research that has illustrated the unreliability of pharmaceutical industry-associated data, claims, and marketing (43, 79, 80). Over the same time period there were significant increases in opioid use, poisonings, and related mortality in these populations.

Pharmaceutical industry efforts to market opioids to children primarily relied on unbranded campaigns, which sidestep FDA regulations on traditional pharmaceutical advertisements (23). These campaigns used appeals to authority to influence children's understanding of pain and opioids, recruiting adults they would be perceive as credible, including coaches and school nurses. Two specific unbranded campaigns, *Growing Pains* and *Smart Moves, Smart Choices*, were designed to sell more opioids despite being presented as public health campaigns. These approaches were likely to have been influential given that past research has shown that advertisements in school settings affect children because they are associated with authority figures such as teachers (37). However this kind of marketing is problematic because children and adolescents may have difficulties understanding the fundamental purpose of advertisements, due to still-developing executive functioning and critical thinking skills, as well as a lack of skepticism among those of younger age

(81). Opioid manufacturers also explicitly targeted women and provided financial support for advocates that supported opioid use among pregnant women. Appeals to policymakers made through the industry-sponsored Pain Care Forum used selective information and anecdotes to develop claims that opioids were needed to address untreated pain among women. One suggestion made through the Forum, that Oxycontin use during pregnancy is safe, was particularly concerning given that it failed to describe the risks of neonatal abstinence syndrome (NAS) due to *in utero* opioid exposure (74, 75). In the years following these presentations the incidence of NAS quintupled (6). Opioid manufacturers also developed direct appeals to women based on the desire for self-empowerment, emotions and fears surrounding disability and pregnancy, and social desirability. This marketing may help explain the disproportionate opioid-related health risks among women; by 2014 opioid-related hospitalizations rates for women surpassed those of men in a majority of states (82).

Our study has limitations. The documents in the DIDA do not represent all documents created by the pharmaceutical companies involved during the development, production, marketing, and distribution of opioid products. While these documents were considered significant during the process of legal discovery, they may not include other relevant material, particularly documents that never existed in electronic form**.** Some documents were presentation aids such as PowerPoint decks and sales pitch outlines that may not have been presented or used. Our findings may not be generalizable to companies that were not included in the settlement or to marketing for non-opioid products. Despite these limitations, we identified sufficient evidence to show a pattern of marketing to women and children.

CONCLUSION

In previous research, findings from industry documents research have been critical in generating discussion and scrutiny about the role of industry funding and influence in scientific publications and health policy, and critical in generating changes in policy and practice that protect public health (28, 83, 84). To our knowledge, this study represents the first analysis of internal industry documents drawn from lawsuits against opioid manufacturers that describes marketing children and women. Findings from previous pharmaceutical industry documents research have illustrated the unreliability of industry-associated data, claims, and marketing (29, 79, 80) and detailed efforts by manufacturers to influence physicians (39-41). This work builds on this previous research by providing new insight into how pharmaceutical companies sought to increase opioid use among women and children. Our results serve as a warning to clinicians and policymakers about the direct-to-consumer advertising, and particularly the use of unbranded campaigns. The opioid industry's ability to sidestep regulation originally intended to limit pharmaceutical advertising suggests that regulatory changes are needed to reduce marketing of addictive medications to children and women, particularly given that rapid increase in negative health outcomes associated with opioid use in these groups.

Figure legends

Fig 1. Excerpt from the October 2011 "Imagine the Possibilities Pain Coalition" meeting. The coalition served as group of leaders in pain management and Janssen professionals that aimed to influence the perception of pain among target groups which included youth and military veterans.

Source: UCSF Drug Industry Documents Archive

Fig 2. Screenshots from the "About Us" page of smartmovessmartchoices.org. Archive of the webpage from August 25, 2016 (right) included the Janssen logo as partner and sponsor. The June 2020 webpage (left) no longer included Janssen as a sponsor.

Source: Internet Archive

Fig 3. Screenshots from the "Talking with Health Care Providers" webpage (left) and "Ask for Help" webpage (right) as of June 12, 2020 from growingpains.org. Created by the American Chronic Pain Association and funded by Janssen Pharmaceuticals, *Growing Pains* was a disease awareness campaign targeting chronic pain in adolescent patients.

Source: Internet Archive

Declarations

Acknowledgements: The authors acknowledge Rachel Taketa at the UCSF library for assistance with searching for documents.

Competing interests: The authors declare they have no actual or potential competing financial interests.

Funding: This work was supported by National Institutes of Health #DA046051 (Apollonio) and a Pathway Project Grant from the University of California, San Francisco (Yakubi and Gac). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability: The data analyzed for the current study are available from the Drug Industry Documents Archive repository, https://www.industrydocuments.ucsf.edu/drug/.

Ethical approval: Not applicable; findings are based on data in a public repository.

Author statement: HY, BG, and DA worked together to design the study, analyze the data, interpret the results, and revise the manuscript. HY drafted the manuscript and HY and BG completed the initial review of the documents.

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SRQR checklist[1]

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BMJ Open

Industry strategies to market opioids to children and women in the United States: A content analysis of internal industry documents from 1999 to 2017 released in State of Oklahoma v. Purdue Pharma, L.P. et al

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052636.R1
Article Type:	Original research
Date Submitted by the Author:	14-Feb-2022
Complete List of Authors:	Yakubi, Hanna; University of California San Francisco, Department of Clinical Pharmacy Gac, Brian; University of California San Francisco, Department of Clinical Pharmacy Apollonio, Dorie; University of California San Francisco, Department of Clinical Pharmacy
Primary Subject Heading:	Public health
Secondary Subject Heading:	Addiction, Health policy, Paediatrics
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PAEDIATRICS, QUALITATIVE RESEARCH, PUBLIC HEALTH, PAIN MANAGEMENT

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Title: Industry strategies to market opioids to children and women in the United States: A content analysis of internal industry documents from 1999 to 2017 released in State of Oklahoma v. Purdue Pharma, L.P. et al

Running title: Marketing opioids to children and women

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Word count: 298 abstract/ 4449 manuscript

Number of tables: 0

Number of figures: 3

Number of references: 95

Number of supplementary files: 1

ABSTRACT

Objective: Identify advertising strategies used to market opioids to women and children

Design: Qualitative content analysis of internal pharmaceutical industry documents released in litigation, dated between 1999 and 2017

Setting: United States

Participants: Opioid manufacturers (Janssen, Ortho-McNeil, Purdue, Teva (Actavis), Janus, Cephalon); women; children

Primary and secondary outcome measures: Advertising campaigns, industry executive statements regarding marketing goals

Methods: We examined documents released in *State of Oklahoma v. Johnson & Johnson (2019)* to identify marketing strategies and campaigns developed by opioid manufacturers that focused on children and women, as well as public records, including websites developed by manufacturers and their allies, to confirm whether marketing campaigns proposed in internal industry documents were implemented. Documents identified as relevant were coded for themes based on expectations drawn from previous research on marketing using internal industry documents, which included making emotional appeals and understating the risks of addiction.

Results: We found that opioid manufacturers sought to recruit coaches and school nurses to encourage opioid use by children, developed unbranded initiatives suggesting adolescents ask providers for pain care medications, suggested that opioid use could reduce health risks associated with untreated pain among women, and advocated to policymakers that women faced unmet needs for pain medication.

Conclusions: The US strictly regulates direct marketing of medications but does not place the same restrictions on indirect marketing and unbranded campaigns, which encourage people to seek

treatment without indicating the names of specific products. Opioid manufacturers in the early 21st century appear to have relied largely on unbranded campaigns for marketing, which they described externally as public health promotion and internally as a way to increase sales of opioids. The rapid increase in opioid use concomitant with these campaigns suggests that additional scrutiny of this kind of marketing may be needed in order to protect vulnerable groups.

Keywords: Analgesics, Opioid; Advertising; Drug Industry; Public Policy

Strengths and limitations of this study

- A major strength of this study is that it used new data, specifically internal industry documents released in litigation against pharmaceutical companies, to identify how opioid manufacturers market to consumers.
- An additional strength was that it validated the existence of marketing strategies mentioned in internal industry documents by checking public records.
- The main limitation is that documents released during legal discovery are likely incomplete and may exclude relevant material.

INTRODUCTION

Since 1999, nearly 841,000 people have died in the US from drug overdoses and in 2019 roughly 70% of all drug overdose deaths involved opioids (1). Between 21% and 29% of people who use opioids report misuse and 8% to 12% advance to addiction (2). The 2019 National Survey on Drug Use and Health (NSDUH) found that 3.3.% of women aged 12 and older misused opioids (3), and women are more likely to misuse prescription opioids than men (4, 5). Sixty-five percent of opioid prescriptions are held by women and their use has led to negative health consequences during pregnancy; the incidence of neonatal abstinence syndrome (NAS) increased five-fold from 2004 to 2014 in the United States, with the incidence of maternal opioid use disorder rising by a similar rate (6, 7). Data drawn from NSDUH in 2015 and 2016 found that 3.8% of adolescents misused opioids (8); this misuse is linked to parental medical use of prescription opioids (9). Parental prescriptions are also linked with overdoses among children ages 0-5 years (10, 11). However research on the risks of opioids has paid relatively limited attention to children (12-14), despite the fact that by 2015 one-fourth of US high school seniors reported using opioids (15, 16). Younger children also use opioids; in one study of children ages 2-17 enrolled in Medicaid in Tennessee from 1999-2014, 15% had filled an opioid prescription annually (17). Among those prescribed opioids for pain, prescriptions were frequently given for conditions that were not severe, one in every 2611 prescriptions was associated with an emergency department visit, hospitalization, or death, and 89% of those adverse events were related to therapeutic use (17, 18). Pediatric hospitalizations for opioid poisonings doubled between 1997 and 2012 (12), representing over a quarter of all opioid poisonings as of 2018 (19), and mortality rates from pediatric opioid exposures nearly tripled from 1999 and 2016 (13). As with adults, opioid misuse among adolescents typically follows medical use by prescription (15, 18).

On June 30, 2017, the state of Oklahoma brought a lawsuit against Johnson & Johnson, Purdue Pharma, and 11 other pharmaceutical manufacturers, claiming that they overestimated the efficacy and underestimated the safety risks of opioids and encouraged physicians to prescribe more of these medications, even when patients exhibited signs of addiction (20). In 2019 these manufacturers were fined $465 million for intentionally overstating the clinical benefit and minimizing the addictive potential of opioids (21, 22), and since then additional litigation has led to fines of over $355 million (23). The Oklahoma verdict specifically referenced issues with unbranded campaigns, a form of direct-to-consumer marketing that highlights disease awareness and the need to seek medical care but do not reference specific brands and as a result are not subject to US Food and Drug Administration (FDA) regulations that require a "fair balance" of both positive and negative information in advertising (24). This advertising has been found to misinform patients about disease causes and prevalence, overemphasize drug benefits, sensationalize natural or trivial conditions, and lead to inappropriate prescribing (25, 26), especially among women (27). By encouraging patients to seek prescriptions, they can also increase sales for manufacturers (28, 29).

Studying industry marketing is frequently challenging, in part due to difficulties in collecting data. Research on other industries has addressed this limitation by reviewing internal documents released in litigation (30, 31). Although industry documents are often first reported on in the popular media, past document-based research has identified ways that industries seek to influence consumers, clinicians, and researchers to increase sales and profits (30). Studies using internal industry documents have found that other industries, such as tobacco and sugar companies, have marketed directly to vulnerable groups, including children (32-34) and women (35), among others (36-38). Children are particularly susceptible to predatory marketing tactics (39), which in the case of tobacco included tailored slogans and emotional appeals (40), misrepresentation of the potential for

addiction (37), and sponsorship of popular brands and events (36). Prior research on opioid industry marketing has primarily focused on efforts by manufacturers to influence physicians (41-45), with little study of industry efforts to market directly to population groups that have been disproportionately affected. The extent of opioid industry marketing is an area of concern given increasing mortality attributed to opioid use. In this study we reviewed and analyzed internal industry documents released in the State of Oklahoma lawsuit to identify strategies used to market opioids to children and women. We hypothesized that like the tobacco and food industries, opioid manufacturers advertised directly to these groups in an effort to increase their consumption of opioids.

METHODS

Our study relied on a retrospective qualitative content analysis of pharmaceutical industry documents. Since 2005, internal documents released during lawsuits against pharmaceutical companies have been stored in the Drug Industry Document Archive (DIDA) at the University of California, San Francisco, a public, open access repository ([DATASET] link: https://www.industrydocuments.ucsf.edu/drug/) (46). In January 2020, DIDA released 503 documents totaling 62,703 pages drawn from the State of Oklahoma lawsuit brought against 13 opioid manufacturers including Purdue Pharma, Janssen and Ortho-McNeil (both subsidiaries of Johnson & Johnson, merged into a single entity in August 2011), Johnson & Johnson, Teva (Actavis), Cephalon, Allergan, and Watson (20, 47). While sources disagree on the share of the opioid market controlled by these companies, Actavis was identified as the highest-volume manufacturer of opioids in Oklahoma, with Purdue ranked fifth; Johnson & Johnson was identified as producing active ingredients used in 60% of oxycodone available in the US (48). Documents

produced in the lawsuit included reports of relevant clinical trials, witness declarations, internal corporate communications, and marketing strategy outlines regarding opioids through 2017. The 503 documents constituting the Oklahoma Opioid Litigation Document Collection were the primary database for the study.

Two authors (HY, BG) independently read and coded all of the 503 documents included in the archive and created a master file from them containing key quotes, figures, and concepts. To ensure every document was examined, each author involved (HY, BG) individually checked each of the 503 documents' unique identification codes to ensure it was represented in the master document shared by all authors. After this review, one investigator (HY) copied documents from the master file identified as relevant to the industry's targeting of vulnerable populations, defined as patients with psychosocial characteristics that could make them more vulnerable to pharmaceutical industry marketing and that included, but were not limited to, populations historically exploited by the tobacco industry (37, 38, 49, 50). Targeting was defined as any explicit reference to business, marketing, outreach, or advertising strategies that focused on increasing opioid sales or creating favorable perceptions of opioid products among these groups. Opioid manufacturers listed target markets in these documents, which included women and children (as well as a handful of other groups, including veterans (51), but not men or adults explicitly). The same investigator (HY) then reviewed each document again for explicit references to either children or women.

Following this assessment, all authors generated a list of relevant search terms, including "adolescent", "school", "coaches", "sports", "pregnancy", "RSD", and "fibromyalgia". As a verification strategy, two authors (HY, BG) searched for these terms in the online archive of all 503 documents to ensure no relevant documents had been missed; no additional documents were identified.

Documents were coded using modified grounded theory, an inductive methodology that uses source material to identify hypotheses and that has previously been used in the analysis of pharmaceutical industry documents (51, 52), to categorize evidence based on general themes. A preliminary categorization of themes was based on those identified in research on tobacco, specifically emotional appeals, misrepresentation of the potential for addiction, and efforts to influence policymakers (36, 37, 40). In addition, referencing past research using pharmaceutical industry documents, the documents were assessed for references to marketing to consumers such as unbranded campaigns (53-55). The industry's targeted marketing to groups that had been disproportionately affected by the opioid epidemic was independently identified by all authors as a unique category for coding. When multiple documents made similar claims or presented similar ideas they were categorized together. If there was question of a document's relevance to the study or its categorization, it was discussed by all three authors until consensus was reached. Documents were excluded from analysis if they did not contain information due to redaction prior to release or when it was impossible to identify whether they were relevant. Additional details on methodology are provided in the Supplemental File.

To triangulate and verify these findings, one author (DA) checked the Internet Archive "Wayback Machine" (https://archive.org/web/) to track changes in industry-sponsored websites for unbranded campaigns identified in the documents. Another (HY) searched Dollars for Docs from ProPublica (https://projects.propublica.org/docdollars/) and Open Secrets (https://opensecrets.org) for payments made from pharmaceutical companies to physicians and policymakers named in the documents.

Patient and public involvement: No patient involvement.

RESULTS

We reviewed industry strategies to market opioids to two groups: children (including adolescents) and women (including pregnant women). For each of these groups, the following results first review corporate marketing plans, and assess how they were implemented based on two themes identified: advocacy to policymakers and unbranded campaigns.

Opioid industry targeting of children

Corporate strategic planning

In 2003, Janssen (the pharmaceutical division of Johnson & Johnson) generated an internal summary of their Duragesic® (fentanyl patch) brand that targeted young patients as a source of franchise expansion. Analysis of the marketplace for Duragesic listed "pediatric exclusivity" as a growth opportunity and indicated that a "pediatric extension request" was submitted to the FDA as part of an initiative to "continue development of products to maximize the pain franchise." (56)

Janssen's focus on young patients was not limited to their Duragesic brand. In an October 2011 meeting of the Imagine the Possibilities Pain Coalition, a group of professionals within Janssen who aimed to "create a broad-based community in the field of Pain Management," repeatedly identified youth as a desired target (57). The Coalition's Media Outreach team was tasked with targeting three separate groups: "youth, military veterans, public" and sought to "destigmatize pain." (57) The team targeted children as young as elementary school in an initiative to "reach early" and designed a "practical message" of "pain is your body telling you something is important" to be delivered "via respected channels, e.g., coaches." (57) A slide from the presentation is shown in Figure 1.

Figure 1 here

In a May 2012 meeting, the Coalition's Public Policy/Advocacy team, with the stated goal of "chang[ing] the conversation about pain," (57) also identified adolescents as a target audience. Like the Media Outreach team, the Public Policy/Advocacy team proposed emphasizing the role of pain in "sports and activities" with the tagline "LESSONS LEARNED – HEALTH MATTERS [emphasis in original]." (58)

Advocacy to policymakers

We identified documents from multiple companies, most involved in the Oklahoma litigation, that undertook advocacy to policymakers: Janssen, Ortho-McNeil (both subsidiaries of Johnson & Johnson, merged into a single entity in August 2011), Johnson & Johnson itself, Purdue, Teva (Actavis), Cephalon, and Janus. One of the leaders of Janssen's Public Policy/Advocacy team, Bob Twillman, had historically worked closely with other pharmaceutical companies to advocate opioid-friendly policy positions. In 2012, Twillman led a task force development a "Pain Care Forum" to create and urge CDC approval of "Clinical guidelines for the use of Chronic Opioid Therapy in Chronic Non-Cancer Pain" (59) and in 2013, Twillman spoke at a FDA public hearing to argue that the reclassification of hydrocodone products from Schedule III to Schedule II would be too costly (60). The Pain Care Forum was a coalition of pharmaceutical companies and advocacy organizations that aimed to be the "voice on pain care issues in Washington," (61) and in 2010, was compromised of 60 organizations including the companies named above as well as Pfizer and Allergan, and the American Pain Foundation, American Academy of Pain Management, and American Pharmacists Association (62). The executive committee was compromised of industry leaders from Purdue Pharma and Ligand Pharmaceuticals, as well as leaders from American Pain Foundation and National Hospice and Palliative Care Organization (62, 63). In a 2008 email from Howard R. Udell, Executive Vice President and Chief Legal Officer at Purdue Pharma, to Burt

Rosen, Vice President of Government Affairs at Purdue Pharma, Udell noted that "The PCF [Pain Care Forum] has become 'a force' to be courted by members of Congress." (64)

In June 2006, the American Pain Foundation and the Pain Care Forum presented a briefing on the "Epidemic of Pain in America" to members of Congress on Capitol Hill (65). The presentation was in cooperation with Representative Mike Rogers, who had received over $600,000 in contributions from the pharmaceutical industry from 1995 to 2015 (66). Supporting material from the Epidemic of Pain in American briefing showed that the Pain Care Forum advocated for pain treatment in young patients. The Forum emphasized that "pain affects people at all stages of life – including infants, children, young adults, and the elderly." (65)

Research!America, an advocacy organization that promotes medical research, included a flyer in the briefing noting, "as many as 20 percent of children experience chronic pain." (65) Research!America was extensively involved with the pharmaceutical and opioid industry; a November 2008 internal memo from the Pain Care Forum showed that Research!America was actively "looking for industry financial (and planning) support" for a 2009 Pain Summit (59), and an internal email from Jon Sackler of Purdue indicated that Research!America had a long term relationship with the Sackler family and until February 2018 named their national leadership award the "R&BS [Raymond and Beverley Sackler] award." (67)

Unbranded campaigns

Companies named in the Oklahoma lawsuit also created unbranded campaigns to target adolescents. In June 2007, an Ortho-McNeil internal presentation titled "Non-Branded Promotions" indicated that it sought to partner with advocacy groups in unbranded campaigns to "establish instant credibility," "develop good will," and "alleviate regulatory anxiety." (68) A 2008 strategy

document for the marketing of Janssen's Nucynta® (tapentadol) indicated that the goal of direct-to-patient unbranded campaigns was "to increase patient origination." (69)

A separate 2008 Janssen internal presentation titled "Pain Non-Branded Campaign Market Research" described an unbranded initiative with the outward-facing message of bringing awareness to physicians about undertreated acute pain, but indicated that the expected impact was "PCPs [primary care providers] stat[ing] that they will be more aggressive in their treatment and use more opioids." (70) This unbranded initiative focused on the negative consequences of undertreated acute pain and emphasized multi-pathway pain treatment in order to encourage physicians to adopt a "more aggressive approach to treating (stronger dosing and meds)." (70) The campaign also attempted to address physician concerns about addiction by "refocusing them from addiction to side effect concerns." (70) The marketing research concluded with the identification of "the elderly, younger patients, post-operative and post-trauma patients" as target groups (70).

Two specific unbranded campaigns centered on young patients. In 2008, Janssen partnered with the National Association of School Nurses to launch *Smart Moves, Smart Choices*, a program that proposed bringing awareness to prescription drug abuse among teenagers (71, 72). However, internal Janssen documents classified *Smart Moves, Smart Choices* as an unbranded campaign (73). *Smart Moves, Smart Choices* was also included as part of Janssen's "Pain Franchise" public relations program and for their opioid product Nucynta (74), specifically as part of a larger strategic approach to "redirect dialogue from *drug control* to *controlling pain* [emphasis in original]" (75) and to "educate/influence to maintain physician/patient access." (74) At the end of 2020, *Smart Moves, Smart Choices* still existed as an outreach program run by the National Association of School Nurses, but Janssen was no longer listed as a partner or sponsor (76); screenshots from the program website are shown in Figure 2.

Figure 2 here

In December 2011, Janssen and Janus partnered with the American Chronic Pain Association (ACPA) to launch a separate unbranded campaign, *Growing Pains*. Robyn Kohn, Director of Medical Education at Janssen, noted this was a "significant contribution to the understanding of pain among the child and adolescent populations." (77) The ACPA described *Growing Pains* as a "a new social networking site for young people with pain" and allowed children as young as 13 years old to become members (78). This unbranded campaign encouraged adolescent patients to seek help for pain and provided information on how to talk to health care providers (79); a screen shot is shown in Figure 3. At the end of 2020 *Growing Pains* was still an active website listing funding by Janssen.

Figure 3 here

Opioid industry targeting of women

Corporate strategic planning

In a presentation to increase its European sales after 2001, Johnson & Johnson emphasized that one of its "major franchises" was "women's health." (80) In 2012, Janssen (a subsidiary) expanded its marketing to women with a new "Mainstream Media Pitch." (81) In 2013, Teva created an "Advocacy Mapping" plan to "understand potential alliances and detractors… to engage and/or minimize them" which specifically noted potential allies that focused on women's health (82).

Advocacy to policymakers

The Pain Care Forum developed by multiple opioid manufacturers also advocated for opioid use by women. Documents from the Pain Care Forum's June 2006 briefing with lawmakers, described above, indicated it sought to establish a perceived need for painkillers among women.

While describing the demographics of pain, the Forum specified "women's pain reports are taken less seriously than men's" and "women receive less aggressive treatment than men for their pain."(65)

As part of their message that chronic undertreated pain disproportionately affects women, the Pain Care Forum shared stories of women suffering from unresolved chronic pain due to reflex sympathetic dystrophy (RSD), which it spotlighted as a pain condition that affected women more than men (65). Documents used as supporting material from the Pain Care Forum briefing showed a pattern of using personal anecdotes about RSD to warn of the disastrous effects of untreated chronic pain among women. One story focused on Barbara, who suffered from RSD, and warned "when the pain rises up, I think it is not really worth living." (65) The story featured Barbara's female friend who "probably had RSD" and "eventually committed suicide." (65) Another story focused on Alexandra, a sixteen-year-old woman suffering from RSD since the age of ten, who grieved the loss of her childhood due to untreated chronic pain and noted that her senior year had been spent "tak[ing] more medications than my grandparents" and spending time in the hospital "just wishing to walk." (65) Although the Pain Care Forum claimed that pain stories like Alexandra's are "told 50 million times," (65) there was no accompanying context: RSD is a rare disease and likely not representative of how most women experience pain or their resulting levels of disability (83, 84).

The same briefing included a 2006 article from *The Washington Post* which focused on physician Howard Heit. It highlighted his decision to prescribe Oxycontin® to his pregnant daughter-in-law and that her infant did not experience withdrawal symptoms, implying that opioid use could be safe for pregnant women and their newborns (65). The article noted, "she [Heit's daughter-in-law] knew she could never get through the pregnancy without the medication [Oxycontin]." (65) At the time of the article's publication, the risk of neonatal abstinence syndrome

in infants exposed *in utero* to opioids was known and characterized (85, 86). The article failed to mention that in 2004 Dr. Heit had provided consulting services promoting Actiq®, a fentanyl transmucosal lozenge sold by Cephalon.(87) Dr. Heit continued to consult for Cephalon and Johnson & Johnson in 2011 (88, 89).

A separate *New York Times* article titled "When it Comes to Severe Pain, Doctors Still Have Much to Learn" was also included in the supporting material for the briefing and focused on "clueless or unnecessarily cautious" doctors and their reluctance to prescribe opioids (65). The article included a quote from a 1995 entry into *The Journal of the American Medical Association*: "Bringing about significant change may depend on empowering patients to demand adequate pain treatment. This empowerment will not come easily, especially if opioids must be used for pain relief and the pain is of nonmalignant origin." (65)

Unbranded campaigns

Consistent with efforts to market opioids as a form of patient empowerment, the American Pain Foundation brainstormed techniques to target women for a fibromyalgia disease awareness campaign funded by a $10,000 check from Pfizer in July 2007 (65). The notes claimed that the "empowerment angle can be used with any program [emphasis in original]" and that the disease awareness program aimed to "create patient demand for proper pain diagnosis and treatment." (65) The Foundation planned to use "viral tactics/word of mouth education (sic)" by "let[ting] women educate women in their natural setting (e.g., Tupperware parties, garden groups, e-cards)." (65) The Foundation also proposed to share this outreach message via communication channels such as "women's books" and "the National Women's Health Resource Center." (65)

In 2012, Janssen proposed similar strategies to target women as part of a public relations program for its pain franchise and specifically to market Nucynta. Janssen's pitch stated, "Women are feeling the pain, study says—what every woman needs to know," and the message was targeted to "women's books" among other advertising venues (74).

DISCUSSION

Summary of the evidence

This study of internal opioid industry documents detailed how opioids were marketed to children and women at the beginning of the 21st century through targeted advocacy directed to policymakers and by using unbranded campaigns intended to increase demand for opioids. It builds on previous documents research that has illustrated the unreliability of data, claims, and marketing produced by the pharmaceutical industry (51-54). Over the same time period there were significant increases in opioid use, poisonings, and related mortality in these populations.

Pharmaceutical industry efforts to market opioids to children primarily relied on unbranded campaigns, which sidestep FDA regulations on traditional pharmaceutical advertisements (27). These campaigns used appeals to authority to influence children's understanding of pain and opioids, seeking to recruit adults they would be perceive as credible, including coaches and school nurses. Two specific unbranded campaigns, *Growing Pains* and *Smart Moves, Smart Choices*, were explicitly developed and launched as a means to market opioids despite being presented to the public as public health campaigns. These approaches were likely to have been influential given that past research has shown that advertisements in school settings affect children because they are associated with authority figures such as teachers (39). This kind of marketing is problematic

because children and adolescents may have difficulties understanding the fundamental purpose of advertisements, due to still-developing executive functioning and critical thinking skills, as well as a lack of skepticism among those of younger age (90).

Opioid manufacturers also developed direct appeals to women based on the desire for self-empowerment, emotions and fears surrounding disability and pregnancy, and social desirability. This marketing may help explain the disproportionate opioid-related health risks among women; by 2014 opioid-related hospitalizations rates for women surpassed those of men in a majority of states (91). Appeals to policymakers made through the industry-sponsored Pain Care Forum used selective information and anecdotes to develop claims that opioids were needed to address untreated pain among women. Companies also provided financial support for advocates that supported opioid use among pregnant women. One suggestion made through the Pain Care Forum, that Oxycontin use during pregnancy is safe, was particularly concerning given that it failed to describe the risks of neonatal abstinence syndrome (NAS) due to *in utero* opioid exposure (85, 86). Although opioid use in limited doses during pregnancy may be warranted for treatment of some specific conditions (e.g., terminal cancer), American Pain Society guidelines recommend no use or minimal use due to adverse effects on fetal development (92, 93). In the years following these presentations the incidence of NAS quintupled (6).

Strengths and limitations

Our study has strengths and limitations. Internal industry documents provide a unique perspective on industry behavior with implications for public health that is "not available from any other source" (30). However the Drug Industry Documents Archive does not include all documents created by the pharmaceutical companies involved during the development, production, marketing, and distribution of opioid products. While the documents included in the archive were considered

significant during the process of legal discovery, they may not include other relevant material, particularly documents that never existed in electronic form**.** For example, although we identified marketing materials explicitly targeting women as a group, we did not find comparable materials intended to reach men as a group; nonetheless, these documents may have existed. Some documents were presentation aids such as PowerPoint decks and sales pitch outlines that may not have been presented or used, although we searched public records for validation that campaigns were launched and provide that information where available. Our findings may not be generalizable to companies that were not included in the settlement or to marketing for non-opioid products, although they are drawn from multiple companies that both sold their own opioid products to consumers and that provided active ingredients to multiple opioid manufacturers. Due to the delay in releasing documents related to litigation, some of the materials cited in the manuscript are date back over two decades, and reveal a pattern of pharmaceutical company behavior that has remained largely unresolved; the FDA has been criticized by multiple sources for failing to change its regulatory policies to address opioid marketing over this time period (94).

Recommendations for research

Litigation against opioid manufacturers continues, as does the release of new documents identified in legal discovery. Further review and analysis of pharmaceutical industry documents is needed to understand the industry's ongoing marketing strategies, what portions of the population may be targeted, and whether pharmaceutical companies may market other products using similar campaigns, particularly given that FDA regulations remain unchanged.

Conclusion

In previous research, findings from industry documents research have been critical in generating discussion and scrutiny about the role of industry funding and influence in scientific publications and health policy, and in generating changes in policy and practice that protect public health (30, 95, 96). To our knowledge, this study represents the first analysis of internal industry documents drawn from lawsuits against opioid manufacturers that describes marketing to children and women. Findings from previous pharmaceutical industry documents research have illustrated the unreliability of industry-associated data, claims, and marketing (31, 53, 54) and have detailed efforts by manufacturers to influence physicians (41-45). This work builds on this previous research by providing new insight into how pharmaceutical companies sought to increase opioid use among women and children. Our results serve as a warning to clinicians and policymakers about the risks of direct-to-consumer advertising and particularly the use of unbranded campaigns. The opioid industry's use of unbranded campaigns to promote opioid use, despite the existence of regulation intended to limit pharmaceutical advertising, suggests that additional regulatory oversight may be needed to discourage inappropriate marketing of addictive medications.

Figure legends

Fig 1. Excerpt from the October 2011 "Imagine the Possibilities Pain Coalition" meeting. The coalition served as group of leaders in pain management and Janssen professionals that aimed to influence the perception of pain among target groups which included youth and military veterans.

Source: UCSF Drug Industry Documents Archive

Fig 2. Screenshots from the "About Us" page of smartmovessmartchoices.org. Archive of the webpage from August 25, 2016 (right) included the Janssen logo as partner and sponsor. The June 2020 webpage (left) no longer included Janssen as a sponsor.

Source: Internet Archive

Fig 3. Screenshots from the "Talking with Health Care Providers" webpage (left) and "Ask for Help" webpage (right) as of June 12, 2020 from growingpains.org. Created by the American Chronic Pain Association and funded by Janssen Pharmaceuticals, *Growing Pains* was a disease awareness campaign targeting chronic pain in adolescent patients.

Source: Internet Archive

Declarations

Acknowledgements: The authors acknowledge Rachel Taketa at the UCSF library for assistance with searching for documents.

Competing interests: The authors declare they have no actual or potential competing financial interests.

Funding: This work was supported by National Institutes of Health #DA046051 (Apollonio) and a Pathway Project Grant from the University of California, San Francisco (Yakubi and Gac). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability: The data analyzed for the current study are available from the Drug Industry Documents Archive repository, [DATASET] https://www.industrydocuments.ucsf.edu/drug/.

Ethical approval: Not applicable; findings are based on data in a public repository.

Author statement: HY, BG, and DA worked together to design the study, analyze the data, interpret the results, and revise the manuscript. HY drafted the manuscript and HY and BG completed the initial review of the documents.

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Title: Industry strategies to market opioids to children and women in the United States: A content analysis of internal industry documents from 1999 to 2017 released in State of Oklahoma v. Purdue Pharma, L.P. et al

Running title: Marketing opioids to children and women

Supplemental file

Our study relied on a retrospective content analysis of pharmaceutical industry documents (1). On January 24, 2020, the University of California San Francisco Industry Documents Library released 503 documents totaling 62,703 pages drawn from *State of Oklahoma, ex. rel. Hunter v. Purdue Pharma, L.P., et. al. (Okla. Dist. Ct. Aug. 26, 2019),* a lawsuit brought by the state of Oklahoma against companies manufacturing and selling opioids, including Purdue, Teva (Actavis), Cephalon, Janssen, Ortho-McNeil-Janssen, Allergan, and Watson (2). Documents include reports on clinical trials, witness declarations, internal corporate communications, short videos taken at conferences, and marketing campaign materials.

Our approach to documents review relied on previously validated standards for research using tobacco industry documents (3, 4). Two authors (HY, BG) who had completed training provided by the UCSF Industry Documents Library on search strategies and documents analysis (the Annual Tobacco Documents Workshop) conducted the preliminary analysis; this team independently reviewed all 503 documents in the archive. Both coders and an independent third reviewer (DA) with experience analyzing industry documents and who has served as an instructor for the UCSF Library Annual Tobacco Documents workshop, created a master text file with information on all 503 documents that summarized key points drawn from each document along with supporting information including quotes, figures, and concepts, and in the case of short videos,

transcriptions. To ensure that no documents were excluded, each was marked with the unique identification code provided by the library.

We reviewed documents using modified grounded theory, an inductive methodology that uses source material to identify hypotheses and to categorize evidence based on general themes, an analytical strategy previously used in the analysis of pharmaceutical industry documents (5). Authors of industry documents used consistent terminology (e.g., "youth") when referring to groups that they identified as target markets, allowing comparison across multiple companies and documents. Our expectations were that opioid manufacturers used strategies similar to those used by the tobacco industry, specifically: seeking to influence policymakers, making emotional appeals to potential users, and understating the risk of addiction.

We noted the strategies mentioned in the documents we reviewed and provided specific quotes and screenshots in the master file to aid understanding of our classifications. When questions arose regarding a document's relevance, it was discussed by all three authors until agreement was reached. Discussions were conducted in weekly meetings of one to three hours each held May-August 2020. When the two coders disagreed regarding interpretation, the designated reviewer read the document and made a final decision; documents for which there were disagreements were then reviewed again by all three authors before making a decision to include or exclude them. Documents were excluded if the authors were unable to identify whether they were relevant (e.g., spreadsheets tracking sales by region that were described only by proprietary identification codes). After this initial review, one investigator (HY) extracted all materials relating to industry marketing to women and children from the master file as a resource for the manuscript. These documents referenced advocacy and marketing campaigns, business plans, and advertising strategies focused on increasing opioid sales or creating favorable perceptions of opioid products.

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BMJ Open

Industry strategies to market opioids to children and women in the United States: A content analysis of internal industry documents from 1999 to 2017 released in State of Oklahoma v. Purdue Pharma, L.P. et al

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-052636.R2
Article Type:	Original research
Date Submitted by the Author:	21-Jul-2022
Complete List of Authors:	Yakubi, Hanna; University of California San Francisco, Department of Clinical Pharmacy Gac, Brian; University of California San Francisco, Department of Clinical Pharmacy Apollonio, Dorie; University of California San Francisco, Department of Clinical Pharmacy
Primary Subject Heading:	Public health
Secondary Subject Heading:	Addiction, Health policy, Paediatrics
Keywords:	Health policy < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, PAEDIATRICS, QUALITATIVE RESEARCH, PUBLIC HEALTH, PAIN MANAGEMENT

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Title: Industry strategies to market opioids to children and women in the United States: A content analysis of internal industry documents from 1999 to 2017 released in State of Oklahoma v. Purdue Pharma, L.P. et al

Running title: Marketing opioids to children and women

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Word count: 298 abstract/ 4504 manuscript

Number of tables: 0

Number of figures: 1

Number of references: 102

Number of supplementary files: 1

ABSTRACT

Objective: Identify advertising strategies used to market opioids to women and children

Design: Qualitative content analysis of internal pharmaceutical industry documents released in litigation, dated between 1999 and 2017

Setting: United States

Participants: Opioid manufacturers (Janssen, Ortho-McNeil, Purdue, Teva (Actavis), Janus, Cephalon); women; children

Primary and secondary outcome measures: Advertising campaigns, industry executive statements regarding marketing goals

Methods: We examined ([DATASET] link: https://www.industrydocuments.ucsf.edu/drug/) documents released in *State of Oklahoma v. Johnson & Johnson (2019)* to identify marketing strategies and campaigns developed by opioid manufacturers that focused on children and women, as well as public records, including websites developed by manufacturers and their allies, to confirm whether marketing campaigns proposed in internal industry documents were implemented. Documents identified as relevant were coded for themes based on expectations drawn from previous research on marketing using internal industry documents, which included making emotional appeals and understating the risks of addiction.

Results: We found that opioid manufacturers sought to recruit coaches and school nurses to encourage opioid use by children, developed unbranded initiatives suggesting adolescents ask providers for pain care medications, suggested that opioid use could reduce health risks associated with untreated pain among women, and advocated to policymakers that women faced unmet needs for pain medication.

Conclusions: The US strictly regulates direct marketing of medications but does not place the same restrictions on indirect marketing and unbranded campaigns, which encourage people to seek treatment without indicating the names of specific products. Opioid manufacturers in the early 21st century appear to have relied largely on unbranded campaigns for marketing, which they described externally as public health promotion and internally as a way to increase sales of opioids. The rapid increase in opioid use concomitant with these campaigns suggests that additional scrutiny of this kind of marketing may be needed in order to protect vulnerable groups.

Keywords: Analgesics, Opioid; Advertising; Drug Industry; Public Policy

Strengths and limitations of this study

- A major strength of this study is that it used new data, specifically internal industry documents released in litigation against pharmaceutical companies, to identify how opioid manufacturers market to consumers.
- An additional strength was that it validated the existence of marketing strategies mentioned in internal industry documents by checking public records.
- The main limitation is that documents released during legal discovery are likely incomplete and may exclude relevant material.

INTRODUCTION

Since 1999, nearly 841,000 people have died in the US from drug overdoses and in 2019 roughly 70% of all drug overdose deaths involved opioids (1). Between 21% and 29% of people who use opioids report misuse and 8% to 12% advance to addiction (2). The 2019 National Survey on Drug Use and Health (NSDUH) found that 3.3.% of women aged 12 and older misused opioids (3), and women are more likely to misuse prescription opioids than men (4, 5). Sixty-five percent of opioid prescriptions are held by women and their use has led to negative health consequences during pregnancy; the incidence of neonatal abstinence syndrome (NAS) increased five-fold from 2004 to 2014 in the United States, with the incidence of maternal opioid use disorder rising by a similar rate (6, 7). Data drawn from NSDUH in 2015 and 2016 found that 3.8% of adolescents misused opioids (8); this misuse is linked to parental medical use of prescription opioids (9). Parental prescriptions are also linked with overdoses among children ages 0-5 years (10, 11). However research on the risks of opioids has paid relatively limited attention to children (12-14), despite the fact that by 2015 one-fourth of US high school seniors reported using opioids (15, 16). Younger children also use opioids; in one study of children ages 2-17 enrolled in Medicaid in Tennessee from 1999-2014, 15% had filled an opioid prescription annually (17). Among those prescribed opioids for pain, prescriptions were frequently given for conditions that were not severe, one in every 2611 prescriptions was associated with an emergency department visit, hospitalization, or death, and 89% of those adverse events were related to therapeutic use (17, 18). Pediatric hospitalizations for opioid poisonings doubled between 1997 and 2012 (12), representing over a quarter of all opioid poisonings as of 2018 (19), and mortality rates from pediatric opioid exposures nearly tripled from 1999 and 2016 (13). As with adults, opioid misuse among adolescents typically follows medical use by prescription (15, 18).

On June 30, 2017, the state of Oklahoma brought a lawsuit against Johnson & Johnson, Purdue Pharma, and 11 other pharmaceutical manufacturers, claiming that they overestimated the efficacy and underestimated the safety risks of opioids and encouraged physicians to prescribe more of these medications, even when patients exhibited signs of addiction (20). In 2019 these manufacturers were fined $465 million for intentionally overstating the clinical benefit and minimizing the addictive potential of opioids (21, 22), and since then additional litigation has led to fines of over $355 million (23). The Oklahoma verdict specifically referenced issues with unbranded campaigns, a form of direct-to-consumer marketing that highlights disease awareness and the need to seek medical care but do not reference specific brands and as a result are not subject to US Food and Drug Administration (FDA) regulations that require a "fair balance" of both positive and negative information in advertising (24). This advertising has been found to misinform patients about disease causes and prevalence, overemphasize drug benefits, sensationalize natural or trivial conditions, and lead to inappropriate prescribing (25, 26), especially among women (27). By encouraging patients to seek prescriptions, they can also increase sales for manufacturers (28, 29).

Studying industry marketing is frequently challenging, in part due to difficulties in collecting data. Research on other industries has addressed this limitation by reviewing internal documents released in litigation (30, 31). Although industry documents are often first reported on in the popular media, past document-based research has identified ways that industries seek to influence consumers, clinicians, and researchers to increase sales and profits (30). Studies using internal industry documents have found that other industries, such as tobacco and sugar companies, have marketed directly to vulnerable groups, including children (32-34) and women (35), among others (36-38). Children are particularly susceptible to predatory marketing tactics (39), which in the case of tobacco included tailored slogans and emotional appeals (40), misrepresentation of the potential for

addiction (37), and sponsorship of popular brands and events (36). Prior research on opioid industry marketing has primarily focused on efforts by manufacturers to influence physicians (41-45), with little study of industry efforts to market directly to population groups that have been disproportionately affected. The extent of opioid industry marketing is an area of concern given increasing mortality attributed to opioid use. In this study we reviewed and analyzed internal industry documents released in the State of Oklahoma lawsuit to identify strategies used to market opioids to children and women. We hypothesized that like the tobacco and food industries, opioid manufacturers advertised directly to these groups in an effort to increase their consumption of opioids.

METHODS

Our study relied on a retrospective qualitative content analysis of pharmaceutical industry documents. Since 2005, internal documents released during lawsuits against pharmaceutical companies have been stored in the Drug Industry Document Archive (DIDA) at the University of California, San Francisco, a public, open access repository ([DATASET] link: https://www.industrydocuments.ucsf.edu/drug/) (46). In January 2020, DIDA released 503 documents totaling 62,703 pages drawn from the State of Oklahoma lawsuit brought against 13 opioid manufacturers including Purdue Pharma, Janssen and Ortho-McNeil (both subsidiaries of Johnson & Johnson, merged into a single entity in August 2011), Johnson & Johnson, Teva (Actavis), Cephalon, Allergan, and Watson (20, 47). While sources disagree on the share of the opioid market controlled by these companies, Actavis was identified as the highest-volume manufacturer of opioids in Oklahoma, with Purdue ranked fifth; Johnson & Johnson was identified as producing active ingredients used in 60% of oxycodone available in the US (48). Documents

produced in the lawsuit included reports of relevant clinical trials, witness declarations, internal corporate communications, and marketing strategy outlines regarding opioids through 2017. The 503 documents constituting the Oklahoma Opioid Litigation Document Collection were the primary database for the study.

Two authors (HY, BG) independently read and coded all of the 503 documents included in the archive and created a master file from them containing key quotes, figures, and concepts. To ensure every document was examined, each author involved (HY, BG) individually checked each of the 503 documents' unique identification codes to ensure it was represented in the master document shared by all authors. After this review, one investigator (HY) copied documents from the master file identified as relevant to the industry's targeting of vulnerable populations, defined as patients with psychosocial characteristics that could make them more vulnerable to pharmaceutical industry marketing and that included, but were not limited to, populations historically exploited by the tobacco industry (37, 38, 49, 50). Targeting was defined as any explicit reference to business, marketing, outreach, or advertising strategies that focused on increasing opioid sales or creating favorable perceptions of opioid products among these groups. Opioid manufacturers listed target markets in these documents, which included women and children (as well as a handful of other groups, including veterans (51), but not men or adults explicitly). The same investigator (HY) then reviewed each document again for explicit references to either children or women.

Following this assessment, all authors generated a list of relevant search terms, including "adolescent", "school", "coaches", "sports", "pregnancy", "RSD", and "fibromyalgia". As a verification strategy, two authors (HY, BG) searched for these terms in the online archive of all 503 documents to ensure no relevant documents had been missed; no additional documents were identified.

Documents were coded using modified grounded theory, an inductive methodology that uses source material to identify hypotheses and that has previously been used in the analysis of pharmaceutical industry documents (51, 52), to categorize evidence based on general themes. A preliminary categorization of themes was based on those identified in research on tobacco, specifically emotional appeals, misrepresentation of the potential for addiction, and efforts to influence policymakers (36, 37, 40). In addition, referencing past research using pharmaceutical industry documents, the documents were assessed for references to marketing to consumers such as unbranded campaigns (53-55). The industry's targeted marketing to groups that had been disproportionately affected by the opioid epidemic was independently identified by all authors as a unique category for coding. When multiple documents made similar claims or presented similar ideas they were categorized together. If there was question of a document's relevance to the study or its categorization, it was discussed by all three authors until consensus was reached. Documents were excluded from analysis if they did not contain information due to redaction prior to release or when it was impossible to identify whether they were relevant. Additional details on methodology are provided in the Supplemental File.

To triangulate and verify these findings, one author (DA) checked the Internet Archive "Wayback Machine" (https://archive.org/web/) to track changes in industry-sponsored websites for unbranded campaigns identified in the documents. Another (HY) searched Dollars for Docs from ProPublica (https://projects.propublica.org/docdollars/) and Open Secrets (https://opensecrets.org) for payments made from pharmaceutical companies to physicians and policymakers named in the documents.

Patient and public involvement: No patient involvement.

RESULTS

We reviewed industry strategies to market opioids to two groups: children (including adolescents) and women (including pregnant women). For each of these groups, the following results first review corporate marketing plans, and assess how they were implemented based on two themes identified: advocacy to policymakers and unbranded campaigns.

Opioid industry targeting of children

Corporate strategic planning

In 2003, Janssen (the pharmaceutical division of Johnson & Johnson) generated an internal summary of their Duragesic® (fentanyl patch) brand that targeted young patients as a source of franchise expansion. Analysis of the marketplace for Duragesic listed "pediatric exclusivity" as a growth opportunity and indicated that a "pediatric extension request" was submitted to the FDA as part of an initiative to "continue development of products to maximize the pain franchise." (56)

Janssen's focus on young patients was not limited to their Duragesic brand. In an October 2011 meeting of the Imagine the Possibilities Pain Coalition, a group of professionals within Janssen who aimed to "create a broad-based community in the field of Pain Management," repeatedly identified youth as a desired target (57). The Coalition's Media Outreach team was tasked with targeting three separate groups: "youth, military veterans, public" and sought to "destigmatize pain." (57) The team targeted children as young as elementary school in an initiative to "reach early" and designed a "practical message" of "pain is your body telling you something is important" to be delivered "via respected channels, e.g., coaches." (57) A slide from the presentation is shown in Figure 1.

Figure 1 here

In a May 2012 meeting, the Coalition's Public Policy/Advocacy team, with the stated goal of "chang[ing] the conversation about pain," (57) also identified adolescents as a target audience. Like the Media Outreach team, the Public Policy/Advocacy team proposed emphasizing the role of pain in "sports and activities" with the tagline "LESSONS LEARNED – HEALTH MATTERS [emphasis in original]." (58)

Advocacy to policymakers

We identified documents from multiple companies, most involved in the Oklahoma litigation, that undertook advocacy to policymakers: Janssen, Ortho-McNeil (both subsidiaries of Johnson & Johnson, merged into a single entity in August 2011), Johnson & Johnson itself, Purdue, Teva (Actavis), Cephalon, and Janus. One of the leaders of Janssen's Public Policy/Advocacy team, Bob Twillman, had historically worked closely with other pharmaceutical companies to advocate opioid-friendly policy positions. In 2012, Twillman led a task force development a "Pain Care Forum" to create and urge CDC approval of "Clinical guidelines for the use of Chronic Opioid Therapy in Chronic Non-Cancer Pain" (59) and in 2013, Twillman spoke at a FDA public hearing to argue that the reclassification of hydrocodone products from Schedule III to Schedule II would be too costly (60). The Pain Care Forum was a coalition of pharmaceutical companies and advocacy organizations that aimed to be the "voice on pain care issues in Washington," (61) and in 2010, was compromised of 60 organizations including the companies named above as well as Pfizer and Allergan, and the American Pain Foundation, American Academy of Pain Management, and American Pharmacists Association (62). The executive committee was compromised of industry leaders from Purdue Pharma and Ligand Pharmaceuticals, as well as leaders from American Pain Foundation and National Hospice and Palliative Care Organization (62, 63). In a 2008 email from Howard R. Udell, Executive Vice President and Chief Legal Officer at Purdue Pharma, to Burt

Rosen, Vice President of Government Affairs at Purdue Pharma, Udell noted that "The PCF [Pain Care Forum] has become 'a force' to be courted by members of Congress." (64)

In June 2006, the American Pain Foundation and the Pain Care Forum presented a briefing on the "Epidemic of Pain in America" to members of Congress on Capitol Hill (65). The presentation was in cooperation with Representative Mike Rogers, who had received over $600,000 in contributions from the pharmaceutical industry from 1995 to 2015 (66). Supporting material from the Epidemic of Pain in American briefing showed that the Pain Care Forum advocated for pain treatment in young patients. The Forum emphasized that "pain affects people at all stages of life – including infants, children, young adults, and the elderly." (65)

Research!America, an advocacy organization that promotes medical research, included a flyer in the briefing noting, "as many as 20 percent of children experience chronic pain." (65) Research!America was extensively involved with the pharmaceutical and opioid industry; a November 2008 internal memo from the Pain Care Forum showed that Research!America was actively "looking for industry financial (and planning) support" for a 2009 Pain Summit (59), and an internal email from Jon Sackler of Purdue indicated that Research!America had a long term relationship with the Sackler family and until February 2018 named their national leadership award the "R&BS [Raymond and Beverley Sackler] award." (67)

Unbranded campaigns

Companies named in the Oklahoma lawsuit also created unbranded campaigns to target adolescents. In June 2007, an Ortho-McNeil internal presentation titled "Non-Branded Promotions" indicated that it sought to partner with advocacy groups in unbranded campaigns to "establish instant credibility," "develop good will," and "alleviate regulatory anxiety." (68) A 2008 strategy

document for the marketing of Janssen's Nucynta® (tapentadol) indicated that the goal of direct-to-patient unbranded campaigns was "to increase patient origination." (69)

A separate 2008 Janssen internal presentation titled "Pain Non-Branded Campaign Market Research" described an unbranded initiative with the outward-facing message of bringing awareness to physicians about undertreated acute pain, but indicated that the expected impact was "PCPs [primary care providers] stat[ing] that they will be more aggressive in their treatment and use more opioids." (70) This unbranded initiative focused on the negative consequences of undertreated acute pain and emphasized multi-pathway pain treatment in order to encourage physicians to adopt a "more aggressive approach to treating (stronger dosing and meds)." (70) The campaign also attempted to address physician concerns about addiction by "refocusing them from addiction to side effect concerns." (70) The marketing research concluded with the identification of "the elderly, younger patients, post-operative and post-trauma patients" as target groups (70).

Two specific unbranded campaigns centered on young patients. In 2008, Janssen partnered with the National Association of School Nurses (NASN) to launch *Smart Moves, Smart Choices*, a program that proposed bringing awareness to prescription drug abuse among teenagers (71, 72). However, internal Janssen documents classified *Smart Moves, Smart Choices* as an unbranded campaign (73). *Smart Moves, Smart Choices* was also included as part of Janssen's "Pain Franchise" public relations program and for their opioid product Nucynta (74), specifically as part of a larger strategic approach to "redirect dialogue from *drug control* to *controlling pain* [emphasis in original]" (75) and to "educate/influence to maintain physician/patient access." (74) The program launched a website in 2010 as a partnership between NASN and PriCara (76) (later Janssen (77, 78)) and continued to list Janssen as a partner through November 2018 (79). In January 2019, the website contained the same

materials but stopped listing Janssen as a sponsor (80). As of July 2022, *Smart Moves, Smart Choices* website address redirected to the NASN main page (81).

In December 2011, Janssen and Janus partnered with the American Chronic Pain Association (ACPA) to launch a separate unbranded campaign, *Growing Pains*. Robyn Kohn, Director of Medical Education at Janssen, noted this was a "significant contribution to the understanding of pain among the child and adolescent populations." (82) The ACPA described *Growing Pains* as a "a new social networking site for young people with pain" and allowed children as young as 13 years old to become members (83). This unbranded campaign encouraged adolescent patients to seek help for pain. The program website, launched in 2013, listed funding by Janssen and included a page on "Talking With Health Care Providers" that stated "you can manage [pain] by improving the quality of your life, increasing your function, and reducing your sense of suffering," claims similar or identical to those made in other opioid marketing campaigns (51, 84). The *Growing Pains* website was maintained through at least 2021 (85).

Opioid industry targeting of women

Corporate strategic planning

In a presentation to increase its European sales after 2001, Johnson & Johnson emphasized that one of its "major franchises" was "women's health." (86) In 2012, Janssen (a subsidiary) expanded its marketing to women with a new "Mainstream Media Pitch." (87) In 2013, Teva created an "Advocacy Mapping" plan to "understand potential alliances and detractors… to engage and/or minimize them" which specifically noted potential allies that focused on women's health (88).

Advocacy to policymakers

The Pain Care Forum developed by multiple opioid manufacturers also advocated for opioid use by women. Documents from the Pain Care Forum's June 2006 briefing with lawmakers,

described above, indicated it sought to establish a perceived need for painkillers among women. While describing the demographics of pain, the Forum specified "women's pain reports are taken less seriously than men's" and "women receive less aggressive treatment than men for their pain."(65)

As part of their message that chronic undertreated pain disproportionately affects women, the Pain Care Forum shared stories of women suffering from unresolved chronic pain due to reflex sympathetic dystrophy (RSD), which it spotlighted as a pain condition that affected women more than men (65). Documents used as supporting material from the Pain Care Forum briefing showed a pattern of using personal anecdotes about RSD to warn of the disastrous effects of untreated chronic pain among women. One story focused on Barbara, who suffered from RSD, and warned "when the pain rises up, I think it is not really worth living." (65) The story featured Barbara's female friend who "probably had RSD" and "eventually committed suicide." (65) Another story focused on Alexandra, a sixteen-year-old woman suffering from RSD since the age of ten, who grieved the loss of her childhood due to untreated chronic pain and noted that her senior year had been spent "tak[ing] more medications than my grandparents" and spending time in the hospital "just wishing to walk." (65) Although the Pain Care Forum claimed that pain stories like Alexandra's are "told 50 million times," (65) there was no accompanying context: RSD is a rare disease and likely not representative of how most women experience pain or their resulting levels of disability (89, 90).

The same briefing included a 2006 article from *The Washington Post* which focused on physician Howard Heit. It highlighted his decision to prescribe Oxycontin® to his pregnant daughter-in-law and that her infant did not experience withdrawal symptoms, implying that opioid use could be safe for pregnant women and their newborns (65). The article noted, "she [Heit's daughter-in-law] knew she could never get through the pregnancy without the medication

[Oxycontin]." (65) At the time of the article's publication, the risk of neonatal abstinence syndrome in infants exposed *in utero* to opioids was known and characterized (91, 92). The article failed to mention that in 2004 Dr. Heit had provided consulting services promoting Actiq®, a fentanyl transmucosal lozenge sold by Cephalon.(93) Dr. Heit continued to consult for Cephalon and Johnson & Johnson in 2011 (94, 95).

A separate *New York Times* article titled "When it Comes to Severe Pain, Doctors Still Have Much to Learn" was also included in the supporting material for the briefing and focused on "clueless or unnecessarily cautious" doctors and their reluctance to prescribe opioids (65). The article included a quote from a 1995 entry into *The Journal of the American Medical Association*: "Bringing about significant change may depend on empowering patients to demand adequate pain treatment. This empowerment will not come easily, especially if opioids must be used for pain relief and the pain is of nonmalignant origin." (65)

Unbranded campaigns

Consistent with efforts to market opioids as a form of patient empowerment, the American Pain Foundation brainstormed techniques to target women for a fibromyalgia disease awareness campaign funded by a $10,000 check from Pfizer in July 2007 (65). The notes claimed that the "empowerment angle can be used with any program [emphasis in original]" and that the disease awareness program aimed to "create patient demand for proper pain diagnosis and treatment." (65) The Foundation planned to use "viral tactics/word of mouth education (sic)" by "let[ting] women educate women in their natural setting (e.g., Tupperware parties, garden groups, e-cards)." (65) The Foundation also proposed to share this outreach message via communication channels such as "women's books" and "the National Women's Health Resource Center." (65)

In 2012, Janssen proposed similar strategies to target women as part of a public relations program for its pain franchise and specifically to market Nucynta. Janssen's pitch stated, "Women are feeling the pain, study says—what every woman needs to know," and the message was targeted to "women's books" among other advertising venues (74).

DISCUSSION

Summary of the evidence

This study of internal opioid industry documents detailed how opioids were marketed to children and women at the beginning of the 21st century through targeted advocacy directed to policymakers and by using unbranded campaigns intended to increase demand for opioids. It builds on previous documents research that has illustrated the unreliability of data, claims, and marketing produced by the pharmaceutical industry (51-54). Over the same time period there were significant increases in opioid use, poisonings, and related mortality in these populations.

Pharmaceutical industry efforts to market opioids to children primarily relied on unbranded campaigns, which sidestep FDA regulations on traditional pharmaceutical advertisements (27). These campaigns used appeals to authority to influence children's understanding of pain and opioids, seeking to recruit adults they would be perceive as credible, including coaches and school nurses. Two specific unbranded campaigns, *Growing Pains* and *Smart Moves, Smart Choices*, were explicitly developed and launched as a means to market opioids despite being presented to the public as public health campaigns. These approaches were likely to have been influential given that past research has shown that advertisements in school settings affect children because they are associated with authority figures such as teachers (39). This kind of marketing is problematic

because children and adolescents may have difficulties understanding the fundamental purpose of advertisements, due to still-developing executive functioning and critical thinking skills, as well as a lack of skepticism among those of younger age (96).

Opioid manufacturers also developed direct appeals to women based on the desire for self-empowerment, emotions and fears surrounding disability and pregnancy, and social desirability. This marketing may help explain the disproportionate opioid-related health risks among women; by 2014 opioid-related hospitalizations rates for women surpassed those of men in a majority of states (97). Appeals to policymakers made through the industry-sponsored Pain Care Forum used selective information and anecdotes to develop claims that opioids were needed to address untreated pain among women. Companies also provided financial support for advocates that supported opioid use among pregnant women. One suggestion made through the Pain Care Forum, that Oxycontin use during pregnancy is safe, was particularly concerning given that it failed to describe the risks of neonatal abstinence syndrome (NAS) due to *in utero* opioid exposure (91, 92). Although opioid use in limited doses during pregnancy may be warranted for treatment of some specific conditions (e.g., terminal cancer), American Pain Society guidelines recommend no use or minimal use due to adverse effects on fetal development (98, 99). In the years following these presentations the incidence of NAS quintupled (6).

Strengths and limitations

Our study has strengths and limitations. Internal industry documents provide a unique perspective on industry behavior with implications for public health that is "not available from any other source" (30). However the Drug Industry Documents Archive does not include all documents created by the pharmaceutical companies involved during the development, production, marketing, and distribution of opioid products. While the documents included in the archive were considered

significant during the process of legal discovery, they may not include other relevant material, particularly documents that never existed in electronic form**.** For example, although we identified marketing materials explicitly targeting women as a group, we did not find comparable materials intended to reach men as a group; nonetheless, these documents may have existed. Some documents were presentation aids such as PowerPoint decks and sales pitch outlines that may not have been presented or used, although we searched public records for validation that campaigns were launched and provide that information where available. Our findings may not be generalizable to companies that were not included in the settlement or to marketing for non-opioid products, although they are drawn from multiple companies that both sold their own opioid products to consumers and that provided active ingredients to multiple opioid manufacturers. Due to the delay in releasing documents related to litigation, some of the materials cited in the manuscript are date back over two decades, and reveal a pattern of pharmaceutical company behavior that has remained largely unresolved; the FDA has been criticized by multiple sources for failing to change its regulatory policies to address opioid marketing over this time period (100).

Recommendations for research

Litigation against opioid manufacturers continues, as does the release of new documents identified in legal discovery. Further review and analysis of pharmaceutical industry documents is needed to understand the industry's ongoing marketing strategies, what portions of the population may be targeted, and whether pharmaceutical companies may market other products using similar campaigns, particularly given that FDA regulations remain unchanged.

Conclusion

In previous research, findings from industry documents research have been critical in generating discussion and scrutiny about the role of industry funding and influence in scientific publications and health policy, and in generating changes in policy and practice that protect public health (30, 101, 102). To our knowledge, this study represents the first analysis of internal industry documents drawn from lawsuits against opioid manufacturers that describes marketing to children and women. Findings from previous pharmaceutical industry documents research have illustrated the unreliability of industry-associated data, claims, and marketing (31, 53, 54) and have detailed efforts by manufacturers to influence physicians (41-45). This work builds on this previous research by providing new insight into how pharmaceutical companies sought to increase opioid use among women and children. Our results serve as a warning to clinicians and policymakers about the risks of direct-to-consumer advertising and particularly the use of unbranded campaigns. The opioid industry's use of unbranded campaigns to promote opioid use, despite the existence of regulation intended to limit pharmaceutical advertising, suggests that additional regulatory oversight may be needed to discourage inappropriate marketing of addictive medications.

Figure legends

Fig 1. Excerpt from the October 2011 "Imagine the Possibilities Pain Coalition" meeting. The coalition served as group of leaders in pain management and Janssen professionals that aimed to influence the perception of pain among target groups which included youth and military veterans.

Source: ([DATASET] link: https://www.industrydocuments.ucsf.edu/drug/) UCSF Drug Industry Documents Archive (CC BY-NC-ND 3.0)

Declarations

Acknowledgements: The authors acknowledge Rachel Taketa at the UCSF library for assistance with searching for documents.

Competing interests: The authors declare they have no actual or potential competing financial interests.

Funding: This work was supported by National Institutes of Health #DA046051 (Apollonio) and a Pathway Project Grant from the University of California, San Francisco (Yakubi and Gac). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability: The data analyzed for the current study are available from the Drug Industry Documents Archive repository, ([DATASET] link: https://www.industrydocuments.ucsf.edu/drug/) .

Ethical approval: Not applicable; findings are based on data in a public repository.

Author statement: HY, BG, and DA worked together to design the study, analyze the data, interpret the results, and revise the manuscript. HY drafted the manuscript and HY and BG completed the initial review of the documents.

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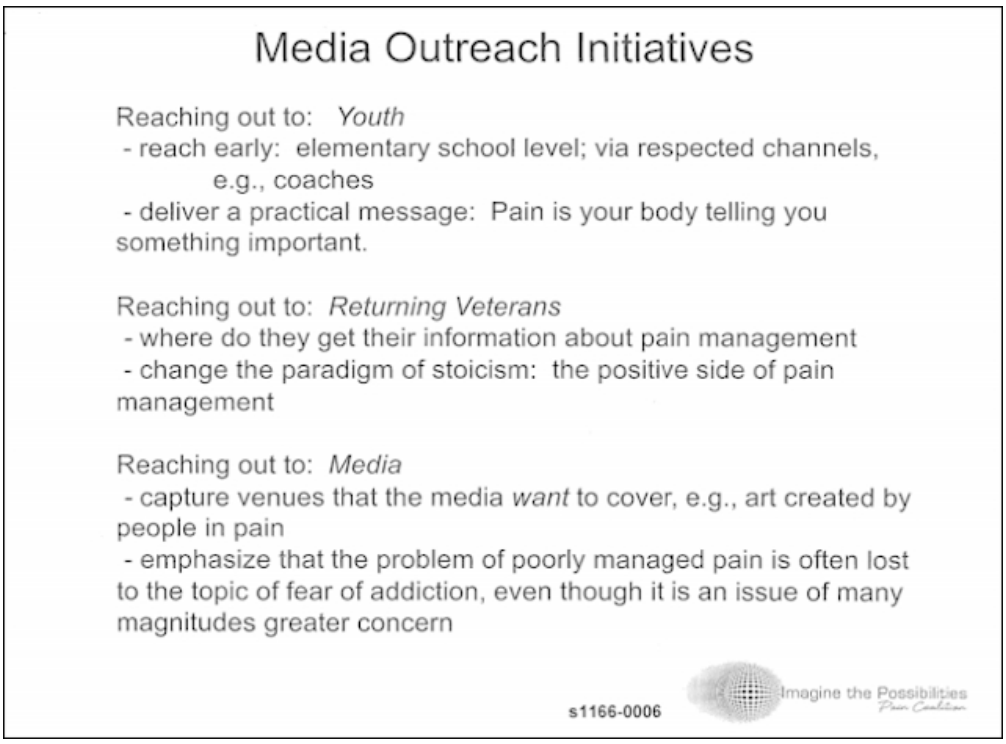

Fig 1. Excerpt from the October 2011 "Imagine the Possibilities Pain Coalition" meeting. The coalition served as group of leaders in pain management and Janssen professionals that aimed to influence the perception of pain among target groups which included youth and military veterans.
Source: UCSF Drug Industry Documents Archive (CC BY-NC-ND 3.0)

Title: Industry strategies to market opioids to children and women in the United States: A content analysis of internal industry documents from 1999 to 2017 released in State of Oklahoma v. Purdue Pharma, L.P. et al

Running title: Marketing opioids to children and women

Supplemental file

Our study relied on a retrospective content analysis of pharmaceutical industry documents (1). On January 24, 2020, the University of California San Francisco Industry Documents Library released 503 documents totaling 62,703 pages drawn from *State of Oklahoma, ex. rel. Hunter v. Purdue Pharma, L.P., et. al. (Okla. Dist. Ct. Aug. 26, 2019),* a lawsuit brought by the state of Oklahoma against companies manufacturing and selling opioids, including Purdue, Teva (Actavis), Cephalon, Janssen, Ortho-McNeil-Janssen, Allergan, and Watson (2). Documents include reports on clinical trials, witness declarations, internal corporate communications, short videos taken at conferences, and marketing campaign materials.

Our approach to documents review relied on previously validated standards for research using tobacco industry documents (3, 4). Two authors (HY, BG) who had completed training provided by the UCSF Industry Documents Library on search strategies and documents analysis (the Annual Tobacco Documents Workshop) conducted the preliminary analysis; this team independently reviewed all 503 documents in the archive. Both coders and an independent third reviewer (DA) with experience analyzing industry documents and who has served as an instructor for the UCSF Library Annual Tobacco Documents workshop, created a master text file with information on all 503 documents that summarized key points drawn from each document along with supporting information including quotes, figures, and concepts, and in the case of short videos,

transcriptions. To ensure that no documents were excluded, each was marked with the unique identification code provided by the library.

We reviewed documents using modified grounded theory, an inductive methodology that uses source material to identify hypotheses and to categorize evidence based on general themes, an analytical strategy previously used in the analysis of pharmaceutical industry documents (5). Authors of industry documents used consistent terminology (e.g., "youth") when referring to groups that they identified as target markets, allowing comparison across multiple companies and documents. Our expectations were that opioid manufacturers used strategies similar to those of the tobacco industry, specifically: seeking to influence policymakers, making emotional marketing appeals, and understating the risk of addiction.

We noted strategies mentioned in the documents we reviewed and provided specific quotes and screenshots in the master file to aid understanding of our classifications. When questions arose regarding a document's relevance, it was discussed by all three authors until agreement was reached. Discussions were conducted in weekly meetings of one to three hours each held May-August 2020. When the two coders disagreed regarding interpretation, the designated reviewer read the document and made a final decision; documents for which there were disagreements were then reviewed again by all three authors before deciding to include or exclude them. Documents were excluded if the authors were unable to identify whether they were relevant (e.g., spreadsheets tracking sales by region that were described only by proprietary identification codes). After this initial review, one investigator (HY) extracted all materials relating to industry marketing to women and children from the master file as a resource for the manuscript. These documents referenced advocacy and marketing campaigns, business plans, and advertising strategies focused on increasing opioid sales or creating favorable perceptions of opioid products.

Supplement references

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SRQR checklist[1]

Section/topic	#	Item	Page #
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Title	1	Concise description of nature and topic of study	1
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Conflicts of interest	20	Potential sources of influence on study conduct and conclusions	21
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