Thematic Analysis

Increase your Confidence in Opioid Prescribing: Marketing Messages in Continuing Medical Education Activities on ER/LA Opioids

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Background: Overprescription of opioids has fueled an epidemic of addiction and overdose deaths. The FDA required manufacturers of extended-release/long-acting (ER/LA) opioids to fund continuing medical education (CME) on opioids as part of a Risk Evaluation and Mitigation Strategy (REMS).

Objectives: We sought to determine whether industry-funded REMS on long-acting opioids were consistent with the FDA's goal to reduce serious, adverse outcomes resulting from inappropriate prescribing, misuse, and abuse.

Study Design: In 2018, we analyzed all internet-based REMS CME activities funded by the REMS Program Companies (RPC), a consortium of ER/LA opioid manufacturers.

Methods: We utilized systematic narrative thematic analysis, an inductive approach that allows for mapping of concepts and meanings across a body of data by identifying, recording, analyzing, and refining key narrative points, called "themes". Authors viewed all REMS activities multiple times.

Results: Ten themes were identified, all of which were at least somewhat incongruent with federal guidelines and their goals:

1. Chronic pain is a common, under-treated problem.
2. Chronic pain is a chronic disease.
3. Opioids are an appropriate treatment for chronic pain.
4. ER/LAs are more appropriate than immediate-release (IR) opioids for chronic pain.
5. Tolerance is normal, expected, and beneficial.
6. "Opioid rotation" can maximize analgesia and minimize adverse effects.
7. There is no population for whom opioids are absolutely contraindicated or inappropriate.
8. Screening and monitoring tools are effective for preventing opioid-related problems.
9. Opioid related adverse effects, such as respiratory depression and addiction, are due only to misuse and abuse.
10. Addiction, overdose, and death are due to street drugs such as heroin and fentanyl, not prescription opioids.

Themes and statements repeated in these activities were inconsistent with current medical knowledge, evidence-based federal guidelines, and FDA goals.

Limitations: We evaluated only online, not live, CME. We also did not evaluate individual conflicts of interest of faculty.

Conclusions: Industry-funded REMS-compliant CME on opioids contain messages that misrepresent scientific evidence and may foster overprescribing of opioids.

Key words: Opioids, REMS, continuing medical education, pharmaceutical industry, marketing messages, prescribing behavior, chronic pain, addiction

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Overprescription of opioids has fueled addiction and overdose deaths (1). To mitigate harms, the Food and Drug Administration (FDA) required opioid manufacturers to propose and implement a Risk Evaluation and Mitigation Strategy (REMS) for extended-release and long-acting (ER/LA) opioids (2). In 2012, the FDA approved the first REMS to require manufacturers to fund Continuing Medical Education (CME) (3). Core messages were mandated in a FDA Blueprint (4) which the industry helped develop (2,5).

The REMS Program Companies (RPC), a consortium created by ER/LA opioid manufacturers, awarded independent educational grants to accredited CME providers to produce and assess activities "designed to ensure that the benefits of ER/LA opioid analgesics outweigh the risks in patients whose clinicians have determined these medications to be an appropriate treatment option" (6).

The first, most popular, RPC activity was called Safe and Competent Opioid Prescribing Education (SCOPE of Pain) (7). By May 2018, over 150,000 people had registered for live or online SCOPE of Pain training; 85% completed the training. Overwhelmingly, people chose online training (8).

By May 30, 2018, RPC had funded 97.1% (866 of 892) of past, current, or planned ER/LA opioid REMS-compliant activities; 93,192 active prescribers and more than 300,000 others successfully completed an activity by REMS CME providers. Although numerically there were more live activities, internet activities accounted for more than 70% of participation (1).

No REMS has been shown to reduce harms (10-12). The REMS for transmucosal immediate-release products failed to reduce inappropriate fentanyl prescribing (13). Although the ER/LA REMS claimed to decrease prescribing (14), prescriptions for immediate-release (IR) opioids also decreased during a period when there was no REMS for IR opioids. At the time, many efforts were made to reduce opioid prescribing.

Industry-funded CME contains promotional messages (15,17-21). Commercial bias in industry-funded CME is not obvious, and current tools for identifying bias (22,23) fail to identify covert marketing messages. The few studies that examined subtle biases consistently found subjective information favoring sponsored drugs (15,17,24,25).

The potential audience for opioid-related education is vast. Forty-seven states (all except Colorado, Montana, and South Dakota) and the District of Columbia require CME for medical license renewal. Thirty-eight states require CME pertaining to controlled substances, pain management, opioids, and/or addiction; 17 of these specifically require opioid-related CME (16).

Our study assessed whether information in industry-funded REMS CME on ER/LA opioids was consistent with the FDA's stated goals regarding opioids. We systematically identified and analyzed thematic commonalities, repeated statements, and points of information among all available REMS activities, and compared these themes with the current state of knowledge on opioids.

Methods

In July 2018, we identified all internet-based REMS CME activities available on RPC's ER-LA-OPIOIDREMS website (26). After an extensive internet search, we were unable to identify any additional REMS-compliant CME. Every activity available at the time of analysis was included. All internet searches led to RPC activities, including links from state medical boards, the National Institute of Drug Abuse, and the Accreditation Council on Continuing Medical Education.

We analyzed all activities for consistency with the FDA's stated goal "to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death" (4).

We utilized systematic narrative thematic analysis to identify and elucidate major teaching points within the REMS activities, both individually and across the corpus. While quantitative research relies on the concept of absolute truth, the epistemological foundation of qualitative research relies on the concept that reality is constructed by social, historical, and individual contexts.

Qualitative research is ideal for exploring complex issues in medical education because it examines phenomena in real-world settings, and interprets these phenomena in terms of the meanings attributed to them (27). Thematic analysis, an inductive approach that allows for an intricate mapping of the concepts and meanings being communicated across a heterogenous body of spoken or written data, requires identifying, recording, analyzing, and refining key narrative points called themes within a data set.

Guided by Braun and Clarke's 6 step method (28), our process entailed: 1. close familiarization with data through multiple viewings of activities by 2 or more analysts; 2. extraction and annotation of important teaching points relevant to our stated research interests, each assigned a unique alphanumeric code for

ease and consistency of data management; 3. creating summary-statement definitions of specific themes (those that emerged repeatedly and encompassed multiple codes) in the body of CME examined (e.g., "Opioids are an appropriate treatment for chronic pain"); 4. collective comparative review, and repeated refinement of the total list of themes; 5. developing, by consensus, a detailed analysis of each theme's overt messages and more subtle connotations; and 6. creation of the academic paper, using verbatim quotes to illustrate analytic points.

Five authors (BG, HDL, JB, DP, MD) each watched or read a subset of REMS activities. All authors collectively created a preliminary list of assertions and teaching points within individual CME activities and across the entire body of the CME activities. These we identified as themes. As additional activities were viewed, the list of themes was refined and a set of codes was created for teaching points (Appendix Table 1). Each code represented an indivisible semantic unit. For example, under the theme, "ER/LAs are more appropriate than IR opioids for chronic pain," Code O5 referred to an assertion made by a speaker, author, or slide that, "ER/LA opioids are convenient and may lead to better adherence."

Two or more researchers individually analyzed each activity for the presence of specific themes; the number of times a theme appeared in an activity was not counted. Only themes noted by 2 or more researchers were included in the data set, which was subsequently coded for data management purposes. Assessment proceeded in an additive chronological sequence, during which new assertions and teaching points emerged, as the corpus of texts reviewed expanded. In this recursive process, themes were added, deleted, split, expanded, or re-defined as more activities were evaluated and previously viewed activities were reviewed with newer findings in mind. Data saturation was reached when the entire corpus of identified CME activities had been assessed and all emerging themes had been recorded.

After the set of themes was finished, we evaluated messages against current medical knowledge and comprehensive, systematic review-based federal guidelines, including the Centers for Disease Control (CDC) Guideline for Prescribing Opioids for Chronic Pain and the Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guideline for Opioid Therapy for Chronic Pain. We also compared themes with newly available marketing materials revealed in litigation against opioid manufacturers.

Results

We identified 15 enduring (online) activities from the ER/LA REMS website. Two were unavailable, 1 was not an ER/LA REMS, and 2 were duplicates, leaving 10 activities available for analysis (29-38). All activities were available without cost and were accredited for 1 to 3 years. Release dates of the activities ranged from April 11, 2016 to January 31, 2018.

Eight of 10 activities included the word "safe" in the title. Seven were videos or slide shows with audio (29,31,32,34,36-38) and 3 were text based, sometimes with embedded videos (30,33,35). The format of 1, REMS Playbook for Opioid Prescribing, was closely modeled on ESPN programming (34).

The same faculty appeared across several activities. Four activities (31,33,37,38) were produced as part of the Collaborative for REMS Education (CO*RE), a partnership of medical and healthcare provider organizations (39). CO*RE trainers all used the same basic slide set, modified for different audiences (e.g., nurse practitioners, physician assistants).

REMS-compliant activities appear to be government-endorsed educational materials. Although several activities invoked FDA involvement (1 inaccurately referred to "the grant… that's funded through the FDA for this program…" (36)), the FDA did not in fact fund, approve, or endorse specific activities.

Themes

We identified 10 distinct themes in the online RPC-funded REMS activities that were, in at least some elements, incongruent with federal guidelines and their goals:

1. Chronic pain is a common, under-treated problem.
2. Chronic pain is a chronic disease.
3. Opioids are an appropriate treatment for chronic pain.
4. ER/LAs are more appropriate than IR opioids for chronic pain.
5. Tolerance is normal, expected, and beneficial.
6. "Opioid rotation" can maximize analgesia and minimize adverse effects.
7. There is no population for whom opioids are absolutely contraindicated or inappropriate.
8. Screening and monitoring tools are effective for preventing opioid-related problems.
9. Opioid related adverse effects, such as respiratory depression and addiction, are due only to misuse and abuse.
10. Addiction, overdose, and death are due to street

drugs such as heroin and fentanyl, not prescription opioids.

Identification of Themes

Themes and illustrative quotes are listed below. Additional examples of quotes supporting themes and supporting codes, are in Appendix Table 1. Contravening facts and relevant marketing messages from other sources are noted.

1. Chronic pain is a common, under-treated problem.

Activities exaggerated the prevalence of significant pain. A typical statement was, "Undertreatment of pain is a serious problem in the United States...and pain should be treated aggressively…" (35). The concept that chronic pain is an undertreated epidemic was deliberately perpetuated by opioid manufacturers (40). For example, a pamphlet by Purdue, manufacturers of OxyContin, states that, "[u]ndertreatment of pain is a serious problem" and "pain should be treated aggressively" (41).

Many activities stated that 40% of Americans, or 100 million people, have chronic pain. The author of the study cited for this statistic has publicly rejected this interpretation as misleading, explaining that this figure included mild, everyday pain from conditions such as arthritis and low back pain. The cited study shows that 10%-15% of Americans have substantial work disability because of chronic pain (33,42).

All activities included ER/LA opioids as a reasonable option for treating chronic pain.

2. Chronic pain is a chronic disease.

Many activities compared chronic pain to other chronic illnesses and opioids to other medication for chronic diseases. A typical statement was, "We need to treat our pain patients the same way we treat our patients with other chronic medications" (32).

While the question of whether chronic pain can be considered a disease remains under debate (43,44), comparing chronic pain to diabetes, hypertension, and other chronic diseases may normalize lifelong opioid treatment.

3. Opioids are an appropriate treatment for chronic pain.

Every activity reassured clinicians about starting and continuing opioids in patients with chronic pain. "This module is designed to help increase your confidence in opioid prescribing," declared the Real CME Get Smart activity (30).

Some activities described opioids as the most effective medication for chronic pain; others described opioids as "one of many tools in the toolbox." A Medscape activity states, "The initial therapeutic trial of an ER/LA opioid may last from several weeks to several months" (33). "You can never go wrong with opioids if you start low and go slow," states ASAM's activity (31). Four other activities also advised "start low and go slow".

Statements such as, "Opioid medications are an effective option for many patients and can be safely used for short- and long-term pain control," (30) imply that initiating long-term use of opioids is safe. "Go slow" suggestions imply that upward dose titration is safe, if done gradually. In fact, both addiction risks (1) and mortality increase with both dose and duration of therapy in chronic pain patients (45-47).

Every activity presented opioid therapy as an efficacious or the most efficacious treatment for chronic pain. In contrast, systematic reviews conducted by the CDC (48), the VA/DOD (49), and others (50,51) conclude that no evidence supports the efficacy of long-term opioid therapy for chronic, nonmalignant pain. Notably, a systematic review that included 9 trials with 1,431 patients found that NSAIDs were as effective as —and safer than— opioids for chronic noncancer pain (52).

Chronic opioid use can cause hyperalgesia, which may be seen within a month of opioid initiation (53). Additionally, withdrawal can cause pain and end-of-dose withdrawal pain may be interpreted as a need for more opioids (1). Tapering down opioids may actually decrease pain (54).

Statements such as "[opioids] can certainly improve function and quality of life for people suffering from real pain" (37) are contradicted by studies showing that opioids decrease functioning (55,56). Purdue's own study on OxyContin CR in osteoarthritis patients showed no benefit for function, little benefit for pain —10 mg twice daily was no better than placebo— and a very high rate of adverse effects (57).

4. ER/LAs are more appropriate than immediate-release (IR) opioids for chronic pain.

Activities suggested that ER/LA opioids are superior to IR preparations for chronic pain management. For example, one activity suggested that , "[F]or the long acting opioids, there's a thought that there's a more consistent plasma concentration [that limits end-of dose failure] …Convert[ing] to a long acting

[formula produced] more stable pain relief" (36). Although inconsistent with evidence (48), this concept is consistent with promotional messaging. A legal complaint from Massachusetts cites Purdue marketing claims that OxyContin provided more consistent pain relief, comparing ER/LA opioids to a "full tank of gas", while immediate-release opioids required "stopping at each exit to refuel" (41).

Although ER/LA opioids may increase addiction risk (48), 1 activity implied that ER/LA opioids are less addictive, stating,"…IR/short-acting opioids are pretty fast in onset,…so they're a bit more rewarding to people who are vulnerable to those reward effects than the sustained-release opioids" (29).

5. Tolerance is normal, expected, and beneficial.

Tolerance to opioid analgesic effects can lead to increased doses and increased harms, but was often normalized in these activities, which presented tolerance as a beneficial adaptive mechanism. Representative statements included, "Keep in mind that tolerance does not equal addiction. Tolerance to and dependence on opioids are normal physiological responses to long-term treatment," (30) and, "Opioid-tolerant patients also develop tolerance to many opioid side effects, like drowsiness and respiratory depression" (30). The normalization of dependence and tolerance echo industry messages: a Purdue publication, Providing Relief, Preventing Abuse, compares dependence on opioids to dependence on antihypertensives or decongestants (58).

Although tolerance is expected, and while opioid-tolerant patients can survive higher doses of opioids than non-tolerant patients, opioid tolerance does not protect against harms (1). Higher doses, even in opioid-tolerant patients, increase the risk of addiction, respiratory depression, and death.

6. "Opioid rotation" can maximize analgesia and minimize adverse effects.

Activities encouraged switching opioids when 1 was ineffective or caused adverse effects. A typical statement was "Current evidence does not clearly indicate an optimal choice for the new opioid; multiple rotations may be necessary to achieve satisfactory outcomes" (30).

The FDA Blueprint required REMS activities to discuss differences in potency among opioids, stating that, "prescribers should be knowledgeable about converting patients from…one ER/LA opioid product to another ER/LA opioid product" (4). Instead, these activities endorsed switching opioids even after 1 – or several – were ineffectual, or caused harms. Activities implied, without evidence, that "opioid rotation" could minimize adverse effects while maximizing analgesia. For example, 1 activity recommended "a trial of several opioids…to find an acceptable balance between the analgesia and tolerability" (29). Another activity summarized, "the key point is that, in any given patient, the absence of benefit or side effects with one opioid does not predict similar responses to another opioid" (30). A Cochrane systematic review found that no reliable evidence supported opioid rotation; all reports were anecdotal, observational, or uncontrolled studies (59).

7. There is no population for whom opioids are absolutely contraindicated or inappropriate.

Activities normalized the prescription of opioids in vulnerable subpopulations. Although pregnant women, patients over 65 years old, patients with mental health conditions, and patients with substance use disorder are all at increased risk of harms from opioids (48), these activities invoked individualized therapy to reassure clinicians.

For example, an activity stated, "A substance abuse history does not necessarily prohibit opioid therapy, but it does warrant additional monitoring and assistance from persons with expertise in managing pain, addiction, or other mental health concerns" (33). "Mary Williams," a case study highlighted in Scope of Pain, is a pack-a-day smoker with an alcohol use disorder, whose mother died from alcoholic cirrhosis. The activity concludes that she is "moderate risk" on the Opioid Risk Tool (ORT) and that it is acceptable to prescribe opioids (29). This advice perpetuates adverse selection; patients with mood disorders and substance abuse disorders are more likely to receive opioids at higher doses and for longer periods (60,61).

Activities noted, accurately, a dearth of data regarding opioids and pregnancy, but did not discourage prescribing opioids to pregnant women. One activity stated that, "...there are no data from well-controlled studies of ER/LA opioids in pregnancy on which to base clinical decisions" (30). Precautions for elders and children were minimized or omitted. As 1 activity stated, "So, uh, older adults are at higher risk for respiratory depression. Doesn't mean you can't use an opioid" (31).

"Personalization" of pain therapy was ubiquitous. One activity denigrated research, stating, "studies don't study real patients" (32). Focusing on individualized treatment effectively advocates for continued prescribing of opioids in vulnerable populations. This echoes

Purdue's "individualize the dose" campaign, which was allegedly designed to "increase the dose" (41).

Providers were cautioned not to apply addiction criteria to chronic pain patients. "… We need to be careful even applying the opioid use disorder criteria from the DSM-V when it applies to our patients with chronic pain on long-term opioid therapy" (29). One activity stated that, "Addiction is a psychological state does not relate to normal physiological processes [sic]" (30).

8. Screening and monitoring tools are effective for preventing opioid-related problems.

The concept that addiction-prone patients could be easily identified and managed was common. An exemplary statement included, "…the good news is the majority of patients are going to screen negative and you're done" (29).

Screening and monitoring tools, including the ORT, urine drug testing, patient prescriber agreements, and pill counts, are presented as simple, effective means to prevent addiction, misuse, and diversion. However, none of these measures have been shown to be effective. Urine drug testing, exhaustively reviewed in each REMS, and opioid treatment agreements are supported by only weak evidence (62). The ORT was developed by a paid consultant to opioid manufacturers (63), and the CDC found results from the ORT "extremely inconsistent" (48).

The overarching message in these REMS activities seems to be that standardized tools can help justify initiating or continuing opioid therapy, but when a tool raises an alarm, opioids can still be justified. As 1 module stated, "Now you can still treat people with opioids even if they have a high risk, but you would monitor them differently" (31). A key message in a Purdue publication plan was, "opioid overdose is controlled by good prescribing practice and patient monitoring, not by arbitrary dosage limitations" (41).

9. Opioid-related adverse effects, such as respiratory depression and addiction, are due only to misuse and abuse.

Fewer than a third of activities mentioned that opioids are dangerous even when used as prescribed. Opioid overdose, the first risk cited in the FDA Blueprint, was not emphasized in any activity. Addiction risks and other major adverse effects in pain patients were minimized, while minor adverse events, especially constipation, were highlighted.

Severe adverse effects (respiratory depression and addiction) were presented as occurring only under specific conditions: in patients with sleep apnea or who combined opioids with benzodiazepines or alcohol. Opioids were portrayed as supporting actors. A typical statement was, "…there is a concern about overdose, especially when opioids [–especially at high doses–] are combined with other sedatives like benzodiazepines or alcohol" (29). In fact, opioids used exactly as prescribed and without concomitant medications can cause addiction, respiratory depression, and death (1).

10. Addiction, overdose, and death are due to street drugs such as heroin and fentanyl, not prescription opioids.

A consistent message in these activities is that only heroin and illicit fentanyl —not prescription opioids— cause addiction, overdose deaths, and other adverse events. Activities often contained a figure illustrating the plateauing of deaths from prescription opioids, while heroin- and fentanyl- related deaths skyrocketed. This seems to imply that the problems with prescription opioids are over.

In fact, prescription opioid deaths remain high: in 2017, there were 14,495 non-heroin and non-fentanyl overdose deaths in the U.S. (65). The risk-benefit ratio for chronic non-cancer pain is highly unfavorable; 1 in 15 (7.5%) chronic opioid users suffers a serious adverse event (66). Also, illicit opioid overdoses are driven by prescription opioids. Four of 5 heroin users began with a prescription opioid (67).

Some REMS activities imply that prescribing opioids to "legitimate pain patients" will actually prevent addiction, because refusing to prescribe enough opioids may force patients to turn to heroin. This was described as the "squeezing the balloon phenomenon" (29). A typical statement was, "When a legitimate pain patient is improperly managed they often find the streets" (37).

In fact, overprescribing feeds addiction in 2 ways. Some patients prescribed opioids will become addicted. Also, leftover opioids can be diverted. One activity implied that even diverted prescription opioids protected users against harm: "as you make prescription opioids less available and harder to obtain for those that are misusing them, it's being taken over by easily accessible high-purity heroin and people are dying from that" (29).

A key message in a Purdue publication plan for marketing OxyContin was, "It's not addiction, it's abuse" (41). In an email disclosed in litigation, Richard Sackler, former chairman and president of Purdue Pharmaceuticals, the manufacturer of OxyContin, said "we

have to hammer on the abusers in every way possible. They are the culprits and the problem. They are reckless criminals" (41).

Discussion

Our study found that themes and statements in industry-funded REMS CME activities on ER/LA opioids did not support the FDA's goals and were inconsistent with current medical knowledge and evidence-based federal guidelines. Although opioids are valuable for end-of-life care, cancer-related pain, and acute pain, evidence is consistent that daily opioids for chronic, nonmalignant pain is both ineffective and dangerous. Addiction and overdose deaths aside, long-term opioid therapy for chronic noncancer pain —even when taken exactly as prescribed— decreases function and worsens quality of life (48).

Several activities stated that, "the pendulum has swung too far," implying that undertreatment of pain was a more pressing problem than over-prescription of opioids. Activities inaccurately presented prescription opioids as safe and effective for chronic nonmalignant pain and only dangerous when misused, abused, or combined with other drugs. They suggested, incorrectly, that serious adverse effects occurred only within specific, predictable circumstances; implied, against evidence, that ER/LA opioids are less likely to cause misuse or addiction than IR opioids; and inappropriately reassured prescribers that prescribing opioids in high-risk populations was safe. Overtly false statements were made regarding risks of prescribed opioids. These activities morally license health care providers to initiate opioids to treat chronic pain (an unproven use) even in high-risk patients, to ignore signs of opioid use disorder, and escalate doses without worrying about addiction, respiratory depression, or death.

"Personalized" pain therapy was invoked to justify irrational prescribing. Activities distinguished "legitimate pain patients" from users of street drugs. Pain patients exhibiting addictive behavior were called pseudo-addicted (32,33) a discredited condition (64) used to justify increasing opioid doses. Opioids were justified, even in frankly addicted patients, to save patients from street drugs.

The themes identified could easily be overlooked in a single activity, but when viewed as a corpus the commonalities become strikingly obvious. The factually incorrect and misleading themes identified in multiple activities appear to be aimed at increasing prescriber comfort with starting and maintaining chronic pain patients on opioids. Several themes we identified have subsequently been exposed as marketing messages in court documents. Purdue's efforts to enhance sales by positioning OxyContin as safe, effective, and non-addicting for chronic, non-malignant pain have been well-documented (71,72).

Limitations

We did not evaluate live CME. It is possible that themes would be different in live CME events; however, given that almost all live REMS CME on ER/LA opioids were RPC-funded (9), messaging is likely to be similar.

Although a Mother Jones investigation found 7 of 24 faculty members on ER/LA opioids REMS activities received a total of $1.6 million from opioid manufacturers (70), we did not evaluate individual conflicts of interest of faculty or the effect of these conflicts of interest on opinions expressed.

Conclusion

This is the first study to identify misleading messages in CME on opioids and is consistent with other studies that have found marketing messages in industry-funded CME. Consistent, unified messages that contradict federal guidelines were identified in all online ER/LA REMS activities. The FDA's purpose in requiring REMS-compliant CME was to decrease inappropriate prescribing, but these activities reassure clinicians that starting or continuing long-term opioids is safe and effective, easing prescriber concerns about increasing doses.

Under the guise of objective, FDA-mandated education, industry-funded REMS-compliant CME on opioids contain marketing messages that misrepresent scientific evidence, provide moral license for prescribers to continue overprescribing opioids and support commercial goals, while undermining public health goals. Clinicians, regulators, legislators, policymakers, and consumers should join forces to end industry funding of CME.

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Appendix Table 1. *Representative quotes from RPC-funded CME activities*

Theme	Typical codes (number of modules code appeared in)	Representative Quotes
1. Chronic pain is a common, under-treated problem.	a) Pain is common (n = 5) b) Chronic pain patients are under-treated (n = 3)	"Undertreatment of pain is a serious problem in the United States…and pain should be treated aggressively…" (34). "According to the Institute of Medicine report in 2011, 100 million people in the US have [pain that has lasted more than 3-6 months]" (28). "The prevalence of chronic pain in our country is very high" (31). "Clearly chronic pain is the problem…Low back pain is the leading cause of years lived with disability in the U.S. and accounts still for ⅓ of all work loss" (35).
2. Chronic pain is a chronic disease.	a) Chronic pain is like other chronic illness (n = 4) b) Pain can be managed but not cured (n = 4) c) Opioids are just like other medication for chronic illness (n = 3)	"Unlike acute pain, which is [a self-limiting symptom serving a] protective biological function, …chronic pain…is a disease process" (36). "…low back pain is similar to congestive heart failure…[in that treatment is] not one-size-fits all…assuming that…one drug will fit all the needs is erroneous" (31). "… chronic pain should be considered like a disease in itself; it's multi-dimensional just like other chronic diseases that we manage" (28). "…pain is like other chronic conditions and we need to treat it as such" (28). "Chronic pain is a true chronic disease condition…And those who experience chronic pain may have a syndrome of multiple chronic pain conditions" (35).
3. Opioids are an appropriate treatment for chronic pain.	a) Opioids are one of many tools in the toolbox (n = 4) b) Opioid prescriptions help some patients and harm some patients (n = 4) c) Opioids are the most effective medication for chronic pain (n = 3)	"For many patients, opioid analgesics – when used as recommended by established pain management guidelines – are…often the only treatment option that provides significant relief" (34). "Obviously the overall benefits are that opioids…can certainly improve function and quality of life for people suffering from real pain" (36). "[If we are going to] prescribe opioids, [we have] to do it in a safe manner…[E}ven though the risks [are high], some of [the] benefits are very important – such as improved function and improved quality of life, …for some people" (30). "The widespread use of opioids derives from the high prevalence of chronic pain" (29).
4. ER/LAs are more appropriate than IR opioids for chronic pain.	a) ER/LA opioids are better than IR for chronic pain management (n = 6) b) ER/LA opioids are convenient and may lead to better adherence (n = 5)	"…for the patient who is opioid naive […or whose pain is intermittent or only occasional…], you would consider a short-acting opioid…But what about extended-release/long-acting? Well, certainly if the person already has some tolerance to the CNS and respiratory effects; certainly if they have constant, severe, around-the-clock pain; and if you want to stabilize pain relief in someone who's using lots of short-acting opioids" (28). "[T]here may be a potential benefit of using a long-acting opioid in patients who need reliable, around-the-clock…titrated dosages so that they're not having…breakthrough pain…[It's also possible that] patients will adhere to the regimen better if they only have to take the medication once a day…" (31). "ER/LA opioids may be more appropriate for people who are known or expected to be at high risk for aberrant behavior" (29).

Appendix Table 1. *Representative quotes from RPC-funded CME activities (continued)*

Theme	Typical codes (number of modules code appeared in)	Representative Quotes
5. Tolerance is normal, expected, and beneficial.	a) Tolerance is not only normal but necessary to initiate ER/LA regimen (n = 9) b) Tolerance is determined by specific dosage and duration (n = 6) c) Tolerance to adverse effects occurs relatively quickly (n = 5) d) Tolerance or dependence does not equal addiction (n = 3)	"Tolerance to the sedating and respiratory-depressant effects is critical to the safe use of certain products and dosage unit strengths" (32). "Opioid-tolerant patients also develop tolerance to many opioid side effects like drowsiness and respiratory depression. When a patient is tolerant to opioids, there are no restrictions on which products can be used" (29). "So, tolerance means you need an increased dose to produce a specific effect. We know that it develops readily for CNS and respiratory depression, but less so for constipation" (28). "We know that there are other medications that also develop tolerance and physical dependence, like benzodiazepines, beta blockers, SSRIs. So, it's not unique to opioids. And our patients need to understand that tolerance and physical dependence is [sic] not the same as addiction" (28). "Opioid-tolerant patients often need a higher dose of opioid to achieve the same level of analgesia. This is a normal physiologic response to chronic opioid use. The development of tolerance is why some people with significant chronic pain sometimes take very large doses of opioids – doses that could be dangerous in an opioid-naive patient" (29). "Yes, the patient may become tolerant to the medication and they may need more of it. And the example that I use is – you know we take showers in the morning, and the shower's very hot when we first get in, and then a few minutes into it we find ourselves turning up the hot water. That doesn't mean we're hot water addicts – it means we've developed tolerance to the effect" (32).
6. "Opioid rotation" can maximize analgesia and minimize adverse effects.	a) Opioid rotation can be useful for minimizing adverse effects and/or maximizing analgesia (n = 8) b) Adverse effects may arise in specific patients due to differences in opioids (n = 6) c) Cross tolerance is incomplete (n = 6) d) The absence of benefit or occurrence of adverse effect with 1 opioid does not predict similar response(s) to another (n = 3) e) Multiple rotations may be necessary to achieve satisfactory results (n = 2)	"…opioid rotation – switching to another opioid as a means of restoring analgesic efficacy or limiting adverse effects –…[is] based on large inter-individual variation in response to different opioids" (28). "…in any given patient, the absence of benefit or side effects with 1 opioid does not predict similar responses to another opioid" (29). "Differences in pharmacological or other effects make it likely that a switch will improve outcomes" (30).

Appendix Table 1. *Representative quotes from RPC-funded CME activities (continued)*

Theme	Typical codes (number of modules code appeared in)	Representative Quotes
7. There is no population for whom opioids are absolutely contra-indicated or inappropriate.	a) Certain patient populations are more vulnerable to the potential risks of opioids (n = 10) b) Risk must be balanced with benefit (n = 8) c) Additional monitoring/expert consultation may be necessary with high-risk patients (n = 8) d) Only prescribe during pregnancy if the benefits [to the pregnant woman] outweigh the risk to the fetus (n = 8) e) Chronic pain requires multimodal/ interdisciplinary/multidimensional care (n = 7) f) Prescribers should refer patients to pain specialists if out of their comfort zone (n = 7) g) Pain symptoms and treatments are highly dependent on the biopsychosocial perspective of each individual patient (n = 5) h) There are no well-controlled data to inform clinical decisions for ER/LA use during pregnancy (n = 5) i) ER/LA opioid prescription is not necessarily prohibited for patients in recovery from opioid use disorders (n = 4) j) Practice in the clinic is different than what non-clinicians understand (n = 2)	"For patients at high risk of aberrant drug-related behaviors, a trial must be in conjunction with frequent monitoring and follow-up" (32). "This is the Opioid Risk Tool…and at the end of the day, you are categorized into low risk, moderate risk, or high risk. So even a score of 0 [is not entirely without] risk. [E]veryone has some risk...And that's important to recognize. It doesn't mean you can't prescribe" (31).
8. Screening and monitoring tools are effective for preventing opioid-related problems.	a) Certain patient populations are more vulnerable to the potential risks of opioids (n = 10) b) Urine drug tests enable monitoring to reduce misuse behavior (n = 9) c) Proper documentation helps to ensure safe prescribing (n = 9) d) PDMPs are a good tool to track potential misuse/abuse/diversion (n = 8) e) Universal precautions should be tailored to the risk level of each individual patient (n = 6) f) Simple screening tools exist to prevent abuse/ misuse (n = 6) g) Pill counts can be useful for monitoring abuse (n = 6) h) Continually assess the need for opioids (n = 5) i) Patients at risk are easy to identify (n = 4) j) High doses may be appropriate, even in high-risk patients, if justifiable and carefully monitored (n = 3)	"So, here's an example…–the Opioid Risk Tool, which I think is popular because it's relatively simple and straightforward and easy to use. It doesn't take a long time to fill out" (30). "When prescribing opioids, we can help reduce our patients' risk for abuse by performing a thorough assessment and understanding the key issues related to appropriate and safe use of opioids" (29). "Talk to them about the importance of the tool, how we use the tool, how it doesn't matter what the score is, we'll work through that…" (30). "I would say that higher doses may be indicated for some of your patients, but…they need to be considered higher risk and they need more monitoring and support" (28). "Misuse risk can be assessed using a systematic approach, which includes validated risk assessment questionnaires" (28). "A substance abuse history does not necessarily prohibit opioid therapy, but it does warrant additional monitoring and assistance from persons with expertise in managing pain, addiction, or other mental health concerns" (32).

Appendix Table 1. *Representative quotes from RPC-funded CME activities (continued)*

Theme	Typical codes (number of modules code appeared in)	Representative Quotes
9. Opioid-related adverse effects, such as respiratory depression and addiction, are due only to misuse and abuse.	a) 'Dose dumping' occurs with concomitant alcohol and or benzodiazepine use (n = 7) b) Constipation is the most common adverse effect (n = 6) c) MAOI use with certain opioids can increase respiratory depression and cause serotonin syndrome (n = 6) d) Opioids contribute to overdose deaths related to CNS depressants (n = 6) e) Tolerance to adverse effects occurs relatively quickly (n = 5) f) The risk of respiratory depression is highest when initiating or increasing the dose of ER/LA opioids (n = 5)	"…respiratory depression is the 1 that we really fear, especially in our patients with [either obstructive or central] sleep apnea" (28). "So, let's remember what the risk factors [for respiratory depression] are, and remembering that, you know, it's usually preceded by sedation" (31). "…sometimes the families are concerned about behaviors the patient has that are not addictive behaviors but they are pseudo-addictive behaviors... [We try] to clarify to them that…pseudo-addictive behaviors are an outcome of people who [are] afraid of… being in pain" (32).
10. Addiction, overdose, and death are due to street drugs such as heroin and fentanyl, not prescription opioids.	a) The real problem is illicit heroin and fentanyl (n = 5) b) Restricting access to appropriate opioid use does not correlate to reduced addiction deaths (n = 2) c) Drug abuse starts with alcohol and marijuana (n = 2) d) Abuse deterrent formulations are safer to use (n = 2)	"[When oxycodone was made tamper-resistant in 2010, street use] went down pretty dramatically …but you know what went up in a mirror image fashion?…heroin use…[S]o there are always unintended consequences" (30). "[It's] kind of a squeezing the balloon phenomenon…as you make prescription opioids less available and harder to obtain for those that are misusing them, [they turn to] easily accessible high-purity heroin and people are dying from that" (28). "Opioid-involved…overdose deaths in 2015 were estimated at just over 33,000…[up from] 28,000 in 2014…[I]llicit opioids – so not prescribed opioids only – significantly contributed to the increase…[W]e do have to keep in mind that, there is this whole other side to this that we cannot control, and is not related to our trying to help our patients" (31).