Canadian Agency for Drugs and Technologies in Health

RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

TITLE: Tamper-Resistant Oxycodone: A Review of the Clinical Evidence and Cost-effectiveness

DATE: 25 June 2015

CONTEXT AND POLICY ISSUES

Oxycodone is a prescription opioid used for chronic and acute pain control.[1] Although it has legitimate value for the treatment of pain, oxycodone is also associated with misuse and abuse,[1-3] which is of particular concern among younger users (for example, in 2012, 7 to 9% of 12 to 21 year olds used oxycodone for non-medical use).[4] Adverse events related to non-medical use of oxycodone include overdose, injection-related harms, and dependence.[2] There is some evidence that Canada has one of the highest rates of per-capita oxycodone misuse.[2]

The misuse of oxycodone often involves crushing the pills in order administer the product intranasally or via injection.[1] Developing tamper-resistant products is a way in which to deter this misuse. Tamper resistance can take the form of physical barriers (which prevent the drug from being crushed, cut, or dissolved), the addition of aversive agents (which are released when the drug is tampered with and result in an unpleasant drug experience for the user), and the addition of antagonistic agents (these are released if the drug is tampered with and reduce the 'high' associated with the drug without having an impact on pain relief.[5]

Prior to 2010, oxycodone was available in an extended release (ER) formulation, that used a time-release mechanism to provide long-term pain relief without frequent dosing[6] and an immediate release (IR) formulation, that requires frequent dosing.[7] Historically, the ER formulations were more attractive for non-medical use due being available in higher doses.[5,7] Therefore, tamper resistant formulations for ER oxycodone were developed and entered the American market in 2010.[6,7]

One of the earlier reformulations to enter the American market was Remoxy, oxycodone ER in a gel-cap was resistant to crushing, breaking, freezing, dissolving, and heat alteration.[6] Targin, an oxycodone/naloxone combination, is potentially less attractive for non-medical use due to the reduction in euphoric feelings that accompany its use.[8] An oxycodone/niacin formulation, which does not decrease the analgesic effect but does increase the potential for unpleasant effects,

has also been developed.[9] These and other abuse deterrent formulations (ADF) have the potential to reduce the misuse of oxycodone.

Requiring tamper-resistant properties for products that contain particular controlled substances in order to be sold can be part of efforts to address prescription drug abuse. The purpose of this review is to evaluate the effectiveness of tamper-resistant formulations in curbing abuse and misuse of oxycodone.

RESEARCH QUESTIONS

1. What is the clinical evidence on the harms associated with non-tamper-resistant oxycodone formulations in adults, including misuse and abuse?

2. What is the clinical evidence on the harms associated with tamper-resistant oxycodone formulations in adults, including misuse and abuse?

3. What is the evidence for the reduction of misuse, abuse, and related harms with tamper-resistant oxycodone compared with non-tamper resistant formulations?

4. What is the cost-effectiveness of tamper-resistant oxycodone?

5. What are the evidence-based guidelines for the use of tamper-resistant oxycodone?

KEY FINDINGS

Evidence from RCTs and observational studies suggest that tamper-resistant oxycodone has the potential to reduce misuse, abuse and their associated harms. Tamper-resistant oxycodone formulations may also decrease healthcare costs associated with the misuse and abuse of oxycodone.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, safety data, economic studies, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 01 2011 and May 28 2015.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for

inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults using oxycodone (with a prescription or recreationally)
Intervention	Q1, 3-5: Tamper-resistant oxycodone (e.g. OxyNEO) Q2: Non-tamper-resistant oxycodone (e.g. extended release oxycodone, OxyContin)
Comparator	Q1, 2,4, 5: Any Q3: Non-tamper-resistant oxycodone (e.g. extended release oxycodone, OxyContin)
Outcomes	Safety: hospitalizations, deaths, rates of overdose, abuse or misuse, harms avoided (e.g. reductions in overdose or harms related to misuse), cost-effectiveness, recommendations
Study Designs	HTA, SR, RCT, NRS, Evidence-based Guidelines

HTA = health technology assessment; NRS = non-randomized study; RCT = randomized controlled trial; SR = systematic review

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to January 2011. Guidelines were excluded if it was not clear that the methodology was based on a systematic review of the evidence.

Critical Appraisal of Individual Studies

The included randomized and non-randomized studies were critically appraised using the Downs and Black checklist,[10] and economic studies were assessed using the Drummond checklist.[11] Critical appraisal of qualitative studies was conducted by assessing whether there was ethics approval, the suitability of the topic to qualitative methods, the adequacy of sampling strategies, the data collection and analysis strategies, as well as the confirmability, transferability, credibility and dependability of the results. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 517 citations were identified in the literature search. Following screening of titles and abstracts, 486 citations were excluded and 31 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, ten publications were excluded for various reasons, while 21 publications met the inclusion criteria and were included in this report. Appendix 1 contains the PRISMA flowchart of the study selection.

Summary of Study Characteristics

A detailed summary of study characteristics is provided in Appendix 2.

Study Design

Clinical studies

Twenty studies reporting clinical outcomes were included in the review. Of these, five were randomized controlled trials[9,12-15] with multiple treatment arms that employed a crossover design. Fourteen observational studies[2,7,8,16-18,18-25] were included. Five[7,17,18,20,22] of the observational studies used a time series or interrupted time series design, two[2,16] used a cross-sectional design, one was a cohort study,[19] and seven used descriptive methods either to describe etiology,[25] post-marketing surveillance,[8] abuse and abuse-related exposures,[16,23,24] or death rates.[21,26] One qualitative study, that used a structured interview, was included.[27]

Cost studies

Two cost studies were identified.[20,28] One study provided a budget impact model for healthcare utilization and cost savings[28] and one examined medical cost savings associated with the tamper resistant formulation.[20] Both studies used the payer perspective, one from a single payer (commercial drug plan)[28] and the other from the perspective of multiple payers (Medicare, Medicaid, and commercial drug plans).[20] One of the cost studies also provided observational data for abuse rates, and was thus included in the clinical review as well.[20]

Country of Origin

Clinical studies

The majority of the included studies (fourteen) were American,[7,9,14-16,18-25,27] three[2,8,26] were Australian, and two of the clinical studies,[12,13] both of which were RCTs, were Canadian.

Cost studies

Both of the included cost studies were from the United States.[20,28]

Patient Population

Clinical studies

The included randomized trials included healthy patients with a history of recreational opioid use but who were not dependent on opioids.[9,12-15] Patients did not require medication for pain management, but rather were recruited to evaluate their reactions to the abuse deterrent properties of the study drugs. The mean age of participants ranged from 24.2[14] to 34.9[12] and all were either only[14] or predominantly[9,12,13,15] male. All of the RCT populations were predominantly white. The number of included patients ranged from 19[14] to 49.[9]

Two[16,18] of the included observational studies examined patients diagnosed with opioid use disorders, two[22,25] examined those who had entered treatment programs related to opioid use problems, and six[2,7,17,19,20,24] examined data regarding opioid use or prescriptions. One study[29]

examined data from supervised injection sites and needle exchange sites, and three[17,21,23] studies examined poison control and/or death reports. The qualitative study examined participants who self-reported as misusing oxycodone.

Cost studies

One of the cost studies examined a group of continuous users of ER opioids[20] and the other examined database records regarding opioid misuse.[28]

Interventions and Comparators

Clinical studies

All of the included randomized studies examined multiple comparisons and included a placebo comparison (Table 2). One study examined two dosing strategies of oxycodone/naloxone IV solution versus placebo formulations,[12] one examined intranasal administration of various oxycodone formulations,[13] one study examined an oxycodone/niacin formulation,[9] one study compared immediate and controlled release oxycodone formulations,[14] and one study compared whole and chewed Remoxy with crushed immediate and extended release oxycodone.[15]

Table 2: Interventions and Comparators Examined in the Included Randomized Trials

Comparison	Number and type of study
IV oxycodone (0.07 mg/kg) + naloxone (0.035 mg/kg) solution vs. IV oxycodone (0.07 mg/kg) + placebo vs. IV placebo + placebo	1 RCT[12]
Intranasal administration of: finely crushed ADF oxycodone (30 mg) vs. coarsely crushed ADF oxycodone (30 mg) vs. finely crushed original oxycodone (30 mg) vs. oxycodone powder (30 mg) vs. placebo (30 mg)	1 RCT[13]
Oral administration of: oxycodone HCl-niacin (40/240 mg and 80/480 mg) vs. oxycodone (40 mg and 80 mg) vs. placebo	1 RCT[9]
Multiple routes of administration. Oxycodone IR (40 mg) vs. oxycodone CR (40 mg, 40 mg crushed, 80 mg)	1 RCT[14]
Remoxy whole tablet (40 mg) vs. Remoxy chewed tablet (40 mg) vs. oxycodone ER crushed (40 mg) vs. oxycodone IR crushed (40 mg) vs. placebo	1 RCT[15]

ADF = abuse deterrent formulation; CR = controlled release; ER = extended release; IR = immediate release; IV = intravenous; kg = kilogram; mg = milligram; RCT = randomized controlled trial

Four[16,17,20,22] of the included observational studies included a comparison of ADF oxycodone with other opioids, ten[7,8,17-24] compared ADF oxycodone with original oxycodone, one study[8] included a comparison of Targin (oxycodone-naloxone) versus oxycodone, one[25] study compared ER with IR oxycodone use prior to the reformulation and one study reported trends in the use of oxycodone CR prior to the reformulation.[2] One study examined oxycodone-related deaths without referencing a comparator drug.[26]

Cost studies

Both of the included cost studies compared ADF ER oxycodone with original formulation ER oxycodone.[20,28]

Outcomes

Clinical Studies

The included randomized studies reported drug liking,[9,12-15] desire to take the drug again,[9,12] subjective monetary value of the drug,[12] drug high,[14] abuse potential,[7,13,14] and safety.[9,12,13,15] The included observational studies examined abuse or abuse rates,[7,16,18,20,23,24] drug sales or dispensing,[17,29] use of oxycodone (prevalence or frequency),[8,19,22] overdose,[2,17] abuse or overdose related death,[2,21,26] oxycodone prescriptions,[2] accidental exposure to oxycodone or therapeutic errors,[23,24] abuse risk,[25] and switch rates to the ADF formulation.[7]

The included qualitative study examined user perceptions regarding changes in local and individual drug use patterns.[27]

Cost studies

The included cost studies reported medical costs associated with abuse,[20] and reductions in healthcare costs due to the introduction of ADF oxycodone.[20,28] Some key assumptions made in the White *et al.* study[28] that examined the budget impact of ADF oxycodone and included direct medical and prescription costs were that the ADF would be priced at par with the branded opioid, would replace the branded opioid 100 percent, and that the prescription volume would remain stable. The other cost study,[20] that did not include prescription costs, made the assumptions that the rate of prescription pain reliever abuse and dependence was 0.7%, that the ratio of diagnosed to undiagnosed abusers was 1:5, that continuous and non-continuous users of ER oxycodone would be affected by the reformulation in the same way, and that the costs of the Medicare-eligible population reflected the actual costs of Medicare patients.

Summary of Critical Appraisal

A detailed summary of critical appraisal of individual studies is provided in Appendix 3.

Clinical Studies – Randomized Trials

Overall, the included RCTs were well-reported with respect to the objectives, interventions, patient characteristics, and outcomes and compliance was reliable in all of the trials.[9,12-15] Double-blinding was reported in all of the trials and it was clear that there was blinding of the patients to the treatment, however it was not always clear whether it was the outcome assessor or those running statistical tests who were blinded.[12,15] Exact *P*-values were reported in four trials[9,12,13,15] and those values were adjusted for multiple comparisons in two studies.[9,15] A power calculation was reported in two of the studies.[14,15] Although RCTs are often underpowered to detect safety, adverse events related to oxycodone use were frequent, thus it is likely that the safety events reported in the trials were valid.

The primary limitations of all of the randomized trials related to the included population and conditions for the use of the interventions.[9,12-15] The highly selected recreational drug users

included in the trials could not (among other characteristics) be on other medications, be diagnosed with substance abuse disorders, and were otherwise healthy.[9,12-15] Additionally, the populations were predominantly white males. It is therefore unlikely that the study populations reflected the real-world oxycodone-using population. Furthermore, the use of the study drugs occurred under supervision, which is also not representative of real world use. [9,12-15]

Clinical Studies – Observational Studies

The methods, objectives, and main findings were clearly described in all of the included observational studies.[2,7,8,16-26] The study sample was drawn from large databases in four studies[8,16,22,24] and therefore selection bias is likely reduced in those studies (though it is likely that the databases themselves do not fully represent the population who uses oxycodone for non-medical use) . Four studies[7,18,21,22] specifically reported using sensitivity analyses or other steps to minimize potential biases (e.g. reporting bias,[7,22] geographical,[18,22] time period[7,21]).

Due to the nature of coding exposures and entering information into databases, misclassification of exposures related to ER or IR oxycodone and ADF or original formulation oxycodone was possible in studies that drew data from databases.[8,16,22,24] Three studies relied on the voluntary reporting of deaths and overdoses,[21,23,26] and thus it is possible that not all outcomes were reported or not coded as oxycodone-related. This could lead to an underestimation of oxycodone deaths outcomes.

Clinical Studies – Qualitative Study

Authors of the included qualitative study[27] stated clear objectives that were congruent with qualitative methods. The sampling strategy was clearly described, as were the participants and results. The sample was likely representative of the population from which it was taken (those who engage in non-medical use of opioids within a region of Appalachia), however, the population itself is likely not representative of the broader misusers of opioids. It was unclear if ethics approval was sought, however, as it was part of a larger quantitative study, it was likely that there was indeed ethics approval. As it was a small sample in a small geographical area, it is unlikely generalizable to a larger population. The study relied on self-reported behaviours that are considered socially undesirable and could therefore be subject to responder bias. It was unclear how data was checked for credibility or whether techniques were used to enhance dependability.

Cost Studies

Both cost studies used real-world data to inform their estimates.[20,28] The study that examined medical cost savings from multiple payers' perspectives used sensitivity analyses at different percentages of abuse rates and found the estimates to be robust to those changes.[20] The budget impact study employed multiple models and found the estimates to be robust.[28]

The cost studies were not full economic evaluations. One study did not include prescription drug costs,[20] and although the other did, it did not include general medical costs associated with opioid abuse.[28] One study assumed that ADF would be the same price as the brand-name non-deterrent alternative;[28] if the ADF is more costly, the study estimates for cost saving are likely too high.

Summary of Findings

A detailed summary of findings is provided in Appendix 4.

What is the clinical evidence on the harms associated with non-tamper-resistant oxycodone formulations in adults, including misuse and abuse?

In an Australian study that examined the misuse and abuse of oxycodone prior to the reformulation,[26] there were 320 oxycodone related deaths (deaths in which post-mortem biological evidence of oxycodone use was found) from 2003 to 2009, 172 of which were attributed to oxycodone toxicity. Authors also found that the oxycodone supply to the area had increased from 7.5 mg to 67.5 mg per capita from 2000 to 2009. Another Australian study found that outpatient treatment for problematic oxycodone use doubled between 2002 and 2008.[2] They found 465 oxycodone related deaths between 2001 and 2009, 10% of which were due to oxycodone toxicity.

An American study examining the abuse risk of ER and IR oxycodone prior to the introduction of the ER reformulation[25] found that the prescription adjusted relative risk of abuse of ER versus IR oxycodone was 5.821 ($P < 0.0001$).

What is the clinical evidence on the harms associated with tamper-resistant oxycodone formulations in adults, including misuse and abuse?

Results from observational studies suggest that although the introduction of tamper resistant oxycodone may have the potential to reduce oxycodone use, it may be associated with some harm. In one observational study, 33.3% of those surveyed indicated that they replaced oxycodone abuse with abuse of another drug (70% of who switched to heroin) and some indicated they were able to find information on how to abuse the ADF.[16] Some patients surveyed in the qualitative study indicated that they were able to tamper with the ADF product, however they did not like the results.[27] Most respondents indicated that they sought out other oxycodone formulations.[27]

What is the evidence for the reduction of misuse, abuse, and related harms with tamper-resistant oxycodone compared with non-tamper resistant formulations?

Results from randomized trials and observational studies suggest a reduction in misuse, abuse, and related harms with tamper-resistant formulations.

Randomized Trials

Patients had lower drug liking for oxycodone/naloxone ($P < 0.001$ vs. original oxycodone),[12] drug liking was lower and drug disliking was higher for oxycodone-niacin formulations than for oxycodone-only,[9] the abuse quotient for ADF oxycodone was lower for ADF formulations of intranasal oxycodone than for the original formulation ($P < 0.001$),[13] crushed ADF oxycodone was not as well liked as IR oxycodone ($P \leq 0.05$),[14] and Remoxy was associated with lower drug liking scores than oxycodone IR ($P \leq 0.0461$).[15] The most common treatment emergent adverse events (the majority of treatment emergent adverse events were mild to moderate in all of included RCTs[9,12-15]) were pruritus,[9,13-15] somnolence,[9,12,13] and nausea.[14,15]

Observational Studies

One 2015 observational study found that the introduction of ADF resulted in a lower demand for safe injection equipment and a decreased number of visits to safe injection sites.[8] The same study found that prior to the reformulation, 56% of those surveyed had used OxyContin 80 mg in the previous 30 days and that following the reformulation, 8% had used the OxyContin 80 mg in the previous 30 days. Among other things, ADF oxycodone was found to be potentially associated with:

- a reduction in dispensing rate for ER oxycodone,[17]
- a decline in the abuse of any ER oxycodone product (Relative Risk [RR] = 0.78, *P* < 0.0001),[19]
- lower abuse rates compared with IR oxycodone (RR = 0.34, 95% confidence interval [CI] 0.28 to 0.42),
- lower rates of diagnosed abuse (22.7% decrease in commercially insured patients),[20]
- a reduced number of ER oxycodone-related fatalities (87% decrease following the reformulation; 95% CI -93% to -78%) ,[21]
- reduced frequency of ER oxycodone abuse (30% decrease following the reformulation; 95% CI -34.90 to -25.98, *P* < 0.0001),[22]
- Reduction in therapeutic errors (20%; 95% CI -26 to -9%, *P* < 0.0001 vs. prior to the reformulation)[23] and fewer unintentional therapeutic errors vs. other opioids (*P* <0.001)[24]
- Reduction in intentional misuse(21%; 95% CI -29 to 2, *P* = 0.0076 [numbers as reported in the publication]) and abuse (36%; 95% CI -40 to -23%, *P* < 0.0001vs. prior to the reformulation)[23]
- Reduction in oxycodone related suspected suicide (21%; 95% CI -26 to -10%, *P* < 0.0001vs. prior to the reformulation).[23]

What is the cost-effectiveness of tamper-resistant oxycodone?

The two included cost studies suggest that tamper-resistant oxycodone may result in cost-savings with respect to the payer.[20,28] ADF ER oxycodone was associated with a projected total annual medical cost savings of $430 million in the US (based on national database data),[20] and in lower healthcare resource utilization[28] in the two included studies. Both studies were American, however, and may not be generalizable to the Canadian setting.

What are the evidence-based guidelines for the use of tamper-resistant oxycodone?

No evidence-based guidelines were identified.

Limitations

Although two of the included randomized trials were conducted in the Canadian setting, none of the included observational studies used Canadian data. The RCTs provide estimates of the potential impact of ADF products on highly selected patient populations (and men were overrepresented in all of the RCTs) whereas observational or post-marketing surveillance studies are better suited toward estimating the real-world effects. Thus, it is uncertain whether or not the American and Australian studies are generalizable to the Canadian public and healthcare system. Due to the fact that in general, the RCT evidence from both the Canadian and American studies were congruent, it is possible that the observational evidence from the

United States could be applicable to the Canadian population with respect to the overall trends toward ADF having the potential to reduce ER oxycodone abuse.

A further limitation of the RCT data is that the study participants were recreational users who were exposed to each of the study drug formulations one time, under highly controlled and supervised conditions in order to determine drug liking and potential for abuse. Although this allowed for comparison versus placebo and versus multiple formulations, it is unlikely that the population or conditions generalize to a real-world setting.

As much of the evidence included is observational, conclusions cannot be made with respect to causation. The ADF products seem to be associated with a reduction in misuse and abuse of oxycodone, however, it is possible that other factors (such as prescription monitoring systems) could have contributed to the effects seen in the observational studies. Since the results of the randomized trials and the observational studies are fairly congruent, it is likely that ADF products were large contributors to the observed reduction in misuse and abuse of oxycodone.

Only two cost studies were identified and neither contained a full economic evaluation and neither contained both direct and indirect medical costs associated with oxycodone misuse and abuse. While both found reductions in medical costs associated with ADF oxycodone and it is likely that the general trend for reduced costs may generalize, it is how generalizable the results are to the Canadian setting and it is certain that the exact costs are not transferrable.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

All of the included studies examining the potential for misuse and abuse of ADF oxycodone suggest that there is reduced potential for misuse and abuse of tamper-resistant formulations. In some studies this reduced misuse of ADF ER oxycodone was associated with an increase in demand for other prescription opioids that did not have tamper-resistant formulations (such as IR oxycodone and other ER opioids) and in others, it was associated with increased use of illegal opioids (such as heroin). It is likely that although ADF ER oxycodone has the potential to reduce abuse and misuse of ER oxycodone, a greater reduction in prescription opioid use will not be seen unless the majority of prescription opioids are available in tamper-resistant formulations. ADF oxycodone formulations may result in cost savings in the Canadian setting, however it is unclear how large those savings will be due to the lack of Canadian data. Tamper-resistant oxycodone is likely to be an effective contributor to a broad opioid abuse and misuse strategy.

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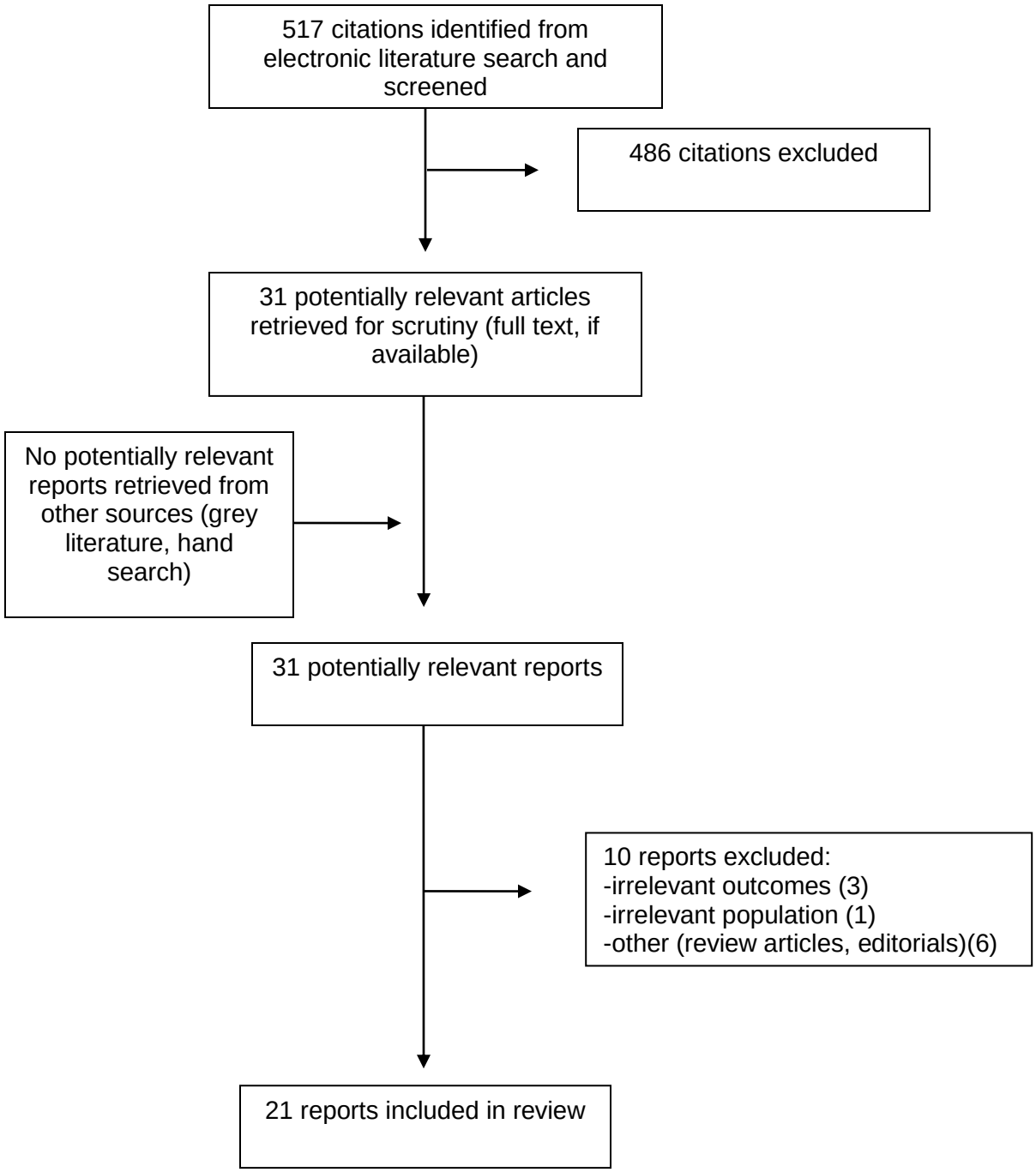
APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Clinical Studies

First Author, Publication Year, Country, Study Name	Study Design	Patient Characteristics	Intervention(s)	Comparator(s)	Clinical Outcomes
Randomized Controlled Trials					
Colucci, 2014,[12] Canada	RCT, crossover (single centre, double blind)	Moderate experience but not dependent on opioids. Had to pass naloxone challenge. 42 subjects initially met inclusion criteria; 24 subjects qualified for treatment. Mean age 34.9 years; 87.5% male; 87.5% white; 22 completed the study.	Oxycodone 0.07 mg/kg + naloxone 0.035 mg/kg solution (sOXN)[1]	Oxycodone 0.07 mg/kg + naloxone placebo (OXY)[1] Placebo oxycodone + placebo naloxone[1]	Drug liking Desire to take drug again Subjective monetary drug value Safety
Harris, 2014,[13] Canada	RCT, crossover (double blind)	History of non-medical opioid use, intranasal administration, absence of opioid physical dependence. Had to pass naloxone challenge. 30 subjects met initial inclusion criteria; 27 started treatment. Mean age 32.1 years (±8.99) (range 18 to 48 years). 86.7% male, 86.7% white. A history of recreational opioid use. Most patients used other drugs recreationally as well.	30 mg reformulated oxycodone tablet – finely crushed[2] 30 mg reformulated oxycodone tablet – coarsely crushed[2]	30 mg finely crushed original oxycodone[2] 30 mg oxycodone powder (Oxy API)[2] 30 mg placebo powder[2]	Abuse potential Drug liking Safety

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Webster, 2012,[9] USA	RCT, crossover (single centre, placebo and active controlled)	Men and women aged 18 to 55 who were in generally good health and recreational opioid users. Had to pass naloxone challenge. 49 patients entered the treatment phase; 47 completed all 5 treatments. 78% male, 94% white, median age 23 (18 to 47)	oxycodone HCl-niacin 40/240 mg oxycodone HCl-niacin 80/480 mg (oral)	Oxycodone 40 mg Oxycodone 80 mg placebo (oral)	Drug liking Desire to take drug again Abuse potential Safety
Webster, 2012,[14] USA	RCT, crossover (single centre, placebo and active controlled)	Males, recreational opioid users (5 occasions in the last 12 months, at least 1 in the last 90 days). Had to pass naloxone challenge. 19 patients entered the treatment phase, Mean age 24.2 years (SD 3.4), 18 of 19 were white.	Oxycodone IR 40 mg	Oxycodone CR 40 mg Oxycodone CR 40 mg crushed Oxycodone CR 80 mg	Abuse potential Drug liking Drug high
Stenik, 2011,[15] USA	RCT, crossover (single site, placebo and active controlled)	Men and women, 18 to 50 years, healthy, use recreational opioids. Needed to pass	Remoxy 40 mg whole Remoxy 40 mg chewed	Oxycodone ER 40 mg whole Oxycodone ER 40 mg crushed Oxycodone IR	Drug liking Safety Chewing duration

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
		naloxone challenge. 45 patients entered treatment phase; 43 completed. 32 completed treatment under 'fasting' conditions. Demographics for fasting patients. Mean age 25.2 (SD 4.65), 78% men, 94% white.		40 mg crushed Placebo	
Observational Studies					
Cicero, 2015,[16] USA	Observational, descriptive, cross-sectional	Patients with diagnosed opioid use disorder (primary drug of abuse a prescription opioid or heroin). Data from ongoing SKIP[3] (N = 11,782) program, part of the RADARS (N = 244) system. SKIP: 50.6% male; mean age 34.1; 78.4% white. RAPID: 46.4% male; mean age 35.9; 90.4% white.	Reformulated OxyContin	Other opioids	Abuse rates
Degenhardt, 2015,[8] Australia, NOMAD study	Observational, descriptive, post-marketing surveillance study	Drug sales, clients at supervised injection sites, clients at needle exchange sites	Reformulated OxyContin Targin (oxycodone-naloxone)	Oxycodone (oral, solution)	Drug sales Use of oxycodone

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Larochelle, 2015,[17] USA	Observational, interrupted time series	Open cohort of 31.3 million American commercially insured adults aged 18 to 64. January 2003 to December 2012. Median follow-up 20 months.	Abuse deterrent OxyContin	Opioids, non-abuse deterrent oxycodone	Dispensing Overdose rate
Cassidy, 2014,[18] USA	Observational, cross sectional, interrupted time series	Sentinel sample of adults assessed for substance abuse treatment within the NAVIPPRO surveillance system. ≥18 years either entering treatment or assessed for substance abuse problems 232,874 adults at 437 facilities between January 2008 and December 2011 64.5% male, median age 32	Abuse deterrent oxycodone	ER oxycodone	Estimated rates of past 30 day abuse
Havens, 2014,[19] USA	Observational, Cohort Structured interviews	189 patients between December 2010 and September 2011. ≥18 years, used ER oxycodone in the 6 months prior to the reformulation. 54.5% male, 97.9% white	Abuse deterrent formulation of oxycodone	IR oxycodone	Prevalence and frequency of use

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Michna, 2014,[7] USA	Observational, before and after the introduction of ADF oxycodone Examination of pharmacy claims	2010 to 2012 Truven MarketScan de-identified pharmacy and medical claims. Patients aged 18 to 64 who received at least a 120 day supply of opioids and primary opioid leading up to reformulation was ER oxycodone. N = 15,162	ADF ER oxycodone	ER oxycodone	Switch to ADF formulation Abuse rates
Rossiter, 2014,[20] USA	Observational, time series. Before and after the introduction of the reformulated ER oxycodone. Study period divided: February 2010 to August 2010; November 2010 to May 2011.	Commercially-insured, Medicaid, and Medicare-eligible patients who had at least one prescription drug claim for prescription opioids from 2009–2011[4] 18 years and older, continuously enrolled in non-capitated/non-HMO healthcare plans. Data included inpatient and outpatient pharmacy claims from members in 50 states.	Introduction of tamper-resistant ER oxycodone	ER oxycodone; other ER opioids	Rates of diagnosed abuse.

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Sessler, 2014,[21] USA	Observational, review of case reports of death	326 fatalities reported to the manufacturer (240 mentions of overdose, 206 mentions of abuse behavior) Between 2009 and 20113 (1 year pre-reformulation, 3 years post-reformulation)	ADF ER oxycodone	ER oxycodone prior to the reformulation	Abuse or overdose related deaths
Butler, 2013,[22] USA	Observational, time series. Before and after the introduction of ADF oxycodone.	Sentinel surveillance sample, assessed for substance abuse treatment at 357 U.S. centers. 14-month period preceding launch of ORF (June 1, 2009, through August 8, 2010); 20 months following release of ORF (August 9, 2010, through March 31, 2012. N = 140,496 55.6% male, 66.2% white.	ADF oxycodone	ER oxycodone ER morphine and ER oxymorphone also examined	Prevalence and prescription-adjusted prevalence rates of past-30-day abuse via any route Frequency of abuse
Coplan, 2013,[23] USA	Observational, descriptive	National Poison Data System data. ! year preceding and 2 years following introduction of ADF	ADF ER oxycodone	Other single entity oxycodone heroin	Abuse Accidental exposure Poison centre

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Severston, 2013,[24] USA	Observational, descriptive	RADARS data used Percentage of the US population covered by the data ranged from 85.1% in 2008 to 90.0% at the start of 2012.	ADF ER oxycodone	ER oxycodone	Abuse Therapeutic errors Price
Butler, 2011,[25] USA	Observational, descriptive, (etiological?)	Assessments of 59,792 patients entering treatment for substance use disorders at 464 treatment facilities in 34 states (NAVIPPRO data) No specific demographic data available for oxycodone users (was not disaggregated from opioid users)	ER oxycodone	IR oxycodone	Abuse risk
Rintoul, 2011,[26] Australia	Observational, population-based, descriptive	Cases identified using National Coroners Information System Victorian Drugs Module and toxicology databases. From 2000 to 2009. 320 total deaths, 172 attributed to drug toxicity alone (58% male, mean age intentional death 47, mean age unintentional death 39.2 years)	Oxycodone	N/A	Oxycodone-related death

Table A1: Characteristics of Included Clinical Studies					
First Author, Publication Year, Country, Study Name	**Study Design**	**Patient Characteristics**	**Intervention(s)**	**Comparator(s)**	**Clinical Outcomes**
Roxburgh, 2011,[2] Australia	Observational, cross-sectional, population-based	Australian patients prescribed oxycodone/	Oxycodone CR tablets Oxycodone CR capsules 5 mg, 10 mg, and 20 mg.	Morphine (IR, CR, Sustained release)	Report trends in: (i) prescribing of morphine and oxycodone; (ii) hospital separations for overdose; (iii) presentations for treatment of problems associated with these drugs; and (iv) oxycodone-related mortality data in Australia.
Qualitative Study					
Buer, 2014,[27] USA		25 participants recruited from a quantitative study of 192 self-reported OxyContin users. 48% male, 92% non-hispanic white, mean age 32.4 years, 68% had been previously incarcerated.	ADF OxyContin	N/A	User perceptions regarding: perceived changes in county drug use patterns, changes in individual drug use patterns, sources of prescription drugs, and past and current illicit and prescription drug use

ADF = abuse deterrent formulation; CR = controlled release; ER = extended release; IR = immediate release; N/A = not applicable; NAVIPPRO = National Addictions Vigilance Intervention and Prevention Program; RADARS = Researched Abuse, Diversion and Addiction-Related Surveillance; RCT = randomized controlled trials; SKIP = Survey of Key Informants Patients; USA = United States of America

[1]Naloxone or placebo administered as a bolus injection followed by infusion of oxycodone or placebo within 1 minute.

[2]Intranasal

[3] key informants from more than150 public and privately funded treatment centers in 48 states

[4]Truven Health Analytics database of de-identified medical and pharmacy claims data

Table A2: Characteristics of Included Cost Studies					
First author, Publication Year, Country	**Type of Analysis, Perspective**	**Intervention, Comparator**	**Study Population**	**Time Horizon**	**Main Assumptions**
White, 2015.[28] USA	Econometric model Budget impact model for healthcare utilization and cost savings	ADF ER oxycodone ER oxycodone	Medical misuse of opioids NSDUH and DAWN data used for hospitalizations and emergency room visits. IMS data used for prescriptions	Per percent decrease in abuse rate	Reductions in abuse rates could be associated with reductions in non-medical use rates. ADF being priced at par with the branded opioid, replacing the branded opioid 100 percent, and prescription volume remaining stable.
Rossiter, 2014,[20] USA	Medical Cost Savings, Payer perspective	Reformulated (tamper resistant) ER oxycodone vs. ER oxycodone	Continuous users of ER opioids	12 months	Rate of prescription pain reliever abuse and dependence (0.7%)[1] 1:5 ratio of diagnosed to undiagnosed abusers Assumed continuous and non-continuous ERO users would be affected by the reformulation in the same way. Assumed that costs of Medicare-eligible population reflected actual costs of Medicare patients.

DAWN = Drug Abuse Warning Network ER = extended release; NSDUH = National Survey on Drug Use and Health; USA = United States of America

[1]From 2011 National Survey on Drug Use and Health

APPENDIX 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[10]

Strengths	Limitations
Colucci[12]	
• Objectives, interventions, patient characteristics clearly described. • Exact *P*-values reported • Subjects were blinded to what injection they were receiving. Study described as double blind – likely the outcome assessors (not those running statistical tests) were blinded. However, part of the inclusion protocol required patients to be able to identify the difference between OXY and placebo. • Important treatment emergent adverse events reported • Compliance reliable	• Unclear if industry sponsorship had an effect on the results • Population likely not representative of those with substance abuse disorders. • Power calculation not reported; unclear if the study had sufficient statistical power to detect differences. • Disposition of patients not clearly described, nor were principle confounders. • Likely that men were overrepresented in the study (men are more often abusers of prescription opioids,[1] but unclear if 87% of abusers are men) • Supervised use not representative of real-world use. • Intended OXY/naloxone ratio was 2:1, however this may not be representative of a real-world setting due to tablet crushing and dissolving.
Harris[13]	
• Study subjects were blinded, however, part of the inclusion protocol required patients to be able to identify the difference between OXY and placebo. • Important treatment emergent adverse events reported. • Objectives, interventions, patient characteristics clearly described. • Actual *P*-values reported • Compliance reliable	• Population likely not representative of those with substance abuse disorders. • Supervised use not representative of real-world use. • Power calculation not reported, unclear if the study had sufficient statistical power to detect differences. • Likely that men were overrepresented in the study (men are more often abusers of prescription opioids,[1] but unclear if 87% of abusers are men)
Webster[9]	
• Objectives, interventions, patient characteristics clearly described • Adequate washout period between treatments • *P*-values adjusted for multiple comparisons using the Benjamini-Hochberg method. • Reasons for discontinuation clearly described. • Important treatment emergent adverse events reported • Outcome measures were valid and appropriate	• Power calculation not reported – authors state that the study is well-powered but do not present their calculation. • Likely that men were overrepresented in the study (men are more often abusers of prescription opioids,[1] but unclear if 78% are men) • While the outcome measures are valid and appropriate for research, they are surrogates for predicting the behavior of those abusing the drugs. • Population likely not representative of those with substance abuse disorders. • Supervised use not representative of real-world use, protocol required fasting – it is unclear if 'full' participants would have the same aversion to niacin (as a high fat meal is known to reduce the negative effect of niacin)

Table A3: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[10]

Strengths	Limitations
Webster[14]	
• Objectives, interventions, participants clearly described • Participants were blinded – interventions were made to be identical. Primary investigator and research staff were also blinded – pharmacist was not. • Power calculation presented – 88% power to detect a one half SD difference between interventions. •	• Population likely not representative of those with substance abuse disorders. • Included males only. • Supervised use not representative of real-world use, protocol required fasting – unclear if that would be important in real-world use. • Actual *P*-values not reported (just P<0.05 or P≤0.001) • Unclear if study was powered for secondary outcomes or for safety.
Setnik[15]	
• Objectives, interventions, participants clearly described. • Washout periods likely adequate • Power calculation presented • Adjustment for multiple comparisons using Benjamini-Hochberg method. • Losses to follow-up and withdrawals mostly described. • Exact *P*-values reported. • Participants were blinded, assessors likely blinded (unclear which group was blinded other than the participants) • Drugs were administered under both 'fasting' and 'full' conditions.	• Population likely not representative of those with substance abuse disorders. • Men likely overrepresented • Supervised use not representative of real-world use

Table A4: Strengths and Limitations of Observational Studies using Downs and Black[10]

Strengths	Limitations
Cicero[16]	
• Objectives clearly described • The large SKIP sample was likely reasonably representative of a study of opioid abusers, drug use representative of real-life abuse rather than controlled clinical conditions. Data was from a large database sample. • Basic patient characteristics described	• The smaller RAPID sample (more detailed questionnaire of 244 people) may not be representative of the full population as they self-selected into answering the survey. • Exact interventions (dosing etc.) not described. • Descriptive study – therefore, cannot determine causality. • Unclear if the results generalize to a non-treatment seeking population
Degenhardt[8]	
• Multiple data sources used. • Objectives, main findings clearly described.	• Descriptive observational study – cannot determine causality – study was hypothesis generating. • Those who visit safe injection sites or needle exchange programs may not be representative of all drug users. • Time period examined may not be lengthy enough to determine long-term changes in use

Table A4: Strengths and Limitations of Observational Studies using Downs and Black[10]	
Strengths	**Limitations**
Larochelle[17]	
• Patients were able to enter and exit the cohort over the 10 year period. • Objectives, main findings, patient population clearly described. • 95% confidence intervals presented	• Insured patients represent only some of the patients taking non-medically necessary opioids. • Not randomized.
Cassidy[18]	
• Methods clearly described. • Outcomes were clearly described and defined • Model adjusted for potential covariates • Steps taken to minimize geographical, and other covariate confounding	• Estimates using logistic regression • Those seeking treatment may not be representative of the entire drug using population • Power calculation not reported, however there was a large sample size so power was not likely an issue.
Havens[19]	
• Authors explored factors related to the time of the interview and whether that would result in confounding bias. • Single interviewer was used so if events were misclassified, they were likely consistently misclassified. • Self-reported drug use is considered a valid measure of drug use; 30 day time frame was likely short enough to reduce problems with recall.	• Recall bias a potential issue due to being a self-reported survey – used anchoring to attempt to reduce recall bias. • Population being studied lived in an area where opioid abuse was considered epidemic – may not be generalizable to other populations.
Michna[7]	
• Objectives, methods, outcomes clearly described. • Classification of exposures well described. • Sensitivity analyses performed in order to control for potential confounders (time, primary opioid, coding of abuse)	• Commercially-insured continuous users may not be representative of the broader oxycodone-using population. • Observational study – direct causation difficult to determine.
Rossiter[20]	
• Objectives, measures, interventions clearly described. • Same inclusion and exclusion criteria applied to all included patients • Pre- post- formulation change acted as a way to match patients; population-based study allowed for analyzing a large portion of users; pre-post- acted as a quasi-experimental design. • Authors allowed for a washout period. • Cases and controls well-matched • Outcomes unlikely to be misclassified.	• No randomization. • Assumed that continuous and non-continuous users were the same. • Non-experimental design – cannot assume causation. • Number of people abusing or misusing opioids likely underrepresented.
Sessler[21]	
• Sensitivity analyses conducted (included prescription numbers, reporter type or source, formulation specificity, missing date of death, and reporting time lag) • Authors examined non-fatal reports and	• No randomization • Possibility that not all fatalities associated with oxycodone use were coded as such. • Voluntary reports of adverse events do not capture all events. (However, there was a large

Table A4: Strengths and Limitations of Observational Studies using Downs and Black[10]	
Strengths	**Limitations**
comparator reports and determined that there was no temporal bias. • Outcomes were validated, definitions of outcomes well reported.	magnitude of change, and reporting of other adverse events did not decrease, therefore, it is more likely that the change seen was a real change and not a change in the way events were reported) • Longer-term follow-up may be needed to capture more permanent changes in death rates.
Butler[22]	
• Sensitivity analyses conducted using a national database. • Objectives, measures, main findings clearly described • Selection bias unlikely to account for changes in oxycodone but not other opioids. • Data was collected uniformly across time and collection sites. • Steps were taken to reduce reporting bias (pictures of the different formulations were shown to patients in order to accurately identify which drug was taken) • Confidence intervals, exact *P*-values reported. • Steps taken to minimize geographical, and other covariate confounding.	• Patients being assessed for substance abuse may be different from other oxycodone users • Results may not be generalizable to the general population of prescription drug abusers. • Relied on self-reported data. • Not randomized • May not reflect patterns of abuse of the new formulation after more time has passed.
Coplan[23]	
• Objectives, methods, main findings clearly described. • Exposure classifications well described • Confidence intervals and exact *P*-values reported	• Possible that changes in poison centre reporting, misclassification of original or ADF oxycodone occurred during the study period • Unclear if there was a representative sample, however, it was a large national sample.
Severston[24]	
• Large percentage of the US population was part of the surveillance. Therefore the results are likely generalizable to the US population. • 95% confidence intervals and exact *P*-values reported. • Demographic characteristics (such as gender, ethnicity, and age) of the source population did not change throughout the study.	• Is a descriptive study, therefore it is difficult to determine causation. • Depended on voluntary reporting and therefore it is likely that not all cases were reported. • Misclassification of product exposure was possible. • Other interventions (such as prescription drug monitoring programs) may gave accounted for some of the reductions in abuse.
Butler[25]	
• Objectives, methods, main findings clearly described. • Exact *P*-values reported • Population likely fairly representative those seeking treatment.	• Self-reported data – recall bias possible, however, patients entering treatment tend to report fairly accurately. • May not generalize beyond patients seeking treatment and who have access to a treatment facility. • Descriptive study, therefore cannot determine causality.

Table A4: Strengths and Limitations of Observational Studies using Downs and Black[10]	
Strengths	**Limitations**
Rintoul[26]	
• Objectives, methods, main findings clearly described. • Confidence intervals and exact *P*-values reported.	• Descriptive study – cannot determine causation. • Possible that not all deaths were identified or that drug-related deaths were misclassified.
Roxburgh[2]	
• Objectives, methods, main findings clearly described • Exposures well described	• Descriptive study – cannot determine causation. • Likely that not all exposures were identified – some were likely classified as 'opioid' or misclassified as another opioid event.

Table A5: Strengths and Limitations of the Included Qualitative Study	
Strengths	**Limitations**
Buer[27]	
• Research objectives clearly stated and congruent with qualitative methods. • Sampling strategy clearly described – and was altered when it became clear that the youngest age group was underrepresented. • Participants described with sufficient detail. • Results consistent with the data. • Data collection clearly described and was congruent with the research objectives.	• Ethics approval not reported, however it was likely sought as it was part of a larger quantitative study. • Small sample in a small geographic area – results may not generalize to other populations. • Self-reported data – therefore may be subject to recall bias. • Reporting socially undesirable behavior – therefore may be subject to responder bias. • Unclear how the data was checked for credibility (the interviews were audio-recorded and transcribed, but unclear if the transcriptions were checked or if there was another method of credibility checking) • Unclear if techniques were used to enhance the dependability

Table A6: Strengths and Limitations of Economic Studies using Drummond[11]	
Strengths	**Limitations**
White[28]	
• Multiple models used. • Models checked for robustness • Used real population data to inform estimates	• Multiple data sources – exposures and drug formulations may be coded differently so data may not be consistent. • NSDUH past-year or past-month measures were not available and would likely be better predictors than the lifetime use that they used. • Small sample size, therefore results may not be generalizable. • Misclassification of data possible while coding entries into database. • Does not include general medical costs. • Likely not generalizable beyond the single payer perspective
Rossiter[20]	
• Their base case was set at 75% of the abuse rate found in the database and sensitivity analyses included 50% and 100% rates. ADF oxycodone was cost saving at all estimates. • Used real population data to inform estimates.	• Not a full economic analysis • Indirect costs not considered • Based on data from an observational study (evaluation of claims data) – we cannot conclude the relationship was causal. • Cost estimates likely only relevant to the US population (however reductions likely in other jurisdictions, but monetary values not transferrable due to differences in price)

ADF = abuse deterrent formulation

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A7: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusions
Randomized Controlled Trials	
Colucci,2014[12]	
Drug Liking • Overall drug liking were highest after receiving oxycodone (vs. sOXN or placebo) • Pairwise comparisons were all statistically significant : OXY vs. placebo, P<0.001; sOXN vs. OXY, *P* < 0.001; sOXN vs. placebo, *P* = 0.05 Take Drug Again • Scale of whether the patient would take the drug again were highest after oxycodone (compared with sOXN and placebo) • Pairwise comparisons were all statistically significant: OXY vs. placebo, *P* ≤ 0.001; sOXN vs. OXY, *P* ≤ 0.001 Subjective Monetary Drug Value • OXY: US$25.06, sOXN: US$3.38, placebo: US$0.86 Safety • Incidence of TEAE: 95.7% for OXY, 29.2% for sOXN, 20.8% for placebo. (Most common were euphoric mood, feeling hot, somnolence, and headache) • Serious TEAE: 2 cases of ventricular tachycardia (one after sOXN and one after placebo)	• The concentration of naloxone (0.035 mg/kg) in the sOXN was sufficient to decrease the degree of drug liking when compared with conventional oxycodone (administered intravenously) • More data is needed to determine the abuse deterrent properties of sOXN in a real-world setting.
Harris,2014[13]	
Abuse Quotient • AQ 5 times higher in Oxy API (102.15 ng/mL/h) and original oxycodone (94.75 ng/mL/h) than finely (17.57 ng/mL/h) and coarsely crushed tamper resistant oxycodone (16.96 ng/mL/h). • Differences in AQ for both finely and coarsely crushed tamper resistant oxycodone vs. OXY API and original oxycontin were statistically significant (*P* < 0.001) Drug Liking • Highest drug liking occurred within 1 hour of administration • For global measures of drug effect, both finely and coarsely ground reformulated oxycodone had lower E_{max} than the non-reformulated oxycodone powders (*P* ≤ 0.002). Subjective Monetary Drug Value • Reformulated, finely crushed: $17.01 (±$16.39); Reformulated, coarsely crushed: $17.25 (±$17.39); Original oxycodone (crushed): $27.95 (±$16.03); Oxy API: $27.30	• Intranasal administration of reformulated oxycodone resulted in lower abuse potential than the original formulation of oxycodone.

Table A7: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
(±$17.40); Placebo: $0.37 (±$0.60) Safety • No serious TEAEs, or serious AEs. • Incidence of AEs: 96.4% for finely crushed oxycodone, 89.7% for Oxy API, 86.2% for finely crushed reformulated oxycodone, 75.0% for coarsely crushed reformulated oxycodone, 41.4% for placebo. • Most common AEs were euphoric mood, somnolence, pruritus, and nasal congestion.	
Webster, 2012[9]	
• Drug liking at 0 to 1 h, 0 to 2 h, and 0 to 3 h was less for both doses of oxycodone with niacin than for oxycodone and drug dislike was higher for oxycodone with niacin than without. ($P < 0.0001$ for most comparisons. P value statistically significant for all comparisons) • Percentage of participants who disliked the drug at 30 min: 60% (40/240 mg), 64% (80/480 mg), 15% (40 mg/0), 4% (80 mg/0) • Decreases in "take drug again" were statistically significant at all assessments (1, 2, and 8 h) comparing oxycodone + niacin with the respective oxycodone doses. • Patients found oxycodone with niacin less desirable than oxycodone alone (55% at the 40/240 mg vs. 40 mg/0 dosing and 72% at the 80/480 mg vs. 80 mg/0 dosing) Safety • The majority of TEAEs were mild to moderate • Any TEAE (% patients): 77% 40 mg/0; 98% 80 mg/0; 98% 40/240 mg; 100% 80/480 mg; 13% placebo • Most common TEAEs were pruritus, somnolence, and flushing.	• The initial lower 'drug liking' of oxycodone with niacin compared with oxycodone supports the lower abuse potential of the combination, as those taking the drug recreationally expect a positive effect within the first hour. • The relative aversive reaction to the niacin versus the oxycodone alone after 8 and 12 hours is promising in deterring abuse. • The stronger dislike for the higher dose of oxycodone plus niacin may be a deterrent for abuse and may help prevent overdose.
Webster, 2012[14]	
Drug liking • Drug liking was similar for 80 mg CR, 40 mg of IR, and 40 mg CR crushed oxycodone. • When compared with 40 mg of IR, 40 mg CR of crushed oxycodone, and 80 mg CR oxycodone, drug liking was significantly less for 40 mg CR ($P \leq 0.05$) • For the intervals assessed, drug liking was similar for 40 mg IR and 40 mg crushed CR oxycodone. Drug high • All oxycodone formulations resulted in greater ratings of "do you feel high" than placebo. • The maximum high was similar for 40 mg IR, 40 mg crushed CR, and 80 mg CR oxycodone.	• Intact CR oxycodone tablets have reduced abuse potential relative to IR formulation. • When CR formulation was crushed, the reduced abuse potential was defeated. • Oxycodone CR resulted in lower subjective scores of drug liking and high than IR oxycodone. Further, a twofold difference between doses of oxycodone CR and IR oxycodone that yielded comparable subjective effects was observed.

Table A7: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
These were all significantly higher than for 40 mg CR oxycodone ($P < 0.05$) • For each time interval assessed after the first hour, the mean assessment of drug high was similar for the 40 mg IR oxycodone, 40 mg crushed oxycodone CR, and 80 mg oxycodone CR, which were all greater than 40 mg oxycodone CR. • Mean time to maximum drug high was shorter for 40 mg IR (1.5 h) than for 40 mg CR (2.4 h) ($P < 0.05$); no other comparisons were significant. Safety • TEAEs were mild to moderate • Most common TEAEs were pruritus, nausea, headache, and decreased oxygen saturation.	
Setnik, 2011[15]	
Drug Liking • Remoxy 40 mg (whole and chewed, both on 'fed' stomachs) was associated with statistically significantly lower scores of drug liking when compared with Oxycodone IR 40 mg (fasting) and Oxycodone ER 40 mg (crushed, fasting). ($P \leq 0.0461$) • Time to drug liking was significantly delayed for Remoxy (both whole and chewed) when compared with oxycodone IR and ER crushed ($P \leq 0.0193$) TEAEs: • All were mild to moderate, most common were pruritus, dizziness, somnolence, nausea, and vomiting.	• Remoxy (whole or crushed) was associated with reduced abuse than IR or ER crushed oxycodone. • Remoxy has the potential to lower rates of oxycodone abuse.
Observational Studies	
Cicero, 2015[16]	
• 45% of patients entering drug treatment from January to June 2009 (prior to the introduction of the ADF), used OxyContin for non-medical use in the 30 days before entering treatment. After the introduction of ADF OxyContin, 26.0% used OxyContin for non-medical use in the 30 days before entering treatment. (95% CI, 23.6% to 28.4% in July to December 2012; $\chi 2 = 230.83$; $P < .001$) • This decrease remained consistent – from January to June 2014, 26.7% used OxyContin prior to seeking treatment (95% CI, 23.7% to 29.6%). • 33.3% of RAPID respondents indicated that the ADF had no effect on drug selection and continued to abuse OxyContin; a separate 33.3% indicated that they replaced OxyContin with other drugs as a result of the ADF. 3.3% of	• OxyContin ADF was successful in reducing abuse of the drug, however a residual level of abuse remains.

Table A7: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
respondents indicated that the ADF influenced their decision to stop taking drugs. • Of the patients who switched drugs after the introduction of ADF OxyContin, 70% of respondents switched to heroin. • Comments from patients included that they had to learn how to make the ADF injectable and that they were able to search the internet for information on how to inject or take the ADF.	
Degenhardt, 2015[8]	
• Following the introduction of reformulated OxyContin, there was a lower demand for safe injection equipment. • Following introduction of reformulated OxyContin, the reformulated OxyContin was the opioid least injected among users at safe injection sites • The number of visits to safe injection sites decreased overall after the introduction of reformulated OxyContin. • Prior to the introduction of reformulated OxyContin, 56% of interviewed opioid users had used OxyContin 80 mg in the previous month; following the introduction, 8% had used OxyContin 80 mg in the previous 30 days. • There was a low level of Targin use both pre- and post-introduction of reformulated OxyContin (2%, and 0.4% had used in the last month respectively). • No clear increase in the use of other drugs.	• Short term data suggest that the introduction of reformulated OxyContin resulted in reductions in the use of injected OxyContin in Australia. • Reformulated OxyContin did not appear to be as attractive for injection drug users.
Larochelle, 2015[17]	
• Dispensing rates of ER oxycodone products increased from 22.9 to 27.7 mg MED between 2003 and 2010. • Immediately following the release of abuse deterrent oxycodone, the prescribing rate dropped by 4.56 mg MED per member per quarter (95% CI -5.91 to -3.21). • 2 years after the formulation change, the dispensing rate for ER oxycodone decreased 39% • Following the reformulation, no change was detected with respect to the out of pocket cost of OxyContin. • Prescription opioid overdose decreased following the reformulation of OxyContin, however, data specific to oxycodone was not presented.	• Opioid prescription patterns and rates of overdose decreased after the introduction of abuse deterrent oxycodone and the removal of propoxyphene from the market. • Market interventions may be helpful in reducing opioid abuse.

Table A7: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
Cassidy, 2014[18]	
• Abuse of any ER oxycodone product declined in the post-ADF period by 22% (RR = 0.78, *P* < 0.0001)	• Abuse of ER oxycodone decreased following the introduction of ADF. • This had little effect on broader opioid use.
Havens, 2014[19]	
• In the month prior to the introduction of ADF oxycodone: 74% reported ER oxycodone abuse, 74% reported IR oxycodone abuse. • In the 30 days preceding the interview, the prevalence of use ADF oxycodone was 33%, IR oxycodone (not available in ADF) was 96% • Abuse of ADF oxycodone was significantly lower than IR oxycodone for all time periods. (RR = 0.34, 95%CI 0.28 to 0.42). • Prevalence of injecting (5%) and snorting (1%) ADF oxycodone was low. • Heroin abuse not common in the study population.	• Following its release, ADF ER oxycodone abuse was infrequent and remained infrequent throughout the study period. • Abuse of ER oxycodone did not replace abuse of original ER oxycodone, especially for those who chose injection or intranasal routes of administration. • There was some shift from ER to IR oxycodone use following the ADF ER introduction.
Michna, 2014[7]	
• Abuse rates among patients who switched from ER oxycodone to a non-abuse deterrent formulation following the introduction of the ADF were higher than in those who switched to the ADF. (6.7% vs. 3.5%, relative risk 1.9, *P* < 0.001) • ER oxycodone patients who discontinued ER opioid treatment following the introduction of reformulated ER oxycodone had a higher rate of diagnosed opioid abuse compared with patients who switched to reformulated ER oxycodone (10.9% vs. 3.5%, relative risk 3.1, *P* < 0.001)	• 31% of ER oxycodone users avoided switching to the abuse-deterrent formulation. • Opioid abusers may seek out formulations that are more easily abusable and some may switch from legal to illegal substances.
Rossiter, 2014[20]	
• In the 6 months following the reformulation of ER oxycodone, rates of diagnosed abuse decreased by 22.7% in commercially insured and 18.0% in Medicaid patients. Change rate was not significantly different from the pre-study period among Medicare-eligible patients.[1]	• Abuse deterrent ER oxycodone is an appropriate component of a multi-faceted approach to the reduction in prescription opioid abuse.
Sessler, 2014[21]	
• A reduced number of ER oxycodone-related fatalities were reported following the introduction of the ADF. This decrease began the first year following the introduction of ADF and became more pronounced the subsequent years. • Fatalities involving ER oxycodone decreased 82% (95% CI -89% to -73%) (from 32.8 to 5.8 per quarter) between the year prior to the reformulation and the third year following reformulation.	• The number of spontaneous reports of death that involved ER oxycodone decreased after the introduction of an abuse deterrent formulation. In context with the findings of previously reported studies, authors suggest that there are fewer fatalities associated with the misuse or abuse of ADF ER oxycodone.

Table A7: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
• ER oxycodone overdose-related fatalities decreased by 87% (95% CI -93% to -78%) (from 26.0 to 3.3 reports per quarter) between the year prior to the reformulation and the third year following reformulation.	
Butler, 2013[22]	
• In the pre-ADF period, 24.0% of opioid abusers reported ER oxycodone abuse in the past 30 days. In the post ADF period, 12.1% of opioid abusers reported ADF oxycodone abuse. • A significant difference was not found between the abuse of oxycodone pre and post-ADF formulation (*P* = 0.06). When authors controlled for the time period when both ER non-reformulated and ADF oxycodone were both available, a significant difference was found (*P* = 0.003) • 33% decline in prescription-adjusted past-30-day abuse of ADF compared with ER oxycodone prior to the reformulation. • Frequency of ER oxycodone abuse decreased 30% following the introduction of ADF. 95% CI -34.90 to -25.68, *P* <0.0001 • Reduction in other opioid abuse was not seen during the same study period.	• The 'real-world' results of this post-marketing surveillance study are consistent with the results of controlled trials. • The reduction in the use of ER oxycodone following the introduction of the ADF was likely not the result of a trend toward less opioid abuse, as the abuse of oxymorphone and morphine increased, or remained consistent. • The study was conducted early after the introduction of the ADF and patterns may change once users learn to use the new formulation. • Substantially lower rates of ADF abuse were seen when compared with historical use of ER oxycodone.
Coplan, 2013,[23]	
Change in intentional exposures following introduction of ADF: • Abuse: 36% reduction (95% CI -40 to -23, *P* < 0.0001) • Suspected Suicide: 21% reduction (95% CI -26 to -10, *P* < 0.0001) • Misuse: 21% reduction (95% CI -29 to 2, *P* = 0.0076) Change in unintentional exposures following introduction of ADF: • Misuse: 26% reduction (95% CI -58 to 37, *P* = 0.2826) • General: 39% reduction (95% CI -49 to -29, *P* < 0.0001) • Therapeutic errors: 20% reduction (95% CI -26 to -9, *P* < 0.0001) Change in: • Adverse reactions: 34% reduction (95% CI -50 to -17, P = 0.0005) • Withdrawal: 67% reduction (95% CI -74 to -37, *P* < 0.0001) Rates of change of other agents (oxymorphone, heroin) were not reduced (mostly increased).	• With respect to events that were reported to poison centres, abuse, therapeutic errors affecting patients, and accidental exposures decreased following the introduction of ADF ER oxycodone. • Physiochemical barriers can likely decrease abuse of oxycodone, however may not decrease abuse of opioids in general.

Table A7: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
Severston, 2013,[24]	
• Mentions of abuse for ADF ER oxycodone decreased progressively each quarter throughout the time period of the study. (Reduction of 38% post-ADF introduction; 95% CI 31 to 45, *P* < 0.001) • Abuse rates of other opioids following the introduction of ADF ER oxycodone were not significantly different. • There was a reduction in the number of prescribing errors after the introduction of ADF ER oxycodone. • Street cost of ADF ER oxycodone was 22% lower than that of ER oxycodone prior to the reformulation (95% CI: 9 to 33, *P* = .002 • Fewer unintentional therapeutic errors were observed following the introduction of ADF ER oxycodone. The decline was larger for ADF ER oxycodone than for other opioids (*P* < 0.001)	• Tamper resistant products may be an important component of abuse reduction programs. • Due to the ease of switching, it is difficult to determine the public health implications of ADF ER oxycodone unless other opioids also have tamper resistant formulations.
Butler, 2011[25]	
IR oxycodone: • Abuse risk: 0.375 • Abuse risk per 100,000 prescriptions: 0.0055 • Relative Risk of abuse: ER oxycodone: • Abuse risk: 0.374 • Abuse risk per 100,000 prescriptions: 0.0320 • Prescription adjusted Relative Risk of abuse vs. IR oxycodone: 5.821 (*P* < 0.0001)	• Establishing baseline abuse risk is important in determining the impact of ADF drugs.
Rintoul, 2011[26]	
• From 2003 to 2009 320 deaths were oxycodone-related • 172 deaths were attributed to oxycodone toxicity alone. • Highest number of drug toxicity deaths occurred in areas with the lowest socioeconomic status (55.2%). • 19.9% of all narcotic use was oxycodone use. • Oxycodone supply to the area had increased from 7.5 mg to 67.5 mg per capita from 2000 to 2009	• The number of oxycodone deaths increased drastically in the region from 2000 to 2009. • The association between increased supply of oxycodone and increased deaths should be explored.
Roxburgh, 2011[2]	
• Outpatient treatment for problematic oxycodone use doubled between 2002 and 2008 (0.01 per 1000 people in 2002–03 to 0.02 per 1000 population in 2007–08) • 465 oxycodone-related deaths between 2001 and 2009 (largest number in 2007) • 10% of deaths were due to oxycodone-only toxicity. • Median age of death due to oxycodone: 41 years. 57% were male. The 40 to 49 years age group had the highest incidence of oxycodone related death (31%). • Oxycodone	• Prescriptions for oxycodone increased in Australia, some of which likely reflected proper pain management prescribing. • Deaths due to oxycodone had not reached the proportions seen in the United States.

Table A7: Summary of Findings of Included Clinical Studies	
Main Study Findings	**Author's Conclusions**
Qualitative Study	
Buer, 2014,[27] USA	
• Since the formulation change in August 2010, respondents said that OxyContin had become unpopular. They indicated that this was due to not being able to inject or snort the new formulation. • Those who used ADF OxyContin orally or claimed to be able to snort (n = 6) or inject (n = 3) the formulation indicated that they did not find the ADF to be 'as strong' as the previous formulation. • Respondents said that people were willing to pay less for the ADF and therefore were asking for prescriptions for IR formulation, as they were able to sell it for more. They indicated that ADF was therefore, more difficult to find on the black market. • Those who did claim to have injected or snorted the ADF did not like the experience. • All participants claimed that single ingredient IR oxycodone hydrochloride had replaced OxyContin as the most misused prescription drug.	• It appeared that reformulating OxyContin had successfully deterred misuse and abuse of the drug in Appalachia. • However, the reformulation did not decrease overall opioid misuse or abuse, as use of other opioid (particularly IR oxycodone) formulations increased. • The results provide strong support for the development of further reformulations in order to deter intranasal and intravenous administration of prescription opioids.

ADF = abuse deterrent formulation; AE = adverse event; AQ = abuse quotient; CI = confidence interval; ER = extended release ; h = hour; IR = immediate release; ng = nanogram; MED = morphine equivalent dose; mL = milliliter; OXY = oxycodone; sOXN = oxycodone plus naloxone solution; TEAE = treatment emergent adverse event
[1]Medicare-eligible patients do not typically represent a population in which opioid abuse is as common as in other groups.

Table A8: Summary of Findings of Included Economic Studies	
Main Study Findings	**Author's Conclusions**
White, 2015[28]	
• Estimated that between 18,017 and 74,913 emergency room visits avoided per percentage decrease abuse rates of ADF ER oxycodone. • Estimated that between 11,932 and 49,613 hospitalizations avoided per percentage decrease in abuse of ADF ER oxycodone. • Estimated cost savings per percentage decrease in abuse rate of ADF ER oxycodone $230.5 to 958.5 million	• ADF oxycodone formulations likely result in lower medical resource utilization and overall cost savings to the payer.
Rossiter, 2014[20]	
• Excess per patient costs associated with opioid abuse: $9,456 for commercially insured, $10,046 for Medicare-eligible, $11,501 for Medicaid patients • Total annual cost savings from reductions in diagnosed abuse: $86 million across all payers. ($35 million commercially insured, $16 million Medicaid, and $35 and uninsured) • Total annual cost savings from reductions in undiagnosed abuse: $344 million ($139 million commercially insured, $63 million Medicaid, and $142 uninsured) • No significant reduction in Medicare-eligible abuse rates, therefore no cost-savings estimated. • Sensitivity analyses ranged from $286 to $573 million in annual medical cost savings.	• Not including prescription drug costs,[1] reformulated ER oxycodone was associated with total annual medical cost savings of $430 million in the US. • Indirect costs were not part of the analysis. • Results from their claims data analyses were consistent with previous research.

ADF = abuse deterrent formulation; ER = extended release; US = United States
[1]excess prescription drug costs that were associated with the diagnosis and treatment of opioid abuse were not statistically significant