

1 The iatrogenic opioid crisis: an example of “institutional corruption of pharmaceuticals”?

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63 Ethical approval is not required for this study

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77 **Abstract**

78 Rationale

79 Prescribed opioids are major contributors to the current international public health opioid
80 crisis. Such iatrogenic calamities usually result from collective decision failures of healthcare
81 organizations rather than solely of individual organizations or professionals. Findings from a
82 system-wide safety analysis of the iatrogenic opioid crisis that includes roles of pertinent
83 healthcare organizations may help avoid or mitigate similar future tragedies. In this exploratory
84 study, we report on such an analysis.

85 Methods

86 Root cause analysis, incorporating recent suggestions for improvement, was used to
87 retrospectively identify possible causal factors from the literature. Based on their mandated roles
88 and potential influences to prevent or mitigate the iatrogenic crisis, relevant organizations were
89 grouped and stratified from most to least influential.

90 Results

91 The analysis identified a chain of multiple interrelated causal factors within and between
92 organizations. The most influential organizations were: pharmaceutical, political and drug
93 regulatory; next: experts and their related societies, and publications. Less influential:
94 accreditation, professional licensing and regulatory, academic and healthcare funding bodies.
95 Collectively, their views and decisions influenced prescribing practices of frontline healthcare
96 professionals and advocacy groups. Financial associations between pharmaceutical and all other

97 organizations/groups were common. Ultimately, patients were adversely affected. There was a
98 complex association with psychosocial variables.

99 Limitations

100 Our analysis suggests associations not causality.

101 Conclusions

102 The iatrogenic crisis has multiple intricately linked interacting roots. The major catalyst:
103 pervasive pharma-linked financial conflicts of interest (CoIs) involving most of the other
104 healthcare organizations. These extensive financial CoIs were likely triggers for a cascade of
105 erroneous decisions and actions that adversely affected patients. The actions and decisions of
106 pharma ranged from unethical to illegal. The iatrogenic opioid crisis exemplifies widespread
107 “institutional corruption of pharmaceuticals.”

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119 **Introduction**

120 Since the 1990s, prescribed opioids have resulted in an escalating international
121 iatrogenic public health problem that has mainly affected the USA, Canada and Australia.¹⁻⁷ Data
122 from the United Kingdom have signaled similar risk.⁸⁻¹⁰ This prescribed opioid crisis is complex
123 in nature and associated with underlying mental health challenges, socio-economic and
124 geographic variables.^{7, 11-15} Those with post-traumatic stress disorder, especially combat
125 veterans, are at high risk.^{16,17} A subset of patients who are initially prescribed opioids transition to
126 illicit opioids.^{1,18-21} In many ways, the current iatrogenic opioid crisis is a replay of the late
127 1800s' opioid epidemic in the USA.^{1,2}

128 Adverse events (AEs) with prescribed opioids are now well-documented.^{1,7,22-29}
129 However, children, adolescents and the elderly are also at risk.³⁰⁻³³ Even short courses of opioids
130 prescribed in emergency departments for acute pain or after surgery and dental procedures may
131 increase the odds of AEs including opioid use disorder (OUD).³⁴⁻³⁹

132 The iatrogenic opioid crisis may be the worst preventable medication disaster in recent
133 times. A patient safety analysis is warranted to prevent or mitigate future iatrogenic medical
134 tragedies. Patient safety is one of six inter-related components of quality of care.⁴⁰ Drug safety is
135 integral to patient safety, and institutional corruption of pharmaceuticals a major threat to drug
136 safety.^{41,42}

137 Safety is strongly influenced by decisions of several “upstream” healthcare-influencing
138 organizations; hence, a systems approach has been advocated by safety experts and organizations

to identify and correct deficiencies at the appropriate organizational levels of the complex healthcare system.^{40, 43–50} A system-wide analysis is particularly necessary when dealing with AEs of national, international or global magnitude since upstream organizational factors are more likely to be responsible for such events rather than the actions of individual hospitals, healthcare teams or professionals. Therefore, we analyzed the iatrogenic opioid crisis (henceforth referred to as “the iatrogenic crisis”) from an international systems safety perspective. We are unaware of any established method to undertake such a system-wide analysis in healthcare. Hence, we based our study on the traditional approach to patient safety: root cause analysis (RCA).^{47–49}

Methods, concepts and definitions

Methods

This exploratory, narrative, retrospective system-wide RCA incorporated other recent suggestions to improve RCAs:^{46–49} assess for multiple contributors rather than a single (root) cause and aggregated analyses. Aggregated (collective) information on specific groups or categories can reveal patterns so corrective action can be taken at the appropriate levels of the healthcare system. Aggregated data cannot provide information on individuals or specific groups within a category. Hence, unless specified, the analysis does not reflect on specific individuals, teams or organizations.

Several principles were adopted for retrieving references for complex heterogeneous evidence:⁵¹ (i) use of relevant Medical Subject Headings (MeSH) including “opioids or opiates, oxycodone, OxyContin, fentanyl, patient safety, drug or pharmaceuticals’ safety, root cause

analysis,” etc.; (ii) snowballing; (iii) serendipity, and (iv) personal knowledge.⁵¹ Databases used included PubMed, Psych INFO, Google and Google Scholar, search being limited to English publications. Search was conducted between May 2018 and June 1, 2020; SSS was primarily responsible but co-authors also contributed references.

Concepts and definitions

Chronic pain: defined as pain lasting > 3months, caused by diverse etiologies, excluding malignancy.²⁸

Organization: group of people with common goals, vision, views and/or mission. “Institutions,” “societies,” and “groups” were considered “organizations.” The highest levels of management make strategic decisions and set the tone for organizational culture and ethical framework.

Organizations involved in the iatrogenic crisis were identified through literature review. They were grouped and stratified by consensus according to their mandated roles. These roles determined their potential ability to prevent or mitigate the extent of the crisis: (I) Critical influencers; (II) important but lesser influencers; (III) organizations exerting important but more indirect influences; (IV) strongly influenced by organizations in I-III categories, and (V) patients and caregivers: dependent on decisions of organizations in the I-IV categories.

Frontline healthcare professionals: physicians, nurse practitioners, physician assistants, dentists, and pharmacists involved in prescribing or dispensing opioids.

Iatrogenic: AEs such as mortality and morbidity, including OUD,⁵² secondary to prescribed opioids. In DSM-V, addiction is incorporated into the concept of OUD.⁵²

P(p)harma: collective term for pharmaceutical industry. *Purdue Pharma*- a specific pharmaceutical company.

Results

The introduction, approval, and widespread use of controlled-release (CR) oxycodone were central to the iatrogenic opioid crisis.^{27,53} Following the enactment of oxycodone-focused restrictions, hydromorphone and fentanyl prescriptions increased in Canada, as did heroin and illicit synthetic opioid use.^{19,21,54} In a Canadian multi-center study of opioid-related hospitalizations (2015-2016), 34%-52% of 2599 patients had an active prescription for opioids; the most common were hydromorphone, codeine, oxycodone and methadone.²⁶ In the USA (2015), the most commonly used were hydrocodone, oxycodone and morphine;⁷ and in England (2016) fentanyl, morphine and oxycodone were the most common long-acting opioids prescribed in high doses.¹⁰ AEs were greater with high doses of opioids and co-prescribed central nervous/respiratory depressants.^{15,27,39,55-56} Precise incidence and prevalence of AEs from prescribed opioids are not available.²² Documented incidence of iatrogenic OUD has ranged from 0.2% to 5% and prevalence of dependence or OUD from 0.05% to 26%.^{28,57} Tamper- (abuse-) deterrent formulations have not clearly been found to reduce OUD.⁵⁸

The organizations involved in influencing the iatrogenic opioid crisis were identified by literature review and stratified as follows:

203 **Category I Organizations - Critical Influencers**

204 Rational, prompt, and ethical decisions from these organizations could have prevented
205 and mitigated the crisis.

206 • *Pharmaceutical industry*

207 Purdue Pharma's (*Stamford, CT., USA*) OxyContin (CR oxycodone) played a pivotal
208 role in the crisis; subsequently, other pharmaceutical companies were also involved.^{1,2,53,59-64}

209 Purdue Pharma (and then other pharmaceutical companies) exerted the following forms of
210 influence:⁶² (i) Purdue Pharma falsely and aggressively marketed OxyContin as a long-acting
211 effective oral opioid with low addiction risk. (ii) Purdue promoted OxyContin through pain
212 experts as paid speakers and consultants, and fully funded symposia for healthcare professionals
213 and students through universities, professional societies, patient advocacy groups, hospitals,
214 clinics etc.^{2,53,59,65} Purdue Pharma also delayed responding to reports of abuse,⁶⁶

215 Approximately one in 12 American physicians received opioid-related payments between
216 August 2013 and December 2015, the top 1% of recipients getting 82% of the total.⁶⁷ Opioid-
217 related companies have generally reached out-of-court settlements, thereby avoiding criminal
218 prosecution and ensuring sealing of critical evidence.⁶⁴ However, in 2020, the founder of *Insys*
219 (marketing *Subsys*, a fentanyl nasal spray) was imprisoned in the USA for charges of
220 racketeering.⁶⁸

221 • *Political systems*

Pharmaceutical companies influence political systems through campaign contributions and lobbying.⁶⁹ In the USA, legislators at various levels of government received contributions from opioid companies.⁶⁴ Political decisions have eroded public funding for regulatory agencies, promoted industry's interests, and restricted powers of enforcing agencies.^{2,63, 64,70} Pharmaceutical policies in Canada are strongly influenced by regional politics and agreements with the USA.⁶⁹

• *Drug regulatory agencies*

In 1996, the Federal Drug Administration (FDA) in the United States approved OxyContin (CR oxycodone) for chronic pain treatment. Comparable agencies in Canada and elsewhere,⁶⁵ followed. To the best of our knowledge, the FDA: failed to independently critically appraise evidence for safety, accepted Purdue Pharma's claims that OxyContin had little addiction risk, and did not mandate randomized controlled trials for efficacy and post-marketing surveillance for effectiveness and long-term side-effects.^{53,61,64,65,70} Collectively, several factors likely contributed to regulatory agencies' failure to prevent or mitigate the crisis, the most important being inadequate resources due to underfunding.^{2,64,65,71} Other factors included: (i) uncritical approval of OxyContin² and fentanyl, (ii) inadequate control of misleading marketing,⁶⁵ (iii) political and public pressure, and (iv) financial and intellectual conflicts of interest (CoIs) of reviewers and staff.^{2,41,53,60,65,72–75} The team medical review officer for the FDA (USA) recommended approval of OxyContin and discouraged competitive products; two years later, he joined Purdue Pharma.² Increased industry funding, now the norm for regulatory agencies, can result in regulators becoming industry's advocates.⁷¹ In both Canada and the USA, representatives of industry sit on decision-making bodies of regulatory agencies, a move labelled “regulatory capture.”^{64, 69}

Among the actions of regulators, the FDA's uncritical approval of OxyContin played the most key role in the iatrogenic crisis.²

Category II Organizations - Important Influencers

Rational, prompt and ethical decisions from these organizations may not have prevented the crisis but would likely have restricted the extent of the crisis.

• *Pain experts and societies*

Until the 1980s, opioids were rarely prescribed long-term because of a collective concern about the risk of addiction. In the 1980s-90s, several pain experts suggested addiction was rare in patients with both malignant and chronic pain treated long-term with opioids; some qualified their remarks by advising careful selection of candidate patients, thorough assessment (particularly psychological), and regular follow up.⁷⁶⁻⁸¹ Subsequently, several additional factors catalyzed the more uncritical use of opioids for chronic pain. In 1995, the American Pain Society's designation of pain as the 5th vital sign was widely adopted and implemented, resulting in increased scrutiny of perceived undertreatment of pain.^{2,63,82} With the marketing of CR oxycodone, many experts and professional societies became promoters of pharma's view of its effectiveness and safety.^{2,53,63,65,83} The World Health Organization's (WHO's) ladder treatment for cancer pain, including escalating high doses of opioids, was extrapolated beyond cancer treatment to chronic non-malignant pain.⁸⁴ Pain management was declared a human right, and advocates of judicious opioid use were accused of "opiophobia" and "opioignorance."^{67,85-91}

264 Affected countries were likely slow to develop evidence-informed guidelines to respond to the
265 crisis.^{28,92,93}

266 It is very likely that pain experts were genuinely interested in minimizing pain. However,
267 opioid-related payments from pharma may have influenced decisions of some experts and
268 societies.^{53,67,94}

269 • *Healthcare publication industry*

270 The healthcare publication industry is responsible for reviewing and disseminating
271 evidence that influences care.^{95,96} A 1980 one paragraph letter in the *New England Journal of*
272 *Medicine* titled “Addiction rare in patients treated with narcotics” was uncritically cited 608
273 times.^{60,97} A critique of the letter was not published until 2017.⁹⁷ The citation pattern exemplifies
274 replication publication bias which can serve to entrench erroneous information.^{95,98} The quality
275 and integrity of published research have been questioned.^{95,96,99–104} Even high impact journals
276 have neither promptly retracted or corrected flawed studies, nor issued timely warnings. Hence,
277 misleading and harmful information may not only linger but may be reinforced.^{96,105} It is worth
278 noting, for example, that concerns about CR oxycodone were first reported in the news media
279 rather than in medical journals.^{67,106}

280 Declarations of financial CoIs in publications, including treatment guidelines, remain
281 inconsistent.^{107–111} Financial CoIs of journals, reviewers and editors are often opaque or
282 unaddressed,^{94, 112–114} with an explicit example being the undeclared financial CoI of a patient
283 safety expert and (now former) editor-in-chief of a leading patient safety journal.¹¹²

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285 **Category III Organizations - Important but Indirect Influencers**

286 Rational, ethical and prompt decisions by any of the following organizations may have
287 mitigated the magnitude of the crisis.

288 • *Accreditation, licensing and regulatory bodies*

289 In 2001, The Joint Commission (TJC), a leading accrediting body for healthcare
290 organizations in the USA, issued pain management standards. TJC did not directly advocate
291 opioids, but it ignored evidence-informed suggestions to explicitly advise using them
292 judiciously.^{59,115–118} TJC admitted to: (i) receiving funds from Purdue Pharma, (ii) allowing
293 possible financial CoIs among its experts, (iii) failing to recognize erroneous pharmaceutical
294 industry's claims, and (iv) acting slowly to respond to the crisis.^{59,115,116} The USA's Federation of
295 State Medical Boards (FSMB), which was involved in producing opioid use guidelines, also
296 received grants from Purdue Pharma.^{2,63}

297 • *Academic institutions*

298 Financial CoIs of healthcare academic institutions, including teaching hospitals, can
299 compromise integrity of research, education, and patient care.^{119–121} Of 58 teaching hospitals
300 examined in the United States, 5.8% received opioid-related payments.¹²⁰ Prestigious universities
301 and academic centers in the USA and one in Canada received grants/donations from opioid
302 companies and, in one instance, privately from the Sackler family (Purdue Pharma); monies were
303 used to create and fund a graduate school, pain centers, a master's program in pain, and pain
304 management courses. Lecturers associated with opioid pharmaceutical companies, focused on

specific brands and minimized AEs.^{64, 65, 83} A group at the University of Wisconsin that contributed to FSMB's policies on opioid use received \$ 2.5 million in grants from Purdue Pharma and other pharmaceutical companies.^{2, 64} University-industry partnerships and industry funding of healthcare-related education and institutions have become common.^{64, 69, 119, 121}

• *Funders*

Management of chronic pain is complex and requires comprehensive biopsychosocial assessment, timely and affordable multi-disciplinary care, including non-pharmacologic management and long-term follow-up. Financial disincentives in both publicly and privately-funded healthcare systems created and continue to create significant barriers for the provision of effective care of chronic pain.^{7, 12, 122–125} Opioid prescribing has been described as a “surrogate for inadequate pain resources.”¹²³

Category IV Organizations - Strongly Influenced by Category I-III Organizations

• *Pain advocacy organizations*

Pain advocacy organizations were likely influenced by decisions of organizations in the I-III categories. Several influential pain advocacy organizations, such as the American Pain Foundation, received funding from opioid manufacturers; these organizations downplayed AEs of opioids, minimized side-effects and opposed guidelines that advocated evidence-informed opioid use.^{1, 2, 60, 63, 122, 126}

324 • *Frontline professionals*

325 The crisis would likely have been worse but for timely actions of health care
326 professionals who drew attention to AEs early in the crisis (examples Davies, Stravino and Van
327 Zee).⁶⁶

328 Some physicians may have been influenced by opioid-related industry payments.⁶⁷ Most
329 were likely misled by views of upstream organizations and industry's marketing (category I-III
330 organizations) promoting CR oxycodone's long-term effectiveness and safety even when given
331 in high doses (discussed earlier).^{53,60,65,97,127-129} Lack of access to non-opioid treatments for pain
332 was a barrier for health care professionals.^{123,130}

333 Individual professional-related factors contributing to AEs include: excess number of
334 pills prescribed post-surgery,⁷ failure to follow national guidelines for more judicious use,
335 failure to screen for patients with OUD risk factors, co-prescribing depressant drugs like
336 benzodiazepines and gabapentinoids,^{11,15,26,27,56,131} and prescribing opioids to pregnant women or
337 those of child-bearing age,¹³²⁻¹³⁴ thereby also risking perinatal side-effects.^{135,136}

338 Unsafe and unethical practices of some physicians, clinics, drug distributors and
339 pharmacists contributed to diversion for illicit use,^{2,122,137} as could have drug losses from
340 hospitals and pharmacies.¹³⁸

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342 **Category V Organizations - Patients and Caregivers**

Patients and caregivers were influenced by upstream (category I-IV) organizations collectively to believe that opioids were effective and safe for use in chronic pain. Direct consumer pharma-marketing in some countries likely contributed.^{122,127,128} Financial and health care access constraints or personal beliefs may have been barriers to seeking and receiving non-pharmacological treatment.^{124,130} Concomitant use of alcohol or other depressants contributed to AEs.²⁷ Some patients exaggerated or falsified pain to obtain opioids for personal illicit use or diversion.¹³⁷

Thus, patients with chronic pain were placed at risk mainly by influences, decisions and actions of upstream organizations.

Discussion

Analysis of the crisis illustrates the complex reciprocal, often hierarchical, relationships between healthcare organizations and their individual and collective influences on patient safety.^{40,45,139} The healthcare system is complex, but some categories of healthcare organizations have a wider influence on patient safety than others. Failures in organizations such as political systems, drug regulatory agencies, and pharmaceutical companies are likely to impact larger segments of the population than failures in organizations/groups such as frontline teams and professionals.

Figure 1 here

The analysis also demonstrates the chain of potential reinforcing, often covert, intricately connected systemic multi-factorial and multi-organizational contributors to AEs in general and to the iatrogenic crisis in particular.^{7,40, 43–48-50} Root cause analysis is better termed root causes analysis. The methodology used in this study may offer a template for analyzing patient safety, especially drug safety, at regional, national, and global levels. However, the methodology is exploratory and requires refinement and independent validation.

Pervasive industry-associated financial CoIs were likely principal catalysts for the iatrogenic opioid crisis. Industry (especially pharma) is at the epicenter of widespread financial CoIs in the healthcare system,^{64, 73,96,119,140} and several critical healthcare-influencing organizations are financially dependent on industry.^{42, 64, 71,121} This codependence, termed “institutional corruption of pharmaceuticals,” is a global threat to patient safety.^{41,42} “Institutional corruption” refers to systemic, often legalized, practices that undermine an institution’s integrity; individual financial CoIs often associate with institutional corruption^{41,42,141,142, 143, 144}.

Disclosure of financial CoIs have revealed the “wide web of influence” of pharmaceutical companies.⁶⁴ Conventionally, physicians have been the focus of policies to address corporate influences. Our review highlights the crucial importance of also addressing institutional corruption. Suggestions to address institutional corruption have been discussed elsewhere,^{41,42,64, 121,145–147} a major one being adequate public funding of drug regulatory agencies and their independence from industry’s influence. The recent imprisonment of John Kapoor, the first convicted opioid pharmaceutical founder found guilty of racketeering strongly suggests that there may be a fine line between illegal and legalized “institutional corruption.”^{64, 68}

Lessons learned from the iatrogenic opioid crisis will likely apply to the current Covid-19 pandemic. Political influences may have been covert in the iatrogenic opioid crisis. However,

387 politicians across the world, and especially in the USA, have played an overt controlling role in
388 the response to the Covid-19 pandemic. The resulting constraints and pressures on “downstream”
389 healthcare influencing organizations should not be minimized. Hofmann has warned against the
390 temptation of taking “scientific and ethical short-cuts” in efforts to tackle the pandemic.¹⁴⁸

391 The complex psychosocial determinants of the iatrogenic crisis and the biopsychosocial
392 management of those adversely affected by it were not examined here and deserve dedicated
393 studies. Risks in perinatal, pediatric, adolescent and geriatric periods, and of even short courses
394 of opioids need specific attention as well. Evidence-informed guidelines should be updated
395 rapidly as new information emerges. However, guidelines should always be person-centered.¹⁴⁹
396 Well-designed prospective randomized controlled and pragmatic trials are needed to better
397 define efficacy, effectiveness and short-and long-term AEs of opioids for chronic pain.⁷⁰

398 Our analysis has several limitations. Limitations in the iatrogenic opioid-related
399 literature include: absence of population-based studies; most reported from information in
400 databases; methodologies and definitions were not uniform; few studies specified type of
401 prescribed opioid or stratified iatrogenic and illicit use; and the majority of references were
402 American. Some iatrogenic AEs were classified by DSM-IV and a few by DSM-V. Almost all of
403 the references pertinent to organizations are USA-focused. The methodology is exploratory.
404 Stratification of organizations in this analysis is subjective, although based on the organizations’
405 recognized roles and influences in healthcare. Intellectual bias and potential bias in selecting
406 references can influence argumentation. Hence, readers are encouraged to critically appraise the
407 sources on which our analysis is based and determine relevance to their respective healthcare
408 settings. Our analysis was based on current best evidence, albeit qualitative and interpretive.
409 Strength of evidence was enhanced by diversity of cited authors and sources. However, at best,

the analysis demonstrates associations rather than causality. Advancing arguments for causality is a major challenge in drug safety.¹⁵⁰

Conclusions

Pharmaceutical companies are multi-national. As western countries limit illegal and unethical practices, opioid manufacturing and marketing companies are expanding to other countries and allegedly using similar unethical practices.⁶⁴ The WHO must act promptly to avoid further spread of the iatrogenic opioid crisis across all age groups, while avoiding industry-associated financial CoIs that may have influenced 2012 guidelines for pain management in children.⁶⁴

The crisis resulted from a cascade of several complex interacting factors, with “institutional corruption of pharmaceuticals” being a major catalyst.^{41,42,121} Only urgent global efforts can help to improve organizational integrity for safer drugs. However, tackling entrenched institutional corruption at the levels of crucial healthcare influencing organizations will not be an easy task. The damage caused by the iatrogenic crisis has been enormous.⁶⁴ and failure to tackle institutional corruption in healthcare risks future crises with similar human and economic tolls.

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433 **Authors' Contributions**

434 All authors: provided essential perspectives from their respective countries of residence and
435 disciplines; contributed to revisions and approved final version for submission.

436 MM & SSS: principal role in developing the final manuscript. Co-ordinated input of co-
437 authors. Guarantors.

438 SSS: core concepts including methods. Principal role in reference retrieval and review.

439 GBY: major role in helping to refine concepts and the manuscript.

440 PAS: personal experience as a family physician during the early part of the crisis; special
441 interest and involvement in patient safety, healthcare organizational management and
442 influences, healthcare education and patient-oriented research.

443 KS: principal contribution to the complex hierarchical organizational influences on
444 healthcare and healthcare education; Evidence-based Medicine (EBM) expertise.

445 ING: provided UK perspective.

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830 **Figure 1 Legend.**

831 Simplified flow diagram representing “Institutional corruption of pharmaceuticals.” Black
832 arrows: financial conflicts of interest (CoIs) ultimately affected individuals and populations.
833 Light colored arrow represents how organizations accepting financial support from pharma
834 become advocates for them. In reality, the interactions within and between organizations and the
835 resulting cascade of reinforcing influences are far more complex than depicted. Psychosocial
836 determinants have a bidirectional association (hatched arrow) with individuals and population at
837 risk for or adversely affected by prescribed opioids.