

Iatrogenic opioid crisis

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.<sup>1-7</sup> Data  
122 from the United Kingdom have signaled similar risk.<sup>8-10</sup> This prescribed opioid crisis is complex  
123 in nature and associated with underlying mental health challenges, socio-economic and  
124 geographic variables.<sup>7, 11-15</sup> Those with post-traumatic stress disorder, especially combat  
125 veterans, are at high risk.<sup>16,17</sup> A subset of patients who are initially prescribed opioids transition to  
126 illicit opioids.<sup>1,18-21</sup> In many ways, the current iatrogenic opioid crisis is a replay of the late  
127 1800s' opioid epidemic in the USA.<sup>1,2</sup>

128           Adverse events (AEs) with prescribed opioids are now well-documented.<sup>1,7,22-29</sup>  
129 However, children, adolescents and the elderly are also at risk.<sup>30-33</sup> 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).<sup>34-39</sup>

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.<sup>40</sup> Drug safety is  
135 integral to patient safety, and institutional corruption of pharmaceuticals a major threat to drug  
136 safety.<sup>41,42</sup>

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

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

148

## 149 **Methods, concepts and definitions**

### 150 Methods

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

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

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

165

### 166 Concepts and definitions

167 *Chronic pain*: defined as pain lasting > 3months, caused by diverse etiologies, excluding  
168 malignancy.<sup>28</sup>

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

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

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

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

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

185

## 186 **Results**

187 The introduction, approval, and widespread use of controlled-release (CR) oxycodone  
188 were central to the iatrogenic opioid crisis.<sup>27,53</sup> Following the enactment of oxycodone-focused  
189 restrictions, hydromorphone and fentanyl prescriptions increased in Canada, as did heroin and  
190 illicit synthetic opioid use.<sup>19,21,54</sup> In a Canadian multi-center study of opioid-related  
191 hospitalizations (2015-2016), 34%-52% of 2599 patients had an active prescription for opioids;  
192 the most common were hydromorphone, codeine, oxycodone and methadone.<sup>26</sup> In the USA  
193 (2015), the most commonly used were hydrocodone, oxycodone and morphine;<sup>7</sup> and in England  
194 (2016) fentanyl, morphine and oxycodone were the most common long-acting opioids prescribed  
195 in high doses.<sup>10</sup> AEs were greater with high doses of opioids and co-prescribed central  
196 nervous/respiratory depressants.<sup>15,27,39,55-56</sup> Precise incidence and prevalence of AEs from  
197 prescribed opioids are not available.<sup>22</sup> Documented incidence of iatrogenic OUD has ranged from  
198 0.2% to 5% and prevalence of dependence or OUD from 0.05% to 26%.<sup>28,57</sup> Tamper- (abuse-)  
199 deterrent formulations have not clearly been found to reduce OUD.<sup>58</sup>

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

202

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.<sup>1,2,53,59-64</sup>

209 Purdue Pharma (and then other pharmaceutical companies) exerted the following forms of  
210 influence:<sup>62</sup> (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.<sup>2,53,59,65</sup> Purdue Pharma also delayed responding to reports of abuse,<sup>66</sup>

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.<sup>67</sup> Opioid-  
217 related companies have generally reached out-of-court settlements, thereby avoiding criminal  
218 prosecution and ensuring sealing of critical evidence.<sup>64</sup> However, in 2020, the founder of *Insys*  
219 (marketing *Subsys*, a fentanyl nasal spray) was imprisoned in the USA for charges of  
220 racketeering.<sup>68</sup>

221 • *Political systems*

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

227   •*Drug regulatory agencies*

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

244            Among the actions of regulators, the FDA’s uncritical approval of OxyContin played the  
245 most key role in the iatrogenic crisis.<sup>2</sup>

246

247 **Category II Organizations - Important Influencers**

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

250 • *Pain experts and societies*

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

264 Affected countries were likely slow to develop evidence-informed guidelines to respond to the  
265 crisis.<sup>28,92,93</sup>

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.<sup>53,67,94</sup>

269 • *Healthcare publication industry*

270 The healthcare publication industry is responsible for reviewing and disseminating  
271 evidence that influences care.<sup>95,96</sup> 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.<sup>60,97</sup> A critique of the letter was not published until 2017.<sup>97</sup> The citation pattern exemplifies  
274 replication publication bias which can serve to entrench erroneous information.<sup>95,98</sup> The quality  
275 and integrity of published research have been questioned.<sup>95,96,99–104</sup> 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.<sup>96,105</sup> 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.<sup>67,106</sup>

280 Declarations of financial CoIs in publications, including treatment guidelines, remain  
281 inconsistent.<sup>107–111</sup> Financial CoIs of journals, reviewers and editors are often opaque or  
282 unaddressed,<sup>94, 112–114</sup> 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.<sup>112</sup>

284

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.<sup>59,115-118</sup> 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.<sup>59,115,116</sup> 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.<sup>2,63</sup>

297 • *Academic institutions*

298 Financial CoIs of healthcare academic institutions, including teaching hospitals, can  
299 compromise integrity of research, education, and patient care.<sup>119-121</sup> Of 58 teaching hospitals  
300 examined in the United States, 5.8% received opioid-related payments.<sup>120</sup> 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

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

309 • *Funders*

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

316

### 317 **Category IV Organizations - Strongly Influenced by Category I-III Organizations**

318 • *Pain advocacy organizations*

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

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).<sup>66</sup>

328           Some physicians may have been influenced by opioid-related industry payments.<sup>67</sup> 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).<sup>53,60,65,97,127–129</sup> Lack of access to non-opioid treatments for pain  
332 was a barrier for health care professionals.<sup>123,130</sup>

333           Individual professional-related factors contributing to AEs include: excess number of  
334 pills prescribed post-surgery,<sup>7</sup> 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,<sup>11,15,26,27,56,131</sup> and prescribing opioids to pregnant women or  
337 those of child-bearing age,<sup>132–134</sup> thereby also risking perinatal side-effects.<sup>135,136</sup>

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

341

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

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

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

352

### 353 **Discussion**

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

361

362 **Figure 1 here**

363

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

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

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

385           Lessons learned from the iatrogenic opioid crisis will likely apply to the current Covid-19  
386 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.<sup>148</sup>

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.<sup>149</sup>  
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.<sup>70</sup>

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,

410 the analysis demonstrates associations rather than causality. Advancing arguments for causality  
411 is a major challenge in drug safety.<sup>150</sup>

412

### 413 **Conclusions**

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

420           The crisis resulted from a cascade of several complex interacting factors, with  
421 “institutional corruption of pharmaceuticals” being a major catalyst.<sup>41,42,121</sup> Only urgent global  
422 efforts can help to improve organizational integrity for safer drugs. However, tackling  
423 entrenched institutional corruption at the levels of crucial healthcare influencing organizations  
424 will not be an easy task. The damage caused by the iatrogenic crisis has been enormous.<sup>64</sup> and  
425 failure to tackle institutional corruption in healthcare risks future crises with similar human and  
426 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.