Comprehensive Review

Pharmacovigilance: A Review of Opioid-Induced Respiratory Depression in Chronic Pain Patients

Albert Dahan, MD, PhD[1], Frank Overdyk, MD[2], Terry Smith, PhD[1], Leon Aarts, MD, PhD[1], and Marieke Niesters, MD[1]

From: [1]Leiden University Medical Center, Department of Anesthesiology, Leiden, Netherlands; and [2]Department of Anesthesiology, Hofstra North-Shore-LIJ School of Medicine, Hempstead, New York

Address Correspondence:
Albert Dahan, MD, PhD
Leiden University Medical Center
Department of Anesthesiology
Albinusdreef 2, 2333 ZA Leiden
Leide, Netherlands
E-mail: a.dahan@lumc.nl

Background: Opioids may induce life-threatening respiratory depression, but limited knowledge is available on factors that contribute to opioid-induced respiratory depression (OIRD). This is especially true for patients with chronic pain on prolonged opioid therapy. There are no good quality case control studies or randomized controlled trials available on this topic. Here we present and analyze all case series since 1980 on OIRD in chronic pain patients extracted from PubMed.

Objective: To describe and understand clinically identified factors involved in life-threatening OIRD in patients receiving opioids for chronic pain relief.

Study Design: A literature search was performed for all relevant case reports on OIRD in chronic pain.

Methods: We searched PubMed (www.ncbi.nlm.nih.gov) for all available case reports/series on OIRD in adolescent (12 years and older) and adult patients treated with opioids for chronic pain, from which we identified specific commonalities that contributed to OIRD (akin to closed claims analyses). The dataset was post-hoc divided into 2 distinct categories: cases published from 1980 to 1999 and those from 2000 to 2012.

Results: Thirty-four reports describing 42 chronic pain patients experiencing OIRD were retrieved. Cases published before the year 2000 (pre-2000) predominantly involved morphine in cancer patients, whereas cases since 2000 (post-2000) predominantly involved methadone or transdermal fentanyl in non-cancer pain patients. Specific factors that contributed to OIRD were elevated opioid plasma levels due to renal impairment and sensory deafferentiation in pre-2000 cases, and elevated plasma levels due to drug interactions on the cytochrome P450 in post-2000 cases.

Limitations: The case series analysis of published case reports imposes limitations in terms of the types of cases presented (only severe cases are published or cases with specific precipitating factors), the journal-related publication strategy, and changes in clinical practice.

Conclusions: Our case review confirms that life-threatening OIRD in chronic pain patients involves a series of complex often-interacting factors. In spite of the factors identified in this cases series, OIRD remains unpredictable and safe opioid prescribing requires careful titration of opioid dosages and continuous monitoring to prevent life-threatening OIRD.

Key words: Opioids, opioid-induced respiratory depression, toxicity, pain, chronic pain, case series

Pain Physician 2013; 16:E85-E94

Opioids are potent analgesics used for the treatment of moderate to severe acute and chronic cancer and non-cancer pain. Opioid analgesics have a number of side effects, of which, respiratory depression is the only one that is potentially life threatening.

Literature reviews summarizing the results of mostly retrospective studies on acute and chronic opioid use indicate that respiratory depression is relatively uncommon, although respiratory depression is rarely the primary end-point of these studies. From one such review, it appears that about 1 in 200 postoperative patients develops opioid-induced respiratory depression (OIRD) requiring rescue, such as the administration of naloxone (1). These figures regarding the overall safety of opioids may be misleading (1). A recent retrospective study on "code blue" emergencies revealed that opioids play an important determinant role in about 50% of non-CardioPulmonary Resuscitation events in hospitals (2).

Many reviews and textbooks describe the characteristics of patients at increased risk for OIRD, and these include obese patients, patients with lung diseases and/or sleep-related breathing disorders, and elderly patients. However, these subsets have not been verified by randomized clinical trials (RCTs) or case control studies (1). Since 1980, a large number of case reports on opioid-OIRD have been published and these show considerable overlap in specific factors such as gender and age, opioid type, underlying disease, and drug-drug interaction.

Furthermore, with the recent exponential rise in opioid consumption related to prescriptions for chronic pain indications, the number of opioid-related respiratory complications has increased exponentially, although exact numbers are not available (3-6). Hence, we found it appropriate to reassess our understanding of OIRD in patients taking opioids for chronic pain. With the objective to describe and understand clinically identified factors involved in life-threatening OIRD in patients receiving opioids for chronic pain relief, we searched PubMed for all relevant case reports in patients over 12 years of age. The reports were analyzed for specific commonalities, which were then interpreted as to whether they comprised specific contributing factors for OIRD. This approach is similar to published closed claims analyses.

Case reports constitute less than 10% of the scientific literature and contain a low level of evidence compared to other types of publications such as RCTs,

case control studies, or meta-analyses (7,8). However, given the absence of such latter studies/analyses, we performed a systematic analysis of case reports rather than search for case control studies or RCTs for the simple reason that high quality RCTs and case control studies on OIRD are not available. We extracted reports from the literature where the intervention was opioid administration for chronic pain and the unexpected outcome was one of the following:

1. respiratory depression or upper airway obstruction/sleep disordered breathing requiring some form of rescue or intervention (naloxone or doxapram administration, resuscitation, intubation, admission into the intensive care unit, opioid withdrawal), or
2. death related to the opioid intake.

METHODS

In October 2012 we searched the electronic database, PubMed (www.ncbi.nlm.nih.gov), for case reports describing one or more patients that developed OIRD after receiving opioids prescribed by medical personnel for the treatment of chronic pain (Appendix I).

We defined OIRD as a compromise of respiratory function that required one of the following interventions:

1. administration of naloxone or doxapram;
2. intubation and/or positive pressure ventilation;
3. unplanned admission to an intensive care or monitored setting.

We also checked relevant review papers and the contents of available case report journals for additional papers. Case report journals included Case Reports in Anesthesiology, BMJ Case Reports, Journal of Medical Case Reports, and International Medical Case Reports Journal.

The search strategy contained several exclusion criteria:

1. case reports in languages other than English, French, German, or Dutch with the exception of foreign language papers with comprehensive abstracts in English;
2. case reports that describe OIRD in an acute setting, such as emergency rooms and perioperative locations;
3. case reports on patients < 12 years or published prior to 1980;

4. papers that describe reports of suicide or homicide by opioid-overdose, OIRD related to opioid abuse, inadvertent intake/application of oral or transdermal opioids;

5. case reports that involved medical personnel and/or device errors.

All relevant papers were read in full and the bimodal causality (strong, weak) between opioid treatment and subsequent respiratory depression was ascertained by 2 authors (AD, MN). Cases with weak causality were discarded, and differences in opinion were resolved by consensus.

The following variables were extracted from the papers that were included in the final database: year of publication, patient gender and age, opioid, opioid dose, co-medication, route of opioid administration, the use of reversal agents, comorbidities, and genetic data (if available). The dataset was post-hoc divided into 2 distinct categories: a) cases published from January 1, 1980, to December 31, 1999, and b) cases published since January 1, 2000.

The causality analysis of the data was subjective and descriptive and intended to find patterns that could identify contributing factors for OIRD. These factors were searched in each of the 2 data subsets within the following fields: age, gender, type of opioid, underlying disease, and drug interactions.

Results

The search resulted in 4,667 unique papers of which 4,633 were discarded (Fig. 1). Thirty-four papers describing 42 chronic pain patients (ie. individual case reports) with OIRD were retrieved and further analyzed (9-42). Papers discarded included 27 pediatric cases (43), 120 acute pain cases, and 35 cases on error-related OIRD. Most other papers discarded were on opioid abuse and/or suicide.

Date of Publication

Fifteen cases were published between 1980 and 2000 (pre-2000) (9-22), and 27 cases between 2000 and 2013 (post-2000) (23-42) (Fig. 2A).

Gender and Age

Nineteen men and 23 women are described, with equal distributions pre- and post-2000 (pre-2000: 7 men and 8 women, post-2000 12 men and 15 women). The median age (range) of the total population was 59 years (28 – 92 years). This distribution was similar in the cases
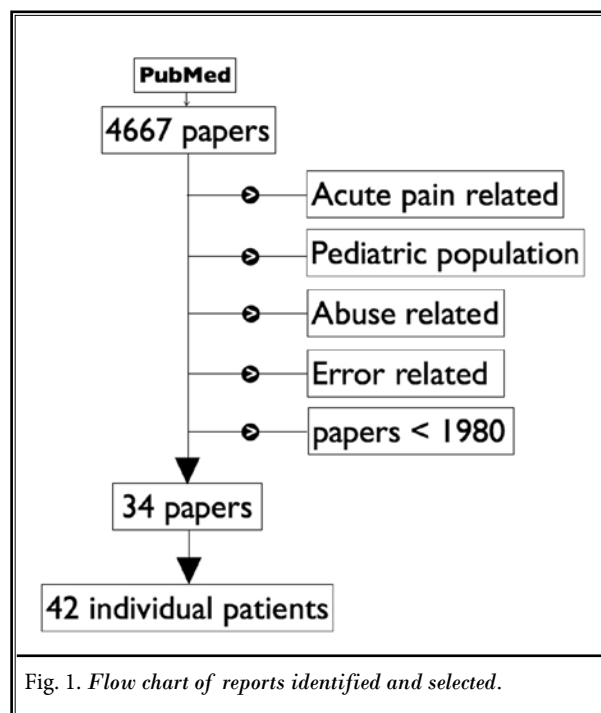

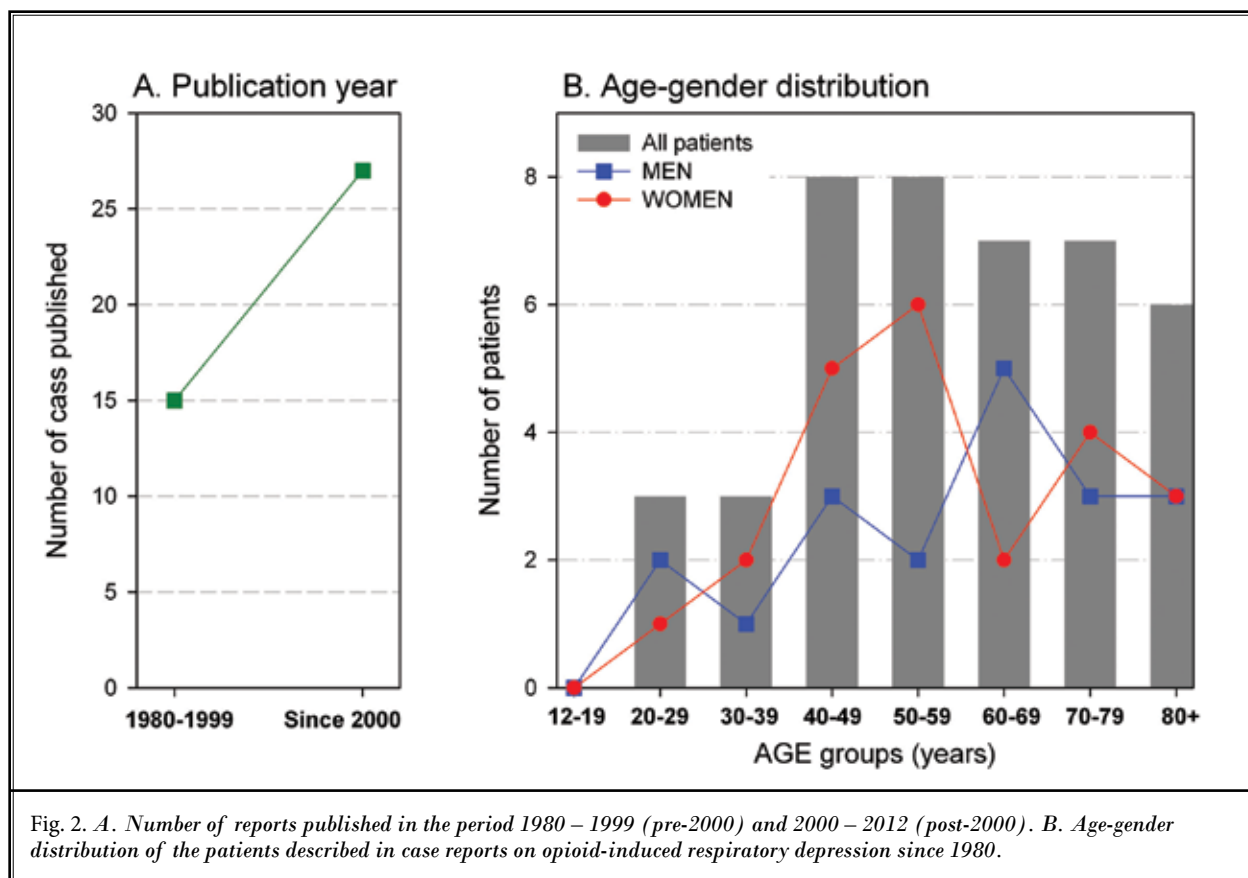Fig. 1. *Flow chart of reports identified and selected.*

reported before and after 2000: pre-2000 60 years (44 – 92 years), post-2000: 57 years (28 – 81 years). The age-gender distribution is given in Fig. 2B, showing, compared to men, a small increase in the number of cases in women between the ages of 40 and 60.

Opioid Type

Pre-2000 the opioid involved in the majority of cases of OIRD was morphine (80% of cases, Fig 3A). Since 2000 the contribution of morphine in OIRD has declined to just 19%. Transdermal fentanyl and methadone now contribute the majority of cases (30% each). Oxycodone was the opioid in 17% of cases (Fig. 3B). In most cases additional circumstances contributed to the development of OIRD (see below). The route of opioid administration was predominantly oral or transdermal (fentanyl, buprenorphine) with just 4 cases involving neuraxial opioids.

Indication for Opioid Therapy

The indication for opioid use was cancer pain in 67% of the cases pre-2000, but dropped to 41% post-2000 (Fig. 3C and D). Post-2000 the indication for opioid prescriptions for non-cancer pain was 59%, most commonly for treatment of musculoskeletal pain (33%) followed by neuropathic pain and complex regional pain syndrome (11%) (Fig 3D).

Fig. 2. *A. Number of reports published in the period 1980 – 1999 (pre-2000) and 2000 – 2012 (post-2000). B. Age-gender distribution of the patients described in case reports on opioid-induced respiratory depression since 1980.*
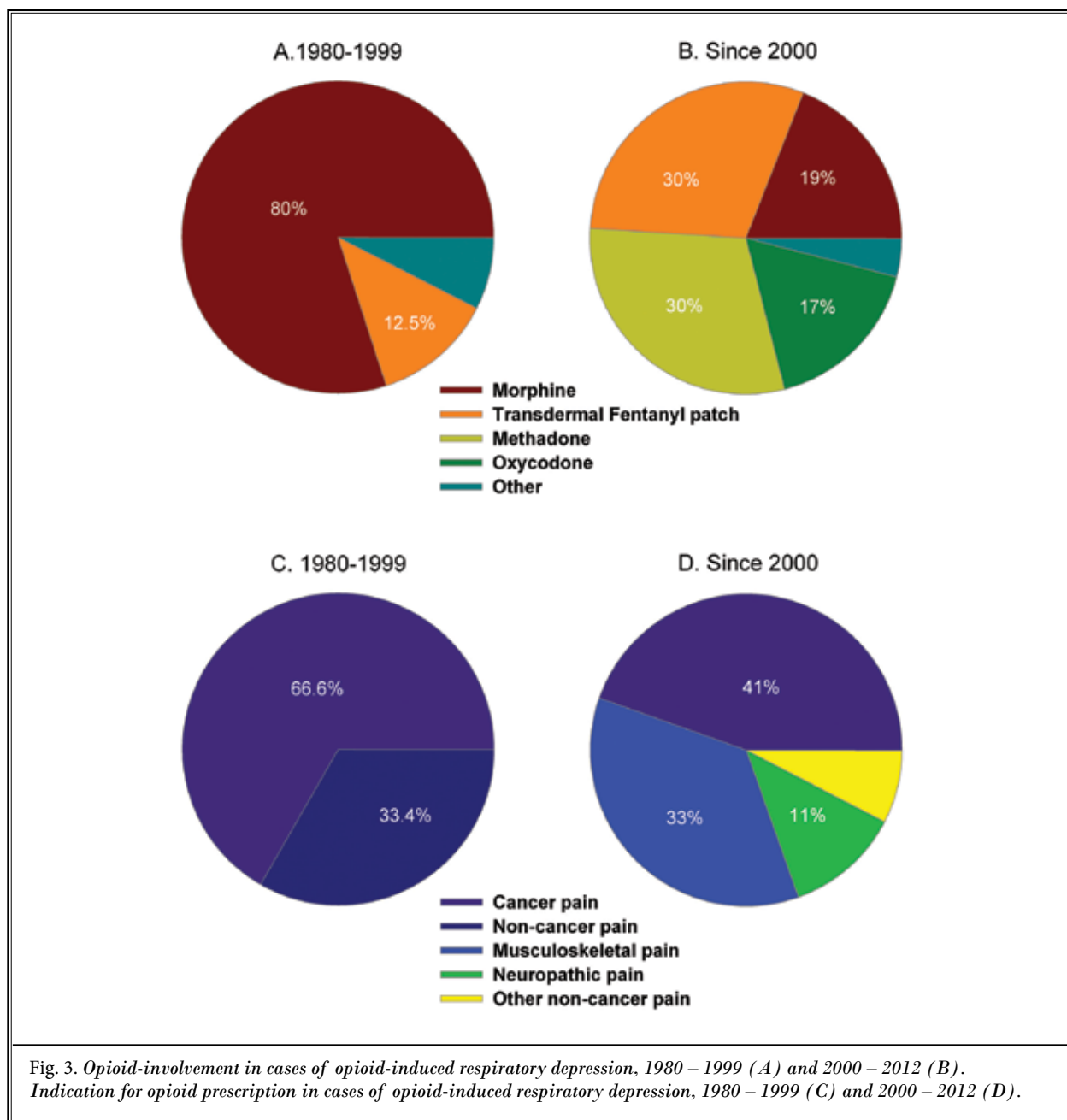
Additional Circumstances

Pre-2000, 2 patterns in the data are apparent. In one-third of the cases morphine-induced respiratory depression was due to the loss of pain-induced stimulation of breathing due to deafferentiation. Deafferentiation was induced by administration of a nerve block or spinal anesthetic, the application of a cordotomy or progression of metastatic disease with full spinal cord compression (10,11,19,22). One-third of the cases pre-2000 with morphine-induced OIRD involved patients with varying degrees of renal failure (14,15,21). The most important etiology of OIRD in the post-2000 data was interference with opioid metabolism from secondary drugs (including polycyclic aromatic hydrocarbons in tobacco smoke) that induce or inhibit the cytochrome P450 metabolic pathway of the opioid, making opioid plasma levels unpredicatbale (Table 1) (23,26,30-33,38,41).

Obesity, sleep disordered breathing, and lung disease did not play a prominent role in pre-2000 cases whereas 5 cases post-2000 describe patients that developed sleep disordered breathing from chronic opioid use (29,35).

Discussion

Herein we analyze 34 case reports describing OIRD in 42 adolescent and adult patients treated for chronic cancer and non-cancer pain from 1980 to 2012. The number of cases is relatively small compared to OIRD in acute pain patients (120 cases), but there is a substantial increase in the incidence of cases post-2000 (pre-2000: 0.8 cases/year versus post-2000: 2.3 cases/year). This reflects the increased use of opioids in patients with non-cancer pain in the last decade. There is currently a certain awareness of the problem of OIRD. The increased morbidity and mortality from opioids in chronic pain patients apparent from case control studies, postmortem forensic studies, retrospective studies on opioid effect, expert opinions, and anecdotal evidence (1-5) has prompted the Federal Drug Administra-

Fig. 3. *Opioid-involvement in cases of opioid-induced respiratory depression, 1980 – 1999 (A) and 2000 – 2012 (B). Indication for opioid prescription in cases of opioid-induced respiratory depression, 1980 – 1999 (C) and 2000 – 2012 (D).*

tion (FDA) and the Centers for Disease Control and Prevention (CDC) to take action in the United States (6,44). As part of their strategy to reduce opioid-related morbidity and mortality, the FDA requires opioid manufacturers to devise a Risk Evaluation and Mitigation Strategy (REMS) prior to marketing a new opioid (44). Only a few studies have investigated specific patient- and non-patient-contributing factors of OIRD (3,6,45),

and the literature on OIRD in patients with chronic pain is sparse. We are aware that case reports constitute a relatively small part of the scientific literature with a limited level of evidence compared to other types of publication such as RCTs, case control studies, or meta-analyses (7,8). However, we chose to perform a systematic analysis of case reports rather than of case control studies or RCTs for the simple reason that (good quality)

Table 1. *Drug-drug interaction.*

Ref. (year)	Patient	Opioid (duration of intake)	Disease	Event	Co-medication	Interaction
23 (2000)	42 yr. F	Methadone (6 years)	Chronic intestinal obstruction (Ogilvie's syndrome)	Sedation/respiratory depression responsive to naloxone	Ciprofloxacin	Inhibition of CYP1A2 and 3A4 activity, increasing methadone blood levels
26 (2002)	60 yr. M	Methadone (15 days)	Adenocarcinoma of the stomach	Respiratory depression responsive to naloxone	Fluconazol	Inhibition of CYP3A4 and 2Y9, increasing methadone blood levels
30 (2005)	70 yr. M	Methadone (switch from long-term opioid use, respiratory event after one week of treatment)	Vertebral compression fracture and alcoholism	Respiratory depression responsive to naloxone	Sertraline	Inhibition of the CYP system, increasing methadone blood levels.
31 (2006)	61 yr. F	Methadone (long-term)	Lung cancer with bone metastasis and neuropathic pain	Naloxone-responsive respiratory depression 11 days after carbamazepine withdrawal	Carbamazepine Gabapentin	Induction of CYP3A4 activity. Its withdrawal slows down methadone's metabolism causing an increase in plasma levels
32 (2006)	46 yr. M	Fentanyl TD patch (45 days), morphine, oxazepam	Tonsillar cancer	8 days following start of fluconazole patient died during sleep. Forensic analysis showed high plasma conc. of fentanyl and fluconazole	Fluconazole	Inhibition of CYP3A4 system, increasing fentanyl blood levels
33 (2006)	34 yr. M	Buprenorphine TD patch (12 h)	Skull osteosarcoma and pelvic metastasis	Respiratory depression upon start of chemotherapy with ifosfamide resolved by removal of the patch	Ifosfamide, an alkylating agent	Possible competitive interaction via common metabolic pathway (CYP3A4)
38 (2009)	81 yr. M	Fentanyl TD patch (long-term)	Spinal stenosis and spondylosis, dementia, COPD	36 h after receiving the first dose of clarithromycine he developed naloxone-responsive respiratory depression.	Clarithromycine	Inhibition of the CYP3A4 system, increasing fentanyl's plasma levels
41 (2011)	46 yr. M	Methadone (4 months)	Chronic low back pain	Smoking cessation (after 33 pack years) initiated naloxone-responsive respiratory depression	Smoking cessation	Polycyclic aromatic hydrocarbons in tobacco smoke induce CYP1A2. A relative reduction in CYP1A2 activity upon smoking cessation may have reduced methadone's metabolism.

F = female, M = male; COPD = chronic obstructive pulmonary disease.

case control studies and RCTs on OIRD are not available. Our approach differs from traditional reports such as that of the American Society for Pain Management Nursing (45), in which mostly retrospective studies on OIRD were rated on strength of evidence. The current analysis is comparable to a closed claims analysis (an analysis of closed malpractice claims) (46,47).

A Change in Practice from Pre- to Post-2000

An important pattern observed in our analysis is that pre-2000 morphine was the predominant cause of OIRD in chronic pain patients (Fig. 3A). Post-2000 morphine loses first place to methadone and transdermal fentanyl (each contributed 30%, Fig. 3B). This observation is in line with a recent study by the CDC showing that methadone was involved in 31% of opioid-related deaths in 13 states (6). The large contribution of methadone and fentanyl reflects the increased use of these 2 opioids for treatment of non-cancer chronic pain. Since 2000 non-cancer pain patients have replaced cancer pain patients as the most commonly reported on (Fig. 3C and D). Most of them suffer from musculoskeletal pain (lower back and neck pain) and neuropathic pain (including complex regional pain syndrome). This reflects a major shift in the prescribing behaviors of physicians (especially in the US) and is related to many factors including an increased awareness, diagnosis, and treatment of chronic pain (5). It should be remembered, however, that chronic pain is often undertreated and any tendency to reduce opioid use due to an increased awareness of opioid-induced side effects in non-cancer chronic pain conditions, such as in osteoarthritis, should be offset by the potential risk of inadequately treating pain in such patients (48).

Patterns in Cases Published Pre-2000

Acute pain stimulates breathing (49,50). Such a stimulatory effect may offset OIRD and, in our data set, the removal of such stimulatory effects of pain on breathing is apparent. In 4 chronic pain patients being initially treated with potent opioids, a subsequent sensory deafferentiation, either from a cordotomy, spinal anesthetic, peripheral nerve block, or a full compression of the spinal cord, led to life-threatening OIRD (10,11,19,22). Renal impairment, leading to an accumulation of morphine's active metabolite morphine-6-glucuronide, is also apparent as a factor for morphine-induced respiratory depression, as described in 3 reports pre-2000 (14,15,21). Current practice is to avoid opioids that may accumulate in patients with even mild renal impairment.

Patterns in Cases Published Post-2000

Drug interactions figure prominently during this period as the cause of OIRD (Table 1). Opioids involved are methadone, fentanyl, and buprenorphine. In most cases a secondary drug (antifungal medication, antibiotic, antidepressant, chemotherapeutic) inhibited the metabolic pathway (ie. the Cytochrome P450 [CYP] enzyme system) of these opioids, causing toxic elevations in opioid blood levels and, consequently, OIRD. In one case, carbamazepine (a CYP inhibitor) was withdrawn during long-term methadone treatment (31), and in another case, when a patient with chronic lower back pain quit smoking the polycyclic aromatic hydrocarbons in tobacco smoke that induce the CYP system became absent (41). These data exemplify the need for educating prescribing physicians on the pharmacokinetic drug interactions that are relevant to patients on prescribed potent opioids.

In contrast to cases in the pediatric/perinatal population (43), and in acute pain patients (Dahan, data on file), sleep-disordered breathing (SDB) did not play a significant role in any of the reports on OIRD in chronic pain patients. This was unexpected and suggests that SDB is likely not an important determining factor in the development of OIRD in chronic pain patients; yet, data on this topic are scarce. Interestingly, in 6 patients without cardiac or neurologic disease, chronic opioid therapy contributed (n = 5) or exacerbated (n = 1) their SDB, as evident from increased ataxic breathing, central apneas, hypoxia, delayed arousal responses, and day-time sleepiness (29,35). Therapy consisted of supplemental oxygen and a continuous positive airway pressure mask during sleep. The cause of opioid-induced SDB is probably related to a reduced REM period and marked increase in the number of central and combined central/peripheral rather than obstructive apneas (51,52). Possibly patients that develop sleep-disordered SDB during opioid therapy have a predisposition for this syndrome that becomes apparent during opioid therapy (51).

Most cases that we retrieved from the literature describe patients on relatively high dose opioid therapy. Dose plays an important role in the development of OIRD. In a cohort study, Dunn et al (5) found a prevalence of OIRD of 0.5% of patients on opioids for chronic non-cancer pain that was dose-dependent. Patients receiving 50 – 99 mg/day of morphine equivalents carried a 3.7-fold increase in overdose risk compared to patients receiving 1 – 20 mg/day of morphine equivalents, while 100 mg or more per day carried a 8.9-fold increased risk. In our data set, we note 2 cases in which

severe OIRD developed after a pause in treatment with intrathecal opioids (19,39). These data suggest that tolerance to the respiratory depressant effects of opioids can dissipate quickly, and re-initiation after a pause in opioid treatment must be done with caution.

Finally, we observed no gender predominance in OIRD cases. This is in disagreement with observations of gender differences in morphine analgesia and respiratory depression in acute and experimental settings (53,54).

We acknowledge the bias in our approach in that a) only severe (ie. fatal or near-fatal) cases are published or cases in which specific precipitating factors were involved, b) publication strategy (from editors and authors) determines which cases are published, and c) due to slow changes in clinical practice, the patterns involved in OIRD will vary over time. But we argue that the patterns we detected over the 32 year period of our analysis are valid and do not lose importance in our understanding of OIRD and its prevention. For example, contributing factors in OIRD described in the 1980s retain their validity in present-day patients even though no new cases containing similar contributing factors were published in the 2010s.

Conclusion

In conclusion, we performed a systematic analysis of case reports on OIRD in chronic pain patients, similar to a closed claims analysis (an analysis of closed malpractice claims) (46,47), and observed marked differences in cases published pre-2000 (OIRD due to morphine in chronic cancer pain patients) and since 2000 (OIRD due to alternative opioid use, such as methadone and transdermal fentanyl in a predominant chronic non-cancer pain population). Specific factors that contributed to OIRD were renal impairment as a cause of morphine-induced respiratory depression and sensory deafferentiation as a cause of OIRD in the data set from pre-2000 and pharmacokinetic drug interactions causing the increase in opioid blood concentration to toxic levels in the data set published post-2000. In all cases OIRD was not predictable despite the presence of "risk" factors. It is therefore essential to carefully titrate, observe, and monitor all patients on chronic opioids to prevent development of life-threatening OIRD.

Appendix 1. *The PubMed search strateg. *

(("Analgesics, Opioid"[Pharmacological Action] OR "Narcotics" [Pharmacological Action] OR opiate[tiab] OR opiates[tiab] OR opioid[tiab] OR narcotic[tiab] OR narcotics[tiab]) AND ("poisoning"[Subheading] OR "toxicity"[Subheading] OR intoxication[tiab] OR toxicity[tiab] OR poisoning[tiab] OR "adverse effects"[Subheading] OR adverse[tiab])) OR "Analgesics, Opioid/poisoning"[Mesh] OR "Analgesics, Opioid/toxicity"[Mesh] OR "Analgesics, Opioid/ adverse effects"[Mesh] OR (("Analgesics, Opioid"[Pharmacological Action] OR "Narcotics" [Pharmacological Action] OR opiate[tiab] OR opiates[tiab] OR opioid[tiab] OR narcotic[tiab] OR narcotics[tiab]) AND ("respiratory arrest" OR "respiratory arrests" OR "respiratory depression" OR "Respiration Disorders/chemically induced"[mesh])) AND (case report OR case reports OR case series OR case[ti] OR cases[ti] OR ((case OR cases) AND (report OR reports OR series)))

References

1. Dahan A, Aarts L, Smith TW. Incidence, reversal and prevention of opioid-induced respiratory depression. *Anesthesiology* 2010; 112:226-238.

2. Fecho K, Jackson F, Smith F, Overdyk FJ. In-hospital resuscitation: Opioids and other factors influencing survival. *Ther Clin Risk Manag* 2009; 5:961-968.

3. Dunn KM, Saunders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, Weisner CM, Silverberg MJ, Campbell CI, Psaty BM, Von Korff M. Opioid prescriptions for chronic pain and overdose: A cohort study. *Ann Int Med* 2010; 152:85-92.

4. Vila H Jr, Smith RA, Augustyniak MJ, Nagi PA, Soto RG, Ross TW, Cantor AB, Strickland JM, Miguel RV. The efficacy of pain management before and after implementation of hospital-wide pain management standards: Is patient safety compromised by treatment solely based on numerical pain ratings? *Anesth Analg* 2005; 101:474-480.

5. Okie S. A flood of opioids, a rising tide of deaths. *N Eng J Med* 2010; 363:1981-1985.

6. Paulozzi LJ, Mack KA, Jones CM. Vital signs. Risk of overdose from methadone used for pain relief – United States, 1999 – 2010. *MMWR* 2012; 61:493-497.

7. Gopikrishna V. A report on case reports. *J Conserv Dent* 2010; 13:265-271.

8. Anonymous. Case reports, case series and systematic review (editorial). *Q J Med* 2002; 95:197-198.

9. Jones RDM, Jones JG. Intrathecal morphine: Naloxone reverses respiratory depression but not analgesia. *Br Med J* 1980; 281:645-646.

10. Hanks GW, Twycross RG, Lloyd JW. Unexpected complication of successful nerve block. *Anaesth* 1981; 36:37-39.

11. Wells CJ, Lipton S, Lauerta J. Respiratory depression after percutaneous cervical anterolateral cordotomy in patients on slow-release of morphine. *Lancet* 1984; 323:739.

12. Kageyama S, Sasoh F, Taniguchi I, Homma I, Saito H, Isogai Y. Cardiorespiratory arrest in a patient with advanced diabetic autonomic neuropathy. *Diab Res Clin Prac* 1985; 1:243-246.

13. Pétry T, Cloez O, Pertek JP, Heck M, Auque J. Respiratory depression with spinal morphine: Interest of naloxone in situ (in French). *Ann Fr Anesth Réanim* 1985; 4:424-426.

14. Niazi Z, Mooney B, O'Dohmnaill S. Respiratory depression due to MST: A case report. *Eur J Clin Pharmacol* 1988; 35:685.

15. Hoogslag PAM, van Dijk B, Vinks A. Respiratory depression after intake of morphine-slow-release tablets (in Dutch). *Ned Tijdsch Geneesk* 1989; 133:516-517.

16. Sjøgren P, Jakobsen S, Valentin N. Respiratory depression during epidural morphine treatment. *Acta Anaesthesiol Scand* 1991; 35:553-555.

17. Lang E, Jedeikin R. Acute respiratory depression as a complication of nebulized morphine. *Can J Anaesth* 1998; 45:60-62.

18. Newshan G. Heat-related toxicity with the fentanyl transdermal patch. *J Pain Sympt Mang* 1998; 16:277-278.

19. Piquet CY, Mallaret MP, Lemoigne AH, Barjhoux CE, Danel VC, Vincent FH. Respiratory depression following administration of intrathecal bupivacaine to an opioid-dependent patient. *Ann Pharmacother* 1998; 32:653-655.

20. Clark JD, Edwards T. Severe respiratory depression in a patient with gastroparesis while receiving opioids for pain. *Clin J Pain* 1999; 15:321-323.

21. Dubs A, Wiedemeier P, Caduff B. Morphine intoxication by morphine-6-glucuronide, a pharmacologically active morphine metabolite, in chronic renal failure (in German). *Dtsch Med Wschr* 1999; 124:896-898.

22. Quevedo F, Walsh D. Morphine-induced ventilatory failure after spinal cord compression. *J Pain Sympt Manag* 1999; 18:140-142.

23. Herrlin K, Segerdahl M, Gustafsson LL, Kaiso E. Methadone, ciprofloxacin, and adverse drug reactions. *Lancet* 2000; 356:2069-2070.

24. Oneschuk D, Bruera E. Respiratory depression during methadone rotation in patient with advanced cancer. *J Palliative Care* 2000; 16:50-54.

25. Frölich M, Giannotti A, Modell JH. Opioid overdose in a patient using a fentanyl patch during treatment with a warm blanket. *Anesth Analg* 2001; 93:647-648.

26. Tarumi Y, Pereira J, Watanabe S. Methadone and fluconazole: Respiratory depression by drug interaction. *J Pain Sympt Mang* 2002; 23:148-153.

27. Reeves RR, Mack JE. Possible dangerous interaction of oxycontin and carisoprodol. *Am Fam Physician* 2003; 67:941-942.

28. Regnard C, Pelham A. Severe respiratory depression and sedation with transdermal fentanyl: Four case studies. *Pall Med* 2003; 17:714-716.

29. Farney RJ, Walker JM, Cloward TV, Rhondeau S. Sleep-disordered breathing associated with long-term opioid therapy. *Chest* 2003; 123:632-639.

30. Elsayem A, Bruera E. Methadone-induced respiratory depression in a patient with a history of alcoholism. *J Pall Med* 2005; 8:1062-1066.

31. Benitez-Rosario MA, Martin AS, Gómez-Ontañón E, Feria M. Methadone-induced respiratory depression after discontinuing carbamazepine administration. *J Pain Sympt Mang* 2006; 32:99-100.

32. Hallberg P, Martén L, Wadelius M. Possible fluconazole-fentanyl intoxication – A case report. *Eur J Clin Pharmacol* 2006; 62:491-492.

33. Moro C, Taino R, Mandala M, Labianca R. Buprenorphine-induced acute respiratory depression during ifosfamide-based chemotherapy. *Ann Oncol* 2006; 17:1466-1467.

34. Scherens A, Kagel T, Zenz M, Maier C. Long-term respiratory depression induced by intrathecal morphine treatment for chronic neuropathic pain. *Anesthesiology* 2006; 105:431-433.

35. Mogri M, Khan MIA, Grant BJD, Mador MJ. Central sleep apnea induced by acute ingestion of opioids. *Chest* 2008; 133:1484-1488.

36. Moon JM, Chun BJ. Fentanyl intoxication caused by abused transdermal fentanyl. *J Emerg Med* 2008; 40:37-40.

37. Upadhyay S, Jain R, Chauhan H, Gupta D, Mishra S, Bhatnagar S. Oral morphine overdose in cancer patient antagonized by prolonged naloxone infusion. *Am J Hospice Pall Med* 2008; 25:401-405.

38. Horton R, Barber C. Opioid-induced respiratory depression resulting from transdermal fentanyl-clarithromycine drug interaction in a patient with advanced COPD. *J Pain Sympt Mang* 2009; 37:e2-e5.

39. Ruan X, Couch P, Liu H, Shah R, Wang F, Chiravuri S. Respiratory failure following delayed intrathecal morphine pump refill: A valuable, but costly lesson. *Pain Physician* 2010; 13:337-341.

40. Lu WJ, Zhou W, Kreutz Y, Flockhart DA. Methadone adverse reaction presenting with a large increase in plasma methadone binding: A case series. *J Med Case Reports* 2011; 5:513.

41. Wahawisan J, Kolluru S, Molina C, Speake J. Methadone toxicity due to

smoking cessation – A case report on the drug-drug interaction involving cytochrome P450 isoenzyme 1A2. *Ann Pharmacother* 2011; 45:e34.

42. Sindali K, Sherry K, Sen S, Dheansa B. Life-threatening coma and full-thickness sunburn in a patient treated with transdermal fentanyl patches: A case report. *J Med Case Rep* 2012; 6:220.

43. Niesters M, Overdyk F, Smith T, Aarts L, Dahan A. Opioid-induced respiratory depression in paediatrics: A review of case reports. *Br J Anaesth* 2013;110:175-182.

44. Food and Drug Adminstration. Approved Risk Evaluation and Mitigation Strategies (REMS) www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm

45. Jarzyna D, Jungquist CR, Pasero C, Willens JS, Nisbet A, Oakes L, Dempsey SJ, Santangelo D, Polomano RC. American Society for Pain Management nursing

guidelines on monitoring for opioid-induced sedation and respiratory depression. *Pain Manag Nurs* 2011; 12:118-145.

46. Staender S, Schaer H, Clergue F, Gerber H, Pasch T, Skarvan K, Meister B. A Swiss anaesthesiology closed claims analysis: Report of events in the years 1987-2008. *Eur J Anaesthesiol* 2011; 28:85-89.

47. Caplan RA, Ward RJ, Posner K, Cheney FW. Unexpected cardiac arrest during spinal anesthesia: A closed claims analysis of predisposing factors. *Anesthesiology* 1988; 68:5-11.

48. O'Neil CK, Hanlon JT, Marcum ZA. Adverse effects of analgesics commonly used with older patients with osteoarthritis: Focus on opioid and non-opioid analgesics. *Am J Geriatr Pharmacother* 2012 [Epub ahead of print].

49. Sarton E, Dahan A, Teppema L, Berkenbosch A, van den Elsen, van Kleef. Influence of acute pain induced by activation of cutaneous nociceptors on ventilatory

control. *Anesthesiology* 1997; 87:289-296.

50. Bourke DL. Respiratory effects of regional anesthesia during acute pain. *Reg Anesth* 1994; 18:361-365.

51. Webster LR, Choi Y, Desai H, Grant BJ. Sleep-disordered breathing and chronic pain therapy. *Pain Med* 2008; 9:425-432.

52. Bernards CM, Knowlton SL, Schmidt DF, DePaso WJ, Lee MK, McDonald SB, Baines OS. Respiratory and sleep effects of remifentanil in volunteers with moderate sleep apnea. *Anesthesiology* 2009; 110:41-49.

53. Niesters M, Dahan A, Kest B, Zacny J, Stijnen T, Aarts L, Sarton E. Do sex differences exist in opioid analgesia? A systematic review and meta-analysis of human experimental and clinical studies. *Pain* 2010; 151:61-68.

54. Dahan A, Sarton E, Olievier C. Sex-related differences in the influence of morphine on ventilatory control in humans. *Anesthesiology* 1998; 88:903-913.