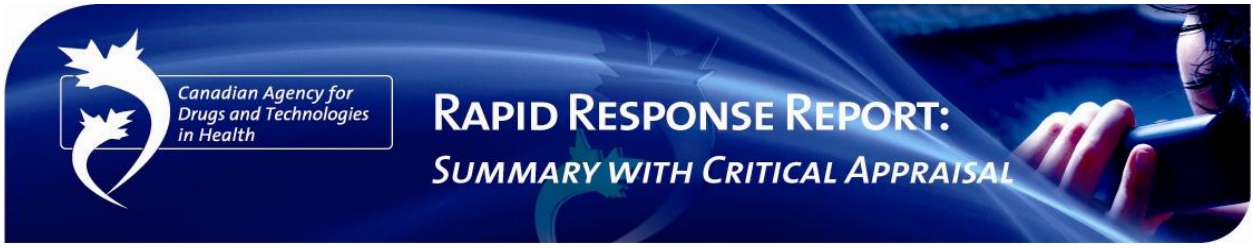

TITLE: Watchful Dosing of Morphine or Morphine Equivalent Dosing in the Treatment of Chronic Non-Cancer Pain: A Review of the Clinical Evidence

DATE: 06 June 2012

CONTEXT AND POLICY ISSUES

The Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain by the National Opioid Use Guideline Group (NOUGG) was published in 2010[1,2] and defines a watchful dose of morphine or equivalent as being in excess of 200 mg/day. The American Pain Society and American Academy of Pain Medicine similarly identify high dose opioid therapy as constituting a total daily oral morphine (or equivalent) dose above 200 mg in their opioid treatment guidelines for chronic non-cancer pain (CNCP).[3]

Although not explicitly stated in the Canadian guidelines,[1] the reason for establishing a threshold dose would appear to have arisen at least in part out of concern over the rising pattern of opioid prescribing that has occurred during the past ten years in Canada and its particular association with overdose and death.[1]

The 'watchful dose' would seem to act as an alert for clinicians contemplating exceeding this threshold to first reassess pain (including potentially, diagnosis), response to opioid therapy, risk for drug-related aberrant behaviors,[2] among other issues such as health status and adherence,[3] before proceeding.[2] What is less clear for policymakers, however, is whether there are important public health safety concerns at morphine-equivalent doses below 200 mg/day.

The present review therefore sought to examine the available safety evidence base for the 200 mg/day watchful morphine (or equivalent) dose in comparison to doses below this threshold.

RESEARCH QUESTIONS

1. What is the clinical evidence regarding the safety of different watchful doses of morphine (or equivalent) for the treatment of chronic non-cancer pain?

2. What are the evidence-based guidelines regarding a watchful dose of morphine (or equivalent) for the treatment of chronic non-cancer pain?

KEY MESSAGE

The evidence base around a watchful dose threshold for morphine or equivalent opioid dosing was limited in both quality and quantity.

The evidence to support a watchful dose of morphine or morphine equivalent opioid dosing of greater than 200 mg/day in chronic non-cancer pain (CNCP) is limited in both quality and quantity; however, there is also little evidence to support a lower threshold dose.

The paucity of evidence for watchful dosing is likely reflective of larger gaps in evidence in the topic of CNCP management in general, including around the appropriate use of opioids.

METHODS

Literature Search Strategy

A focused search (with main concepts appearing in title or major subject heading) was conducted on key resources including PubMed, The Cochrane Library (2012, Issue 4), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2007 and May 8, 2012.

Selection Criteria and Methods

One reviewer screened the titles and abstracts from the list of identified citations. Potentially relevant articles were retrieved and reviewed for final selection. Articles reporting on watchful doses of morphine were selected for inclusion, according to the criteria listed in Table 1.

Table 1: Selection Criteria

Population	Adult patients with chronic, non-cancer pain
Intervention	Morphine (or equivalent) 200 mg/day
Comparator	Morphine (or equivalent) $\geq$ 100 mg/day
Outcomes	Safety issues/adverse events: • Adverse events (i.e., overdose, hospitalization, death) • Addiction potential
Study Designs	• Health technology assessments, systematic reviews and meta-analyses • Randomized controlled trials • Non-randomized studies • Guidelines

Exclusion Criteria

Studies were excluded if the authors did not report on dosing of opioids studied. Similarly, if morphine equivalent dosing was not reported and either could not be calculated[2] or is not well established (e.g., methadone, tramadol, buprenorphine)[2,4], the study was excluded. Studies of children, efficacy (as opposed to safety), or those investigating the use of opioids in indications other than for chronic non-malignant pain (CNCP) were also excluded.

Critical Appraisal of Individual Studies

Critical appraisal of the methodology used in the individual studies was performed using the Downs and Black instrument[5] while clinical practice guidelines were appraised for quality according to the criteria described in the AGREE instrument.[6]

An annotated critical appraisal of the strengths and limitations of the individual included studies and clinical practice guidelines is provided in Appendix 3.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search yielded a total of 640 citations. After screening titles and abstracts, 603 articles were excluded and 37 potentially relevant reports were selected for full-text review. In addition, 13 potentially relevant reports were retrieved from other sources (grey literature, hand search) for a total of 50 potentially relevant reports. Of these 50 reports, 44 did not meet the inclusion criteria and were excluded, leaving a total of six relevant reports comprising four non-randomized studies[7-10] and two clinical practice guidelines[1-3]. No systematic reviews or randomized controlled trials were identified that met the inclusion criteria.

The study selection process is outlined in Appendix 1.

Summary of Study Characteristics

Characteristics of the included reports are summarized below and detailed in Appendix 2.

Country of origin

Of the four included studies,[7-10] two were from Canada[7,8] and two were from the US.[9,10] Of the two clinical practice guidelines included, one was from Canada[1,2] and the other was from the US.[3]

Population

All of the included studies investigated adult populations. The two Canadian studies[7,8] specifically examined socioeconomically disadvantaged patients < 65 years of age covered under the Ontario public drug plan. One US study[9] looked at beneficiaries of the Veterans Health Administration while the other US study[10] examined beneficiaries of two health administrative claims databases – one public and one private.

Both the Canadian and US guidelines[1-3] likewise provide evidence-based recommendations for opioid therapy in the management of CNCP in adults. Primary care clinicians represent the target audience for both sets of guidelines[1-3] while specialists are an additional target for the US guidelines.[3]

Intervention

All of the included studies investigated prescription drug claims data for multiple opioid agents, translating doses of non-morphine drugs into morphine equivalent doses. In the two Canadian[7,8] and one US[9] database studies, the intervention consisted of receipt of ≥1 opioid prescription for CNCP over observation periods ranging from four to nine years. In the other US database study,[10] prescription opioid use for ≥ 90 continuous days over a six-month interval was observed during a total study period of three years.

Methadone was excluded in three of the studies[7-9] because of its predominant use in addiction treatment; parenteral dosage forms were also excluded.[7-9] It is unclear whether specific opioid medications were excluded in the remaining study.[10]

Both sets of guidelines[1-3] include recommendations on patient selection, initiation, titration, and monitoring of opioids in CNCP. The Canadian guideline[2] additionally provides recommendations around misuse and addiction.

Comparators

Categories of average daily morphine equivalent dosing were used to compare outcomes in the two Canadian studies:[7,8] in one study,[7] quintiles were used ranging from 20 to 49 mg/day to >200 mg/day while tertiles were employed in the other study ranging from ≤ 200 mg/day to > 400 mg/day.

In the US studies,[9,10] one[9] drew a random sample of opioid-treated patients from the overall study population to serve as a control for the cases while the other[10] simply compared outcomes between the public and private insurer databases. Categories of morphine equivalent dosing were also used for comparisons between groups. In one study,[9] maximum daily doses were analyzed by quartiles ranging from 1 to 20 mg/day to ≥ 100 mg/day. Tertiles of total 'daily' dose were analyzed in the other study[10] using categories ranging from < median dose (either 32 or 35 mg/day) to > 120 mg/day.

Recommendations from the two included guidelines provide guidance on the use of opioids as a class in the treatment of CNCP.[1-3]

Outcomes

Opioid-related mortality comprised the primary outcome in the two Canadian studies[7,8] while unintentional, fatal prescription opioid overdose was the outcome of interest in one US study.[9] Associations between prescription opioid use and health services utilization, such as emergency department visits and 'alcohol- or 'drug-related encounters', were examined as outcomes in the other US study.[10]

Both sets of guidelines[1-3] developed evidence-based recommendations on the use of opioids in CNCP and include tools to support clinical practice.

Grading of recommendations and levels of evidence

Recommendations from the Canadian guidelines were graded based on an adaptation of the grading system used by the Canadian Task Force on Preventive Health Care.[1,2] By comparison, the US guidelines adapted the methods used by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group.[3] Details of these grading systems can be found in Appendix 6.

Summary of Critical Appraisal

All included studies[7-10] were retrospective and observational in nature, and are therefore subject to the limitations inherent to this experimental design, namely bias from lack of control of potential confounders. One study[10] was a sub-analysis of a larger database study.

The generalizability of the two US studies[9,10] to a Canadian context may be limited by the inclusion of some opioid therapies not approved in Canada. However,most of the agents studied were available in Canada; moreover, transformation of individual drug doses into morphine-equivalent dosing provided a common language for making comparisons. Similarly, there may be some differences in the delivery of pain management services and the approach to opioid prescribing and monitoring between countries as a function of the availability of private and publicly-funded healthcare delivery models and access to pain specialists.

With respect to the two clinical practice guidelines identified[1-3], the Canadian guidelines[1,2] were more thorough in their methodology reporting compared with the US guidelines.[3] Both sets of guidelines[1-3] were multidisciplinary in the composition of their expert advisory panel; both provided a detailed description of their recommendation development process and plans for updating the guidelines; and both used a published grading system for rating the recommendations made. However, only the Canadian guideline[1] clearly stated the status of industry support (i.e., none given), provided a thorough description of their literature search strategy, and highlighted the limitations of their guideline; the Canadian guideline is also distinguished by the additional guidance given on managing opioid misuse and addiction.[2] The target audience for the Canadian guidelines[1,2] was identified as the primary care physician while the US guidelines named both the primary care physician and specialist as their target audience.{11533)

A more detailed review of the strengths and limitations of the individual included studies and clinical practice guidelines is described in Appendix 3.

Summary of Findings

What is the clinical evidence regarding the safety of different watchful doses of morphine (or equivalent) for the treatment of chronic non-cancer pain?

In the population-based nested case-control study by Gomes,{11797} Ontario public drug plan beneficiaries taking $\geq$ 200 mg/day of morphine or equivalent were found to have a nearly threefold higher risk of opioid-related death compared with the reference (<20mg/day) group [Odds ratio (OR): 2.88 (95% confidence interval (CI): 1.79 to 4.63)]. The risk was also approximately twofold higher in patients taking either 100-199 mg/day [OR: 2.04 (95% CI: 1.28 to 3.24)] or 50-99 mg/day [OR: 1.92 (95% CI: 1.30 to 2.85)] compared with the reference group.

In a cross-sectional time series and exploratory cohort analysis of Ontario public drug plan beneficiaries (n=154,411) also conducted by Gomes,[8] 3733 (2.4%) patient deaths from any cause occurred between 2004-2006, in which 302 (8.1%) of these deaths were classified by the Coroner's Office as being opioid-related; 19.3% of these deaths occurred in patients categorized as having taken 'high' or 'very high' doses of opioids with oxycodone (39.2%), morphine (39.2%), and fentanyl (21.6%) being the opioids most often implicated.

In the exploratory analysis, all-cause mortality was observed to be five times higher in the drug plan beneficiaries who received an opioid prescription [20.05 (95% CI: 19.38 to 20.73) vs 4.00 (95% CI: 3.95 to 4.04) per 1000 population] compared with Ontarians aged 15 to 64 years not prescribed an opioid. When these rates were examined in the context of mean daily opioid dosing category (i.e., moderate: $\leq$ 200 mg/day; high: 201-400mg/day; very high: >400 mg/day), the rate more than doubled among very high- [44.93 per 1000 (95% CI: 32.42 to 60.67)] and high- dose [42.24 per 1000 (95% CI: 35.34 to 50.08)] categories compared with the moderate-dose category [19.28 per 1000 (95% CI: 18.61 to 19.97)] When the rate of opioid-related mortality was specifically explored, rates were similarly highest in the very high dose category [9.94 per 1000 (95% CI: 2.78 to 25.12)] compared with the high [7.92 per 1000 (95% CI: 5.25 to 11.49)] or moderate dose [1.63 per 1000 (95% CI: 1.42 to 1.85)] categories.

In a case cohort study of Veterans Health Administration beneficiaries by Bohnert,[9] the unadjusted rate of fatal prescription opioid overdose for patients with CNCP taking a maximum daily dose of $\geq$100 mg/day (the highest quintile) was 1.24 (95% CI: 1.04 to 1.48) per 1000 person-months. Cox proportional hazards modeling showed a dose-response relationship between maximum prescribed daily opioid dose and risk of opioid overdose death compared with the reference group (1 to <20 mg/day); in the subgroup of CNCP patients prescribed $\geq$100 mg/day, this corresponded to a hazard ratio of 7.18 (95% CI: 4.85 to 10.65).

In a sub-analysis of public and private insurance claims from a larger audit study, Braden[10] found that morphine-equivalent daily dosing (MED) was inconsistently associated with emergency department (ED) visits, such that private insurance recipients taking either 32 to 120 mg/day [Relative risk (RR): 1.30 (95% CI: 1.26 to 1.34); P < 0.001] or > 120 mg/day [RR: 1.08 (95% CI: 1.02 to 1.15); P < 0.01] had a slightly elevated risk for ED visits compared with the reference group (< 32 mg/day); by contrast, there was no association between ED visits and MED in public insurance recipients. Alcohol or drug-related encounters were associated with MED > 120 mg/day in both the private [RR: 2.18 (95% CI: 1.58 to 3.00); P < 0.001] and public [RR: 2.06 (95% CI: 1.15 to 3.67); P < 0.05] insurance recipients, but only in the private insurance recipients at MED of 32 to 120 mg/day [RR: 1.66 (95% CI: 1.35 to 2.03); P < 0.001].

Findings from the individual studies are presented in greater detail in Appendix 4.

What are the evidence-based guidelines regarding a watchful dose of morphine (or equivalent) for the treatment of chronic non-cancer pain?

The Canadian Guideline for Safe and Effective Use of Opioids for Chronic Non-Cancer Pain[1,2] define a watchful dose as morphine or a morphine equivalent dose > 200 mg/day.[2] The recommendation states that most patients with CNCP can be managed at doses $\leq$ 200 mg/day (grade A), and that a reassessment of pain, response to opioid therapy, and risk of aberrant drug-related behavior should be undertaken if considering dosing > 200 mg/day (grade C). A summary of guideline recommendations and the grading of recommendations and levels of evidence are provided in Appendix 5 and 6 respectively.

The American Pain Society (APS) and the American Academy of Pain Medicine (AAPM) Clinical Guidelines for the Use of Chronic Opioid Therapy in Noncancer Pain[3] acknowledge that there is no universally accepted definition of a 'high' dose therapy, but developed an operational definition by panel consensus of > 200 mg/day of oral morphine or equivalent. Similar to the Canadian guideline,[2] the APS and AAPM[3] recommend more frequent monitoring, including response to therapy, adverse effects, adherence, and health status in patients who require high dose therapy (strong recommendation, low-quality evidence).

Limitations

The evidence base around a watchful dose threshold for morphine or equivalent opioid dosing was limited in quantity and quality, with only observational studies being identified. Likewise, the included studies analyzed claims data in aggregate for multiple opioid drugs (according to levels of morphine equivalent dosing) as opposed to looking at individual agents, thereby limiting the ability to draw conclusions about specific drugs; however, Gomes[8] does include some brief, descriptive (graphical) utilization data on long-acting oxycodone and transdermal fentanyl.

Two Canadian observational studies were identified out of a total of four. The paucity of evidence for watchful dosing is likely reflective of larger gaps in evidence in the topic of CNCP management in general — including around the appropriate use of opioids — acknowledged by both guideline groups.[1,3] Moreover, inconsistency was noted between the guidelines with respect to the definitions employed for chronicity of pain, where the APS and APM referred to persistence of pain in excess of three months while the Canadian guideline referred to persistent pain of more than six months in duration.[1]

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There was a paucity of studies from which to make unequivocal conclusions about an appropriate watchful dose of morphine (or equivalent); the outcomes specifically examined in the four included studies were opioid-related mortality, unintentional fatal opioid overdose, and health resource utilization (i.e., emergency department visits, alcohol- and drug-related encounters), not all of which suggested a relationship with increasing opioid dosing.

There is limited evidence to support a watchful dose of morphine or equivalent opioid dosing of >200 mg/day in chronic non-cancer pain; however, there is also little evidence to support a lower threshold dose.

The two clinical practice guidelines similarly consider a morphine or equivalent opioid dose of more than 200 mg/day as constituting a high dose; the Canadian guidelines assert that most patients with CNCP should not require doses in excess of 200 mg/day.

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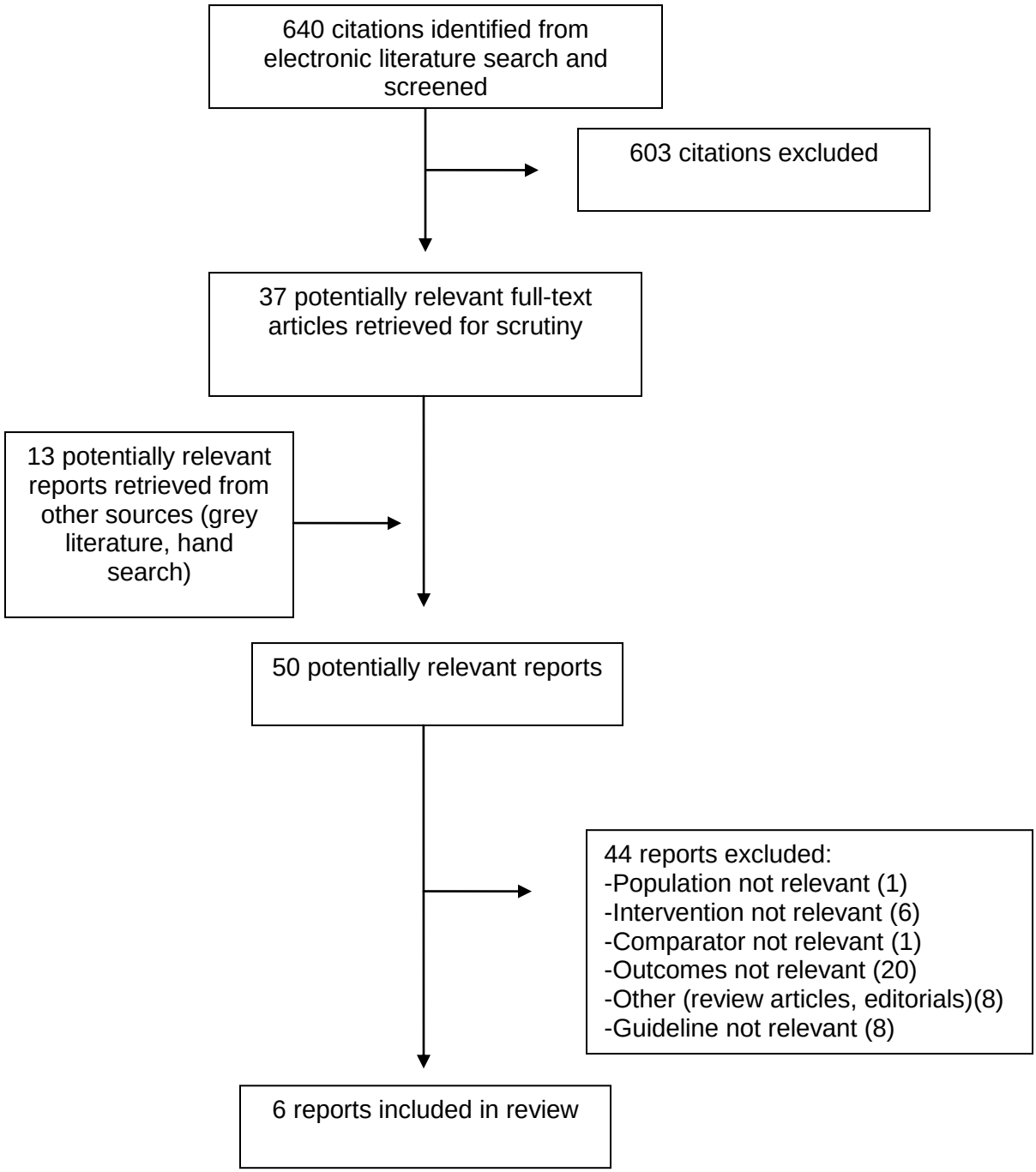
Appendix 1: Selection of Included Studies



Appendix 2: Summary of Study Characteristics

First Author, Publication Year, Country	Study Design	Population	Intervention	Comparator	Outcomes
Gomes, 2011a, Canada[7]	Population-based nested case-control study	Ontario Drug Benefit Program beneficiaries aged 15-64 years old who received ≥1 opioid prescription (i.e., codeine, morphine, oxycodone, hydromorphone, meperidine, transdermal fentanyl) for chronic non-cancer-related pain.	≥1 opioid prescription(s) (i.e., codeine, morphine, oxycodone, hydromorphone, meperidine, transdermal fentanyl) for chronic non-cancer-related pain over the course of the study period (August 1, 1997 to December 31, 2006)	Five categories of mean daily morphine equivalent dosing: < 20 mg; 20 to 49 mg; 50 to 99 mg; 100 to199 mg; >200 mg	Opioid-related mortality
Gomes, 2011b, Canada[8]	Cross-sectional time series analysis followed by exploratory analysis	Ontario Drug Benefit Program beneficiaries aged 15-64 years old who received ≥1 opioid prescription (i.e., codeine, morphine, oxycodone, hydromorphone, meperidine, transdermal fentanyl) for non-cancer-related pain.	≥1 opioid prescription(s) (i.e., codeine, morphine, oxycodone, hydromorphone, meperidine, transdermal fentanyl) for chronic non-cancer-related pain within the calendar year of their study eligibility over a study period of 5 years (January 1, 2003 and December 31, 2008)	Three categories of mean daily morphine equivalent dosing (based on first 90 days of opioid therapy in each year): 'Moderate': ≤ 200 mg/day; 'High': 201 to 400mg/day; 'Very high': > 400 mg/day	Opioid-related mortality
Bohnert, 2011,	Case-cohort	Patients enrolled in	≥1 opioid	Random sample of	Unintentional fatal prescription

First Author, Publication Year, Country	Study Design	Population	Intervention	Comparator	Outcomes
USA[9]	study	Veterans Health Administration, who died from an unintentional prescription opioid overdose between 2004-2008	medication(s) (i.e., codeine, morphine, oxycodone, hydrocodone, oxymorphone, hydromorphone) received between 2004 to 2008	patients enrolled in Veterans Health Administration, who received an opioid prescription between 2004-2008 for pain Four categories of maximum daily morphine equivalent dosing: 1 to < 20 mg; 20 to < 50 mg; 50 to < 100 mg; ≥ 100 mg	opioid overdose (in subgroup of patients treated for chronic non-cancer pain)
Braden, 2010, USA[10]	Administrative claims data audit; sub-analysis of TROUP (Trends and Risks of Opioid Use for Pain) study.	Adults aged ≥ 18 years without a cancer diagnosis enrolled in either a single state Medicaid plan or a large commercial insurance plan (claims data from 14 states), who received opioid therapy ≥ 90 continuous days over 6 months from January 1, 2001 to December 31, 2004.	Prescription opioid use for ≥ 90 continuous days over a 6-month period from January 2001 to December 31, 2004	Single state (Arkansas) Medicaid plan claims database compared with a large, private database housing commercial insurance claims data for 14 states (HealthCore Integrated Research Database) Three categories of total daily morphine	Emergency Department visits; alcohol or drug-related encounters (i.e., alcohol intoxication, withdrawal, or overdose; drug intoxication or withdrawal; non-opioid or opioid drug overdose) in the 12 months following the index date of the opioid use episode

First Author, Publication Year, Country	Study Design	Population	Intervention	Comparator	Outcomes
				equivalent dosing: <Median* dose; Median* to 120 mg/day; >120 mg/day **Median dose: 32 mg/day for HealthCore (private) group; 35 mg/day for Medicaid (public) group.*	

Appendix 3: Summary of Critical Appraisal of Included Studies and Guidelines

First Author, Publication Year, Country	Strengths	Limitations
Included Studies		
Gomes, 2011a, Canada[7]	• Canadian context of study • Use of well-established databases • Vulnerable population studied (i.e., socio-economically disadvantaged) • Assessment of safety of 'watchful dose' threshold of 200 mg/day as cited in some guidelines,[1] in addition to doses < 200mg/day	• Indications for opioid prescriptions not able to be determined • Possibility of incomplete capture of opioid-related deaths • Out-of-pocket-purchased opioid prescriptions, unused medication, or illicitly obtained drugs not identified • Some differences in baseline characteristics between cases and controls, but the authors indicate they adjusted for 'all potential confounders'.
Gomes, 2011b, Canada[8]	• Canadian context of study • Use of well-established databases • Vulnerable population studied (i.e., socio-economically disadvantaged)	• Indications for opioid prescriptions not able to be determined • Possibility of incomplete capture of opioid-related deaths • Possibility of underestimating the number of patients categorized as receiving 'high' or 'very high' doses of opioid therapy • Out-of-pocket-purchased opioid prescriptions, unused medication, or illicitly obtained drugs not identified • Co-morbid conditions, addiction history were potential confounders that were not controlled; changes in opioid dosing over time were not factored into the analysis.
Bohnert, 2011, USA[9]	• Use of well-established databases • Large, national sample studied prospectively and linked to mortality data • Power calculation performed	• Predominantly white, male population • Population studied not strictly chronic pain, but included patients with acute pain (~30% of cases vs 19% controls) and cancer (~12% of cases vs 24% of controls) • Out-of-pocket-purchased opioid prescriptions, unused medication, or illicitly obtained drugs not identified • Hydrocodone (except as an antitussive) and

First Author, Publication Year, Country	Strengths	Limitations
		oxymorphone are not available in Canada as narcotic analgesics
Braden, 2010, USA[10]	• Two large sources of claims data: public and private • Diverse populations studied (i.e., socioeconomic, regional, and payer differences)	• Retrospective study, no control • Predominantly white, female population • Majority of data (~80%) comes from a large, private commercial health insurance database, the analysis of which may not produce findings generalizable to public drug plans in Canada. • Out-of-pocket-purchased opioid prescriptions, unused medication, or illicitly obtained drugs not identified • Sociodemographic data limited to age and gender; risk of residual confounding from race and income, which were not controlled.
Evidence-Based Guidelines		
Canadian Guideline for Safe and Effective Use of Opioids for CNCP (NOUGG), 2010[1]	• Nationally representative, multidisciplinary advisory panel of experts • Guideline group included jurisdiction-wide representation or support from medical regulatory authorities • Not industry-sponsored • Well-described methodology (e.g., literature search, recommendations development process), scope, target audience, limitations • Used a published grading system adapted from the Canadian Task Force on Preventive Health Care • Examined additional issues of societal importance (e.g., addiction, diversion) • Advisory panels' values and preferences provided • Established process for updating the guideline • Guideline implementation strategy developed (e.g., practice support tools) • Disclosure of competing interests provided	• Unclear whether patient input was sought • Unclear whether guideline was piloted among target users • Unclear whether an independent external review occurred prior to publication • Large gaps in evidence cited; other patient-important outcomes aside from quality of life often not studied (e.g., return to work); mostly non-randomized trials were identified; heavy reliance on expert opinion • No formal analysis of cost implications of guideline implementation performed
Chou, 2009, USA	• Multidisciplinary panel of experts	• Unclear whether patient input was sought

First Author, Publication Year, Country	Strengths	Limitations
(APS and AAPM Guidelines)[3]	• Target audience and scope described • Well-described recommendations development process • External peer review occurred prior to publication • Adapted GRADE profile for rating the recommendations on strength and quality • Plans in place for updating guidelines • Disclosure of competing interests provided	• Unclear whether guideline was piloted among target users • Unclear whether formal guidelines implementation strategy developed • Literature search methods incompletely described, including yield of randomized controlled to non-randomized trials. • Unclear whether industry provided financial support • No formal analysis of cost implications of guideline implementation performed

AAPM: American Academy of Pain Medicine; APS:American Pain Society; CNCP: Chronic Non-Cancer Pain; NOUGG: National Opioid Use Guideline Group

Appendix 4: Summary of Findings of Included Studies

First Author, Publication Year, Country	Main Study Findings	Authors' conclusions
Gomes, 2011a, Canada[7]	A cohort of 607,156 patients aged 15 to 64 years were identified as having had ≥ 1 opioid prescription through the Ontario public drug plan over the 113-month study period; within this cohort,1463 (0.24%) patients of mean age 42.7 ± 8.8 years had an opioid–related death. Accidental death (59.0%) accounted for the majority of cases, followed by suicide (16.8%), and was undetermined in 354 (24.2%) cases. In the primary analysis, in which patients with cancer, those without public plan drug coverage in the preceding 6 months, and those without overlapping opioid prescription(s) on the index date were excluded, 593 deaths were examined. Of these, 498 (84.0%) cases were matched with ≥ 1 control. Coroner toxicology investigations were positive for > 1 opioid in 193 (38.8%) cases. *Risk of opioid related death (compared with <20mg/day):* ≥ 200 mg/day: OR 2.88, 95% CI: 1.79 to 4.63 100-199 mg/day: OR 2.04, 95% CI: 1.28 to 3.24 50-99 mg/day: OR: 1.92 95% CI: 1.30 to 2.85 Sensitivity analyses conducted on the average opioid dose taken over the 4 months preceding the index date were consistent with the findings from the primary analysis.	"… we found that a higher daily dose of opioids is associated with large relative and absolute increases in opioid-related mortality, and that daily doses of 200 mg or more of morphine (or equivalent) are associated with a particularly high risk." (p.690)
Gomes, 2011b, Canada[8]	In 2004 — the index year for the exploratory cohort analysis of opioid-related mortality — 4,370,565 opioid prescriptions were dispensed through the Ontario public drug plan. Of the 154,411 patients included in the exploratory cohort analysis, 3733 (2.4%) died from any cause between 2004-	"Our findings highlight the widespread prescription of very high doses of opioid analgesics, particularly among users of long-acting oxycodone, and indicate a relation between opioid dose and opioid-related mortaliy." (p.e21)

First Author, Publication Year, Country	Main Study Findings	Authors' conclusions
	2006 in whom the median age was 46 years; 302 (8.1%) of these deaths were classified by the Coroner's Office as being opioid-related, with 19.3% occurring in patients categorized as having taken 'high' or 'very high' doses of opioids. Oxycodone (39.2%), morphine (39.2%), and fentanyl (21.6%) were the opioids most often implicated in the deaths. Confirmed suicides (n=45) comprised 15% of the deaths and were most often associated with oxycodone (53.3%), codeine (42.2%), and morphine (26.7%). Age- and sex-adjusted rate of all-cause mortality for drug plan beneficiaries who received an opioid prescription in 2004 compared with Ontarians aged 15-64 years old: 20.05 (95% CI: 19.38 to 20.73) vs 4.00 (95% CI: 3.95 to 4.04) per 1000 population by opioid dosing category: Very high: 44.93 per 1000 (95% CI: 32.42 to 60.67) High: 42.24 per 1000 (95% CI: 35.34 to 50.08) Moderate: 19.28 per 1000 (95% CI: 18.61 to 19.97) by rate of opioid-related mortality per opioid dosing category Very high: 9.94 per 1000 (95% CI: 2.78 to 25.12) High: 7.92 per 1000 (95% CI: 5.25 to 11.49) Moderate: 1.63 per 1000 (95% CI: 1.42 to 1.85)	
Bohnert, 2011, USA[9]	A total of 750 cases or deaths from unintentional opioid overdose in patients prescribed opioid therapy were identified from a base population of 1,834,250 patients	"This study documents a relationship between opioid prescribing and opioid overdose in a large, national, prospective cohort of individuals receiving

First Author, Publication Year, Country	Main Study Findings	Authors' conclusions
	prescribed opioid therapy between 2004-2008 yielding an overdose rate of 0.04%. Descriptively, cases (opioid overdose deaths) were more likely to be Caucasian, middle-aged, have chronic or acute pain, substance use or other psychiatric disorders, and less cancer than controls. Unadjusted rate of fatal prescription opioid overdose per 1000 person-months in subgroup of patients with chronic non-cancer pain by maximum prescribed daily opioid dose: 0 mg/day: 0.09 (95% CI: 0.08 to 0.10) 1 to < 20 mg/day: 0.11 (95% CI: 0.08 to 0.15) 20 to < 50 mg/day: 0.24 (95% CI: 0.19 to 0.28) 50 to < 100 mg/day: 0.66 (95% CI: 0.53 to 0.82) ≥100 mg/day:1.24 (95% CI: 1.04 to 1.48) Cox proportional hazards modeling showed a dose-response relationship between maximum prescribed daily opioid dose and risk of opioid overdose death in the subgroup of chronic non-cancer pain patients compared with the reference dose (1 to < 20 mg/day): 20 to < 50 mg/day: HR: 1.88 (95% CI: 1.33 to 2.67) 50 to < 100 mg/day: HR: 4.63 (95% CI: 3.18 to 6.74) ≥100 mg/day: HR: 7.18 (95% CI: 4.85 to 10.65)	opioid therapy for a variety of medical conditions. The risk of opioid overdose should continue to be evaluated relative to the need to reduce pain and suffering and be considered along with other risk factors." (p.1320)
Braden, 2010, USA[10]	A total of 38,491 enrollees who received opioid therapy for ≥ 90 days over 6 months from January 1, 2000 to December 31, 2005 were identified from the commercial insurance claims database (HealthCore) compared with 10,159 enrollees from the public (Medicaid) insurance database.	"In summary, this report describes clinical and demographic characteristics associated with ED visits and ADEs [alcohol or drug-related encounters] among adult enrollees in a state Medicaid and commercially insured population who used prescription opioids for at least 90 continuous

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	Opioid daily dose (expressed as morphine-equivalent dosing, MED) was found to be associated with emergency department (ED) visits in the HealthCore group only. Compared with doses < 32 mg/day): 32 to 120 mg/day: RR: 1.30 (95% CI: 1.26 to 1.34), p<0.001 >120 mg/day: RR: 1.08 (95% CI: 1.02 to 1.15), p<0.01 Association of alcohol or drug-related encounters with MED: >120 mg/day: HealthCore[a] group: RR: 2.18 (95% CI: 1.58 to 3.00), p<0.001 Medicaid[b] group: RR: 2.06 (95% CI: 1.15 to 3.67), p<0.05 32 to 120 mg/day: HealthCore[a] group: RR: 1.66 (95% CI: 1.35 to 2.03); p<0.001 No association with Medicaid group [a]Reference dose: < 32 mg/day; [b]Reference dose: < 35 mg/day	days." (p.1431)

CI: Confidence interval; HR: hazard ratio; RR: relative risk

Appendix 5: Summary of Guideline Recommendations

Guideline Society or Institute, Year	Recommendations
Canadian Guideline for Safe and Effective Use of Opioids for CNCP (NOUGG), 2010[2]	"Chronic non-cancer pain can be managed effectively in most patients with dosages at or below 200 mg/day of morphine or equivalent (Grade A). Consideration of a higher dosage requires careful reassessment of the pain and of risk for misuse, and frequent monitoring with evidence of improved patient outcomes. (Grade C)." (p.36)
APS and AAPM Guidelines, 2009[3]	"In patients who require relatively high* doses of COT, clinicians should evaluate for unique opioid-related adverse effects, changes in health status, and adherence to the COT treatment plan on an ongoing basis, and consider more frequent follow-up visits (strong recommendation, low-quality evidence)"[3] (p.120) *"...there is no standardized definition of what constitutes a 'high' dose. By panel consensus, a reasonable definition for high dose opioid therapy is >200 mg daily of oral morphine (or equivalent), based on maximum opioid doses studied in randomized trials and average opioid doses observed in observational studies."[3] (p.120)

AAPM: American Academy of Pain Medicine; APS:American Pain Society; CNCP: Chronic Non-Cancer Pain; COT: chronic opioid therapy; NOUGG: National Opioid Use Guideline Group

Appendix 6: Grading of Recommendations and Levels of Evidence

First Author, Publication Year, Country	Grading of Recommendations and Levels of Evidence
Canadian Guideline for Safe and Effective Use of Opioids for CNCP (NOUGG), 2010[1]	Adapted from the Canadian Task Force on Preventive Health Care: **"Grade A**: Recommendations are supported by evidence from RCT(s). **Grade B**: Recommendations are supported by: - Evidence from controlled trial(s) without randomization, or, - Evidence from cohort or case-control analytic studies, preferably from more than one centre or research group, or - Evidence from comparisons between times or places with or without the intervention; dramatic results in uncontrolled experiments could be included here. **Grade C**: Recommendations are supported by consensus opinion of the National Advisory Panel" (p.19)
APS and AAPM Guidelines, 2009[3]	Adapted methods from the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group: • *Strength of the evidence* (e.g., weak, strong): A 'strong' recommendation is one in which benefit outweighs risk; it is expected that most clinicians and patients would opt to implement a strong recommendation. By contrast, a weak recommendation indicates either a closer balance of benefits and harms or a weak evidence base. • *Quality of the evidence* (e.g., low, moderate, high): rates the body of evidence supporting the recommendation based on "type, number, size, and quality of studies; strength of associations or effects; and consistency of results among studies." (p.115)

AAPM: American Academy of Pain Medicine; APS:American Pain Society; CNCP: Chronic Non-Cancer Pain; NOUGG: National Opioid Use Guideline Group