JAMA Clinical Evidence Synopsis

Oxycodone for Cancer Pain in Adult Patients

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CLINICAL QUESTION Is oxycodone associated with greater efficacy and fewer adverse events compared with alternative analgesics for cancer pain?

BOTTOM LINE Oxycodone was not associated with superior cancer pain relief or fewer adverse effects compared with other strong opioids, such as morphine or oxymorphone. However, the quality of the evidence was low.

Many patients with cancer experience moderate or severe pain requiring treatment with strong opioids. However, not all opioids are well tolerated by all patients. This JAMA Clinical Evidence Synopsis summarizes a published Cochrane review[1] that examined the association of oxycodone (any formulation or route of administration) compared with placebo or an active drug (including alternative forms of oxycodone) for treating cancer pain in adults.

Summary of Findings

Because the studies used different scales to measure pain intensity, meta-analysis was performed using the standardized mean difference (SMD) to compare pain intensity across studies. Pain scores were not significantly different between controlled-release (CR) vs immediate-release (IR) oxycodone (SMD, 0.1 [95% CI, −0.06 to 0.26]) or between CR oxycodone vs CR morphine (SMD, 0.14 [95% CI, −0.04 to 0.32]; **Figure**). The most commonly reported adverse events were constipation, drowsiness, and nausea in the studies comparing CR and IR oxycodone (for constipation, 13.9% for CR oxycodone [26/187 patients] vs 19.4% for IR oxycodone [37/191 patients]; for drowsiness, 20.9% for CR oxycodone [39/187 patients] vs 19.9% for IR oxycodone [38/191 patients]; and for nausea, 19.3% for CR oxycodone [36/187 patients] vs 22% for IR oxycodone [42/191 patients] and in the studies comparing CR oxycodone with CR morphine (for constipation, 28.1% for CR oxycodone [50/178 patients] vs 30.6% for CR morphine [53/173 patients]; for drowsiness, 17.2% for CR oxycodone [26/151 patients] vs 23.3% for CR morphine [34/146 patients]; and for nausea, 17.4% for CR oxycodone [31/178 patients] vs 22% for CR morphine [38/173 patients]). There were no or only minor differences in adverse event rates, treatment acceptability or quality-of-life ratings in studies comparing CR oxycodone with either IR oxycodone or CR morphine. The remaining studies reported different drug comparisons and found no consistent differences associated with oxycodone for treating pain intensity, adverse events, or treatment acceptability. The evidence was limited by the methodological quality and small size of the studies.

Evidence Profile

No. of randomized clinical trials: 17 (crossover or parallel group)

Study years: Published, 1978-2014; date of last literature search, March 3, 2014

No. of patients: 1390 (1110 analyzed for efficacy, 1170 analyzed for safety)

Men: 47% **Women:** 45% (unspecified, 8%)

Race/ethnicity: Not reported

Age, mean (range): 58 years (20-91)

Setting: Inpatient and outpatient

Countries: United States, Canada, Finland, Italy, Australia, United Kingdom, Brazil, Japan/Korea

Comparisons: Controlled-release (CR) oxycodone vs (1) immediate-release (IR) oxycodone (4 studies); (2) CR morphine (6 studies); (3) CR hydromorphone (1 study); (4) extended-release (ER) oxymorphone (1 study); (5) ER tapentadol (1 study); intravenous (IV) oxycodone vs rectal oxycodone (1 study); IV oxycodone followed by IR oxycodone vs IV morphine followed by IR morphine (1 study); intramuscular oxycodone vs oral oxycodone (1 study); intramuscular oxycodone vs intramuscular morphine vs intramuscular codeine (1 study)

Primary outcome: Patient-reported pain intensity measured on verbal or visual rating scales

Secondary outcomes: Adverse events, patient preference/treatment acceptability, quality of life

Discussion

Low-quality evidence shows that for adults with cancer pain, oxycodone is not associated with better pain relief or fewer adverse events compared with other strong opioids, including morphine or oxymorphone.

Limitations

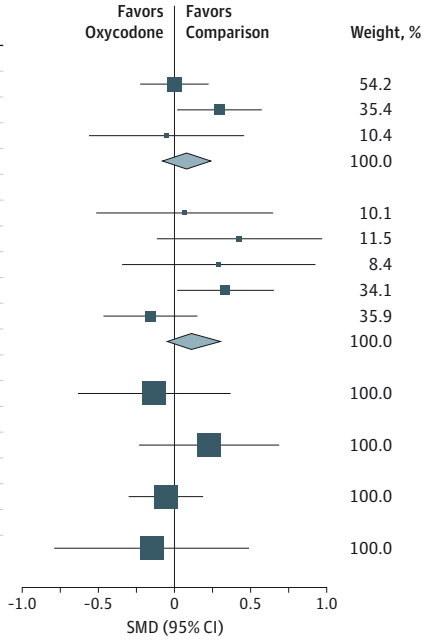
The evidence quality was low due to small sample sizes in some cases and important study limitations in all cases, including heterogeneous definitions of cancer pain and high levels of attrition, with data missing from more than 20% of the patients for pain intensity and more than 15% of the patients for adverse events.

Comparison of Findings With Current Practice Guidelines

The National Institute for Health and Care Excellence recommends morphine as first-line opioid[2] because it is less expensive than other alternatives. The European Association of Palliative Care recommends that any oral opioid is appropriate for first-line use.[3] Our review found no differences in pain control between CR and IR oxycodone; however, CR opioids are generally recommended for maintenance of pain control compared with IR opioids,[2,5,6] and are

Figure. Pain Scores Analyzed as the Standardized Mean Difference (SMD) Between the Treatment Groups

Study	Oxycodone Pain Score, Mean (SD)	Oxycodone Total Patients	Comparator Pain Score, Mean (SD)	Comparator Total Patients	Pain Score, SMD (95% CI)	Weight, %
CR oxycodone vs IR oxycodone[a]						
Kaplan, 1998	1.3 (1.25)	156	1.3 (1.25)	156	0.00 (-0.22 to 0.22)	54.2
Parris, 1998	1.4 (1.01)	103	1.1 (1.01)	103	0.30 (0.02 to 0.57)	35.4
Stambaugh, 2001	2.7 (1.9)	30	2.8 (1.9)	30	-0.05 (-0.56 to 0.45)	10.4
Subtotal		289		289	0.10 (-0.06 to 0.26)	100.0
CR oxycodone vs CR morphine						
Bruera, 1998	24.3 (20)	23	22.9 (21)	23	0.07 (-0.51 to 0.65)	10.1
Heiskanen, 1997	0.99 (0.62)	27	0.77 (0.36)	27	0.43 (-0.11 to 0.97)	11.5
Mercadante, 2010[b]	3.15 (3)	19	2.35 (2.36)	20	0.29 (-0.34 to 0.92)	8.4
Mucci-LoRusso, 1998	1.3 (0.89)	79	1 (0.89)	79	0.34 (0.02 to 0.65)	34.1
Riley, 2014	2.05 (1.71)	80	2.36 (2.18)	85	-0.16 (-0.46 to 0.15)	35.9
Subtotal		228		234	0.14 (-0.04 to 0.32)	100.0
CR oxycodone vs CR hydromorphone						
Hagen, 1997	28 (22.27)	31	31 (22.27)	31	-0.13 (-0.63 to 0.37)	100.0
CR oxycodone vs ER oxymorphone						
Gabrail, 2004	2.8 (1.3)	37	2.5 (1.3)	37	0.23 (-0.23 to 0.69)	100.0
CR oxycodone vs ER tapentadol						
Imanaka, 2013	2.57 (2.03)	139	2.69 (2.22)	126	-0.06 (-0.30 to 0.18)	100.0
IR oxycodone vs IR morphine						
Kalso, 1990	1.3 (1.2)	19	1.5 (1.4)	19	-0.15 (-0.79 to 0.49)	100.0



Source: Data were adapted with permission from Wiley.[1] CR indicates controlled release; ER, extended release; IR, immediate release. SMD was calculated using the inverse variance fixed-effect method. The SMD can be interpreted as an effect size, with small effect size values of 0.2; medium, 0.5; and large, 0.8.[4] The size of the data markers indicates the weight of the study.

[a] IR oxycodone is input as the comparator group in this specific drug comparison grouping.

[b] Week 4 data.

preferred by patients because of the need for fewer daily doses and the ability to enjoy an uninterrupted night's sleep.[7] Our review is consistent with these recommendations such that at a group level, clinicians may select any strong opioid for first-line treatment. For an individual patient, one strong opioid may be tolerated better than another, so regular assessment of pain control is needed.

Areas in Need of Future Study

Current evidence is limited by the absence of high-quality studies. More well-designed and well-powered randomized clinical trials are needed. Developing a single outcome that better reflects patients' experiences of both pain and adverse events would allow a clearer comparison.

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Submissions: We encourage authors to submit papers for consideration as a JAMA Clinical Evidence Synopsis. Please contact Dr McDermott at mdm608@northwestern.edu.

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