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Treating postoperative pain? Avoid tramadol, long-acting opioid analgesics and long-term use.

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Treating postoperative pain? Avoid tramadol, long-acting opioid analgesics, and long-term use.

A recent cohort study investigated "the risk of transitioning from acute to prolonged use" of opioid analgesics in patients undergoing elective surgery. Patients given tramadol or long-acting opioids after discharge were at greater risk of prolonged opioid use than those who were given short-acting opioids.

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EBM Verdict on: Chronic use of tramadol after acute pain episode: cohort study. BMJ 2019 May 14. doi: 10.1136/bmj.l1849.

Strong pain-relieving medicines called opioids are commonly prescribed when patients are discharged from hospitals. However, pain after elective surgery is usually short-lived. This study [1], addresses an important question regarding the prolonged use of opioid analgesics after elective surgery in light of the opioid crisis in the USA and Canada and increased prescribing of opioids in high-income countries [2].

Tramadol is both a weak mu-opioid receptor agonist and a serotonin and noradrenaline (norepinephrine) reuptake inhibitor (SNRI). Its active metabolite, O-desmethyltramadol, is longer acting than tramadol itself and is a more potent mu-opioid receptor agonist. Responses to tramadol, therefore, vary according to the genotype of the main metabolizing enzyme, CYP2D6 [3].

Tramadol has been available for over 30 years in the UK and for 24 years in the USA (see Box 1). It is considered by many to be safer than other opioids. However, deaths from tramadol are increasing [4]. Evidence is emerging that the adverse effects of tramadol are consistent with the adverse effects of stronger opioids such as fentanyl which receive stricter regulations by scheduling authorities than tramadol.

Currently, there is no Cochrane review of the use of tramadol for acute postoperative pain in adults. A summary of the results of two non-Cochrane reviews on tramadol showed that studies in which tramadol was associated with high rates of adverse events were highly susceptible to publication bias [5]. Furthermore, patients taking tramadol have the second highest probability of continued opioid use, after those taking long-acting opioids, at one and three years after the start of opioid treatment [6].

The authors of this study concluded: "People receiving tramadol alone after surgery had similar to somewhat higher risks of prolonged opioid use compared with those receiving short-acting opioids." This conclusion is justified, based on the adjusted risk ratios. However, the interpretation of risk ratios can often amplify findings. To improve the interpretation of findings for the clinical setting, for which this study was intended, the number needed to harm (NNT_H) is a helpful calculation for comparing treatment groups.

The data from this cohort study are abstracted in Table 1, including the values of NNT_H I calculated for all definitions of prolonged opioid use. The NNT_H for persistent use of opioids, comparing tramadol alone with other short-acting opioids is 272 (95% CI: 171 to 566). Thus, for every 272 patients who receive a discharge prescription for tramadol alone, one will continue to use opioids for 90 or more days over 180 days after surgery.

In contrast, the NNT_H for patients discharged taking any long-acting opioid is significantly lower (NNT_H: 31, 95% CI: 26 to 37). The lower the NNT_H, the greater the risk of harm. Despite the study's focus on tramadol, the authors omitted to mention the importance of this significant finding for prolonged use of opioids in people taking long-acting opioids. Therefore, short-acting opioids in the setting of acute pain are preferable to both long-acting opioids and tramadol when discharging patients after elective surgery.

It is well recognized that clinical decision making must take into account patients' values and preferences. However, when there is acute pain, the choice of opioid largely depends on the preferences of the provider. Thus, the NNT_H should be adopted by providers to effectively communicate to patients the risk of prolonged opioid use when treating acute pain after elective surgery.

Limitations of this study highlight the inability of large datasets to ascertain the reason patients receive additional opioid prescriptions and other benefits and/or harms that patients experience from opioids that would further contribute to informed decisions. The latter are particularly important, since there is a paucity of data to allow accurate quantification of the risks of using tramadol in people with acute pain [5]. Although hydrocodone and short-acting oxycodone are the two most commonly prescribed opioids, their potential for long-term use after surgery was not evaluated in this study. This analysis would have provided further insight into the problem of prolonged opioid use.

Tramadol remains poorly regulated in low-income countries and receives lower scheduling in high-income countries. Despite the need for additional research into the clinical benefits and harms of tramadol, the evidence from this study of the greater risk of prolonged use of tramadol should be considered by scheduling authorities and in clinical guidelines for acute pain.

EBM Verdict: Long-acting opioids and tramadol should be avoided when discharging patients from hospital after elective surgery. Alternative short-acting opioids at low doses and for short durations are preferable.

Box 1 - A brief history of tramadol

1963: Tramadol patented
1977: Tramadol launched as 'Tramal' by Grünenthal GmbH in Germany
1988: The first tramadol formulation approved by the MHRA in the UK
1995: Tramadol receives US FDA approval
2014: Tramadol becomes a controlled substance in both the USA (schedule IV) and the UK (schedule 3, class C)

Table 1: Values of NNT_H for prolonged use of opioids after elective surgery

Comparison	Definition of prolonged use of opioids	Adjusted RR (95% CI)	NNT_H (95% CI)
Tramadol alone vs. other short-acting opioids	Additional opioid use *	**1.06 (1.00 to 1.13)**	373 (135 to 544)
	Persistent opioid use †	**1.47 (1.25 to 1.69)**	272 (171 to 566)
	CONSORT definition of chronic opioid use ‡	**1.41 (1.08 to 1.75)**	952 (401 to 8400)
Tramadol and short-acting opioids vs. other short-acting opioids	Additional opioid use *	1.05 (0.96 to 1.14)	43 (32 to 64)
	Persistent opioid use †	1.04 (0.86 to 1.21)	60 (47 to 79)
	CONSORT definition of chronic opioid use ‡	**1.40 (1.05 to 1.74)**	120 (86 to 179)
Any long-acting opioid compared with other short-acting opioids	Additional opioid use *	0.95 (0.87 to 1.03)	36 (28 to 50)
	Persistent opioid use †	**1.18 (1.02 to 1.35)**	31 (26 to 37)
	CONSORT definition of chronic opioid use ‡	**1.69 (1.36 to 2.02)**	54 (44 to 68)

The statistically significant results are in **BOLD**

CI: confidence interval; RR: relative risk, calculated as a ratio of predictive margins after logistic regression, including covariates of year, surgery, female sex, beneficiary type, race/ethnicity, census division, age category, categorical measurement of morphine milligram equivalents at discharge, and flags for each Elixhauser comorbidity [1]

*At least one opioid fill 90-180 days after surgery.

† Any span of opioid use starting in 180 days after surgery and lasting ≥90 days

‡ Opioid episode starting in 180 days after surgery that spans ≥90 days and includes either ≥10 opioid fills or ≥120 days' supply of opioids

Formulae for NNT_H [7], calculated using Stata SE v14.1 [8]

NNT_H = 1/(absolute increase in risk)

e.g. NNT_H = 1/((1066/13,519) - (25,388/333,289))

NNT_H = 1/(0.0789 - 0.0762)

NNT_H = 1/0.0027

NNT_H = 373

e.g. Stata code: *bcii 1066 25388 12453 307901, level(95)*

Stata output: *Risk of improvement for control (p0): 0.076*
Risk of improvement for intervention (p1): 0.079
Risk difference (p1 - p0): 0.003
Newcombe Method 10 95% CI: -0.002-0.007
*Number needed to treat (Improvement): **373.433***
*Bender's 95% CI: **134.649--544.013***

Declaration of interests
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