Therapeutics

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

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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 other short-acting opioids.

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 cohort 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 norepinephrine reuptake inhibitor. 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 metabolising 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 also emerging that tramadol's adverse effects are similar to stronger opioids such as fentanyl, which receive stricter regulations by scheduling authorities than tramadol.

Box 1 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 Medicines and Healthcare products Regulatory Agency in the UK.
1995: Tramadol receives U.S. Food and Drug Administration approval.
2014: Tramadol becomes a controlled substance in both the USA (schedule IV) and the UK (schedule 3, class C).

EBM verdict

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

- 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.

Two systematic reviews 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.[6]

The BMJ cohort study[1] retrospectively analysed USA claims data from a large, private insurance health plan. Included participants (n=444 764) had undergone one of 20 commonly performed, elective surgical procedures and were opioid naïve (ie, had not received a prescription for opioids 6 months before the procedure). The exposures were type of discharge prescriptions which were stratified into five mutually exclusive categorises including no opioids (n=86 880, 19.5%), any long-acting opioids (n=5619, 1.3%), tramadol only (n=13 519, 3%), tramadol and other short-acting opioids (n=5457, 1.2%) or short-acting opioids only, excluding tramadol (ie, the reference group, n=333 289, 74.9%). The outcome was risk of prolonged opioid use defined using three definitions: (1) additional opioid use, (2) persistent opioid use and (3) the CONSORT (CONsortium to Study Opioid Risks and Trends) definition of long-term opioid therapy (full definitions are in the footer of table 1).

The authors of the BMJ cohort 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[1] are abstracted in table 1 with the NNT_H. For every 272 (95% CI 171 to 566) 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. The NNT_H for patients discharged taking any long-acting opioid is significantly lower (NNT_H=31, 95% CI 26 to 37). Short-acting opioids in the setting of acute pain are, therefore, preferable to both long-acting opioids and tramadol when discharging patients after elective surgery.

Confounding and selection biases are the two important aspects to consider in this cohort study. The authors suggested confounding was addressed by including participants with 'minimal clinical complexity'.[1] Although the adjusted risk ratios did take into account various confounding factors including type of surgery and morphine equivalent dose at discharge, the comparison groups are not identical in nature. Thus, other factors such as the duration of discharge prescription may also be associated with the prolonged use of opioids following elective surgery.

Limitations of the cohort study[1] 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

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**.
Formulae for NNT_H,[7] calculated using Stata SE V.14.1[8]
NNT_H=1/(absolute increase in risk)
eg, 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
eg, 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 to 0.007
Number needed to treat (improvement): ***373.433***
Bender's 95% CI 134.649 to ***544.013***
*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.
CONSORT, Consortium to Study Opioid Risks and Trends; NNT_H, number needed to harm; RR, risk ratio.

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.

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