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SEE Question

You serve on the hospital subcommittee for perioperative pain and are asked your expert opinion on gabapentin. According to a recent meta-analysis on gabapentinoids, which of the following statements is MOST likely true?

☐ (A) Gabapentinoids did not have analgesic benefit in the perioperative period.
☐ (B) Pregabalin had better analgesic properties than gabapentin.
☐ (C) Gabapentin prevented the development of postoperative chronic pain.

In the pain literature, few drugs are as polarizing as gabapentin, even though perioperative use of this former anticonvulsant has increased in order to decrease, and perhaps prevent, pain in an opioid epidemic.

A recent systematic review and meta-analysis of gabapentinoids included 281 randomized controlled trials in adults (N=24,682). This study was different from prior systematic reviews because it included both pregabalin and gabapentin, which were initiated between one week before surgery (71% of trials) and 12 hours after surgery (4% of trials); both pre- and postoperative administration occurred in 25% of trials. In addition, this meta-analysis was more exhaustive (no language or type of publication restriction), and the concept of minimally important difference of pain intensity was included. The primary outcomes were acute pain scores at six, 12, 24, 48, and 72 hours postoperatively, as measured by any quantitative pain scale. The surgeries included orthopedic, abdominal, ophthalmic, breast, vascular, and neurosurgical procedures. Regional techniques were not part of the pain regimen in 84% of the trials.

The authors concluded that gabapentinoids (both gabapentin and pregabalin) do not have a noteworthy clinical analgesic benefit for acute pain in the perioperative period. While postoperative pain intensity was lower at six, 12, 24, and 48 hours (but not at 72 hours), this was not clinically significant because it was below the minimally important difference (10 points out of 100) for each time interval. Trials that had a low risk of bias consistently showed small or no effect on pain intensity compared with trials that had a high or unclear risk of bias. Although there might be a statistical difference in postoperative pain – especially in its early use – the proportion of patients with greater than 20 points out of 100 in pain scores was small; when the definition used to consider an appreciable analgesic effect was 30 points or greater, the difference was absent.

In the secondary outcomes, subacute pain intensity after surgery (at four and 12 weeks postoperatively) was slightly lower with the use of gabapentinoids, but the authors did not consider this finding to be clinically relevant. In reviewing postoperative chronic pain (at three and 12 months postoperatively), gabapentinoids were not associated with reducing the risk of the development of chronic pain (risk ratio [RR], 0.89; 95% CI, 0.74-1.07; n=27 trials). These results were consistent whether gabapentin or pregabalin was used, whether single or multiple administrations were used, and regardless of dose regimen. However, the quality of evidence of the primary outcome according to the Grades of Recommendation, Assessment, Development and Evaluation rating was mostly low (Table).

Outcomes	Number of Trials	Number of Patients: Gabapentinoids	Number of Patients: Control	Summary Estimate: Mean Difference or Risk Ratio [95% CI]	Summary Estimate: I², %	Quality of the Evidence: Grades of Recommendation, Assessment, Development, and Evaluation Rating
Postoperative acute pain (100-point scale)*						
6 h	129	5,499	4,710	−10 [−12 to −9]	91	Low†
12 h	130	5,871	5,198	−9 [−10 to −7]	90	Low†
24 h	141	6,593	5,481	−7 [−8 to −6]	88	Low†
48 h	59	3,434	2,778	−3 [−5 to −1]	88	Low†
72 h	32	2,410	1,724	−2 [−4 to 0]	76	Low†
Postoperative subacute pain (100-point scale)	18	650	642	−6 [−9 to −3]	98	Low‡
Postoperative chronic pain	27	1,767	1,431	0.89 [0.74 to 1.07]	42	Moderate§
Postoperative opioid administration, mg of IV morphine equivalent‖						
24 h	117	4,807	4,253	−7.90 [−8.82 to −6.98]	98	Very low#
48 h	24	808	692	−9.79 [−12.81 to −6.78]	93	Very low#
72 h	4	200	173	−29.18 [−46.89 to −11.47]	94	Very low#
Length of stay (h)						
Postanesthesia care unit	10	512	383	−0.01 [−0.09 to 0.07]	73	Low†
Intensive care unit	6	184	184	0.14 [−3.49 to 3.78]	0	Low†
Hospital	17	1,359	1,104	2.96 [0.28 to 5.63]	62	Moderate§
Adverse events						
Ataxia or fall	14	1,228	1,107	1.31 [0.88 to 1.95]	40	Moderate**
Delirium	4	452	454	1.12 [0.85 to 1.47]	0	Low††
Visual disturbance	54	2,494	2,143	1.89 [1.53 to 2.33]	0	Moderate‡‡
Respiratory depression	42	2,251	2,108	0.79 [0.46 to 1.35]	0	Low§§
Nausea and/or vomiting	187	9,337	7,808	0.77 [0.72 to 0.82]	44	Moderate‡‡
Dizziness	134	6,645	5,409	1.25 [1.12 to 1.39]	39	Low‖‖

*Intervals considered for the time point: 6 h, 0 to 6 h; 12 h, 7 to 12 h; 24 h, 13 to 24 h; 48 h, 25 to 48 h; and 72 h, 49 to 72 h. †One level for potential risk of bias and one level for inconsistency. ‡One level for inconsistency and one level for imprecision. §One level for potential publication bias. ‖Intervals considered for the time point: 24 h, 0 to 24 h; 48 h, 0 to 48 h; and 72 h, 0 to 72 h. #One level for potential risk of bias, one level for indirectness, one level for inconsistency, and one level for potential publication bias. **One level for imprecision. ††Two levels for imprecision. ‡‡One level for potential risk of bias. §§One level for potential risk of bias and one level for imprecision. ‖‖One level for potential risk of bias and one level for potential publication bias.

Table: Summary Estimates from Meta-analyses with the Assessment of Statistical Heterogeneity and the Quality of the Evidence

Used with permission, from Verret M, Lauzier F, Zarychanski R, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain: a systematic review and meta-analysis. *Anesthesiology.* 2020;133(2):265-79. doi:10.1097/ALN.0000000000003428

Other notable aspects were found in this meta-analysis. Adverse events associated with gabapentinoids included a longer hospital length of stay (mean difference, 2.96 hours; 95% CI, 0.28-5.63), increased incidence of dizziness (RR, 1.25; 95% CI, 1.13-1.39), and visual disturbance (RR, 1.89; 95% CI, 1.53-2.33). However, gabapentinoids were found to reduce nausea and vomiting (RR, 0.77; 95% CI, 0.72-0.82).

In summary, the routine use of gabapentinoids does not appear to have clinically appreciable benefit in acute postoperative pain and does not prevent the development of postoperative chronic pain. ■

Bibliography:

1. Verret M, Lauzier F, Zarychanski R, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain: a systematic review and meta-analysis. *Anesthesiology.* 2020;133(2):265-79. doi:10.1097/ALN.0000000000003428
2. Egunsola O, Wylie CE, Chitty KM, Buckley NA. Systematic review of the efficacy and safety of gabapentin and pregabalin for pain in children and adolescents. *Anesth Analg.* 2019;128(4):811-9. doi:10.1213/ANE.0000000000003936

Answer: A

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