Pre-emptive Oral Duloxetine Versus Duloxetine with Intravenous Dexamethasone for Postoperative Pain After Laparoscopic Gynecological Surgery: A Randomized Comparative Study

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Abstract

Background: Postoperative pain after laparoscopic gynecological surgery is usually moderate but may increase rescue analgesic requirement. Duloxetine and dexamethasone act through different analgesic mechanisms and may be useful as part of multimodal analgesia.

Materials and methods: This randomized comparative study included 100 female patients aged 18–50 years, ASA grade I or II, undergoing laparoscopic gynecological surgery lasting up to 2 hours. Patients were allocated into two groups of 50 each. Group A received oral duloxetine 30 mg 2 hours before surgery. Group B received oral duloxetine 30 mg with intravenous dexamethasone 0.1 mg/kg 2 hours before surgery. Postoperative pain was assessed using Numerical Rating Scale (NRS) at 0, 1, 2, 4, 8, 12, 18 and 24 hours. Rescue analgesia was given as intravenous tramadol 1 mg/kg when NRS was ≥4. Total tramadol consumption, number of rescue doses and adverse effects were recorded.

Results: Baseline demographic profile, ASA grade, weight category, type of surgery and duration of surgery were comparable between groups. NRS scores were lower in Group B at most time points but were not statistically significant. At 4 hours, NRS was 5.14 ± 1.01 in Group A and 4.72 ± 1.18 in Group B (p=0.056). Total tramadol consumption was 120.47 ± 41.60 mg in Group A and 111.43 ± 37.87 mg in Group B (p=0.258). Rescue doses were also comparable. Adverse effects did not differ significantly.

Conclusion: Addition of intravenous dexamethasone to pre-emptive oral duloxetine showed a small favourable trend in pain score and tramadol requirement but without statistical significance.

Keywords: Duloxetine, dexamethasone, laparoscopic gynecological surgery, postoperative pain, tramadol, NRS score

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Introduction

Postoperative pain is still an important issue after laparoscopic gynecological surgery. Laparoscopy is less invasive than open surgery, but pain is not completely avoided. Pain may occur due to trocar site trauma, peritoneal stretching, tissue handling, pelvic manipulation and residual carbon dioxide pneumoperitoneum. Shoulder tip pain may also occur due to diaphragmatic irritation and referred pain through the phrenic nerve.

Adequate pain control in the early postoperative period improves comfort and allows early mobilisation. Poor pain control may increase rescue analgesic requirement and delay recovery. Opioids are effective for moderate to severe postoperative pain, but repeated use may cause nausea, vomiting, sedation, dizziness and delayed discharge. Because of this, multimodal analgesia has become a routine part of perioperative pain management. It uses drugs acting through different mechanisms and aims to reduce opioid requirement without compromising analgesia.[1,2]

Pain after surgery is not only a local inflammatory response. Peripheral nociception, central sensitisation and descending inhibitory pathways also contribute to pain perception. Pre-emptive analgesia is based on the concept that analgesic administration before surgical stimulus may reduce central sensitisation and postoperative pain intensity.[3] This concept is relevant in laparoscopic gynecological surgery because pain is usually moderate but occurs early and may need rescue opioid analgesia.

Duloxetine is a serotonin and norepinephrine reuptake inhibitor. It increases descending inhibitory modulation of pain at spinal and supraspinal levels. It is used mainly in chronic neuropathic pain, but its use in acute postoperative pain has also been studied. Recent studies and meta-analyses have reported that perioperative duloxetine may reduce

postoperative pain scores and opioid consumption in selected surgical patients.[6-8] However, the magnitude of benefit varies according to type of surgery, dose, timing and background analgesic regimen.

Dexamethasone is commonly used in anaesthesia for prevention of postoperative nausea and vomiting. It also has anti-inflammatory action and may reduce postoperative pain and analgesic consumption. Procedure-specific recommendations for laparoscopic hysterectomy include paracetamol, non-steroidal anti-inflammatory drugs, dexamethasone and opioids as rescue analgesics.[4] Dexamethasone is also supported by guidelines for postoperative nausea and vomiting prophylaxis.[5]

The combination of duloxetine and dexamethasone is pharmacologically reasonable. Duloxetine acts mainly through central pain modulation, while dexamethasone acts through anti-inflammatory and antiemetic mechanisms. Few studies have directly assessed this combination in laparoscopic gynecological surgery. Hence, the present randomized comparative study was planned to compare pre-emptive oral duloxetine alone with oral duloxetine and intravenous dexamethasone for postoperative pain after laparoscopic gynecological surgery. The primary outcomes were postoperative NRS pain score and total tramadol consumption in the first 24 hours. Rescue analgesic doses and postoperative adverse effects were also assessed.

Materials and Methods

This randomized comparative study was conducted in the Department of Anaesthesiology, M.G.M. Medical College and M.Y. Hospital, Indore, after approval from the Institutional Ethics Committee. Written informed consent was obtained from all patients.

A total of 100 female patients aged 18–50 years, belonging to ASA physical status I or II and posted for laparoscopic gynecological surgery lasting up to 2 hours were included. Patients with refusal, hypersensitivity to study drugs, psychiatric illness, substance abuse, chronic pain therapy, systemic glucocorticoid use within 4 weeks and diabetes mellitus on treatment were excluded.

Patients were randomly allocated into two groups of 50 each by chit method. Group A received tablet duloxetine 30 mg orally with a sip of water 2 hours before surgery. Group B received tablet duloxetine 30 mg orally with intravenous dexamethasone 0.1 mg/kg 2 hours before surgery.

In the operation theatre, pulse rate, non-invasive blood pressure, oxygen saturation and end-tidal carbon dioxide were monitored. Premedication was given with glycopyrrolate 0.2 mg IV and midazolam 1 mg IV. After preoxygenation, anaesthesia was induced with fentanyl 2 mcg/kg IV and propofol 1–2 mg/kg IV. Tracheal intubation was facilitated with atracurium 0.5 mg/kg IV. Anaesthesia was maintained with isoflurane, oxygen, nitrous oxide and intermittent atracurium. Thirty minutes before the end of surgery, acetaminophen 1 g IV and ondansetron 4 mg IV were given.

Postoperative pain was assessed using NRS at 0, 1, 2, 4, 8, 12, 18 and 24 hours. Rescue analgesia was given as tramadol 1 mg/kg IV over 15 minutes when NRS was ≥4. Total tramadol consumption, number of rescue doses and adverse effects were recorded for 24 hours.

Data were entered in Microsoft Excel and analysed using SPSS software. Continuous variables were expressed as mean ± SD. Categorical variables were expressed as number and percentage. Unpaired t-test, Mann–Whitney U test and Chi-square test were used as applicable. A p-value <0.05 was considered statistically significant.

Results

Table 1: Baseline demographic and clinical profile of study participants

Variable	Group A (n=50)	Group B (n=50)	Total (n=100)	p-value
Age group, years				0.772
18–26	15 (30.0%)	18 (36.0%)	33 (33.0%)	
27–34	11 (22.0%)	8 (16.0%)	19 (19.0%)	
35–42	7 (14.0%)	9 (18.0%)	16 (16.0%)	
43–50	17 (34.0%)	15 (30.0%)	32 (32.0%)	
ASA grade				1.000
I	40 (80.0%)	40 (80.0%)	80 (80.0%)	
II	10 (20.0%)	10 (20.0%)	20 (20.0%)	
Weight category, kg				0.444
<40	4 (8.0%)	3 (6.0%)	7 (7.0%)	
41–70	28 (56.0%)	34 (68.0%)	62 (62.0%)	
71–100	14 (28.0%)	12 (24.0%)	26 (26.0%)	
>100	4 (8.0%)	1 (2.0%)	5 (5.0%)	

A total of 100 patients were included in the study and were equally divided into two groups of 50 each. Group A received oral duloxetine and Group B received oral duloxetine with intravenous dexamethasone. Age distribution was comparable between both groups. In Group A, 15 patients were in the 18–26 years age group, 11 in 27–34 years, seven in 35–42 years and 17 in 43–50 years. In Group B, the corresponding numbers were 18, eight, nine and 15 respectively. The difference was not statistically significant (p=0.772). ASA physical status was identical in both groups. Forty patients in each group belonged to ASA grade I and 10 patients in each group belonged to ASA grade II (p=1.000). Weight distribution was also comparable between the groups (p=0.444). Most patients were in the 41–70 kg category. This included 28 patients in Group A and 34 patients in Group B. Thus, the two groups were comparable with respect to baseline demographic and clinical profile.

Table 2: Surgical profile of study participants

Variable	Group A (n=50)	Group B (n=50)	Total (n=100)	p-value
Type of surgery				0.234
Adhesiolysis	9 (18.0%)	11 (22.0%)	20 (20.0%)	
Diagnostic laparoscopy	6 (12.0%)	7 (14.0%)	13 (13.0%)	
Salpingectomy	13 (26.0%)	8 (16.0%)	21 (21.0%)	
Hysteroscopy	13 (26.0%)	7 (14.0%)	20 (20.0%)	
Myomectomy	4 (8.0%)	4 (8.0%)	8 (8.0%)	
Ovarian cystectomy	5 (10.0%)	13 (26.0%)	18 (18.0%)	
Duration of surgery, minutes	62.32 ± 15.47	59.08 ± 17.31	—	0.260

The type of laparoscopic gynecological surgery was comparable between the two groups (p=0.234). Adhesiolysis was done in nine patients in Group A and 11 patients in Group B. Diagnostic laparoscopy was done in six and seven patients respectively. Salpingectomy was performed in 13 patients in Group A and eight patients in Group B. Hysteroscopy was done in 13 patients in Group A and seven patients in Group B. Myomectomy was equally distributed with four patients in each group. Ovarian cystectomy was done in five patients in Group A and 13 patients in Group B. The mean duration of surgery was 62.32 ± 15.47 minutes in Group A and 59.08 ± 17.31 minutes in Group B. The difference was not statistically significant (p=0.260). This shows that both groups were comparable with respect to type and duration of surgery.

Table 3: Comparison of postoperative NRS pain scores between the two groups

Time after surgery	Group A	Group B	p-value
0 hour	0.56 ± 0.57	0.50 ± 0.46	0.590
1 hour	3.24 ± 1.52	3.02 ± 1.25	0.424
2 hours	4.79 ± 1.28	4.69 ± 1.78	0.759
4 hours	5.14 ± 1.01	4.72 ± 1.18	0.056
8 hours	3.30 ± 1.10	2.92 ± 1.32	0.118
12 hours	2.42 ± 0.99	2.23 ± 0.93	0.332
18 hours	1.95 ± 1.08	1.64 ± 0.87	0.116
24 hours	1.02 ± 0.77	0.95 ± 0.73	0.630

Postoperative NRS pain scores were recorded at 0, 1, 2, 4, 8, 12, 18 and 24 hours. At 0 hour, the mean NRS score was 0.56 ± 0.57 in Group A and 0.50 ± 0.46 in Group B (p=0.590). At 1 hour, the score was 3.24 ± 1.52 in Group A and 3.02 ± 1.25 in Group B (p=0.424). At 2 hours, NRS score was 4.79 ± 1.28 in Group A and 4.69 ± 1.78 in Group B (p=0.759). The highest mean NRS score was seen at 4 hours in both groups. At this time point, the score was 5.14 ± 1.01 in Group A and 4.72 ± 1.18 in Group B. The p-value was 0.056. This was close to significance but remained statistically non-significant. At 8 hours, the score was 3.30 ± 1.10 in Group A and 2.92 ± 1.32 in Group B (p=0.118). At 12 hours, the score was 2.42 ± 0.99 and 2.23 ± 0.93 respectively (p=0.332). At 18 hours, the score was 1.95 ± 1.08 in Group A and 1.64 ± 0.87 in Group B (p=0.116). At 24 hours, the score was 1.02 ± 0.77 and 0.95 ± 0.73 respectively (p=0.630). NRS scores were numerically lower in Group B at all recorded time points. However, none of the differences were statistically significant.

Table 4: Comparison of tramadol consumption and rescue analgesic doses in first 24 hours

Parameter	Group A	Group B	p-value
Total tramadol consumption in 24 hours, mg	120.47 ± 41.60	111.43 ± 37.87	0.258

Number of rescue analgesic doses in 24 hours	1.77 ± 1.01	1.59 ± 0.95	0.378

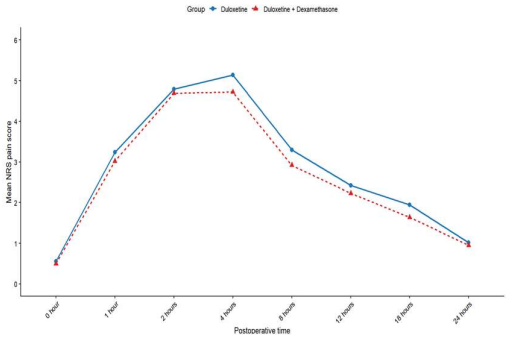
Total tramadol consumption in the first 24 hours was 120.47 ± 41.60 mg in Group A and 111.43 ± 37.87 mg in Group B. The difference was not statistically significant (p=0.258). The mean number of rescue analgesic doses was 1.77 ± 1.01 in Group A and 1.59 ± 0.95 in Group B. This difference was also not statistically significant (p=0.378). Both tramadol consumption and number of rescue doses were lower in the duloxetine with dexamethasone group. However, the reduction was small and did not reach statistical significance.

Table 5: Comparison of postoperative adverse effects between the two groups

Adverse effect	Group A (n=50)	Group B (n=50)	Total (n=100)	p-value
Nausea	8 (16.0%)	4 (8.0%)	12 (12.0%)	0.218
Vomiting	6 (12.0%)	1 (2.0%)	7 (7.0%)	0.112
Dry mouth	8 (16.0%)	9 (18.0%)	17 (17.0%)	0.790
Somnolence	3 (6.0%)	4 (8.0%)	7 (7.0%)	0.695
Dizziness	2 (4.0%)	3 (6.0%)	5 (5.0%)	0.646

Postoperative adverse effects were comparable between the two groups. Nausea was seen in eight patients in Group A and four patients in Group B (p=0.218). Vomiting was seen in six patients in Group A and one patient in Group B (p=0.112). Although nausea and vomiting were numerically lower in Group B, the difference was not statistically significant. Dry mouth was reported in eight patients in Group A and nine patients in Group B (p=0.790). Somnolence was seen in three patients in Group A and four patients in Group B (p=0.695). Dizziness was reported in two patients in Group A and three patients in Group B (p=0.646). No statistically significant difference was observed in any recorded adverse effect. Both regimens showed a comparable postoperative safety profile.

Figure 1: Comparison of mean postoperative NRS pain scores between the two groups



Discussion

The present study compared pre-emptive oral duloxetine alone with oral duloxetine and intravenous dexamethasone for postoperative pain after laparoscopic gynecological surgery. Both groups were comparable at baseline. Age distribution, ASA grade and weight category did not show significant difference. The surgical profile was also comparable. Mean duration of surgery was 62.32 ± 15.47 minutes in Group A and 59.08 ± 17.31 minutes in Group B, with p-value 0.260. This is important because surgical duration and type of procedure can affect postoperative pain intensity and rescue analgesic use.

The main finding was that addition of intravenous dexamethasone to oral duloxetine did not produce a statistically significant reduction in postoperative NRS pain score. Pain scores were numerically lower in the duloxetine with dexamethasone group at most time points. At 4 hours, NRS was 5.14 ± 1.01 in Group A and 4.72 ± 1.18 in Group B. The p-value was 0.056. This was close to statistical significance but did not cross the accepted level. At 8 hours, NRS was 3.30 ± 1.10 in Group A and 2.92 ± 1.32 in Group B. At 24 hours, NRS was 1.02 ± 0.77 and 0.95 ± 0.73 respectively. Thus, the combination group showed a small favourable trend, but statistical superiority was not established.

This result should be interpreted in relation to the study design. The present study did not compare duloxetine with placebo. Both groups received oral duloxetine. Hence, the expected difference between the groups was likely to be smaller. The added benefit of dexamethasone may be modest when a centrally acting analgesic has already been given in both groups. This may explain why the difference remained non-significant despite lower mean NRS scores in Group B.

Kassim et al. directly studied duloxetine and dexamethasone in laparoscopic gynecological surgery. They compared duloxetine 60 mg, duloxetine 60 mg with dexamethasone 0.1 mg/kg and placebo. Time to first rescue analgesia was 200.8 ± 30.4 minutes in the duloxetine group and 326.0 ± 10.4 minutes in the duloxetine with dexamethasone group, compared with 38.2 ± 4.5 minutes in placebo. Total pethidine requirement in 12 hours was 65.0 ± 24.1 mg in the duloxetine group

and 55.0 ± 16.7 mg in the combination group, compared with 108.0 ± 18.7 mg in placebo.[6] Their results favoured the combination group. In the present study also, the combination group had lower pain score and tramadol use numerically. However, the difference was not significant. One possible reason is the lower dose of duloxetine in the present study. We used 30 mg, whereas Kassim et al. used 60 mg.

The analgesic requirement in the present study was also slightly lower in the combination group. Total tramadol consumption in the first 24 hours was 120.47 ± 41.60 mg in Group A and 111.43 ± 37.87 mg in Group B. The p-value was 0.258. The number of rescue analgesic doses was 1.77 ± 1.01 in Group A and 1.59 ± 0.95 in Group B, with p-value 0.378. This shows a small reduction in tramadol consumption and rescue dose frequency in Group B, but the reduction was not statistically significant. It should be reported as a trend only.

The present findings are partly supported by meta-analysis data on duloxetine in laparoscopic surgery. Baradwan et al. analysed four randomized controlled trials with 244 patients undergoing laparoscopic gynecological surgery. Duloxetine significantly reduced postoperative analgesic consumption compared with placebo, with mean difference −41.97 mg and 95% CI −53.23 to −30.72.[7] Barbosa et al. published a recent meta-analysis of four randomized placebo-controlled trials including 227 patients undergoing laparoscopic surgery. Duloxetine reduced pain scores at 2 hours, 4 hours, 8 hours, 12 hours and 24 hours. The mean difference at 4 hours was −1.28 and at 24 hours was −1.05. They also reported longer time to first analgesic requirement by 128.38 minutes and lower risk of nausea/vomiting with RR 0.48.[8] These findings support the analgesic role of duloxetine. But these studies mainly compared duloxetine with placebo. Our study compared two active regimens. Hence, the observed difference was expected to be smaller.

Hatami et al. studied preoperative duloxetine 60 mg in laparoscopic myomectomy. They found reduction in postoperative pain without significant difference in dizziness, nausea, vomiting, blood pressure or heart rate.[9] This is similar to the safety profile observed in the present study. In our study, dry mouth, somnolence and dizziness were comparable between both groups. No increase in adverse effects was seen after adding dexamethasone.

Mansour et al. studied duloxetine 60 mg given 2 hours before laparoscopic cholecystectomy. They reported that the AUC of VAS score was significantly lower in the duloxetine group compared with placebo, 757.89 ± 326.01 mm × hour versus 1005.1 ± 432.5 mm × hour. VAS scores at 4 hours and 24 hours were significantly different with p-values 0.041 and 0.003. However, time to first rescue medication was not significantly different, with p-value 0.665.[10] This is relevant to our findings. Pain score may show numerical or statistical improvement, but rescue analgesic requirement may not always differ significantly. In the present study also, the reduction in tramadol consumption did not reach significance.

Not all trials have shown clear benefit of duloxetine in gynecological surgery. Takmaz et al. evaluated perioperative duloxetine after laparoscopic hysterectomy. They randomized 80 patients and found that median total QoR-40 score was 111/200 in the duloxetine group and 112/200 in the placebo group, with p-value 0.91. Postoperative narcotic dose was also similar, with median 3 doses in both groups.[11] Bastanhagh et al. studied duloxetine 60 mg before abdominal hysterectomy. They analysed 38 patients in each group and found no significant difference in opioid use, but nausea and vomiting were significantly higher in the duloxetine group, 65% versus 34%, with p-value 0.006.[12] These negative studies show that the effect of duloxetine is not uniform. Type of surgery, pain intensity, baseline analgesia and dose schedule can influence the result. A systematic review by Nair et al. on duloxetine premedication in hysterectomy also noted that the available evidence was not sufficient to recommend routine duloxetine premedication for all hysterectomy patients.[13] This supports a balanced interpretation of the present study. The results do not oppose duloxetine use, but they also do not prove that adding dexamethasone to duloxetine gives a statistically superior analgesic effect in all patients.

Broader meta-analyses have also reported procedure-dependent benefit. Govil et al. evaluated duloxetine for acute postoperative pain and found that perioperative duloxetine was better than placebo for pain and analgesic-related outcomes in several surgical models.[14] Schnabel et al. reviewed selective serotonin and norepinephrine reuptake inhibitors for postoperative pain and concluded that they may reduce postoperative pain, but at the cost of increased dizziness in some patients.[15] Azimi et al. studied total hip and knee arthroplasty trials and found lower opioid consumption with duloxetine on postoperative day 2 by −14.35 morphine milligram equivalents and on day 3 by −13.60 morphine milligram equivalents. However, somnolence/drowsiness was increased with RR 1.87.[16] Lin et al. also reported reduced opioid consumption and pain after total hip or knee arthroplasty with duloxetine.[17] These findings suggest that duloxetine may have stronger benefit in high-pain surgeries such as arthroplasty and spine surgery than in short laparoscopic gynecological procedures.

The role of dexamethasone in postoperative analgesia is supported by abdominal surgery data. Mitchell et al. included 52 studies with 5768 participants in a systematic review and meta-analysis. Dexamethasone reduced pain score within

4 hours at rest by MD −0.54 and during 4–24 hours by MD −0.31. It also increased time to first analgesia by 22.92 minutes and reduced opioid requirement by 6.66 mg oral morphine equivalent.[18] These values show that dexamethasone has analgesic benefit, but the size of effect is modest. This matches our finding. In our study, Group B had slightly lower NRS and tramadol use, but the effect size was not large enough to reach statistical significance. The antiemetic effect of dexamethasone is also relevant. In the present study, nausea was seen in 8 patients in Group A and 4 patients in Group B. Vomiting was seen in 6 patients in Group A and 1 patient in Group B. These values were lower in Group B, but p-values were not significant. Dexamethasone is recommended as a standard antiemetic option in PONV guidelines.[5] The PADDI trial included 8880 adult patients and found that postoperative nausea and vomiting in the first 24 hours occurred in 42.2% of dexamethasone patients and 53.9% of placebo patients. Surgical site infection was 8.1% with dexamethasone and 9.1% with placebo.[19] This supports the antiemetic safety of single-dose dexamethasone. In the present study, the lower nausea and vomiting in Group B is clinically consistent with this evidence, but the study was not powered primarily for PONV.

De Oliveira et al. also reported that dexamethasone is effective for prevention of PONV at both 4–5 mg and 8–10 mg dose ranges. They included 60 randomized trials with 6696 subjects and found reduced 24-hour PONV with dexamethasone compared with control.[20] In the present study, ondansetron was given to both groups. This may have reduced the measurable difference in nausea and vomiting between groups. When all patients receive antiemetic prophylaxis, additional antiemetic benefit of dexamethasone may become less obvious. The safety profile in the present study was acceptable. Dry mouth was seen in 8 patients in Group A and 9 patients in Group B. Somnolence was seen in 3 and 4 patients respectively. Dizziness was seen in 2 and 3 patients respectively. None of these differences were significant. This is important because duloxetine may cause nausea, dizziness or sedation in some patients. In the present study, adding dexamethasone did not increase these adverse effects.

The present study has some limitations. It was a single-centre study with 50 patients in each group. There was no placebo group and no dexamethasone-only group. Hence, the independent effect of duloxetine and dexamethasone cannot be separated. Duloxetine dose was 30 mg, while many previous trials used 60 mg. Pain assessment was limited to the first 24 hours. The included surgeries were comparable statistically, but the types of gynecological procedures were clinically heterogeneous. The study may not have been adequately powered to detect small differences in pain scores, tramadol consumption or adverse effects. Overall, the present study showed that duloxetine with dexamethasone had slightly lower postoperative NRS pain scores, lower tramadol consumption and fewer nausea and vomiting episodes compared with duloxetine alone. However, none of these differences were statistically significant. The findings are clinically plausible and are in line with evidence showing modest analgesic benefit of dexamethasone and variable benefit of duloxetine. The result should be presented as a non-significant favourable trend, not as proven superiority of the combination regimen.

Conclusion

Pre-emptive oral duloxetine with intravenous dexamethasone showed slightly lower postoperative NRS pain scores and lower tramadol consumption compared with oral duloxetine alone after laparoscopic gynecological surgery. The difference was closest at 4 hours but did not reach statistical significance. Rescue analgesic doses and adverse effects were also comparable between groups. The combination appeared safe and showed a small favourable trend, but this study does not prove significant analgesic superiority over duloxetine alone.

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