Systematic Review & Meta-Analysis

# Analgesic efficacy and safety of duloxetine premedication in patients undergoing hysterectomy – A systematic review

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## ABSTRACT

**Background and Aims:** Patients undergoing hysterectomy by open or laparoscopic approach experience moderate to severe postoperative pain. A multimodal analgesic approach is recommended for these patients. This study reviews the analgesic efficacy of duloxetine, a selective serotonin and norepinephrine reuptake inhibitor used as an adjuvant for opioid-sparing postoperative analgesia. **Methods:** After registering the protocol in the international prospective register of systematic reviews (PROSPERO), databases like PubMed, Ovid, Scopus, Cochrane Library and clinicaltrials.gov were searched for randomised controlled trials using relevant keywords to find studies in which duloxetine premedication was compared to a placebo in patients undergoing hysterectomy. The revised Cochrane risk-of-bias tool for randomised trials (RoB 2) was used to assess the quality of evidence. **Results:** The qualitative systematic review included five of the 88 studies identified. The overall risk of bias in the included studies was very high. In all the studies, 60 mg oral duloxetine was used, and the control group was placebo. In two studies, duloxetine premedication was administered 2 h before and 24 h after surgery. In the other three studies, a single dose of 60 mg duloxetine was only administered 2 h before surgery. A pooled meta-analysis was not performed due to fewer studies that fulfilled the inclusion criteria and even fewer studies with consistent reporting of various outcomes. **Conclusion:** The evidence is insufficient to advocate routine duloxetine premedication in patients undergoing hysterectomy.

**Key words:** Acute pain, analgesia, premedication, duloxetine, surgery, hysterectomy, quality of recovery, length of hospital stay, systematic review, meta-analysis

## INTRODUCTION

Hysterectomy is a surgical procedure that is often performed to treat conditions such as uterine fibroids, endometrial cancer and uterine prolapse. Hysterectomy is performed either as an open surgery or using a laparoscopic approach. This procedure is performed under spinal, combined spinal–epidural or general anaesthesia. It may cause significant postoperative pain and discomfort for the patient.[1,2] Various pain management strategies like thoracic epidural analgesia, fascial plane blocks, opioid based patient-controlled analgesia (PCA), non-steroidal anti-inflammatory drugs (NSAIDs), local infiltration analgesia (LIA) and adjuvants like gabapentinoids have been used for patients undergoing hysterectomies.[3-5]



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To minimise the pain and discomfort associated with hysterectomy, premedication with duloxetine has been investigated by many researchers.[6] Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) commonly used to treat depression, anxiety and chronic pain. The medication works by increasing the levels of serotonin and norepinephrine in the brain, which can help to reduce pain, improve mood and promote relaxation. Duloxetine has also been found to have a mild analgesic effect and has been investigated as a premedication for various surgical procedures, including hysterectomy. Duloxetine premedication in hysterectomy effectively reduces pain and improves patient satisfaction. Duloxetine has been shown to improve the quality of anaesthesia, reduce the need for additional pain medication and cause lesser adverse events when compared to those who do not receive premedication.[7,8] Despite the potential benefits of duloxetine premedication, there are potential side effects, such as nausea, dizziness and drowsiness, usually encountered in the postoperative period.[9,10]

This systematic review aims to investigate the efficacy and safety of preoperative oral duloxetine premedication as a part of multimodal analgesia in adult patients undergoing hysterectomy by comparing it with placebo or no premedication.

## METHODS

This systematic review was registered with the international prospective register of systematic reviews (PROSPERO registration number: CRD42023399778). It was reported as per the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines.[11] The search for relevant keywords was done from databases from January 2000 till February 2023. The strategy included searches of PubMed/MEDLINE, Ovid, Cochrane Library (CENTRAL) and clinicaltrials.gov. The search strategy for the PubMed database was as follows: 'Duloxetine' AND 'Hysterectomy' AND 'Postoperative pain'. The full search strategy in all databases is provided in Supplementary File 1.

### Participants (inclusion and exclusion criteria)

Randomised controlled trials (RCTs) in which oral duloxetine was compared with a placebo or no premedication in patients undergoing hysterectomy were included. Studies with no control groups, case reports/series, editorials, review articles and conference abstracts were excluded.

The results obtained from the databases were carefully screened for RCTs in which oral duloxetine premedication was compared to a placebo in patients undergoing hysterectomy. The titles and abstracts were separately reviewed, and duplicates were removed by two authors (AN and MT). The studies were chosen after consideration by both authors, who read the complete texts. A third author (NB) settled any disagreement and inconsistency. Data were extracted independently by each author using a standardised format. The finalised articles were assessed for study characteristics and study outcomes. The collected data comprised the author's name, publication year, study design, number of participants, country, age and open versus laparoscopic hysterectomy. We performed the search using the 'PICO' criteria (Population, Intervention, Comparator, Outcomes):

*Population:* Adult females (more than 18 years) undergoing hysterectomy (open or laparoscopic) were considered eligible for inclusion.

*Intervention:* Oral duloxetine premedication administered preoperatively.

*Comparator:* The patients who either received a placebo or did not receive any active premedication.

*Outcomes:* The primary outcome was 24-h opioid consumption. The secondary outcomes were postoperative pain scores, time to first analgesia, patients requiring rescue analgesia, adverse events like postoperative nausea/vomiting (PONV), quality of recovery (QoR)-40 score and length of hospital stay.

### Methodological quality assessment

The revised Cochrane risk-of-bias tool for randomised trials (RoB 2) was used to assess the methodologic quality and risk of bias of the included RCTs. The categories used for bias assessment were bias due to randomisation, bias due to deviation from intended intervention, bias due to missing data, bias due to outcome measurement, bias due to selection of reported result and overall bias.[12] Two authors (AN and UD) independently evaluated all the eligible articles for the risk of bias.

### Data extraction

The reference data, populations and outcomes were extracted from the articles and entered into pre-planned tables. The two authors (AN and MR) used a systematic process for data extraction. Before

being used, the data gathering form underwent a pilot test. Data on the study design, number of arms, primary result, participants' demographics, sample size, surgical approach (open vs. laparoscopic) and the experimental intervention (oral duloxetine premedication) was gathered. The distinction between the presence and absence of a therapeutic or adverse effect was retrieved as a dichotomous outcome. The means and standard deviations (SDs) for continuous data were calculated.

### Data synthesis and analysis

Data pooling was planned if trials were clinically homogenous regarding demographic characteristics and control groups. Review Manager software was used for quantitative meta-analysis (version 5.4.1) if the above criteria were fulfilled.[13]

For the meta-analysis, aggregate-level data were utilised. The Mantel–Haenszel technique was used to assess dichotomous variables, and the risk ratio (RRs) with the associated 95% confidence interval (CI) was determined. If data were expressed as median and interquartile range (IQR), the median was considered mean and the difference of IQR divided by 1.35 was considered SD. We evaluated the heterogeneity between studies using the $I^2$ statistic, which was defined as follows: 0–40%- might not be important, 30%–60%- may represent moderate heterogeneity, 50%–90%- may represent significant heterogeneity and 75%-100%- considerable heterogeneity.[14]

When $P > 0.01$ and $I^2 < 50\%$, the fixed-effects model was used; when $P < 0.01$ and $I^2 > 50\%$, the random-effects model was used for meta-analysis. For comparison purposes between the trials, different opioids were converted to intravenous (IV) morphine equivalents. RR with 95% CI were used to report dichotomous results. A sensitivity analysis was planned by removing each study from the meta-analysis to address the heterogeneity in the outcomes.

## RESULTS

### Results of literature search

We identified 88 articles by searching the databases mentioned in methods section and registries. After removing duplicates and articles that were irrelevant, we identified 20 articles for scrutiny. A total of nine studies were considered eligible. Four studies were excluded (study with no control group- 0, review articles- 2, active control group- 1, unrelated primary and secondary outcomes- 1). Finally, we included five studies with 347 patients for analysis (173 in the duloxetine group and 174 in the control group), as depicted in the PRISMA flowchart [Figure 1].[15-19] All the included studies with study characteristics are summarised in Table 1.

### Risk of bias

The risk of bias within the trials according to RoB 2 and summary plot of the quality assessment was done [Figure 2]. The bias from the randomisation process was low in all five studies.[15-19] Bias due to deviations from intended interventions (allocation concealment) was low in four studies,[15-18] and there was no information in one study.[19] Bias arising due to missing outcome data was low in one study[15] and there needed to be more information in four studies.[16-19] Bias in the measurement of outcome needed to be higher in one study[15] and there was no information in four studies.[16-19] There was no information about bias arising due to the selection of reported results in any study.[15-19] The overall bias was high in all the studies included in the qualitative review.

### Details of included studies

In all the studies, 60 mg of oral duloxetine was used uniformly,[15-19] [Table 1]. In two studies, duloxetine premedication was administered 2 h before surgery and 24 h after surgery,[15,17] and in the other three studies, a single dose of 60 mg duloxetine was administered 2 h before surgery.[16,18,19] The control group was placebo in all the studies. An open approach for hysterectomy was used in four studies,[15,16,18,19] and a laparoscopic approach was used in one study.[17] Surgeries were performed under general anaesthesia in three studies[16-18] and spinal anaesthesia in two.[15,19] In two studies, QoR-40 scores at 24 h were the primary outcome.[15,17] In two studies, postoperative pain scores at 24 h were the primary outcome.[16,19] In one study, postoperative opioid consumption was the primary outcome.

In the study by Castro-Alves *et al*.,[15] in both groups, there was a robust postoperative pain relief strategy which comprised IV ketoprofen 100 mg 8 hourly and metamizole 50 mg 6 hourly, with IV morphine 1–2 mg to limit the pain score to less than 4. Despite that, patients in the duloxetine group had a higher QoR-40 score and lesser opioid consumption than placebo. In the study by Takmaz *et al*.,[17] all patients in both groups received IV paracetamol 1000 mg 8 hourly and metamizole 50 mg 12 hourly. Here, the authors found

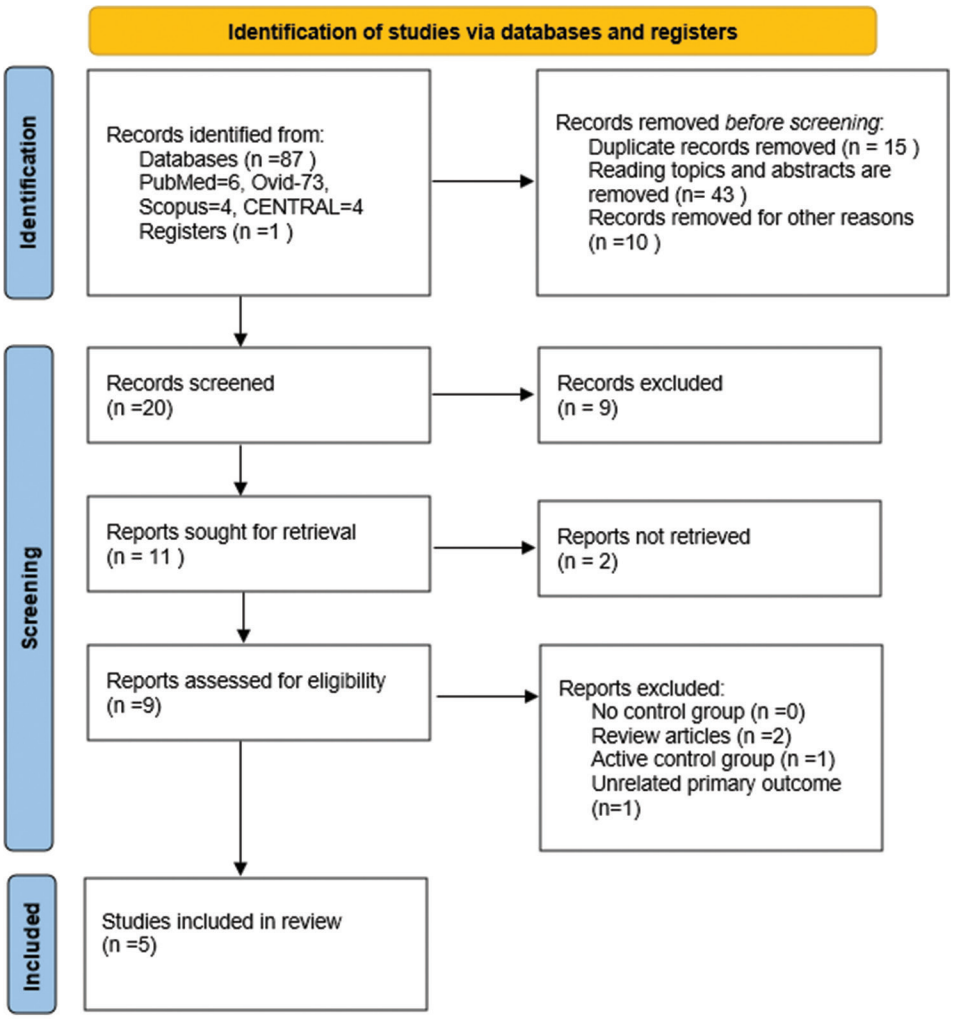


**Figure 1:** Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) flow diagram showing the literature search process

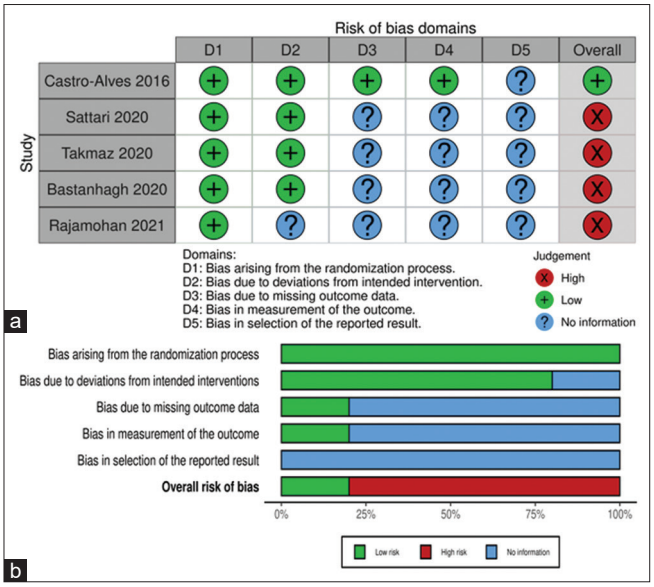


**Figure 2:** Risk of bias and quality assessment: (a) traffic light plot showing the risk of bias within the trials; (b) summary plot showing quality assessment for each included study

comparable QoR-40 scores in both groups undergoing laparoscopic hysterectomy with and without duloxetine premedication, respectively.

In the study by Sattari *et al*.,[16] patients in the duloxetine group had better pain scores (measured at 15 min and 2, 4 and 24 h postoperatively) compared to placebo. The pain management strategy comprised IV pethidine 25 mg for a visual analogue scale (VAS) score of more than four and IV acetaminophen 1000 mg 6 hourly. Also, the QoR-40 scores were higher in patients who received duloxetine than placebo. However, postoperative opioid consumption was comparable between the two groups. In the study by Rajamohan *et al*.,[19] postoperative pain scores at rest and coughing were comparable between both groups. The rescue and total analgesia consumption were comparable between both groups, with a higher PONV in patients who received duloxetine.

**Table 1: Characteristics of all the included studies**

| Authors, year | Country | Type of study | Surgical approach | Number of patients | Comparator | Dose of oral duloxetine used | Primary outcome | Secondary outcome | Conclusions |
|---|---|---|---|---|---|---|---|---|---|
| Castro-Alves *et al.*, 2016[15] | USA | Prospective, randomised, double-blinded, placebo-controlled study | Open | 31 patients-study group, 32 patients-control group | Placebo | 60 mg | Quality of recovery-40 score at 24 h | Opioid consumption, postoperative nausea and vomiting and postoperative pain scores | Duloxetine enhances the postoperative quality of recovery following abdominal hysterectomy and decreases postoperative opioid usage |
| Sattari *et al.*, 2020[16] | Iran | Randomised, double-blind study | Open | 32 patients in each group | Placebo | 60 mg | Postoperative pain scores | Perioperative opioid use, quality of recovery | Preoperative duloxetine improves postoperative pain and the quality of recovery in abdominal hysterectomy |
| Takmaz *et al.*, 2020[17] | Turkey | Randomised, placebo-controlled trial | Laparoscopic | 40 patients in each group | Placebo | 60 mg | Total quality of recovery-40 score | Use of opioids and hospital length of stay | Perioperative duloxetine did not reduce pain, the need for narcotic analgesia or hospital length of stay following laparoscopic hysterectomy |
| Bastanhagh *et al.*, 2020[18] | Iran | Randomised, double-blinded, placebo-controlled trial | Open | 38 patients in each group | Placebo | 60 mg | Perioperative opioid consumption | postoperative nausea and vomiting | Duloxetine was ineffective in controlling pain after abdominal hysterectomy and was also a cause of significant postoperative nausea and vomiting |
| Rajamohan *et al.*, 2021[19] | India | Prospective, randomised, placebo-controlled study | Open | 32 patients in each group | Placebo | 60 mg | Postoperative pain scores | Postoperative analgesic consumption, postoperative nausea and vomiting | Duloxetine premedication for abdominal hysterectomy is no better than placebo in providing better postoperative pain scores |

Bastanhagh *et al*.[18] concluded from their study that duloxetine premedication did not reduce either pain scores or postoperative opioid consumption but was responsible for a higher incidence of PONV. The postoperative pain management strategy comprised ketorolac 15 mg IV every 8 h, and once orals were tolerated, ibuprofen 400 mg orally was administered every 6 h. For a VAS score higher than 3, 2 mg of IV morphine sulphate was administered.

### Data analysis

A meta-analysis of effect estimates is either impossible or inappropriate in various situations. This happens when effect estimates are only reported partially or when research variables (such as study designs, intervention types or outcomes) are too diverse to produce a meaningful summary estimate of the effect.[20] The high risk of bias of the included studies can considerably impact the validity and reliability of the results. It might introduce systematic errors or inaccuracies that jeopardise the precision of the pooled estimate in a meta-analysis. Conclusions that are inaccurate or incorrect can result from including studies with a high risk of bias. We used the synthesis without meta-analysis (SWiM) reporting guidelines in addition to the PRISMA checklist, as a quantitative meta-analysis was not possible with this qualitative systematic review.[21] SWiM includes nine items to guide reporting systematic review without meta-analysis: seven in methods and one each in results and discussion.

## DISCUSSION

### Summary of results

This systematic review investigated the safety and efficacy of oral duloxetine premedication in female patients undergoing hysterectomy, either open or laparoscopic. The qualitative analysis included five RCTs with an overall high bias. A pooled meta-analysis was not performed due to an overall smaller number of studies that fulfilled the inclusion criteria and an even lesser number of studies that consistently reported various outcomes. To the best of our knowledge, this is the first systematic review that has investigated the safety and efficacy of oral duloxetine premedication in patients undergoing open or laparoscopic hysterectomy compared to a placebo.

Several studies investigated the efficacy of duloxetine and compared it to placebo for various surgeries and have obtained variable results. A single-centre, triple-blinded and placebo-controlled trial including 96 patients undergoing surgery for lumbar canal stenosis compared 60 mg duloxetine premedication versus placebo.[22] The authors concluded that in the duloxetine group, the 24-h morphine consumption was significantly less compared to the placebo with a similar time to the first analgesic requirement and comparable adverse events. Kim *et al*.[23] compared the efficacy and safety of duloxetine with opioids in patients undergoing total knee arthroplasty. They found no difference in the pain scores, functional scores and adverse events between both groups. In another RCT, authors compared 60 mg oral duloxetine premedication to placebo in patients undergoing laparoscopic cholecystectomy. They concluded that the use of duloxetine provided better pain scores and lesser PONV when compared to a placebo.[24] In another study, the authors concluded that 60 mg duloxetine premedication leads to better pain scores, lesser rescue analgesia requirement and better haemodynamics in patients undergoing laparoscopic cholecystectomy.[25] Another study compared 60 mg duloxetine premedication to placebo in gall bladder cancer patients undergoing open radical cholecystectomy.[26] The authors concluded that duloxetine premedication provided better pain scores, lesser morphine consumption and comparable patient satisfaction scores. In a systematic review and meta-analysis by Schnabel *et al*.,[27] the authors compared the postoperative pain outcomes of perioperative selective serotonin noradrenaline reuptake inhibitors (SSNRIs) and placebo or other drugs in adults undergoing various surgeries, including hysterectomies. On analysis, they concluded that SSNRI could reduce postoperative pain between 24 and 48 h, but at the cost of dizziness. They also mentioned that duloxetine could be used in individual cases.

The safety and efficacy of duloxetine premedication were attested earlier by Baradwan *et al*.[28] Their systematic review and meta-analysis included four RCTs and 244 patients undergoing laparoscopic gynaecological surgeries. The authors concluded that duloxetine premedication is a safe and effective medication with minimal adverse effects. However, this review considered various gynaecological surgeries such as laparoscopic myomectomy, ovarian cystectomy, ovarian drilling and adhesiolysis, diagnostic laparoscopic interventions for infertility and hysterectomy. The heterogeneity in terms of small sample size and the above-mentioned variable

surgeries was mentioned in the limitations. Another systematic review and meta-analysis quantifying the pooled effects of duloxetine on postoperative pain, analgesic consumption and side effects in the first 48 h postoperatively were reported.[29] Duloxetine had statistically significant impacts on postoperative pain and opioid use in the first 48 h following surgery, but the effect sizes were small. The authors concluded that the available evidence did not support the clinical use of duloxetine to treat acute postoperative pain when the changes were less than the anticipated bare minimum of clinically significant differences. Zorrilla-Vaca *et al*.[30] conducted a meta-analysis that included nine studies to investigate the efficacy of duloxetine in the acute perioperative setting. According to analyses, compared to placebo, duloxetine use was linked to a significant decrease in pain levels as early as 4 h after surgery. Moreover, compared to a placebo, duloxetine was linked to a significant decrease in both PONV and opioid usage at 24 h. A dose of 60 mg duloxetine has been considered optimal for providing opioid-sparing perioperative analgesia. In a clinical study by Bartlett *et al*.,[31] the authors randomised 88 patients undergoing mastectomy into four groups: placebo, 30 mg, 60 mg and 90 mg duloxetine 2 h before surgery. They concluded that although morphine consumption was lesser in 60 and 90 mg groups compared to the 30 mg group and placebo group, adverse events like PONV were more in patients who received 90 mg duloxetine.

The strength of the present review is that studies in which only hysterectomy was performed were included. Moreover, only RCTs were included in this systematic review. However, the small sample size, short duration of follow-up and variable outcomes were the limitations of our review. Outcomes like patient satisfaction scores, length of hospital stay and economic implications of premedication should have been addressed, which are the other limitations. The studies included have variability along with significant clinical heterogeneity regarding indications for hysterectomy and the type of anaesthesia, thus making it one of the limitations.

## CONCLUSION

Based on the results of this systematic review, the current body of research is insufficient to support the routine premedication of hysterectomy patients with duloxetine. Further studies need to be conducted with a robust methodology to explore the effective and tolerable dose and investigate the long-term effects of duloxetine, like the prevention of chronic post-surgical pain in patients undergoing hysterectomy.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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## SUPPLEMENTARY FILE 1

### Search strategy for PubMed database:

("duloxetin"[All Fields] OR "duloxetine hydrochloride"[MeSH Terms] OR ("duloxetine"[All Fields] AND "hydrochloride"[All Fields]) OR "duloxetine hydrochloride"[All Fields] OR "duloxetine"[All Fields] OR "duloxetine s"[All Fields]) AND ("hysterectomy"[MeSH Terms] OR "hysterectomy"[All Fields] OR "hysterectomies"[All Fields]) AND ("pain, postoperative"[MeSH Terms] OR ("pain"[All Fields] AND "postoperative"[All Fields]) OR "postoperative pain"[All Fields] OR ("postoperative"[All Fields] AND "pain"[All Fields]))

### Search strategy for Ovid database:

(Duloxetine and Acute pain and Hysterectomy).mp. [mp=tx, bt, ti, ab, ct,sh, hw, tn, ot, dm, mf, dv, kf, fx, dq, nm,ox, px, rx, an, ui, ds, on, sy, ux, mx, pt]