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Review Article

Selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors as adjuncts for postoperative pain management: systematic review and meta-analysis of randomised controlled trials

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梶原 一絵

Background

- SSRIとSNRIは最も処方されている抗うつ薬である。
- アメリカでSSRIの1/5以上は慢性痛に対して処方されている[1)]。
- SSRIとSNRIは慢性痛に有効[2,3)]、術後疼痛管理には？？？

以前のシステマティックレビュー

- Duloxetineは、術後急性痛とオピオイド使用量↓[4,5)]
- しかし、非常に質の低いエビデンスのために支持できない。

術後疼痛管理の補助薬としてのSSRIとSNRIの効果を評価するために
システマティックレビュー/メタアナリシスを行った。

1) Wong J, Motulsky A, et al. BMJ 2017; 356: j603
2) Patetsos E, Horjales-Araujo E. Pain Res Manag 2016; 2016: 2020915
3) Marks DM, Shan MJ, et al. Curr Neuropharmacol 2009; 7: 331-6
4) de Oliveira Filho GR, Kammer RS, et al. J Clin Aneths 2020; 63: 109785
5) Zorrilla-Vaca A, Stone A, et al. Reg Aneths Pain Med 2019; 44: 959-65

Methods

Data sources and searches 🔍

- ７つのデータベース ＋ ２つの試験登録サイト
- 言語や年齢の制限（－）

Eligibility criteria 👍

種類、投薬量、期間、術式を問わず、

SSRI or **SNRI**　vs　**プラセボ** or **対照薬**

を周術期に投与したRCT

除外基準

- SNDRI（ビシファジン）
- 抄録、進行中の試験
- 手術患者でない
- 精神疾患にSSRI/SNRIを使用
- 必要時、著者に連絡 ➜ 返答（－）

Methods

Risk-of-bias assessment （Cochraneバイアスリスクツール）⛔❓➕

- ランダム化
- 割り付けの隠ぺい化
- 研究参加者・医療提供者の盲検化
- データ収集者・アウトカム測定者の盲検化
- 選択的アウトカム報告
- 不完全なアウトカムデータ （20%以上の症例の減少）

上記のいずれかで、バイアスリスクを特定した場合
➜ バイアスリスクの高い研究

Methods

Data extraction

- **研究の特徴**（著者、出版年、国、言語、資金）
- **患者背景**（年齢、性別、BMI、手術・麻酔の種類、精神疾患の併存）
- **治療の詳細**（SSRI or SNRIの種類、投与量・方法、治療期間）
- **鎮痛補助薬**
- **バイアスリスク**
- **急性** or **慢性術後疼痛**　（術後 6, 12, 24, 48, 72 h, 1 w, 10 d - 1 m, 3, 6 m）
- **オピオイド消費量**　（術後 24, 48 h）
- **最初のレスキュー使用までの時間**
- **患者の満足度**（痛みのコントロール、全体的なケア）
- **回復の質**（Quality of Recovery-40で測定）
- **すべての有害事象**

Methods

Statistical analysis

共通のスケールに変換

- 痛み ➜ **VAS**
- オピオイド消費量 ➜ **経口モルヒネ量**
- 患者満足度 ➜ **リッカート尺度**（4段階）

- 安静時痛を解析 + 感度解析（体動時痛の影響）
- SSRIとSNRIを合わせて解析 +サブグループ解析（SSRI vs SNRI）

Methods

Statistical analysis

- DerSimonian-Laird法 +
- 連続アウトカム ➜ WMD（加重平均差）
  （痛み、オピオイド消費量、患者満足度スコア）
- ２値アウトカム ➜ RR（リスク比）
  （有害事象、慢性痛発生、患者満足度）
- 軽度の痛みの患者の割合 ➜ RD（リスク差）
  （VAS３以下）

Methods

Subgroup analysis, sensitivity analysis, and meta-regression

異質性：χ^2検定、I^2統計量

サブグループ解析

- SNRI vs SSRI
- 治療期間（≦3日 vs ＞3日）
- バイアスリスク（high vs low）
- 痛みスコア（試験終了時 vs スコアの変化）
- 手術の種類
- 麻酔の種類
- 患者満足度（痛みのコントロール vs 全体的なケア）

Methods

Subgroup analysis, sensitivity analysis, and meta-regression

📊 感度分析

- DerSimonian-Laird法 ➜ Hartung-Knapp-Sidik-Jonkman法
- 安静時痛 ➜ 体動時痛
- 嘔気 + PONV ➜ PONV

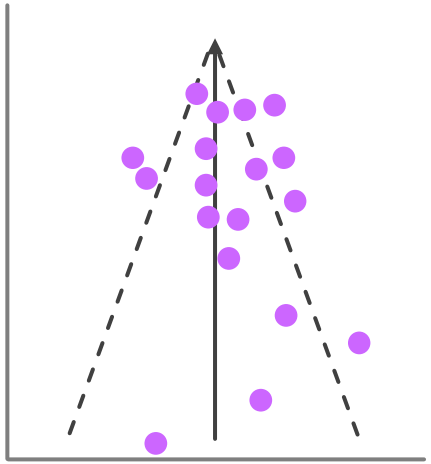
📊 メタ回帰分析

- ICEMANツール
- 治療効果と追跡期間の長さの関連

Methods

Small study effects

- ファンネルプロット ➜ 目視評価
- 連続アウトカム ➜ Eggerの検定
- ２値アウトカム ➜ Harbordの修正検定



Quality of evidence

- GRADEアプローチ

Results

Study identification

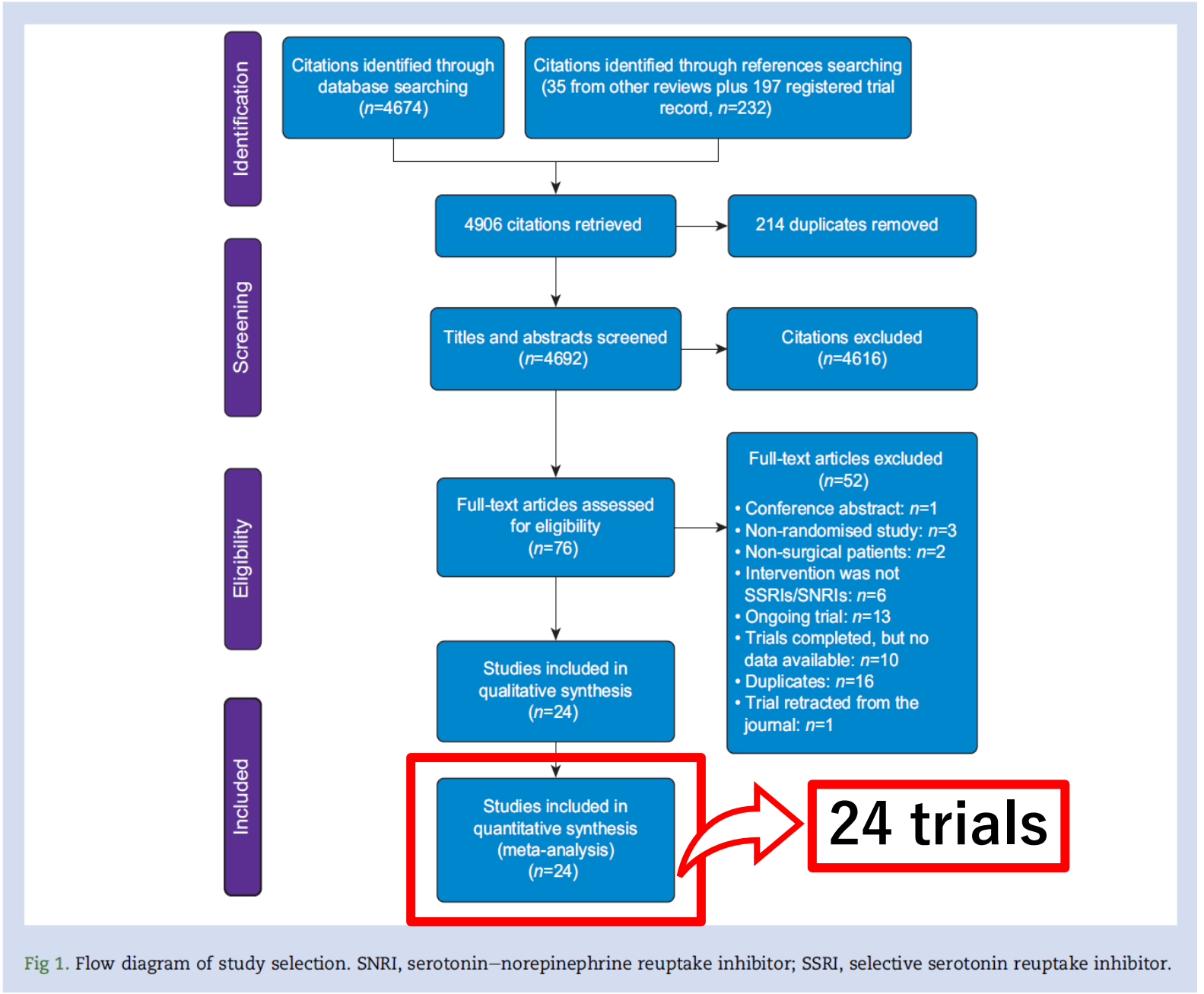


Fig 1. Flow diagram of study selection. SNRI, serotonin–norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Result

Study characteristics

- 整形外科（n=10）
- 婦人科（n=9）
- 一般外科（n=2）
- 心臓外科（n=1）
- 脳神経外科（n=1）
- 歯科（n=1）

Table 1 Baseline characteristics of 24 eligible RCTs. NR, not reported; SD, standard deviation. *If age, BMI, weight, or height was reported as median and inter-quartile range or range, mean and associated SD were estimated.

Author	Year	Age (yr) (mean [SD])*	BMI or weight (kg)/height (cm) (mean [SD])*	Female sex, n (%)	ASA physical status, n (%)	Surgery	Trial arms	Interventions	Duration of treatment (days)
Selective serotonin reuptake inhibitors									
Gordon and colleagues[29]	1994	21.4 [5]	Weight 63.4 [12.4] kg	41 (59)	NR	Removal of bony impacted mandibular third molar		Fluoxetine 10 mg+morphine 6 mg vs placebo+morphine 6 mg vs fluoxetine 10 mg+pentazocine 45 mg vs placebo+pentazocine 45 mg for 7 days (starting 7 days before surgery)	7
Chocron and colleagues[32]	2013	67.1 [8.9]	BMI 27.6 [4.1]	50 (14)	NR	Coronary artery bypass grafting		Escitalopram 10 mg vs placebo starting 14–21 days before surgery to 180 days after surgery	194–201
Lunn and colleagues[36]	2015	67.5 [7.1]	BMI 29.15 [4.1]	58 (49)	1: 30 (25.4) 2: 79 (67) 3: 9 (7.6)	Total knee arthroplasty		Escitalopram 10 mg vs placebo starting on the day of surgery for 7 days	7
Serotonin–norepinephrine reuptake inhibitors									
Amr and Yousef[30]	2010	44 [6]	Weight 83 [6] kg; height 159 [5] cm	150 (100)	1–2: 150 (100)	Mastectomy with axillary dissection		Venlafaxine 37.5 mg vs gabapentin 300 mg vs placebo daily starting the evening before surgery and continued for the first 10 postoperative days	10
Ho and colleagues[31]	2010	65.5 [7.2]	Weight 67.6 [12.1] kg; height 155 [9] cm	33 (70)	1: 3 (6.4) 2: 37 (78.7) 3: 7 (14.9)	Total knee arthroplasty		Duloxetine 60 mg vs placebo starting 2 h before surgery and 1 day after surgery	2
Saoud and Elkabarity[33]	2013	50 [11]	Weight 65.1 [7] kg	25 (56.8)	1: 24 (54.5) 2: 20 (45.5)	Anterior cervical decompression fusion		Duloxetine 60 mg vs placebo starting at least 2 weeks before surgery to 2 weeks after surgery	28
Nasr[34]	2014	42.1 [5.5]	Weight 71.7 [5] kg	50 (100)	1: 35 (74.5) 2: 12 (25.5)	Radical mastectomy with axillary dissection		Duloxetine vs placebo 60 mg for 2 days (starting 2 days before surgery) and then continue for 2 weeks, then taper to 30 mg for 6 months	196

Continued

Result

Study characteristics

薬剤・投与時期

- SNRI（n=21）
- SSRI（n=3）

- 手術前（n=6）
- 周術期（n=18）

Table 1 Continued

Author	Year	Age (yr) (mean [SD])*	BMI or weight (kg)/height (cm) (mean [SD])*	Female sex, *n* (%)	ASA physical status, *n* (%)	Surgery	Trial arms	Interventions	Duration of treatment (days)
Hyer and colleagues[35]	2015	53.3	BMI 31.6	51 (48.5)	NR	Spine neurosurgery (lumbar micro-discectomy, anterior cervical discectomy and fusion, lumbar decompression and fusion)	2	Duloxetine *vs* placebo: 30 mg for 5 days before surgery, and then 60 mg for 90 days after surgery	95
Castro-Alves and colleagues[37]	2016	42.2 [5.2]	BMI 27.3 [3.7]	63 (100)	1: 47 (74.6) 2: 16 (25.4)	Abdominal hysterectomy	2	Duloxetine 60 mg *vs* placebo 2 h before surgery and 24 h after surgery	2
Mantay and colleagues[38]	2016	55.8 [10.5]	BMI 25.33 [5]	50 (100)	1: 15 (30) 2: 34 (68) 3: 1 (2)	Modified radical mastectomy	2	Duloxetine 60 mg *vs* placebo starting the night before surgery until 7 days after surgery	8
YaDeau and colleagues[39]	2016	65 [7.3]	BMI 31.5	54 (51)	1: 6 (5.7) 2: 81 (76.4) 3: 19 (17.9)	Total knee arthroplasty	2	Duloxetine 60 mg *vs* placebo starting from day of surgery for 15 days	15
Attia and Mansour[40]	2017	46.9 [7.5]	Weight 80.8 [14.1] kg; height 165.9 [8.4] cm	54 (45)	1: 68 (56.7) 2: 32 (26.7) 3: 20 (16.6)	Lumbar laminectomy	4	Duloxetine 60 mg *vs* placebo *vs* etoricoxib 120 mg *vs* duloxetine 60 mg+etoricoxib 120 mg starting 1 h before surgery and repeated after 24 h	2
Bedin and colleagues[41]	2017	48 [13]	BMI 28 [5]	31 (54)	1: 18 (31.6) 2: 37 (64.9) 3: 2 (3.5)	Lumbar spinal fusion	2	Duloxetine 60 mg *vs* placebo starting 1 h before surgery and the following morning	2
Altiparmak and colleagues[42]	2018	53.1 [10.8]	BMI 27.7 [3.3]	58 (61.7)	1: 32 (34) 2: 62 (70)	Elective repair of lumbar disc herniation	3	Duloxetine 60 mg (once) *vs* pregabalin 75 mg *vs* placebo starting 1 h before surgery to 1 day after surgery	2
Kassim and colleagues[43]	2018	30.6 [2.0]	Weight 76.3 [4.4] kg; height 174.2 [6.2] cm	75 (100)	1: 71 (94.7) 2: 4 (5.3)	Laparoscopic gynaecological surgery for infertility	3	Duloxetine 60 mg *vs* duloxetine 60 mg+i.v. dexamethasone 0.1 mg kg^{-1} *vs* placebo at 2 h before surgery	1
El-Behairy and colleagues[44]	2019	44.4 [8.1]	BMI 22.4 [2]	27 (45)	1–2: 60 (100)	Hip surgery	2	Duloxetine 30 mg *vs* placebo starting 3	8

Continued

Result

Study characteristics

Duloxetine（n=20）

- 60 mg/day（n=15）
- 30 mg/day（n=1）　vs placebo
- 30-60 mg/day（n=3）
- 30, 60, 90 mg/day（n=1）

- Morphine
- Pentazocine + SSRI or SNRI　vs placebo
- Etoricoxib

- SNRI vs 抗けいれん薬
- Duloxetine vs Etoricoxib

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Continued

Result

Study characteristics

投薬期間

- 中央値：３日間
- 範囲：術前 - 術後 201日
  ≦3日（n=13）
  7 - 201日間（n=11）

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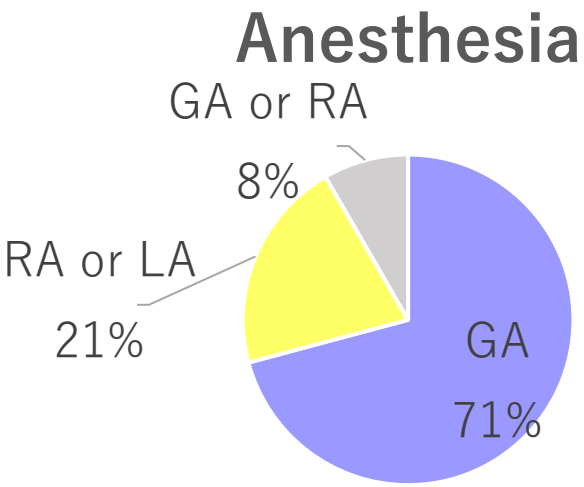
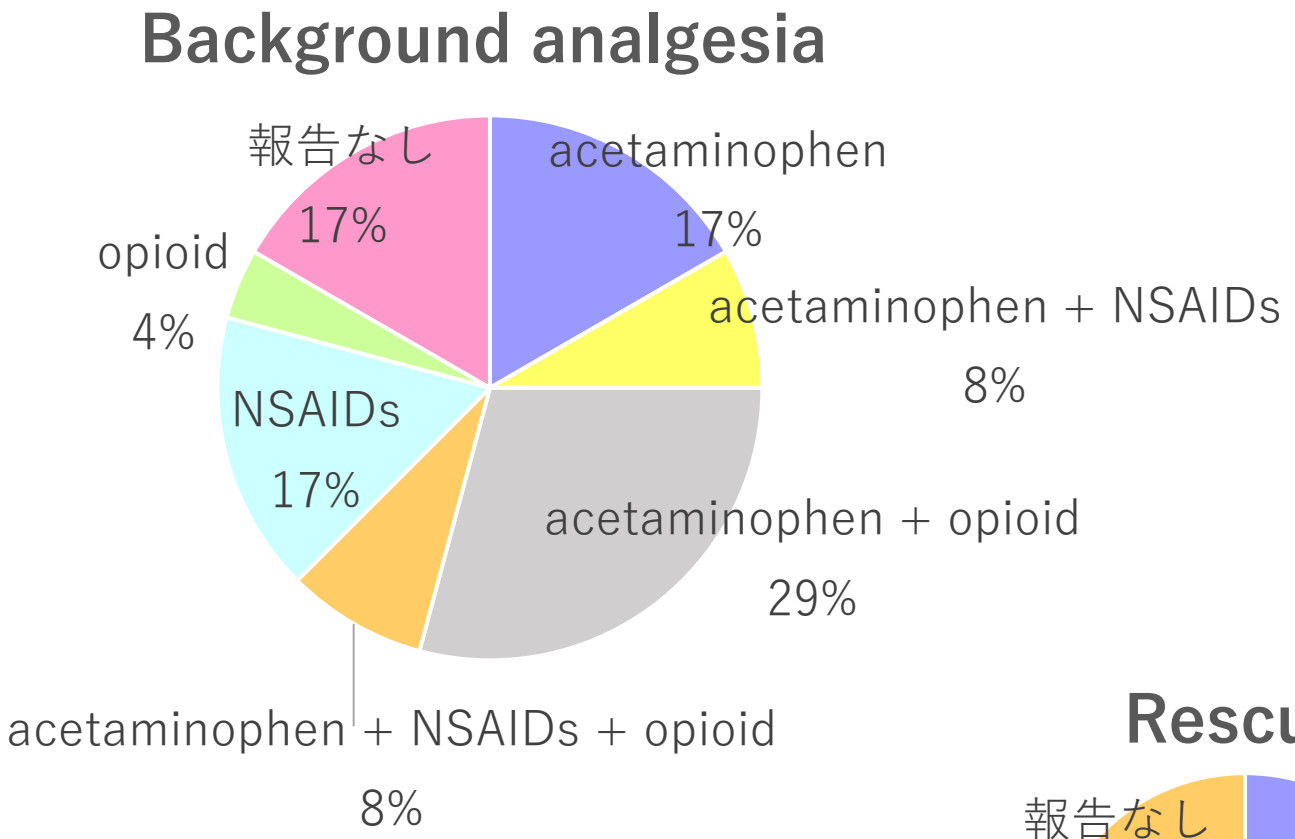
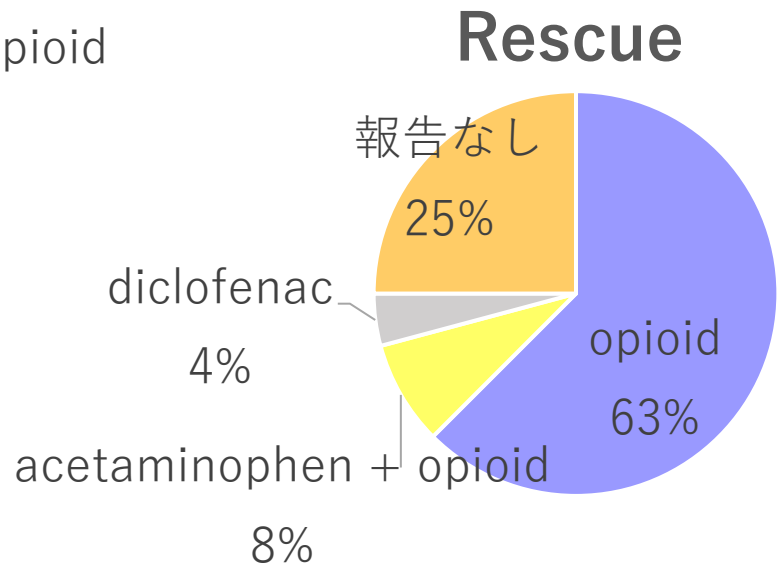
Continued

Result

Study characteristics





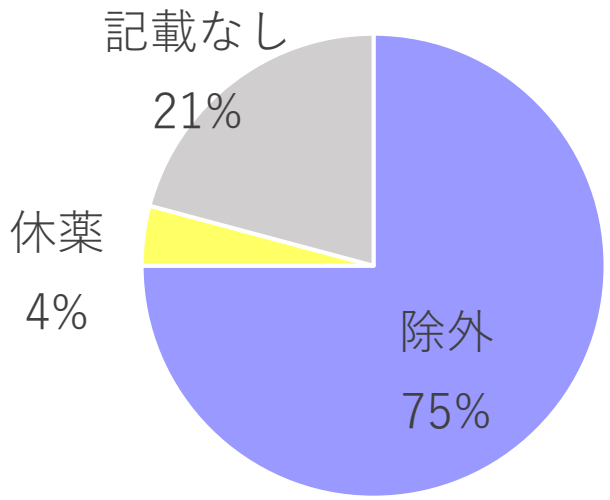


Result

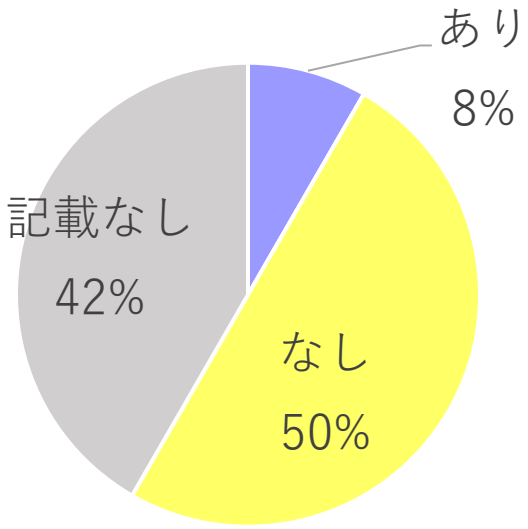
Study characteristics

- サンプルサイズ　44-368（中央値 78; IQR: 60-99）
- 平均年齢　（中央値 47.5; IQR: 43.1-57.5）
- 女性　64 %　（中央値 78%; IQR: 51-100%）
- 追跡期間　（中央値 2 day; 範囲: 6h-1yr）

精神疾患・抗うつ薬内服患者



資金提供



Result

Risk of bias

Low risk ☺

- すべてLow risk ➜ 14 trials（58%）
- ランダム化 ➜ 19 trials（79%）
- 割り付けの隠ぺい化 ➜ 23 trials（96%）
- 研究参加者の盲検化 ➜ 23 trials（96%）
- 医療提供者
データ収集者
アウトカム測定者 } の盲検化 ➜ 21 trials（88%）

High risk ☹

- 選択的アウトカム ➜ 3 trials（12%）
- 20%以上の結果を欠落 ➜ 1 trial（4 %）

Author	Year	Funding	Randomization sequence generation	Allocation concealment	Blinding of patients	Blind of caregivers	Blinding of data collectors	Blinding of outcome adjudicators	Selective outcome reporting	Proportion of loss to follow-up (%)	Overall risk of bias
Selective serotonin reuptake inhibitors (SSRIs)											
Gordon	1994	No industry funding	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0	High risk
Chocron	2013	Industry funded	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	4	Low risk
Lunn	2015	No industry funding	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	5	Low risk
Serotonin and norepinephrine reuptake inhibitors (SNRIs)											
Amr	2010	Not reported	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0	High risk
Ho	2010	Not reported	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	6	Low risk
Saoud	2013	Not reported	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	0	High risk
Nasr	2014	Not reported	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	2	Low risk
Hyer	2015	Industry funded	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	31	High risk
Castro-Alves	2016	No industry funding	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	10	Low risk
Mantay	2016	Not reported	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0	Low risk
YaDeau	2016	No industry funding	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	9	Low risk
Attia	2017	No industry funding	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0	Low risk
Bedin	2017	Not reported	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0	High risk
Altiparmak	2018	Not reported	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0	Low risk
Kassim	2018	No industry funding	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0	Low risk
El-Behairy	2019	Not reported	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0	High risk
Koh	2019	No industry funding	Low risk	Low risk	High risk	Low risk	High risk	High risk	Low risk	0	High risk
Bansal	2020	No industry funding	Low risk	High risk	High risk	High risk	High risk	High risk	Low risk	0	High risk
Bastanhagh	2020	No industry funding	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	5	Low risk
Govil	2020	No industry funding	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	5	High risk
Hatami	2020	Not reported	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	0	Low risk
Hetta	2020	No industry funding	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	8	Low risk
Sattari	2020	Not reported	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	0	High risk
Takmaz	2020	No industry funding	Low risk	Low risk	Low risk	High risk	High risk	High risk	Low risk	4	High risk

Result SSRIs/SNRIs vs placebo（Pain relief）

6 h - 6 mの術後痛を有意に減少させる
（72 h - 1 wを除いて）

Outcome	Duration of follow-up	No. of trials (no. of patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								WMD (95% CI)	RD, % (95% CI)	
Postoperative pain score on a 10 cm VAS (lower is better)*	≤6 h	18 (1126)	Not serious†	Serious I^2=78%	Not serious	Not serious	Undetected; symmetric funnel plot; Egger's test p=0.47	−0.73 cm (−1.04 to −0.42)	18 (11–25)*	Moderate
	12 h	12 (755)	Not serious†	Serious I^2=96%	Not serious	Not serious	Undetected; symmetric funnel plot; Egger's test P=0.16	−0.68 cm (−1.28 to −0.07)	20 (2–37)*	Moderate
	24 h	18 (1242)	Not serious†	Serious I^2=93%	Not serious	Not serious	Undetected; symmetric funnel plot; Egger's test P=0.77	−0.68 cm (−1.16 to −0.20)	16 (5–27)*	Moderate
	48 h	14 (935)	Not serious†	Serious I^2=95%	Not serious	Not serious	Undetected; symmetric funnel plot; Egger's test P=0.82	−0.73 cm (−1.22 to −0.23)	23 (8–37)*	Moderate
⊗	72 h	5 (447)	Not serious†	Serious I^2=96%	Not serious	Serious‡	Uncertain: only five trials	−0.75 cm (−1.78 to 0.28)	22 (−6 to 49)*	Low
⊗	1 week	5 (385)	Not serious†	Serious I^2=95%	Not serious	Serious‡	Uncertain: only five trials	−0.60 cm (−1.34 to 0.14)	12 (−3 to 26)*	Low
	10 days to 1 month	7 (814)	Not serious†	Serious I^2=93%	Not serious	Not serious	Uncertain: only seven trials	−0.71 cm (−1.11 to −0.31)	25 (12–37)*	Moderate
	3 months	5 (608)	Serious¶	Not serious I^2=79%¶	Not serious	Not serious	Uncertain: only five trials	−0.64 cm (−1.05 to −0.22)	16 (6–26)*	Moderate
	6 months	3 (508)	Not serious	Serious I^2=91%	Not serious	Not serious	Uncertain: only three trials	−0.95 cm (−1.64 to −0.25)	23 (7–38)*	Moderate

Result SSRIs/SNRIs vs placebo（Pain relief）

３ｍ＆６ｍの慢性術後痛の発生率を有意に減少させる

Outcome	Duration of follow-up	No. of trials (no. of patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								WMD (95% CI)	RD, % (95% CI)	
Chronic postoperative pain incidence	3 months	2 (90)	Not serious	Not serious I^2=0%	Not serious	Serious[§]	Uncertain: only two trials	0.33 (0.13–0.83)	−22 (−6 to −29)	Moderate
	6 months	3 (190)	Not serious	Not serious I^2=0%	Not serious	Serious[§]	Uncertain: only three trials	0.41 (0.23–0.72)	−20 (−9 to −26)	Moderate

Result SSRIs/SNRIs vs placebo (Opioid consumption and time to first rescue analgesia)

≦24 h, 48 hの術後オピオイド使用量を有意に減少させる
レスキュー使用までの時間を延長する

Outcome	Duration of follow-up	No. of trials (no. of patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								WMD (95% CI)	RD, % (95% CI)	
Opioid consumption (mg, on oral morphine equivalent dose)	≤24 h	13 (877)	Not serious†	Serious I^2=97%	Not serious	Not serious	Undetected; symmetric funnel plot; Egger's test P=0.07	−12 mg (−16 to −8)	NA	Moderate
	48 h	9 (628)	Not serious†	Serious I^2=97%	Not serious	Not serious	Uncertain: only nine trials	−10 mg (−15 to −5)	NA	Moderate
Time to first analgesia (min)	≤6 h	10 (634)	Not serious†	Serious I^2=99%	Not serious	Not serious	Undetected; symmetric funnel plot; Egger's test P=0.23	73 min (27−118)	NA	Moderate

Result SSRIs/SNRIs vs placebo
(Patient satisfaction and quality of recovery)

より良い患者満足度
（痛みのコントロール、全体的なケア）

より良い回復の質（24 h）
➜ 時間経過ともに減少（48 hが境界）

Outcome	Duration of follow-up	No. of trials (no. of patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								WMD (95% CI)	RD, % (95% CI)	
Patient satisfaction score on a 4-point Likert scale (higher is better)	12 h to 6 months	5 (305)	Not serious[†]	Serious I^2=75%	Not serious	Not serious	Uncertain: only five trials	0.49 point (0.09 −0.89)	NA	Moderate
Patient satisfaction: good or excellent	12–48 h	5 (335)	Not serious[†]	Not serious I^2=64%	Not serious	Serious[§]	Uncertain: only five trials	1.32 (1.02–1.72)	18 (1–41)	Moderate
Quality of recovery on Quality of Recovery-40 scale (higher is better)	24 h	3 (204)	Not serious	Serious I^2=86%	Not serious	Serious[§]	Uncertain: only three trials	18.21 points (9.48 −26.94)	NA	Low
	48 h	2 (140)	Serious[‖]	Not serious I^2=0%	Not serious	Serious[§]	Uncertain: only two trials	0.96 point (0.04 −1.88)	NA	Low

Result SSRIs/SNRIs vs placebo(Adverse effects)

有害事象に有意差（－）
（PONV, めまい, 眠気, 頭痛, そう痒）

Outcome	Duration of follow-up	No. of trials (no. of patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								RR (95% CI)	RD, % (95% CI)	
PONV	12 h to 2 weeks	15 (1211)	Not serious*	Not serious I^2=36%	Not serious	Serious†	Undetected; symmetric funnel plot; Harbord's test P=0.41	0.95 (0.72–1.25)	−1.0 (−5.5 to 4.9)	Moderate
Dizziness	12 h to 2 weeks	13 (1072)	Not serious*	Not serious I^2=10%	Not serious	Serious†	Undetected; symmetric funnel plot; Harbord's test P=0.82	1.33 (0.84–2.10)	2.4 (−1.2 to 8.0)	Moderate
Drowsiness	12–48 h	9 (786)	Not serious*	Not serious I^2=27%	Not serious	Serious†	Uncertain: only nine trials	1.11 (0.46–2.68)	0.5 (−2.6 to 8.1)	Moderate
Headache	12–48 h	8 (425)	Not serious*	Not serious I^2=0%	Not serious	Serious†	Uncertain: only eight trials	1.25 (0.63–2.48)	1.4 (−2.1 to 8.3)	Moderate
Pruritus	12–48 h	8 (425)	Not serious*	Not serious I^2=0%	Not serious	Serious†	Uncertain: only eight trials	0.82 (0.38–1.78)	−1.1 (−3.8 to 4.8)	Moderate

Result SNRIs vs anticonvulsants

duloxetine & venlafaxine　　gabapentin & pregabalin

3 trials(231人)

有意差（－）

痛み：2 - 4, 12, 24, 48, 72 h, 1 w, 10 d
患者満足度
PONV・めまい・頭痛

SNRIは抗けいれん薬に比べ

オピオイド消費量（24 h)↑
レスキュー使用までの時間↓
回復の質（24, 48 h)↓
そう痒↑
術後慢性痛のスコア＆オピオイド使用量（6 m)↓

Low-quality evidence

Outcome	Duration of Follow Up	# of Trials (# of Patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								WMD (95%CI)	RD (95%CI)	
Postoperative pain on a 10 cm VAS (lower is better)	2 to 4 hours	2 (161)	Serious [a]	Not serious I^2 = 0%	Not serious	Serious [b]	Uncertain: only two trials	WMD 0.13 (-0.44 to 0.69)	NA	Low
	12 hours	1 (100)	Serious [a]	Not serious	Not serious	Serious [b]	Uncertain: only one trial	WMD 0.10 (-0.39 to 0.59)	NA	Low
	24 hours	3 (231)	Serious [c]	Not serious I^2 = 63%	Not serious	Serious [b]	Uncertain: only three trials	WMD 0.37 (-0.07 to 0.81)	NA	Low
	48 hours	3 (231)	Serious [c]	Not serious I^2 = 68%	Not serious	Serious [b]	Uncertain: only three trials	WMD 0.66 (-0.7 to 2.02)	NA	Low
	72 hours	1 (100)	Serious [a]	Not serious	Not serious	Serious [b]	Uncertain: only one trial	WMD 0.10 (-0.29 to 0.49)	NA	Low
	1 week	1 (100)	Serious [a]	Not serious	Not serious	Serious [b]	Uncertain: only one trial	WMD 0.2 (0.0 to 0.4)	NA	Low
	10 days	1 (100)	Serious [a]	Not serious	Not serious	Serious [b]	Uncertain: only one trial	WMD 0.10 (-0.08 to 0.28)	NA	Low
	6 months	1 (100)	Serious [a]	Not serious	Not serious	Serious [d]	Uncertain: only one trial	WMD -0.90 (-1.26 to -0.54)	NA	Low
Use of opioid for pain management at 6 months	6 months	1 (100)	Serious [a]	Not serious	Not serious	Serious [d]	Uncertain: only one trial	RR 0.47 (0.22 to 0.99)	-18% (-0.3% to -26%)	Low
Opioid consumption (mg)*	24 hours	1 (100)	Serious [a]	Not serious	Not serious	Serious [d]	Uncertain: only one trial	WMD 19 mg (18 to 20)	NA	Low
Quality of recovery on Quality of recovery-40 scale (higher is better)	24 hours	1 (70)	Serious [e]	Not serious	Not serious	Serious [d]	Uncertain: only one trial	WMD -6.00 (-8.80 to -3.20)	NA	Low
	48 hours	1 (70)	Serious [e]	Not serious	Not serious	Serious [d]	Uncertain: only one trial	WMD -7.00 (-8.39 to -5.61)	NA	Low
Time to first analgesia (minutes)	24 hours	2 (161)	Serious [a]	Not serious I^2 = 53%	Not serious	Serious [d]	Uncertain: only two trials	WMD -40 minutes (-71 to -10)	NA	Low
PONV	48 hours	2 (131)	Serious [c]	Not serious	Not serious	Serious [b]	Uncertain: only two trials	RR 1.59 (0.94 to 2.69)	14% (-1% to 41%)	Low
Dizziness	48 hours	2 (131)	Serious [c]	Not serious I^2 =0%	Not serious	Serious [b]	Uncertain: only two trials	RR 1.99 (0.86 to 4.62)	9% (-1% to 33%)	Low
Headache	48 hours	1 (70)	Serious [e]	Not serious	Not serious	Serious [b]	Uncertain: only one trial	RR 3.00 (0.89 to 10.16)	17% (-1% to 79%)	Low
Pruritis	48 hours	1 (70)	Serious [e]	Not serious	Not serious	Serious [d]	Uncertain: only one trial	RR 5.00 (1.18 to 21.19)	23% (1% to 115%)	Low
Patient satisfaction	48 hours	1 (70)	Serious [e]	Not serious	Not serious	Serious [b]	Uncertain: only one trial	RR 0.73 (0.51 to 1.05)	-20% (-36% to 4%)	Low

Result SNRIs vs NSAIDs

duloxetine　　etoricoxib

1 trial(60人) 腰椎椎弓切除術

有意差（－）

術後痛（6, 12, 24, 48 h）
オピオイド消費量（24, 48 h）
レスキュー使用までの時間
患者満足度
PONV・めまい・眠気・頭痛・そう痒

Low-quality evidence

Outcome	Duration of Follow Up	# of Trials (# of Patients)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Treatment association (95% CI)		Overall quality of evidence
								WMD (95%CI)	RD (95%CI)	
Postoperative pain on a 10 cm VAS (lower is better)	6 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	WMD -0.50 (-1.09 to 0.09)	NA	Low
	12 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	WMD 0.0 (-0.37 to 0.37)	NA	Low
	24 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	WMD 0.50 (-0.04 to 1.04)	NA	Low
	48 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	WMD 0.0 (-0.37 to 0.37)	NA	Low
Opioid consumption (mg)*	24 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	WMD -5 mg (-10 to 0.5)	NA	Low
	48 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	WMD -0.8 mg (-6 to 4)	NA	Low
Time to first analgesia (minutes)	24 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	WMD -14 minutes (-30 to 3)	NA	Low
PONV	48 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	RR 1.0 (0.4 to 2.5)	0% (-14% to 35%)	Low
Dizziness	48 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	RR 2.0 (0.40 to 10.11)	7% (-4% to 61%)	Low
Drowsiness	48 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	RR 2.0 (0.19 to 20.9)	3% (-3% to 66%)	Low
Headache	48 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	RR 1.67 (0.44 to 6.36)	7% (-6% to 54%)	Low
Pruritis	48 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	RR 0.75 (0.18 to 3.07)	-3% (-11% to 28%)	Low
Patient satisfaction	24 hours	1 (60)	Not serious	Not serious	Not serious	Very serious [a]	Uncertain: only one trial	RR 0.94 (0.68 to 1.30)	-5% (-24% to 23%)	Low

Result

Small study effects ➜ 検出されず

Subgroup analysis, meta-regression, and sensitivity analysis

サブグループ解析・メタ回帰分析

- SNRI vs SSRI
- 治療期間　≦3日 vs ＞3日
- バイアスリスク（high vs low）
- 痛みスコア（試験終了時 vs スコアの変化）
- 手術の種類
- 麻酔の種類
- 患者満足度（疼痛管理 vs 全体的なケア）

結果は変わらず

感度分析

- DerSimonian-Laird法 ➜ Hartung-Knapp-Sidik-Jonkman法
- 安静時痛 ➜ 体動時痛
- 嘔気 ＋ PONV ➜ PONV

結果は変わらず

SSRI/SNRI vs placebo

- 慢性術後疼痛スコア（6 m）
- 発生率（3, 6 m）
- 患者の満足度

➜ 有意差（－）

Discussion　Main findings

Moderate-quality evidence
(SSRI/SNRI　vs placebo)

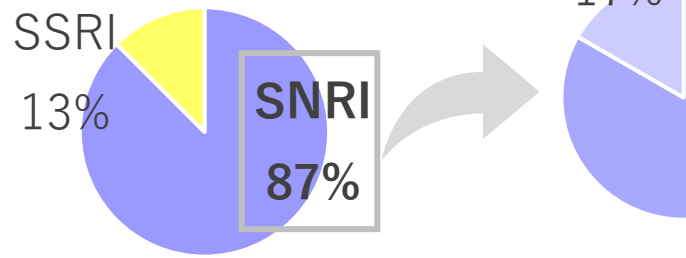
- 急性・慢性術後痛⬇（VAS 0.64-0.95 cm⬇）
- 慢性術後痛：発生率 20%
- オピオイド消費量⬇（24 h: 12 mg⬇, 48 h: 10 mg⬇）
- レスキュー使用までの時間が遅い ＝ オピオイド節約効果（＋）
- 有害事象 ~~⬆~~ ＋ わずかに患者満足度⬆

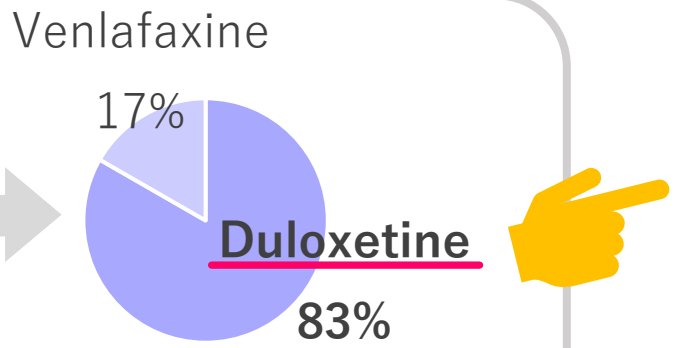
Low-quality evidence
（術後痛）

- duloxetine or venlafaxine ＝ gabapentin or pregabalin(≦10 d)
- duloxetine ＝ etoricoxib

対象：**成人**の外科患者

24 eligible trials





小児やDuloxetine以外では
適用されるもしれないが、
されないかもしれない…

Discussion

Strengths 💪

- すべての言語で検索
- + 11 trials
- 急性 & 慢性術後痛への効果
- ＋ 感度解析・サブグループ分析・メタ回帰
- DerSimonian-Laird法 ＋ Hartung-Knapp-Sidik-Jonkman法
- 個々のtrialでバイアスリスク評価
  ➜ GRADEアプローチでエビデンスの質を評価

Discussion

limitations ⚠

- 小児・青年は調査していない。
- 手術の種類・周術期の薬物療法・研究方法に異質性（＋）
- 有意なサブグループ効果を覆い隠している可能性（＋）
- 結果のいくつかは、95％CIが広く、下限に近い ➜ 有意差がなくなる可能性（＋）
- 最適なSSRI/SNRIの種類、投与時期・期間・量を調査していない。

Discussion　Relation to other studies

- ✓ Pain relief
- ✓ Opioid consumption
- ✓ Statistical analysis

以前のシステマティックレビュー

- 13 trialsのみ
- Duloxetineの急性期（≦術後 48 h）の効果のみ
- 痛みとオピオイド消費量（24 h, 48 h）のエビデンスを不適切に低く評価
- SMD（標準化平均差）*

今回のシステマティックレビュー

- 24 trials
- SSRI / SNRIの亜急性・慢性の効果（10 d - 6 mで痛み↓）
- 痛みとオピオイド消費量（24 h, 48 h)↓
- 検定力× ➜ 3 d, 1 wで痛みに有意差（−）
- 連続アウトカム ➜ 一般的なスケールに変換
- ~~SMD~~ ➜ WMD

Moderate-quality evidence

Low-quality evidence

＊SMDは異質性に弱い

Discussion

Relation to other studies

- ✓ Adverse effects
- ✓ Patient satisfaction

以前のシステマティックレビュー
- 患者の満足度：有意差（−）
- Duloxetine：PONVのリスク↓(1 trialのみ)

今回のシステマティックレビュー

SSRI / SNRI vs placebo

- 患者満足度↑
- 有害事象に有意差（ー）
  - 嘔気と嘔吐が別々に報告された場合は嘔気（嘔吐よりも高頻度）のみを使用

Moderate-quality evidence

Low-quality evidence

Discussion

Relation to other studies

- ✓ Subgroup analysis
- ✓ meta-regression

以前のシステマティックレビュー
- Duloxetine：乳がん患者のオピオイド消費量（24 h, 48 h)↓
  （1 trialのみ）

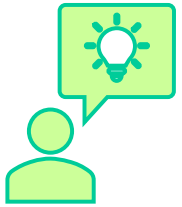
今回のシステマティックレビュー

サブグループ効果（ー）

SSRIはSNRIより…
- 術後痛を軽減する効果が少ない傾向
- SSRIのtrialは非常に数が限られている

➜ RCTが必要

Conclusion



- ✓ 標準的な周術期ケアの補助薬としてのSSRI/SNRIの使用は、有害事象を増加させることなく、急性・慢性の術後疼痛とオピオイド消費量をわずかに減少させ、患者満足度をわずかに改善する。
- ✓ エビデンスが非常に限られており、SSRIの効果は確定的ではない。
- ✓ 将来的には、SSRI/SNRIの効果の検証と、特定の手術に対する最適な薬剤の種類・投与時期・期間・量、およびSNRI、SSRI、その他の鎮痛薬の有効性の比較検討をするために、質の高いRCTが必要である。