Gabapentin and Pregabalin for the Acute Post-operative Pain Management. A Systematic-narrative Review of the Recent Clinical Evidences†

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Abstract: Background: Gabapentin and pregabalin inhibit Ca^{2+} currents via high-voltage-activated channels containing the $\alpha 2\delta$-1 subunit, reducing neurotransmitter release and attenuating the postsynaptic excitability. They are antiepileptic drugs successfully used also for the chronic pain treatment. A large number of clinical trials indicate that gabapentin and pregabalin could be effective as postoperative analgesics. This systematic-narrative review aims to analyse the most recent evidences regarding the effect of gabapentinoids on postoperative pain treatment.

Methods: Medline, The Cochrane Library, EMBASE and CINHAL were searched for recent (2006-2009) randomized clinical trials (RCTs) of gabapentin-pregabalin for postoperative pain relief in adults. Quality of RCTs was evaluated according to Jadad method. Visual analogue scale (VAS), opioid consumption and side-effects (nausea, vomiting, dizziness and sedation) were considered the most important outcomes.

Results: An overall of 22 gabapentin (1640 patients), 8 pregabalin (707 patients) RCTs and seven meta-analysis were involved in this review. Gabapentin provided better post-operative analgesia and rescue analgesics sparing than placebo in 6 of the 10 RCTs that administered only pre-emptive analgesia. Fourteen RCTs suggested that gabapentin did not reduce PONV when compared with placebo, clonidine or lornoxicam. Pregabalin provided better post-operative analgesia and rescue analgesics sparing than placebo in two of the three RCTs that evaluated the effects of pregabalin alone vs placebo. Four studies reported no pregabalin effects on preventing the PONV.

Conclusion: Gabapentin and pregabalin reduce pain and opioid consumption after surgery in confront with placebo, but comparisons with other standard post-operative regimens are not sufficient. Gabapentin and pregabalin seem not to have any influence on the prevention of PONV.

INTRODUCTION

Gabapentin (GBP) [1-(aminomethyl)cyclohexaneacetic acid] – an alkylated analogue of gammaaminobutyric acid (GABA) was introduced in 1993 in Europe and the following year in USA. It was first developed as an anticonvulsant drug and than the GBP potentials as an analgesic drug for the treatment of the neuropathic pain was described in mid 1990s [1, 2]. Pregabalin (PGL) [(S)-(+)-3-(aminomethyl)-5- methylhexanoic acid] was indroduced in Europe and USA a decade after the GBP approval and has a similar pharmacological alkylated GABA analogue structure.

Pharmacology

Similar, in few pharmacological aspects but, different in others, both GBP and PGL produce several pharmacological effects, including interaction with L-amino acid transporter (important for absorption from gastrointestinal tract and distribution across blood-brain barrier) [3, 4], inhibition of Ca^{2+} currents via high-voltage-activated channels containing the $\alpha 2\delta$-1 subunit, leading in turn to reduced neurotransmitter release and attenuation of postsynaptic excitability [5-10]. The decreased Ca^{2+} influx reduces also the excitatory aminoacid [ex: glutamate] and substance P release, leading to suppression of neuronal excitability following nerve or tissue injury [11]. However, their antinociceptive effects occur primarily in the setting of neural sensitization after nerve or tissue injury and it seems to be minimal on normal physiological pain transmission [12].

A recent study in both laboratory animals and humans suggest an interaction between GBP and spinal alpha-2-adrenergic receptor systems in the rat and, furthermore, that GBP administration reduces cerebrospinal fluid norepinephrine levels in humans [13].

GBP exerts its analgesic action through a negative indirect interaction with the glycine binding site of NMDA receptors [14, 15]. SV2A, a ubiquitous synaptic vesicle glycoprotein that may prepare vesicles for fusion and serves as the target for levetiracetam and its analog brivaracetam (which is currently in late-stage clinical development) [16].

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Table 1. Gabapentin and Pregabalin, Both Similar and Different on Mechanisms of Action, Pharmacokinetics, Interactions with Other Drugs, Uses, Dosage and Side Effects

	Gabapentin	Pregabalin
Year of approval	1993 in UK and Europe,1994 in USA	2004 in UK, Europe and USA
Structure	2[1(aminomethyl)cyclohexyl]acetic acid (GABA analogue)	(*S*)-3-(aminomethyl)-5-methylhexanoic acid (GABA analogue)
Mechanisms of action	· Interaction with L-amino acid transporter (important for absorption from gastrointestinal tract and distribution across blood-brain barrier) [3, 4] · Activation of $GABA_B$ receptor (controverse) [17-19] • Inhibition of Ca^{2+} currents via high-voltage-activated channels containing the α2δ-1 subunit, reducing neurotransmitter release and attenuation of postsynaptic excitability [5-10]. The decreased Ca^{2+} influx reduces also the excitatory aminoacid (ex: glutamate) and substance P release, leading to suppression of neuronal excitability after nerve or tissue injury [11] and decrease AMPA receptor activation and noradrenaline release in the brain [97]. Interaction with spinal α-2-adrenergic receptor systems in the rat, and GBP administration reduces cerebrospinal fluid norepinephrine levels in humans [13]. • GBP exerts its analgesic action through a negative indirect interaction with the glycine binding site of NMDA receptors [14, 15]. · SV2A, a ubiquitous synaptic vesicle glycoprotein that may prepare vesicles for fusion and serves as the target for levetiracetam and its analogue brivaracetam (which is currently in late-stage clinical development) [16]. · K_v7/KCNQ/M - K^+ channels that mediate the M-current, which acts a brake on repetitive firing and burst generation [16].	· Interaction with L-amino acid transporter (important for absorption from g.i. tract and distribution across blood-brain barrier) [3, 4] · No evidence of interaction with $GABA_B$ receptor [20] • Inhibition of Ca^{2+} currents via high-voltage-activated channels containing the α2δ-1 subunit, leading in turn to reduced neurotransmitter release and attenuation of postsynaptic excitability [5-10] · The decreased Ca^{2+} influx reduces excitatory aminoacid (ex: glutamate) release leading to decreased AMPA receptor activation and noradrenaline relase in the brain [97]. · Inhibitory modulation in neocortex, amygdale e hippocampus [21].
Pharmaco-kinetics	• Available only as oral preparation. • Absorption dependent by a saturable L-amino acid transport: the bioavailability of GBP varies inversely with dose: 300 mg= 60%; 600 mg= 40%; 1600 mg=35% (steady state). • Plasma peak = 2.7-2.99 mg/l achieved 3-3.2 h after ingestion of 300 mg (because of the dose-dependent absorption, plasma peak increases less than threefold when the dose is tripled) • Volume of distribution: 0.6-0.8 l/Kg; cerebrospinal fluid concentration: 20% of plasma concentration; brain issue concentration: 80% the plasma level. • No hepatic metabolism and it is eliminated unchanged in the urine with first order kinetic mechanism • Elimination half-life: 4.8-8.7 h. • No microsomal enzyme induction. [90, 91, 98-100]	• Available only as oral preparation. • Absorption not saturable (linear pharmacokinetic profile) • Plasma peak (0.04–9.46 mg/L) reached in within 1 h. • Average bioavailability> 90% independent of dose. • Elimination half-life: 5.5-6.7h (independent of dose). • No hepatic metabolism and renal excreted (98% unchanged in urine, 0.9%N-methylated derivative); elimination proportional to creatinine clearance. [92, 93, 101]
Interactions	• No pharmacokinetic interaction with anticonvulsivant drugs [90] • Cimetidine decrease clearance of GBP (because decrease glomerular filtration) of 12% [90] • Antacids reduce bioavailability of GBP when given until 2h post its administration [102].	• No pharmacokinetic interactions • Concurrent intake reduces peak plasma levels by 25–30% and increases the time to peak by 3 hours [92, 93, 101]
Uses	General tonic-clonic seizure, partial seizures, peripheral neuropathic pain, diabetic peripheral neuropathy, post-herpetic neuralgia and acute pain [22].	Peripheral neuropatic pain, partial seizures, diabetic peripheral neuropathy, posterpetic neuralgia, general anxiety disorders, fibromyalgia and acute pain [21].
Dosage and administration	• To give 3 time/day because of the short half-life • Epilepsy in adults 2400 mg/day; • Epilepsy in children 25-35 mg/kg/day • Neuropathic pain: 900-3600 mg/day	• Neuropathic pain: 150-600 mg thrice a day • Acute pain: 50-300 mg/day • Fibromyalgia: 150-300 mg/day
Side effects	· Somnolence (15,2%), dizziness (10.9%), asthenia (6%), convulsions (0.9%), reversible acute renal allograft dysfunction and exacerbation of myasthenia gravis [22] • More frequent nausea and vomiting than PGL [21]	· Somnolence (22%), dizziness (29%), convulsions, weight gain, myoclonus, aterixis and gynecomastia [21]

K_v7/KCNQ/M - K^+ channels that mediate the M-current, which acts a brake on repetitive firing and burst generation [16]. Activation of $GABA_B$ receptor by GBP is almost controversial [17-19], meanwhile no evidence of interaction with $GABA_B$ receptor is reported for PGL [20]. Inhibitory modulation of PGL is also exerted in neocortex, amygdale e hippocampus [21]. A summery of GBP and PGL similarities and differences on mechanisms of action, pharmacokinetics, interactions with other drugs, uses, dosage and side effects is reported in Table **1**.

Gabapentinoids Indication for Use

These anticonvulsants have been used for the treatments of a wide variety of disorders including general tonic-clonic seizure, partial seizures, peripheral neuropathic pain, diabetic peripheral neuropathy, post-herpetic neuralgia and acute pain [22]. Furthermore, GBP and PGL seem to be effective on various forms of pruritus, including uraemic pruritus, intractable hiccups and hot flushes in post-menopausal women [23]. With respect to the GBP benefits on phantom

limb pain the opinions are inconclusive. Bone *et al*. reported that GBP was efficacious to treat this syndrome [24] in discordance with other authors [25, 26]. GBP has been used also for attenuating haemodynamic response to tracheal intubation [27, 28] and on reducing postoperative delirium [28], and like an alternative to benzodiazepines in the treatment of alcohol withdrawal [29].

The first published PGL randomised clinical trials (RCTs) in 2001 [30], and the first published GBP RCTs in 2002 [31, 32] reported cheering results for the treatment of the post-operative pain. The following years, several authors reported their experiences regarding the use of GBP [33-68] and PGL [69-76] for the post-operative pain management.

The main objective of this review is focusing the attention on the recent evidences for the analgesic properties and the adverse effects of GBP and PGL as treatment for the post-operative pain.

METHODS

The Selection of the Studies

The articles research was performed using MEDLINE, Cochrane Controlled Trials Register (CCTR), EMBASE, and CINAHL databases. Reference lists of the retrieved articles were also searched. The period of publication were established from 1990 to 2009. The first studies of PGL use after major surgery pain management were published in 2006 and furthermore previous systematic narrative [11, 28, 77, 78] or meta-analytic [79-85] reviews reported data from GBP clinical trials until 2006 (included). A total of three trials on PGL use for post-operative pain management [30, 69, 71] have been included in only one review [11] and the other three [77-79] included only one trial on postoperative dental pain published in 2001 [30]. Thus, we decided to take in consideration only recent (from 2006-2009) RCTs which investigated the analgesic effects of GBP or PGL in adult patients (age range 18 years and above) underwent to surgical procedures. Trials were included if they were randomized, double-blind, active or placebo controlled, had at least 10 subjects per study group, and reported both analgesic consumption and pain scores. Trials studying both pre and post - operative GBP or PGL were included, also if these drugs were part of a multimodal technique. Works that reported information about use of GBP and PGL in different settings (treatment of epilepsy, neuropathic pain, and other type of pain or that produced by other drugs), non-randomised or experimental pain studies, case reports, and clinical observations and editorials were excluded. No language restrictions were applied and no investigators were contacted. Abstracts published in congresses acts and unpublished studies were not considered. The following search terms were included: gabapentin; pregabalin; postoperative pain; postoperative analgesia; pain measurement; postoperative nausea and vomiting; postoperative outcome. The reference lists of the selected studies and reviews were checked for additional citations. The last search was performed on 30 April 2009.

Literature Information, Outcome Measures

The following information were collected: 1) publication details, 2) patient population, number of patients, age, sex (male/female), settings and surgical procedure, 3) study design, description of drugs administration and follow-up, 5) intra- and postoperative analgesics and type of administration, 6) outcome measures, pain and analgesic consumption, 7) withdrawals and adverse effects. Bibliographic research was performed and data were collected independently by three investigators (S. F, L. C, R. C) and reviewed by the others (M. D, A. G., AF. S). In order to measure the likelyhood of bias in pain research reports, the Jadad score calculation was performed for each of clinical trials included in the review (Table **2**) [86].

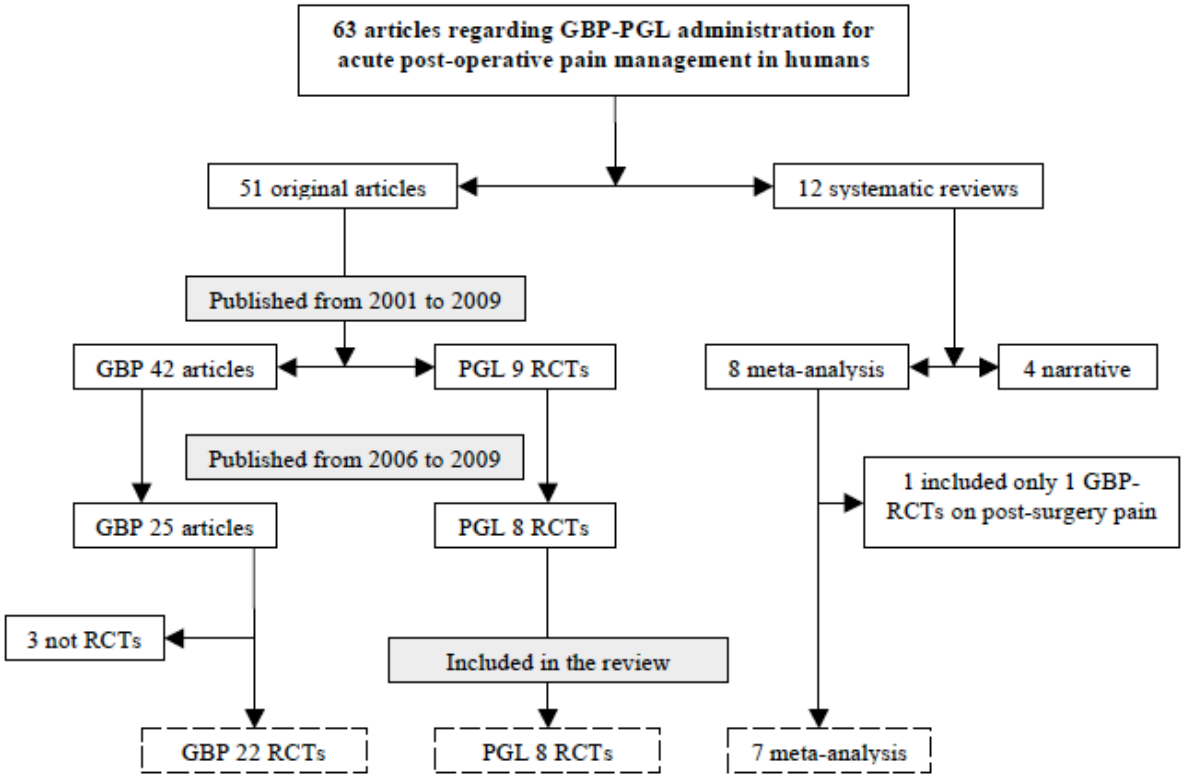
RESULTS

Post-surgical Pain

At the time of writing, we found an overall of 50 original works that reported the gabapentinoids use in 4248 surgical patients [31-76, 87-89]. Nine of them studied the effects of PGL [30, 69-76] and the other 41 those of gabapentin [31-68, 87-89] in different surgical settings as gynaecological, abdominal, neurosurgery, musculoskeletal, thoracic, head, neck and breast. Gabapentin studies involved totally 3343 patients, 1514 of them received gabapentin and were confronted with 282 patients who received combination of

Table 2. Jadad Score Calculation (from 0 to 5). Instrument to Measure the Likelihood of Bias in Pain Research Reports

	Items (based on randomization, blinding, and dropout)	**Score, Yes/No**
1	Was the study described as randomized (this includes words such as randomly, random, and randomization)?	1/0
	Give 1 additional point if: the method to generate the sequence of randomization was described and it was appropriate (table of random numbers, computer generated, etc.)	1/0
	Deduct 1 point if: the method to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.)	-1/0
2	Was the study described as double blind?	1/0
	Give 1 additional point if: the method of double blinding was described and it was appropriate (identical placebo, active placebo, dummy, etc.)	1/0
	Deduct 1 point if: the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	-1/0
3	Was there a description of withdrawals and dropouts?	1/0



GBP - gabapentin
PGL - pregabalin
RCTs - randomised clinical trials

Fig. (1). Flow chart of the review.

gabapentin and other analgesic, 389 patients who received other analgesics and with 1158 patients receiving placebo as controls. PGL studies involved totally 905 patients, 323 of them received gabapentin and were confronted with 194 patients who received combination of PGL and other analgesic, 137 patients who received other analgesics and with 251 patients receiving placebo as controls. Furthermore, we found a total of 4 systematic narrative [11, 28, 77, 78] and 7 meta-analytic [79-85] reviews reporting information from RCTs on gabapentin and PGL use for the treatment of post-operative pain, published from 2004 to 2008. The flow chart in the Fig. (**1**) reports generally the selection of the studies included.

This review focuses particularly the attention to the 25 gabapentin [47-68, 87-89] and 8 PGL [31-76] studies published from 2006 to 2009, which involved a total of 2668 patients and to the meta-analysis [79-85].

Gabapentin RCTs

Three of the 25 gabapentin studies were not RCTs [87-89]. Nissman's *et al.* work was a prospective cohort study that included a total of 141 patients and reported information about analgesic properties of gabapentin after keratectomy [88], meanwhile Parsa *et al.* analyzed the gabapentin and celecoxib combination in aesthetic surgery (118 patients) [89]. In all these works the results were then compared with previous data as control patients concluding that gabapentin administration significantly reduces postoperative pain and opioid requirements. Van Elstraete, found that the median effective dose of pre-emptive gabapentin on postoperative morphine consumption after posterior lumbar spinal fusion was 21.7 mg kg^{-1} (95%CI: 19.9 –23.5 mg kg^{-1}) [87]. More detailed information regarding each of 22 gabapentin RCTs (an overall of 1640 patients) included in the review is reported in Table **3**. There has been tested a large modality of GBP administration for post-surgical analgesia. All the RCTs administered pre-emptive gabapentin or its combination with other analgesic drugs. Thirteen of all presented RCTs evaluated pre (10 RCTs) [50, 52, 54, 56, 58, 61, 63, 64, 67, 68] and both pre/post-operative (3 RCTs) [48, 49, 59] doses of GBP alone vs placebo patients. Eight RCTs studied gabapentin in confront with other analgesics (dexamethasone, lornoxicam, celecoxib, rofecoxib, acetaminophen, clonidine); five of them used only pre-emptive analgesia [53, 55, 57, 62, 65] and 3 considered both pre and post-operative mixture administration [47, 51, 66]. Only one work confronted different dosages of pre-emptive gabapentin, concluding that increasing the dose of gabapentin (300 to 1200 mg), appears to significantly decrease the severity of postoperative pain and total fentanyl consumption during the first 24 hours after myomectomy [60]. Variable GBP pre-emptive doses from 300 mg to 1600 mg were administered achieving the highest dosage of 3200 mg/day at the surgery day in one RCT [59]. No studies considered the comparison of pre-emptive and post-incisional or post-surgery GBP administration. The follow up period was no more than 24 h in thirteen studies [50, 53-58, 60-63, 67, 68]. In the other

nine studies the patients' observation varied from 2 to 7 POD [47-49, 51, 52, 59, 64-66], and four of them inter-viewed the patients by phone also one month [48, 59, 66] and three month [47] post-surgery. No studies established the optimal post surgical GBP treatment duration. Pain assessment has been performed using a Visual Analogue Scale (VAS) in 18 RCTs [48, 50, 52-67], meanwhile three studies used a 11-point [47, 49] or 4-point [51] Verbal Rating Scale (VRS). One study did not consider pain evaluation but only post-operative PCA fentanyl consump-tion, focusing the attention to the anti-emetic gabapentin effects [68]. One study assessed the pain only at rest [56], eleven RCTs evaluated pain both at rest and on movement [48, 50, 51, 53, 55, 58, 59, 61, 63, 64, 66] and the remaining 9 works did not specify whether pain was measured at rest or with movement [47, 49, 52, 54, 57, 60, 62, 65, 67]. The total rescue analgesics consumption has been used as another outcome for the assessment of the post-operative analgesia efficacy. In nine works the patients have been instructed to use an i.v. PCA pump with morphine [47, 48, 53, 55, 59, 62, 65] or fentanyl [64, 68] without continuous infusion. Seven studies reported i.v. morphine [50, 52, 56] or fentanyl [54, 60, 66, 67] boluses on demand administered by the personnel. Two RCTs used an epidural PCA pump with [61] or without continuous anaesthetic infusion [49]. Other rescue analgesics have been administered on demand in 13 studies that was alone [51, 57, 58, 63] or in adjunction to the previous i.v. opioid boluses [47, 48, 52, 54, 59, 64, 66] or epidural PCA [49, 61]. Furthermore, three RCTs have treated all the patients with a standard analgesic regimen as well as the on demand therapy [51, 52, 64]. Three studies [52, 54, 56] registered also the time elapsed from the end of the surgery to the first analgesic demand as a further outcome.

Table 3. Gabapentin for the Postoperative Pain Management. Randomized Clinical Trials

Author, year, setting, Jadad score reference	Demographics, sample size, dosing, active/control, follow-up	Anaesthesia, Intra-operative and post-operative analgesics	Main results
Abdominal and pelvic surgery			
Turan, 2006. **Setting** abdominal hysterectomy. **Jadad score** 5 **Reference** 47	**Sex:** All females **Age: A**, 53±13; **B,** 50±11 **C,** 49±14; **D,** 51±11 **Drugs administration:** Orally 1 h before surgery. Than, the same dosage at the 1st and 2nd POD. **Group A (*n*=25):** GBP 1.2 g + PL, **Group B (*n*=25):** rofecoxib 50 mg + PL. **Group C (*n*=25):** GBP 1.2 g + rofecoxib 50 mg **Group D (*n*=25):** PL **Follow up:** at 1, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 60, and 72 h	**Anaesthesia:** General anesthesia. **Intraoperative:** IV fentanyl, 2 μg kg^{-1} and morphine, 2 mg. **Post-operative:** PCA IV with morphine 2 mg bolus, 10 min lockout interval. Oral acetaminophen 500 mg + codeine 30 mg on demand.	Lower pain scores at rest in groups A, B and C vs D at 4 h, 8 h, 16 h and 20 h (all $p<0.05$) and in groups A and C at 12 h ($p<0.001$) and 24 h ($p<0.05$). The pain with movement was lower in group A at 4 h ($p<0.01$), in groups A, B and C at 8 h (all $p<0.05$) and in groups A and B at 20 h ($p<0.05$) vs group D. Reduced morphine consumption in groups A, B and C at 1, 8, 24, and 30 h after surgery (all $p<0.05$). Total PCA morphine use was decreased by 24%, 43%, and 50% in groups A, B and C vs D. Shorter period of time of opioids requirement in group C vs D. Less oral analgesic consumption in groups B and C vs D. At the 72-h follow-up, all of the patients in group C were completely satisfied vs 32%, 64%, and 72% in groups D, B, and A. Less nausea in group C vs group D, (all $p<0.05$). Ambulation, hospitalization, and recovery's quality were not different.
Bartholdy, 2006 **Setting** laparoscopic sterilization **Jadad score** 5 **Reference** 53	**Sex:** All females **Age: A**, 37 (28–45); **B,** 38 (27–45) **Drugs administration:** Orally 30 min before surgery. **Group A (*n*=38):** GBP 1.2 g + lornoxicam 8 mg, **Group B (*n*=38):** lornoxicam 8 mg + PL **Follow up:** 2h and 4h.	**Anaesthesia:** General anaesthesia **Intra-operative:** remifentanil 0.4 μg·kg-1 min^{-1}, alfentanil 0.5 mg i.v. **post-operative:** PCA morphine, 5 mg initial bolus, supplemental bolus doses of 2.5 mg, 10 min lock-out.	Thirty-two (84%) patients in group A and 37 (97%) patients in group B did require morphine, ($p=0.049$). No difference in the morphine consumption (group A, 10.5±7.1 vs B 13.7±7.4 mg, $p=0.06$) and on VAS. VAS at rest: **At 2h:** group A 13 (7–28) vs B 22.5 (11–35), $p=0.06$; **At 4h:** group A, 4 (0–10) vs B, 6 (1–11), $p=0.22$ VAS on movement: **At 2h:** group A 8 (4.5–26) vs B 20(6.5–29), $p=0.26$; **At 4h:** group A, 3 (0–10) vs B, 5 (1–14) $p=0.49$. Side-effects were similar between groups.
Durmus, 2007 **Setting** abdominal hysterectomy: **Jadad score** 5 **Reference** 55	**Sex:** All females **Age: A**, 48±7; **B,** 49±6; **C,** 48±7 **Drugs administration:** Orally 1 h before the anaesthesia **Group A (n=25):** GBP 1.2 g **Group B (n=25):** GBP 1.2 g + acetaminophen 20 mg kg^{-1} **Group C (n=25):** PL **Follow up:** 1, 2, 4, 6, 24 h	**Anesthesia:** general anesthesia **Intraoperative:** fentanyl 1 μg kg^{-1} at induction, 5 mg morphine 15 min before the end of surgery **Post-operative:** PCA morphine 2 mg bolus, 15 min lock-out, 35 mg maximum 4 h limit.	Higher morphine consumption in group C vs A and B ($p<0.05$), and higher morphine consumption in group A vs B ($p<0.05$) at all time points. Higher VAS scores at rest and at movement at all time points in group C vs A and B ($p<0.05$). SpO_2 at 24 h was lower in group C vs A and B ($p<0.05$). Lower sedation in group C vs A and B until 4 h ($p<0.05$). Higher sedation in group C vs A and B at 24 h, the difference was only statistically significant for group B ($p<0.05$). At all time points, the patient dissatisfaction scores were higher in group C vs groups A and B ($p<0.05$). No significant difference in terms of the side-effects.

(Table 3). contd…..

Author, year, setting, Jadad score reference	Demographics, sample size, dosing, active/control, follow-up	Anaesthesia, Intra-operative and post-operative analgesics	Main results
Fassoulaki 2006; **Setting** abdominal hysterectomy **Jadad score** 5 **Reference** 48	**Sex:** all females **Age: A,** 42±5.6**; B,** 42±6.2 **Drugs administration:** orally, starting at 12.00 pm the day before surgery, than every 6h until the 5th POD **Group A (*n=30):*** GBP 400 mg **Group B (*n=30*)**: PL **Follow up:** at 2, 4, 8, 24, 48, 72, 96, 120 h, and 1 month by phone.	**Anaesthesia:** general anesthesia **Intra-operative:** fentanyl 5 μg kg^{-1} at induction. No other analgesics were described **Post-operative:** PCA with morphine 1mg ml^{-1}, bolus 1mg, lock out of 7 min; acetaminophen 300 mg+ codeine 30 mg	No differences in morphine consumption at each time point and totally in the first 48h (p=0.09). **At 2h:** A, 9.0±4.3; B, 9.7±3.5. **At 4h:** A, 10.5±4.4; B, 13.4±5.1. **At 8h:** A, 13.5±5.5; B, 16.9±6.3. **At 24h:** A, 20.3±7.9; B, 25.7±11.2. **At 48h:** A, 28.4±12.1; B, 33.0±15.7. No difference on tablets of acetaminophen-codeine consumption (*p*=0.42). **At 72h:** A, 1.0 (0-4); B, 1.0 (0-4). **At 96h:** A, 1.0 (0-3); B: 0.5 (0-2). **At 120h:** A, 0.0 (0-2); B: 0.0 (0-3). No differences on pain at rest and after cough (p=0.46, and p=0.34 respectively). Less painful patients, (OR=0.16; 95% CI, 0.05-0.53) and lower pain intensity OR=0.36; 95% CI, 0.16-0.82) 1 month after surgery at group A vs B, p=0.003.
Fassoulaki, 2007, **Setting** abdominal hysterectomy. **Jadad score** 5 **Reference** 59	**Sex:** All females **Age: A,** 40±7.3**; B,** 40±7.7 **Drugs administration** **Group A (n=27):** premedication with GBP 1.6 g, than GBP 400 mg every 6 h, starting at 12.00 p.m. the day before surgery till 7th POD **Group B (n=24):** PL as group A. **Follow up:** at 2, 4, 8, 24 h, the 2th - 7th POD. Than 1 month by phone.	**Anaesthesia:** General anaesthesia. **Intra-operative:** morphine 0.1 mg kg^{-1}, acetaminophen 1.2 g. **Post-operative:** Continuous wound infusion with ropivacaine 0.75% (group A) or normal saline (group B) at 2 mL h^{-1}. PCA morphine 1mg boluses, 7 min lockout. Oral acetaminophen - codeine on demand.	Groups were similar regarding: VAS values at rest and after cough, p=NS, nausea or vomiting, dizziness, and sedation during all the point time follow up. Number of patients who required analgesics at home the first month after surgery did not differ between the two groups, P=NS. Overall cumulative morphine consumption at 48h, group A: 31.6±13.2 mg vs group B: 50.6±20.5 mg, p<0.001. During the postoperative days 3–7, the group A consumed fewer acetaminophen-codeine than group B, p=0.011. Fewer patients experienced pain 1 month after surgery in group A vs group B, P=0.045).
Said-Ahmed 2007 **Setting** myomectomy **Jadad score** 2 **Reference** 60	**Sex:** all female **Age: A,** 35 ± 8; **B,** 39 ± 5; **C,** 38 ± 6**; D,** 36 ± 7 **Drugs administration:** orally, 2h before surgery, **Group A (n=20)**: GBP 300 mg **Group B (n=20):** GBP 600 mg **Group C (n=20):** GBP 1.2 g **Group D (n=20):** PL **Follow up:** 2, 6, 12, 24 h	**Anaesthesia:** general anesthesia **Intra-operative:** fentanyl 2 μg kg^{-1}at induction; no other analgesic were described **Post-operative:** fentanyl 2 μg kg^{-1} on demand	With increasing the dose of GBP (300 to 1200 mg) there was a reduction in VAS scores compared to PL at all time points, which reached significance for group C. **2h:** A, 4.5±1.9; B, 4.4±2.1; C, 3.0±1.4; D, 5.0±1.5 (p= 0.004). **6h:** A, 3.1±1.2; B, 2.8±1.3; C, 1.9±1.2; D, 4.2±1.1, (p<0.001). **12h:** A, 2.5±1.1; B, 2.2±1.1; C, 1.5±0.9; D, 3.3±1.1 (p<0.001). **24h:** A, 1.9±1.1; B, 1.7±0.7; C, 1.3±0.5; D, 2.5±1.2, (p=0.014). Significantly lower fentanyl consumption in group C (μg): A, 270±90; B, 250±85; C, 190±80; D, 340±95 (p<0.001). No difference in side effects (p=NS)
Gilron, 2009 **Setting** ambulatory laparoscopic cholecystectomy. **Jadad score** 5 **Reference** 66	**Sex,** M/F: **A:** 6/24; **B:** 11/19; **C**: 8/21 **Age: A,** 41.5 (21–81); **B,** 49.5 (30–77); **C,** 46 (24–81) **Drugs administration:** **Group A (n=30):** oral meloxicam 15 mg 1 h preoperatively, than the POD 1 and 2 **Group B (n=30)**: oral GBP 1.2 g before surgery, 400 mg on the evening of surgery and GBP 400 mg x 3 on POD 1 and 2 **Group C (n=29):** oral meloxicam 15 mg/day for 3 days+GBP 1600 mg the day of surgery and GBP 1200 mg daily on POD 1 and 2. **Follow up:** every 30 min until discharge, at POD 1, 2, and 30.	**Anaesthesia:** general anaesthesia and trocar insertion sites were infiltrated with up to 15 mL of 0.25% bupivacaine. **Intraoperative:** IV fentanyl 2–5 μg·kg^{-1} **Post-operative:** IV fentanyl 12.5–25 μg every 3 min as needed. Upon discharge from hospital, patients were prescribed either codeine 30–60 mg or morphine 5–10 mg PO every 3 h as needed.	Lower rest pain at 60 min in the group B vs A (*p*=0.003). Pain decreased from 60 to 120 min (*p*=0.0005, 0.005, <0.0001 for pain evoked by peak expiration, sitting, and cough, respectively), but no differences between groups (*p*=0.7, 0.3, 0.3, and 0.08 for shoulder pain, pain evoked by peak expiration, sitting, and cough pain, respectively). Lower cough pain at 60 min in the group B vs A (*p*=0.01). On POD 1, 2, and 30, no differences between groups on pain. No differences among groups in opioid consumption until POD 3. No significant effect of treatment by time interaction for any of the spirometric measures (*p*=0.44, 0.07, and 0.35 for PEF, FEV1, and FVC, respectively). All spirometric measures improved from 60 to 120 min (*p*<0.0003), but groups were not different for PEF, FEV1, and FVC (*p*=0.3, 0.9, 0.9, respectively). PEF was higher in group C vs A at 120 min (*p*=0.02). Less nausea in the group C vs A (*p*=0.016) but not vs B (*p*=0.8). Median time (hours) from PACU admission to meeting PACU discharge criteria was 2.92, 2.83, and 2.75 for group A, B and C, respectively (p=NS). Mean time (days) from surgery to return to work was 13.6, 11.7, and 10.6 for groups A, B, and C respectively (p=NS).

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Author, year, setting, Jadad score reference	Demographics, sample size, dosing, active/control, follow-up	Anaesthesia, Intra-operative and post-operative analgesics	Main results
Pandey, 2006, **Setting** laparoscopic cholecystectomy **Jadad score** 5 **Reference** 68	**Sex,** M/F**: A,** 25/100; **B:** 13/107 **Age: A,** 42.8±11.4; **B,** 41.8±11.1 **Drugs administration:** orally, 2h before surgery, **Group A (*n=125):*** GBP 600 mg **Group B (*n=125):*** PL **Follow up:** 2, 6, 12, 24 h.	**Anaesthesia:** general anesthesia **Intra-operative:** induction with fentanyl 3μg kg^{-1}; manteinance not described **Post-operative:** fentanyl (dosage not described)	Significantly higher fentanyl consumption in group B vs A. **A:** 221.2±92.40 μg ; **B:** 505.9±82.0 μg (*p*=0.01) The incidence of PONV during the first 24 hr was significantly lower in A group (37.8%) than B (60%), (p =0.04). No difference in the PONV severity. A: mild 9 patients, moderate 31 patients, severe 6 patients. B: mild 10 patients, moderate 52 patients, severe 13 patients. Similar incidence of side effects in both groups.
Koç, 2007 **Setting** varicocele surgery **Jadad score** 4 **Reference** 57	**Sex:** All males **Age: A,** 39.5±19.3; **B,** 38.4±17.4; **C,** 35.3±18.0; **D,** 41.1±20.9. **Drugs administration:** 1 h before surgery **Group A (n=20):** oral 800 mg of GBP + IV 2 ml saline **Group B (n=20)**: oral PL + IV 8 mg dexamethasone **Group C (n=20):** 800 mg GBP+8 mg dexamethasone **Group D (n=20):** oral PL + IV 2 ml saline **Follow up:** at 1, 2, 4, 6, 12, and 24 h.	**Anaesthesia:** general anesthesia **Intraoperative:** remifentanil 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at induction then it was reduced to 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. **Post-operative:** When VAS>3, tenoxicam 20 mg IM was administered	Lower HR and MAP in group C at 1, 3, 5, and 10 min after intubation vs A and B ($p<0.05$) and D ($p<0.001$). Hemodynamics were similar in group A and B, but lower than group D ($p<0.05$). Less remifentanil consumption in group C (249.1±85.7 mg) vs A (408.5±139.7 mg) and B (409.2±136.6 mg) ($p<0.05$) and D (745.7±119.7 mg) ($p<0.001$). Values in group D were higher than in group A and B ($p<0.05$) but A and B were similar. Similar MAP and HR among groups at each time point. Less pain in group C at 30 min, 1, 2, 4, 6, and 12 h vs A, B ($p<0.05$) and D ($p<0.001$). Values in group D were higher than in group A and B (p<0.05), but group A and B were similar. Lower tenoxicam consumption in group C (0 mg) vs A (80 mg) and B (80 mg) (p<0.05) and vs D (300 mg) ($p<0.001$). Less PONV in group C vs the other groups ($p<0.001$).PONV in group A and B were similar, but less than in D ($p<0.05$). No differences in other side effects.
Mohammadi, 2008 laparoscopic surgery for reproductive technologies **Jadad score** 3 **Reference 67**	**Sex:** all female **Age: A,** 31.3±5.4; **B,** 31.9±5.6 **Drugs administration:** Orally 1h before surgery **Group A (*n=35):*** GBP 300 mg **Group B (*n=35):*** PL **Follow up:** 0, 1, 2h.	**Anaesthesia:** general anaesthesia **Intra-operative:** induction wit fentanyl 2μg kg^{-1}; manteinance not described **Post-operative:** Fentanyl as rescue analgesic (dose not described)	Significant differences in median VAS score at all time points (p<0.05) At 0 h: A: VAS 1 (0-2), B: VAS 2 (1-3) At 1 h: A, VAS 3 (1-3); vs B, VAS 3 (2-5) At 2 h: A, VAS 3 (2-3); vs B, VAS 3 (3-5) One patient (0.02%) in A group and 10 patients (28%) in B group required additional IV analgesic (p=0.012). Two patients in A group and 9 patients in B group had nausea (p=0.022). None patients in A group and 4 pz in B group had vomiting (p=0.114). No differences in side effects.
Mohammadi, 2008 **Setting** Abdominal (gynaecological/general surgery) **Jadad score** 4 **Reference** 62	**Sex,** M/F**: A,** 24/16; **B,** 23/17; **C:** 25/15 **Age: A,** 39±12**; B,** 35±13 **C,** 40 ±12 **Drugs administration:** orally 1 h before surgery **Group A (*n=40*):** 300 mg GBP **Group B (*n=40*):** 0.2 mg clonidine **Group C (*n=40*):** PL **Follow up:** at 0, 1 and 6 h	**Anaesthesia:** general anesthesia **Intra-operative:** fentanyl 3 μg kg^{-1} for induction; fentanyl 1 μg kg^{-1} h^{-1} for maintenance. **Post-operative:** In the PACU: iv morphine titrated 2 mg every 10 min in order to obtain VAS<3; PCA: bolus 1 mg lockout interval 10 min.	VAS score>3 significantly more frequent in B e C group than in A. **PACU:** A, 2%; B, 13%; C, 29%, (p=0.001). **At 1 h:** A, 19%; B, 36%; C, 29%, (p=0.001). **At 6 h:** A, 33%; B, 37%; C, 39%, (p=0.027) Morphine consumption at the **PACU:** A, 1.56±1.5 mg; B, 1.95±5.5mg; C, 4.75±7.5 mg (A vs B p=0.045; A vs C p=0.024; B vs C p=0.032). Morphine consumption during the first **6 h:** A, 12.1±19.9 mg; B, 13.1±12.6 mg; C, 18.0±15.8 mg (A vs B, p=0.07; A vs C, p=0.023; B vs C, p=0.02. Side effects were not different between the groups.
Ghafari 2009; **Setting** abdominal hysterectomy **Jadad score** 2 **Reference** 65	**Sex:** all female **Age: A,** 45±1; **B:** 44±1; **C:** 44±1 **Drugs administration:** at 10:00 pm the night before and 1 h before surgery **Group A (*n=33*):** 300 mg GBP **Group B (*n=33*):** 100 μg clonidine **Group C (*n=33*):** PL **Follow up:** 1, 4, 8, 12, 24, and 48 h.	**Anaesthesia:** general anesthesia **Intra-operative:** induction with fentanyl 2.5 μg kg^{-1}; maintenance with fentanyl 1μg kg^{-1} every 30 min **Post-operative:** PCA with morphine 1 mg ml^{-1}, bolus 1 mg, 7 min lock out period.	Lower VAS scores in groups A e B vs group C at 1, 12, 24 and 48h (p<0.05). **At 1h:** A, 4.24±0.54; vs B, 4.48±0.58; vs C, 6.39±0.48, (A and B vs C, p<0.05). **At 4h:** A, 4.25±0.35; vs B, 4.62±0.44; vs C, 5.81±0.40, (A vs C, p<0.05); **At 8h:** A, 3.51±0.31; vs B, 4.86±0.41; vs C, 6.10±0.47, (A vs B and C, p<0.05). **At 12h:** A, 2.92±0.32, vs B3.43±0.38, vs C, 4.94±0.40 (A and B vs C, p<0.05). **At 24h:** A, 1.81±0.30; vs B, 1.76±0.30; C, 3.48±0.40 (A and B vs C, p<0.05). **At 48h:** A, 0.64±0.19; vs B, 1.12±0.28; vs C, 2.17±0.38 (A and B vs C, p<0.05). Lower morphine consumption in groups A and B vs C till 24 h after surgery (p<0.05); no difference at 48 h. No differences in side effects.

(Table 3). contd…..

Author, year, setting, Jadad score reference	Demographics, sample size, dosing, active/control, follow-up	Anaesthesia, Intra-operative and post-operative analgesics	Main results
Head, neck, thoracic and breast surgery			
Al-Mujadi, 2006 **Setting** thyroid surgery. **Jadad score** 5 **Reference** 50	**Sex:** M/F **A:** 9/26; **B:** 10/27 **Age:** **A**: 45 ± 13; **B:** 49 ± 15 **Drugs administration:** Orally 2 h before surgery. **Group A (*n*=37):** GBP 1.2 g **Group B (*n*=35):** PL **Follow up:** At 2, 6, 12, 18 and 24 h.	**Anesthesia:** General anesthesia **Intraoperative:** fentanyl 2–3 $\mu g \cdot kg^{-1}$ i.v. at the induction. **Post-operative:** Morphine 3 mg *iv* bolus doses were given every five minutes until VAS pain scores were 4 or less at rest, and 6 or less with swallowing.	**VAS at rest, at 0 h:** group A 3.3±2.8 vs B 4.5±0.9, p<0.01; at 2 h: A, 1.81±1.1 B, 4.4±1.9 p<0.001; **at 6 h**: group A, 1.40±0.7 vs B, 2.41±1.3, p<0.01; **at 12 h:** group A, 1.60±1.3 vs B, 2.60±1.6, p<0.01; **at 18 h:** group A, 1.1±0.7 vs B 2.5±1.8, p<0.01; **at 24 h:** group A, 1.8 ± 1.6 vs B, 2.3±1.3 p<0.01.**VAS during swallowing, at 0 h**: group A, 4.5±1.3 vs B, 5.1±1.8, p<0.01; **at 2 h:** group A, 2.6±1.6 vs B, 5.0±1.7, p<0.001; **at 6 h:** group A, 2.3±1.2 vs B, 3.13±1.5, p<0.01; **at 12 h:** group A, 2.2±1.2 vs B, 3.8±1.5, p<0.01; **at 18 h:** group A, 2.5±1.4 vs B, 3.6±1.9, p<0.01; **at 24 h:** group A, 2.3±1.2 vs B, 3.5±1.1, p<0.01. Les morphine consumption in group A (15.2 ± 7.6 mg) vs B (29.5 ± 9.9 mg), (P < 0.001). No differences on PONV.
Mikkelsen, 2006 **Setting** tonsillectomy in adults **Jadad score** 5 **Reference** 51	**Sex,** M/F: **A,** 9/14; **B,** 7/21 **Age: A,** 31 (18–43); **B,** 27.5 (18–53) **Drug's administration:** **Group A (n=23):** Orally 1 h before surgery GBP 1.2 g+rofecoxib 50 mg, than GBP 600 mg x 2 on the day of operation and GBP 600 mg x 3 for the next 5 days. **Group B (n=28):** rofecoxib 50 mg before anesthesia and PL as group A. **Follow up:** at 2, 4 h and at 1–5 POD	**Anaesthesia:** General anaesthesia **Intra-operative:** Sufentanil or alfentanil **Post-operative:** rofecoxib 50 mg daily. Ketobemidone 2.5 mg as needed. In the PACU, from 0 to 4 h post-operatively, iv morphine in incremental doses of 2.5 mg on request	No statistically significant difference between the groups regarding: pain scores at rest and during swallowing of 50 ml of water, awakenings caused by pain, sedation and nausea, at any time period. Reduced ketobemidone consumption in the first 24 h in group A: 2.0±2.0 vs B: 4.5±3.0 mg, p = 0.003. Three-fold more dizziness in group A vs B, p = 0.002 and gait disturbance four-fold more frequently in group A, p=0.02, five-fold more vomiting in group A vs B (p=0.046).
Brogly, 2008 **Setting** thyroidectomy **Jadad score** 3 **Reference** 63	**Sex,** M/F: **A**, 3/19; **B,** 3/18 **Age: A**, 49 (18–63); **B:** 49 (25–72) **Drugs administration:** Orally 2h before surgery. **Group A (*n*=22):** GBP 1.2 g **Group B (*n*=21):** PL **Follow up:** 1h, 3h, 6h, 9h, 12h, 18h, 24h.	**Anaesthesia:** General anaesthesia and superficial cervical plexus block **Intra-operative:** IV sufentanil 0.2– 0.3 $\mu g \cdot kg^{-1}$ at induction than boluses of 5-10 µg **Post-operative:** IV acetaminophen 1 g or 50 mg IV tramadol.	The total (median, range) analgesic consumption (paracetamol and tramadol) was 3 (0 –5) in group A vs 3 (1–5) in B, p=NS. Tramadol was required in 27.3% patients in group A vs 23.5% in B (p=NS). No significant differences between groups for VAS at rest and during swallowing. After 6 mo, 8 patients presented pain scores $\leq$ 3 vs 2 patients in the preoperative period (p=0.04). It was significantly lower in group A. There was a trend toward greater burning sensation and numbness in group B, but p=NS.
Jeon, 2008 **Setting** tonsillectomy **Jadad score** 3 **Reference** 64	**Sex,** M/F**: A,** 18/14; **B,** 9/17 **Age: A,** 27.7±11.5; **B,** 24.2±6.3 **Drugs administration:** Orally, the night before and 1 h before surgery, **Group A (n=32):** GBP 600 mg **Group B (n=26):** PL **Follow up:** at 1, 2, 4, 8, 12, 24, 36 and 48 h, then for 7 days after discharge.	**Anaesthesia:** General anesthesia **Intraoperative:** No analgesics were reported. **Post-operative:** PCA with 1% fentanyl 2 ml bolus, 10 min lockout time, dicolfenac sodium 75 mg i.m. as needed. Acetaminophen 325 mg and tramadol 37.5 mg daily for 9 POD.	Fentanyl consumption: group A, 28.1±31.5 ml vs B, 59.7±41.5 ml, p=0.002. Diclofenac injections: group A, 0.1±0.3 vs B, 0.8±0.9, p=0.001. The pain score at rest (rVAS) was highest at 2 h (group A: 4.1±2.2, group B: 4.5±2.4) and lowest on 9th POD (group A: 2.1±1.3; B: 2.5±2.2) (p always NS). The swallowing VAS (sVAS) in group B was highest at 1 h: 6.8±2.6 2 and 2h: 6.8±2.4, and lowest to 3.6±2.1 on the 9th POD. In the group A, the sVAS was highest at 8 h (5.8±2.0) and lowest on the 9th POD (3.4±1.5). Lower sVAS in the group A than B only at 2 and 4 h (p= 0.04; p=0.04). No significant differences regarding patients' satisfaction, drowsiness, PONV and headache.
Huot, 2008 **Setting** post-thoracotomy shoulder pain **Jadad score** 4 **Reference** 61	**Sex** M/F**: A,** 11/12; **B,** 17/11 **Age: A,** 60.1±13.6; **B,** 60.0±8.7 **Drugs administration:** Orally 2 hours before surgical incision. **Group A (n=23):** GBP 1.2 g **Group B (n=28):** PL **Follow up:** At 0, 4, 8, 12, 16, 20 and 24 h.	**Anaesthesia:** General anesthesia and thoracic epidural block. **Intraoperative:** fentanyl 2 - 5 $\mu g \cdot kg^{-1}$ or sufentanil 0.2 - 0.5 $\mu g \cdot kg^{-1}$ iv at induction and further boluses as needed. Epidural bupivacaine 0.1% + fentanyl 2 $\mu g \cdot ml^{-1}$ at 0.1 $ml \cdot kg^{-1} \cdot hr^{-1}$ **Post-operative:** Epidural bupivacaine 0.1% + fentanyl 2 $\mu g \cdot ml^{-1}$ at 0.1 $ml \cdot kg^{-1} \cdot hr^{-1}$ + bolus of 0.1 $ml \cdot kg^{-1}$ of epidural solution as needed. S.c. hydromorphone 1–2 mg.	Similar amount of epidural solution in both groups (group A: 281.1 ± 75.8 ml vs group B: 318.1 ± 94.8 ml, p=0.06) and hydromorphone consumption (group A: 2.36 ± 2.5 mg vs group B: 2.65 ± 3.2 mg, p = 0.36). No differences on pain intensity at surgical site and at shoulder between groups, for the entire postoperative period. Twenty-three patients (82%) in Group B experienced shoulder pain vs 21 (91%) in Group A. Nausea, vomiting, and pruritus were similar in the two groups. Seven patients in Group A (30%) and eight patients in Group B (29%) received antiemetic treatment. At four hours, the incidence of sedation scores > 1 was greater in Group A (21/23 patients), vs Group B (18/28 patients; p=0.025). At 24 hr, 5/18 patients in Group B had sedation scores > 1, vs 0/28 patients in Group A (P = 0.05).

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Author, year, setting, Jadad score reference	Demographics, sample size, dosing, active/control, follow-up	Anaesthesia, Intra-operative and post-operative analgesics	Main results
musculoskeletal surgery			
Turan, 2006, **Setting** postoperative epidural analgesia after lower limb surgery **Jadad score** 5 **Reference** 49	**Sex:** not reported **Age: A,** 54 (28–74); **B,** 50 (25–68) **Drug's administration:** Orally 1 h before surgery, than same drugs at 09:00 on the 1st and 2nd POD **Group A (n=20):** GBP 1.2 g. **Group B (n=20):** PL **Follow up:** at 1, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 60, and 72 h.	**Anaesthesia:** General anaesthesia **Intraoperative:** Fentanyl, 2 μg kg^{-1} i.v. Epidural bupivacaine 0.125% 5 ml, with fentanyl 1 μg ml^{-1}. **Post-operative:** epidural PCA with bupivacaine 0.125% and fentanyl 1 μg ml^{-1}, 5 ml bolus, 10 min lockout, or oral 500 mg acetaminophen.	Greater VRS pain scores at 1, 4, 8, 12, and 16 h after operation in group B (P<0.001). AUC for the pain scores showed a statistically significant difference for the first 24 h (P<0.001) but not at 72 h (P=0.7). Less VAS scores at group A until 20 h (P<0.001). Reduced PCEA requirements in the group A at 24, 48, and 72 h. Duration of PCEA usage was shorter in group A (57±9 vs 38±11, p<0.05); less oral analgesic consumption in the group A. (350±400 vs 700±523 mg, p<0.05). Groups were similar in times to the return of bowel function, resumption of dietary intake, and length of hospitalization. Fewer group A patients had motor block (P<0.05). Patient of group A were more satisfied. More dizziness in group A, p<0.05.
Adam, 2006 **Setting** arthroscopic shoulder surgery. **Jadad score** 5 **Reference** 52	**Sex,** M/F**: A,** 18/9; **B:** 18/8 **Age: A**, 43±18; **B,** 47±15 **Drugs administration:** Orally 2 h before surgery **Group A (*n*=27):** GBP 800 mg **Group B (*n*=26):** PL **Follow up: t**wo times the 1st day and four times the 2nd day after hospital discharge.	**Anaesthesia:** brachial plexus block and general anesthesia **intra-operative:** remifentanil 1 μg·kg^{-1} at induction. **post-operative:** ketoprofene 150 mg x 2 and 400 mg acetaminophen + 30 mg dextropropoxyphene as needed.	No statistically significant differences in the VAS score. Cumulative use of supplement analgesics was similar in each group (group A: 6±3, B: 7±3 tablets). Time to the use of the first analgesic tablet was comparable in the two groups (group A: 768 ± 218 min vs B: 719±199 min). Side effects were comparable in both groups, except that headaches were more frequent in the group B (*P*=0.034). About 25%–30% of the patients considered their analgesia insufficient. However, scores for overall satisfaction were high (about 80 mm in both groups) and did not differ between the two groups.
Turan, 2007 **Setting** tourniquet pain and I.V. regional anesthesia. **Jadad score** 5 **Reference** 54	**Sex,** M/F: **A:** 15/5; **B:** 14/6 **Age: A,** 35±12; **B,** 39±14 **Drugs administration:** Orally 1 h before anesthesia **Group A (*n*=20):** GBP 1.2 g **Group B (n=20):** PL **Follow up:** at 1, 2, 4, 6, 12, and 24 h.	**Anaesthesia:** I.V. regional anaesthesia with lidocaine, 3 mg kg^{-1}. **Intra-operative:** Fentanyl 0.5 μg/kg IV boluses if tourniquet pain score > 4 **Post-operative:** Diclofenac, 75 mg i.m. as needed	Reduced VAS scores for tourniquet pain in group A at 30, 40, 50, and 60 min after tourniquet inflation. Prolonged time to intraoperative fentanyl rescue (35±10 min vs 21±13 min, *P* <0.05), and total fentanyl requirement during surgery in group A (83±73 vs 35±47 μg, p<0.05). Higher quality of anesthesia reported by the anaesthesiologist (4 [3– 4] vs 2 [1–2]) and the surgeon (3 [3–3] vs 2 ([2–3]) in group A (*P*<0.05). Prolonged time to first postoperative analgesic request in group A (135±25 min vs 85±19 min, *P*<0.05). Lower VAS at 1 and 2 h after surgery (p<0.01) and decreased diclofenac consumption in group A (30±38 mg vs 60±63 mg, *P*<0.05). No differences regarding to adverse effects.
Montazeri, 2007 **Setting** lower extremity orthopaedic surgery. **Jadad score** 4 **Reference** 56	**Sex,** M/F**: A,** 26/9**; B,** 28/7 **Age: A,** 34.7±18.1; **B,** 34.6±17.8 **Drugs administration:** Orally two hours before induction of anaesthesia. **Group A (n=35):** GBP 300 mg **Group B (n=35):** PL **Follow up: at** 2, 4, 12, and 24 h.	**Anaesthesia:** general anesthesia **Intraoperative:** fentanyl 2 μg kg^{-1} at induction and morphine 0.1 mg kg^{-1}before the start of the surgery **Post-operative:** morphine 0.05 mg kg^{-1} IV on demand.	Lower VAS scores in group A vs B at 2 h: group A, 55.5±15.8 vs B, 72.3±14.0 at 4 h: group A, 57.3±19.3 vs B, 70.5±18.1 at 12 h: group A, 45.7±16.0 vs B, 62.0± 23.3 at 24 h: group A, 44.6±17.6 vs B, 66.5±25.7. All p<0.05. Less required morphine in group A, 15.4±2.5 mg vs group B 17.9±3.0 mg, p<0.05. Significant difference between the two groups in the first time of patients' morphine demand after surgery (group A 31.6 ±15.9 min vs group B 26.7±7.1 min, p<0.05). No significant difference in the recovery duration between the two groups. Postoperatively, the adverse effects were similar between groups.
Prabhakar, 2007 **Setting** Surgical brachial plexus exploration for injury **Jadad score** 4 **Reference** 58	**Sex,** M/F: **A,** 10/0; **B,** 9/1 **Age: A,** 27.5 (18-33); **B,** 31 (20-35) **Drugs administration:** Orally 2 hours before surgery. **Group A (n=10):** GBP 800 mg **Group B (n=10):** PL **Follow up:** Every 1 h for 24 h. For the analysis, the mean values were taken at intervals of 0 - 6, 6 - 12 h, 12 - 18 h, and 18 - 24 h.	**Anaesthesia:** General anesthesia **Intraoperative:** fentanyl 2 μg kg^{-1} at induction, than fentanyl boluses as needed. **Post-operative:** ketorolac iv as demanded by the patient or if VAS score was >50.	Total intraoperative fentanyl requirement, group A: 200 (100-225) μg vs B: 237.5 (100-400) μg, p= 0.03. Intraoperative and postoperative hemodynamics was similar in the 2 groups. The VAS scores at rest: **at 0h:** A, 31.5±11.6 vs B, 46±14.3, p=0.01. **At 6 h:** A, 37.5±11.1 vs B, 47.5±14.4, p=0.01. **At 12 h:** A, 38±10.3 vs B, 49±17.3, p=0.01. **At 18 h:** A, 34.5± 4.4 vs B, 49±14.5, p=0.007. **At 24 h**: A, 38.5±10.0 vs B, 54±13.5, p=0.009. The VAS scores during movement: **At 0h:** A, 52±14.8 vs B, 67±15.7, p=0.04. **At 6 h:** A, 52.5±10.9, vs B, 65±19.6, p=0.04. **At 12 h:** A, 54±11.0 vs B, 66±17.8, p=0.04. **At 18 h:** A, 50.5±10.1 vs B, 63±12.5, p=0.04. **At 24 h:** A, 54.5±10.1 vs B, 66.5±16.3, p=0.04. Rescue analgesic doses in group B, 2.5 (0-4) vs A, 0 (0-3), (p=0.004). No side effects requiring intervention were noted in both groups.

GBP – gabapentin; PL – placebo; VAS – Visual Analogue Scale; I.V. – intravenous; POD – post-operative day; PCA – patient controlled analgesia; PCEA – patient controlled epidural analgesia; HR – heart rate; MAP - mean arterial pressure; AUC- area under the curve

GBP provided better post-operative analgesia and rescue analgesics sparing than placebo in 6 of the 10 RCTs that administered only pre-emptive analgesia [50, 54, 56, 58, 64, 67, 68]. Three studies reported no GBP effects on pain

scores or rescue analgesics sparing [52, 61, 63]. One study that did not assessed pain reported only opioid sparing effect of GBP [68]. Of the 5 RCTs that measured pain with movement, 3 demonstrated significantly reduced movement-related pain in GBP patients [50, 58, 64]. Three RCTs compared pre and post-operative GBP administration with placebo. Turan at al found perioperative GBP treatment useful for pain reduction and epidural PCA solution sparing and oral acetaminophen reduction [49]. Fassoulaki *et al.* did not demonstrate any benefits in early pain management and analgesics sparing with perioperative gabapentin after hysterectomy [48]. The same authors reported opioid sparing but not pain reduction, in the same setting the following year [59]. However, in both works they found a significant pain reduction one month after surgery [48, 59]. Several RCTs compared GBP with other analgesics for post-operative pain management. In adjunction to dexamethasone [57] or to a selective COX-2 inhibitor as rofecoxib [47, 51] or lornoxicam [53] GBP did not seem to offer further benefits on pain management in comparison with GBP, dexamethasone, rofecoxib or lornoxicam alone. However, there were reported reduced intra [57] and post surgery [51, 57] analgesics consumption or number of patients requesting analgesics [53]. Meanwhile, Gilron *et al.* did not find substantial positive effects of GBP-meloxicam mixture with those of GBP and meloxicam alone on pain control and opioid sparing after laparoscopic colecystectomy [66]. Mohammadi *et al.* described positive GBP effects on reduction of pain and PCA morphine consumption when compared with clonidine after abdominal and pelvic surgery [62], but their assertions where not confirmed by Ghafari *et al.* after laparoscopic gynaecological surgery [65]. GBP-acetaminophen combination provides better pain control and reduced PCA-morphine consumption in comparison with GBP alone or placebo after abdominal hysterectomy [55]. Different dosages of gabapentin have been confronted only by Said-Ahmed that reported increasing the pre-emptive dose of gabapentin (300 to 1200 mg), significantly decrease the severity of post-myomectomy pain and total opioid consumption during the first 24 hours after surgery [60]. Two of the 3 trials that evaluated the time elapsed from the end of surgery to the first analgesic request, reported that it was significantly longer in GBP group vs placebo [54, 56] but the other one did not find difference [52].

Related to a specific antiemetic effect, 14 RCTs suggested that GBP did not reduce nausea and vomiting following surgery when compared with placebo [49, 50, 52, 54, 56, 58, 59, 61, 63, 64, 67]. clonidine [62, 65], or lornoxicam [53]. Three RCTs that studied the gabapentin alone [68] or its combination with dexamethasone [57] or rofecoxib [47] reported a significant reduction of PONV in gabapentin patients vs placebo [47, 57, 68]. Furthermore, GBP-dexamethasone combination seems to have a synergic positive effect on PONV reduction in confront with GBP or dexamethasone alone [57]. Combined with COX-2 inhibitors, GBP seems to have similar incidence of PONV where confronted with GBP [47, 66] and rofecoxib [47] alone and less if confronted with meloxicam alone [66]. These findings are in contradiction with those of Mikkelsen at al who reported five-fold more incidence of PONV in GBP-rofecoxib group than rofecoxib alone group [51]. Gilron et al. demonstrated that there are not differences on lung function during treatment with either GBP, meloxicam or both after laparoscopic cholecystectomy as assessed by peak expiratory flow rate [66]. This findings are in contradiction with a previous work of the same authors where these improvements were enhanced even further when GBP was combined with another COX-2 inhibitor for abdominal hysterectomy [41]. Furthermore, they were not able to demonstrate benefits of gabapentin on PACU discharge and return to work [66]. The most frequent other adverse effects were sedation, dizziness, headache. No statistical differences regarding the adverse effects have been observed between GBP, other analgesics, combination or placebo in 17 RCTs [47, 50, 53, 55-68]. Two studies reported less headache in gabapentin group [52, 54] and other two trials found more dizziness with GBP administration [49, 51]. Meanwhile, Fassoulaki *et al.* excluded the patients having PONV or other side effects from the study [48].

Pregabalin RCTs

More detailed information regarding each of the eight PGL RCTs (an overall of 707 patients) included in the review is reported in Table **4**. There has been tested a large modality of PGL administration for post-surgical analgesia. All the RCTs administered pre-emptive PGL or its combination with other analgesic drugs. Three RCTs evaluated pre [70, 75] and both pre/post-operative [73] PGL alone vs placebo patients. The PGL – other analgesic [dexamethasone [74], ibuprofen [72], celecoxib [69], and both acetaminophen-dexamethasone [76], combination has been studied by four RCTs, three of them used only pre-emptive analgesia [72, 74, 76] and one considered a second 12 h post-operative administration of the same pre-emptive drugs [69]. Totally, three different PGL pre-emptive dosages (75 mg, 150 mg and 300 mg) have been studied. Jokela *et al.* confronted different dosages (300 mg and 600 mg) of perioperative of PGL alone with diazepam 10 mg as control group after laparoscopic hysterectomy concluding that only PGL 600 mg, decreases oxycodone consumption postoperatively, and is associated with an increased incidence of dizziness, blurred vision, and headache [71]. However, when the same authors tested the pre-emptive PGL 150 or 75 mg in combination with ibuprofen in a similar setting, they did not found differences about neither the amount of postoperative analgesics required, nor the incidence of side-effects [72]. No studies considered the comparison of pre-emptive and post-incisional or post-surgery PGL administration. The follow up period was no more than 24 h in 6 RCTs [69, 70, 72, 74, 75, 76], one trial followed the patients for 72 hours [71] and the the other once a day till 7 POD [73]. No studies established the optimal post surgical PGL treatment duration. Five studies assessed pain by using VAS [71, 72, 74-76], one study used both VAS and 4-point VRS [70], and the other two used an 11-point VRS [69, 73]. Six RCTs evaluated pain both at rest and on movement [69, 70, 72, 74-76] and the remaining 2 works did not specify whether pain was measured at rest or with movement [71, 73]. All the PGL-studies used the total rescue analgesics consumption as an important outcome for testing post-operative analgesia level. Morphine was delivered by the patients instructed to use an i.v. PCA pump in three RCTs [69, 74, 76], fentanyl [75] or oxycodone [71] in one trial respectively, without

continuous infusion. The other studies reported administration of fentanyl [70, 72] or hydrocodone [73] as needed. In adjunction to the i.v. opioid boluses other rescue analgesics have been administered on demand in 3 studies [70-72]. Furthermore, four RCTs have treated all the patients with a standard analgesic regimen as well as the on demand therapy [71, 72, 74, 76]. Two RCTs registered the time elapsed from the end of the surgery to the firs analgesic demand as a further outcome [72, 73].

Table 4. Pregabalin for the Postoperative Pain Management. Randomized Clinical Trials

Author, year, setting, reference	Demographics, sample size, dosing, active/control, follow-up	Anaesthesia, Intra-operative and post-operative analgesics	Main results
Abdominal and pelvic surgery			
Paech, 2007, **Setting** Day-case minor gynaecological surgery **Jadad score** 5 **Reference** 70	**Sex:** All females **Age:** **A:** 44±11; **B:** 45±13 **Drugs administration:** Pre-medication with: **Group A (n=45):** PGL 100 mg, **Group B (n=45):** PL **Follow up:** at 1, 2, and 24 h	**Anesthesia:** General anesthesia **Intraoperative:** fentanyl 1 μg kg^{-1} at induction, acetaminophen 1 g, boluses of fentanyl 25 μg. **Post-operative:** i.v. boluses 20 or 30 μg of fentanyl, tramadol 50 mg, or oral diclofenac 50 mg. Acetaminophen as needed at home.	No clinical and statistical differences on: VAS between groups at rest and on movement during all the assessment times; the use of postoperative analgesics; the incidence of nausea (A: 20% vs B: 20%) or vomiting (A: 10% vs B: 2%, $P = 0.13$); the need for antiemetics (A: 22% vs B: 16%, $P = 0.45$); sedation scores, the Quality of Recovery Score, satisfaction scores. Group A higher incidence of light- headedness (A: 59% vs B: 33%, p= 0.03), visual disturbance (A: 22%, B: 2%, p= 0.01) and difficulty with walking (A: 45% vs B: 20%, p=0.02)
Jokela, 2008, **Setting** laparoscopic hysterectomy **Jadad score** 5 **Reference** 71	**Sex:** All females **Age: A**: 50±6; **B**: 48±8; **C**: 52±9 **Drugs administration:** Pre-medication with: **Group A (n=27):** PGL 150 mg, **Group B (n=29):** PGL 300 mg, **Group C (n=29):** diazepam 10 mg Than 12 h after the premedication groups A and B received the same dose of the pre-medication whereas group C received PL **Follow up: a**t 1, 2, 4, 6, 8, 12, 24, 48, and 72 h.	**Anesthesia:** General anesthesia **Intraoperative:** Remifentanil infusion, 0.2 mg $kg^{-1}min^{-1}$ at induction than adjusting to as needed. **Post-operative:** PCA oxycodone 1 mg ml^{-1}, 0.04 mg kg^{-1} bolus, lock-out 8–10 min. POD 1st stop PCA and oral ibuprofen 800 mg twice a day, acetaminophen-codeine as needed.	Groups were similar regarding: VAS at rest and on movement, anxiety; times to the 1st rescue dose, and fentanyl doses in the recovery room; oxycodone doses during 0–12 h; patients taking acetaminophen-codeine; PONV, anti-emetics use; other side effects; pain and patients' satisfaction. Less oxycodone use during 12–24 h after surgery in group B vs group A (P = 0.025). Less total oxycodone dose (0–24 h) in group B vs group C (P = 0.046;). More headache in group B vs C during 1-3 POD (P = 0.04). More dizziness in the group B vs C (P <0.05). More blurred vision in group A and B vs C during 0–24 h (p=0.02, p=0.002). Less pruritus in group B vs C (p=0.047)
Agarwal, 2008, **Setting** laparoscopic cholecystectomy **Jadad score** 5 **Reference** 75	**Sex: A:** 23/7; **B:** 18/12 **Age: A,** 46.6 (25–76); **B,** 44.6 (22–69) **Drugs' administration:** 1 h before anesthesia **Group A (n=30):** PGL 150 mg **Group B (n=30):** PL **Follow up:** every 2 h till 24 h after surgery.	**Anaesthesia:** General anaesthesia **Intra-operative:** fentanyl 3 μg kg^{-1} at induction. No other intra-operative analgesic **Post-operative:** PCA fentanyl 20 μg, lockout 5 min, max. dose 2 μg kg^{-1} h^{-1}	Pain reductions during all follow up group A vs B, **0 h**: static 30±20 vs 50±28, dynamic 30±25 vs 70±20; **0–4 h**: static 30±20 vs 40±38, dynamic 40±20 vs 50±28; **4–8 h**: static 30±10 vs 40± 10, dynamic 40±20 vs 50±30; **8–12 h**: static 20±10 vs 30± 18, dynamic 30±15 vs 40±10; **12–24 h**: static 20±20 vs 35±40, dynamic 20±10 vs 30±30. All p<0.05. Less PCA fentanyl consumption in the group A (555.2 ± 124.8 μg) vs B (757.5± 99.3 μg), (P<0.05). No difference on headache, sedation, PONV, antiemetic use and respiratory depression.
Jokela, 2008 **Setting** day-case gynaecological laparoscopic surgery **Jadad score** 5 **Reference** 72	**Sex**: All females **Age: A,** 36±12; **B,** 37±10; **C:** 35±9 **Drugs administration:** Pre-medication with: **Group A (n=28):** PGL 75 mg + ibuprofen 800 mg **Group B (n=30):** PGL 150 mg + ibuprofen 800 mg **Group C (n=26):** diazepam 5 mg + ibuprofen 800 mg **Follow up:** at 1, 2, 4, 6, 8, 12, and 24 h.	**Anesthesia:** General anesthesia **Intraoperative:** Remifentanil 0.2 mg $kg^{-1}min^{-1}$ at induction, than as needed. Fentanyl 75 μg i.v. bolus the end of the surgery. **Post-operative:** ibuprofen 800 mg twice a day. Fentanyl 25 μg i.v. and oral acetaminophen-codeine if needed.	The groups were similar regarding: the patients' score (0–10) for anxiety; the times to the first rescue fentanyl dose, the doses of fentanyl in the RR; and the number of patients taking acetaminophen-codeine. The AUC values for VAS at rest 1–8 h after surgery (P=0.048) and in motion (P=0.046) were lower in the group B than in the group C. The AUC values for VAS at cough, the degree of drowsiness, the incidence of side effects, the patients' satisfaction with anaesthesia and pain management did not differ in the three groups.
Mathiesen, 2009, **Setting** abdominal hysterectomy. **Jadad score** 5 **Reference** 76	**Sex:** All females **Age: A,** 47 (44–52); **B,** 46 (43–50); **C,** 46 (42–51) **Drugs administration:** Pre- medication with: **Group A (n=43):** acetaminophen 1 g + PL + PL **Group B (n=43):** acetaminophen 1 g + PGL 300 mg + PL **Group C** (n=42): acetaminophen 1 g + PGL 300 mg + dexamethasone 8 mg. **Follow up:** at 2, 4 and 24 h.	**Anaesthesia:** General anaesthesia **Intraoperative:** remifentanil 0.5 μg kg^{-1} min^{-1}, morphine 0.2 mg/kg 30 min before the end of the surgery. **Post-operative:** Oral acetaminophen 1 g every 6 h, PCA morphine 2.5 mg bolus, 10 min lockout	The groups were similar regarding: morphine consumption (group A: 42 ± 20 mg; group B: 40 ± 22 mg; group C: 38 ± 24 mg; pain scores either at rest or during mobilization; sedation and dizziness Less nausea score in group C vs. group A (P=0.002). Less total number of vomits in group B vs. group A (P=0.04) and in group C vs. group A (P=0.001), less total number of patients vomiting in group B vs. group A (P=0.038) and in group C vs. group A (P=0.001). Less ondansetron use in group C vs. group A (P<0.001) and B (P=0.001)

(Table 4). contd…..

Author, year, setting, reference	Demographics, sample size, dosing, active/control, follow-up	Anaesthesia, Intra-operative and post-operative analgesics	Main results
neurosurgery			
Reuben, 2006 **Setting** decompressive lumbar laminectomy with posterior spinal fusion. **Jadad score** 5 **Reference** 69	**Sex,** M/F**: A,** 13/7; **B,** 12/8; **C,** 13/7; **D,** 11/9 **Age: A:** 43±14; **B:** 46±18; **C**: 42 ± 12; **D:** 44±16 **Drugs administration:** 1 h before anaesthesia than 12 h after surgery **Group A (n=20):** PGL 150 mg + PL than PGL 150 mg + PL **Group B (n=20):** celecoxib 400 mg + PGL 150 mg than celecoxib 200 mg + PGL 150 mg **Group C (n=20):** celecoxib 400 mg + PL than celecoxib 200 mg + PL. **Group D (n=20):** 2 PL capsules **Follow up:** at 0, 4, 8, 12, 16, 20, 24 h	**Anesthesia:** General anesthesia **Intraoperative:** morphine 0.3 mg kg^{-1} at induction. No other analgesic are reported **Post-operative:** PCA morphine bolus, 2 mg; lockout 8 min; 40 mg 4-h limit. Increasing to 2.5 or 3.0 mg bolus, and 50 mg or 60 mg 4-h limit, as needed.	The group B consumed the least PCA morphine (43.0 ± 1.3 mg) than the groups A (77.4 ± 1.7 mg), C (88.0 ± 2.4 mg), and D (134.0 ± 3.3 mg), p<0.001. Groups A and C vs D also reduced morphine consumption (p<0.01). Less pain on rest (p<0.001), and on movement (p<0.05) in group B. Hemodynamics and respiratory rate did not differ among groups. Significantly less nausea in the group B vs D (p<0.05). Drowsiness was less frequent in B and C groups than D group, p<0.017. Less sedation in the group B and C vs A and D, p<0.05
Breast surgery			
Freedman, 2008, **Setting** mammaplasty **Jadad score** 1 **Reference** 73	**Sex:** All females **Age: A:** 31±8**; B:** 31±8 **Drugs administration:** Orally twice daily beginning 2 h before surgery for 7 days. **Group A (n=40):** PGL75 mg **Group B (n=40):** PL **Follow up: o**nce a day till 7 days	**Anesthesia:** Local anaesthesia and iv sedation with meperidine, thiopenthal, and midazolam. **Intraoperative:** meperidine, dosage non reported. **Post-operative:** 5-mg hydrocodone tablets as needed.	Less VAS pain in group A (3.4 ± 1.2 vs 5.3 ± 1.3, p<0.05). Less hydrocodone consumption in group A 34 ± 27 mg vs B,115 ± 32 mg, (p<0.05). Patients in group A reported nausea on a total of 76 PODs vs 41 days in group B, p<0.05. Eighty percent of patients in group A reported less than expected pain, vs 40% in group B. In group A 25% of patients described pain as sharp and burning vs 78% in group B. Likewise, 75% of patients in group A and 22% in group B described their pain as dull and aching. All p<0.05.
Muscoloscheletal			
Mathiesen, 2008, **Setting** Hip arthroplasty **Jadad score** 5 **Reference** 74	**Sex:** **A:** 18/20; **B:** 14/26; **C:** 22/20 **Age: A:** 66 (63–71); **B:** 67 (62–71); **C:** 68 (64–71) **Drugs administration:** Oral acetaminophen 1 g 1 h before anaesthesia and: **Group A (n=38)**: PL + PL; **Group B (n=40)**: PGL 300 mg + PL; **Group C (n=42):** PGL 300 mg + 8 mg dexamethasone **Follow up:** at 2, 4, and 24 h.	**Anesthesia:** Spinal anaesthesia **Intraoperative:** No intraoperative analgesics. **Post-operative:** Oral acetaminophen 1 g every 8 h, initiated 4 h after operation, PCA morphine 2.5 mg bolus, 10 min lockout time.	No significant differences between groups on: morphine consumption for the first 2 and 4 h after operation; total morphine consumption between groups B and C; VAS pain scores at rest and on movement; nausea; ondansetron consumption; sedation at 24 h; dizziness. Less total 24 h morphine consumption in groups B (24 ± 14 mg) and C (25 ± 19 mg) vs A (47 ± 28 mg), (P<0.003); less number of vomits and number of patients vomiting in group A vs B. Less number of vomits and patients vomiting in group C vs B (P=0.03), but not different vs A; more sedation in group B vs A (p<0.003) and C (p=0.02).

PGL – pregabalin; PL – placebo; PCA – patient controlled analgesia; POD – post-operative day; PONV – post-operative nausea and vomiting

PGL provided better post-operative analgesia and rescue analgesics sparing than placebo in two [73, 75] of the three RCTs [70, 73, 75] that evaluated the effects of PGL alone vs placebo. The other one [73] did not find any differences between PGL and placebo on VAS and PCA opioid consumption. Mathiesen *et al.* studied the triple combination of 300 mg of PGL with dexamethasone and acetaminophen and did not find VAS reduction in confront of PGL-acetaminophen and acetaminophen alone after hip arthroplasty [74] and hysterectomy [76]. The post-surgery morphine consumption was similar in groups after hysterectomy [76] but higher in acetaminophen patients than PGL-acetaminophen and PGL-dexamethasone-acetaminophen patients after total hip arthroplasty [74]. Jokela *et al.* did not demonstrate VAS differences during all the 24 h post-hysterectomy follow up period between peri-operative administration of 300 mg or 600 mg of PGL and 10 mg of diazepam as control group [71]. The overall oxycodone consumption was lower in 600 mg PGL group vs 300 mg PGL group at 12-24 h period and in PGL 300 mg group vs diazepam at 24 h after surgery [71]. In adjunction to ibuprofen and diazepam, 150 mg of PGL provides better analgesia than PGL 75 mg-ibuprofen-diazepam and ibuprofen-diazepam association, but the rescue analgesic consumption was similar between groups [72]. No differences regarding the time elapsed from the end of the surgery and the first analgesic request has been observed both above-mentioned RCTs [71, 72] .Reuben at al reported as the peri-operative PGL-rofecoxib association reduced pain and opioid consumption regarding PGL or rofecoxib alone, after spinal fusion surgery [69]. Four studies reported no PGL effects on preventing the PONV [70-72, 75]. Mathiesen *et al.* [74] and Freedman *et al.* [73] findings suggest that PGL administration increases the incidence of PONV, meanwhile two other trials reported a reduction of PONV in PGL patients [69, 76]. PGL caused significantly more other

side effects than placebo in two trials [70, 71]. In other two RCTs the adverse effects in patients who received PGL were similar with those of the other groups [72, 75, 76]. Mathiesen *et al.* reported more sedation in PGL-acetaminophen group in confront of PGL-dexamethasone-acetaminophen combination and acetaminophen alone [74]. Meanwhile Reuben *et al.* findings suggested that PGL receiving patients reported higher incidence of sedation vs patients who received the combination of PGL-rofecoxib or rofecoxib alone [69]. Freedman *et al.* did not report data about side effects [73].

Meta-analysis

An overall of 7 meta-analysis regarding gabapentin use for apost-operative pain management [79-85] has been included in this review and the most important data of these studies are reported in the Table **5**. All these works findings are in accordance each other regarding the analgesic effects of GBP on the post operative setting. Statistically significant reduction of pain and rescue analgesic consumption has been reported by all the meta-analysis with GBP administration vs placebo during the perioperative period [79-85]. The most studied adverse effects were nausea and/or vomiting, sedation and dizziness. GBP effects on PONV reduction are not conclusive. Both Hurley *et al.* [81] and Seib *et al.* [83] did not find statistically significant difference with GBP administration with respect to reduction of incidence of PONV, in discordance with the other authors who described a significant reduction of nausea and vomiting [79, 80, 82, 84, 85]. The GBP-related sedation is reported in 5 of the 7 meta-analysis [79-82, 84]. The other two authors did not find any increase of the sedation incidence associated with GBP administration [83, 85]. More dizziness has been described by three authors in GBP patients [84, 79, 82] in discordance with Hurley *et al.* [81] who did not find any difference.

DISCUSSION

Both past and recent evidences (included in this review) with respect to the benefits of GBP/PGL administration for post-operative pain management are generally in favour of these drugs when confronted with placebo. Especially, due to the large number of the RCTs currently available, the GBP vs placebo efficacy on pain reduction and opioid sparing is clear. However, the meta-analysis included in the Table **5**

Table 5. Gabapentin and Pregabalin for the Postoperative Pain Management. Meta-Analysis

Author, year, trials included, reference	Patients included, outcome measures, dosages	Main results	Conclusions
Seib, 2006 8 RCTs, Reference 83	**Outcome measures** Pain scores, analgesic consumption, and side effects. **Patients included** A total of 663 subjects, 333 of whom received GBP, **GBP dosages** from 300 to 1200 mg, generally pre-operative single dose.	Statistically significant lower pain scores at rest in the GBP groups (WMD, 11.9; 95% CI: 8.4–15.5). This difference was most pronounced at 12–18 hr postoperatively (WMD 15.9; 95% CI 7.1–24.7). Significant reduction in pain scores on mobilization during the first 24 hr postoperatively (WMD, 11.0; 95% CI: 6.7–15.3). Lower opioid consumption ($P < 0.05$) in the GBP treatment arm (WMD 13.7; 95% CI 8.9–18.5). The incidence of GBP-related side effects (dizziness, light headedness, visual disturbance and headache) was similar in the GBP and control groups. There were no significant differences with respect to the incidence of opioid related adverse effects (nausea, vomiting, sedation, constipation, urinary retention, pruritus, and respiratory depression) between the GBP and control groups.	Preoperative GBP is effective in reducing postoperative opioid consumption in the first 24 hr after surgery and the pain scores a rest and with mobilization. Doses of 1200 mg are more effective in reducing analgesic consumption than doses of 300 or 400 mg. GBP treatment did not reduce the incidence of opioid related side effects.
Ho, 2006 16 RCTs reference 80	**Outcome measures** Pain scores, analgesic consumption, and side effects. **Patients included** Overall of 1151 patients, 614 of them received GBP. **GBP dosages** from 300 to 1200 mg, generally pre-operative single dose.	Preoperative GBP 1200 mg reduced significantly the pain scores at 6 h: WMD, -16.55 (95%CI: -25.66, -7.44) and 24 h: WMD, -10.87 (95%CI: -20.90, -0.84). Total: WMD, -14.17 (95%CI: -21.1, -7.22) and also the morphine consumption at 24 h: WMD, -27.9 mg (95%CI: -31.52, -24.29). The time to first analgesic was reduced by 7.42 minutes, (WMD, 7.42 min; 95%CI: 0.49, 14.34) Preoperative GBP <1200 mg reduced significantly pain scores at 6 h: WMD, -22.43 (95%CI: -27.66, -17.19) and 24 h: WMD, -13.18 (95%CI: -19.68, -6.68), and also the morphine consumption at 24 h: (WMD, -15.98 mg (95%CI: -23.45, -8.50). Significant lower nausea: OR, 0.72 (95%CI: 0.51-1.01), vomiting: OR 0.58 (95%CI: 0.39-0.86) and pruritus: OR 0.27 (95%CI: 0.10-0.74) and more sedation: OR 3.86 (95%CI: 2.5-5.94) in GBP groups.	The perioperative administration of GBP is effective in reducing pain scores, opioid requirements and opioid-related adverse effects in the first 24 h after surgery. Sedation was associated with its use but no serious adverse effects were observed.
Hurley, 2006 12 RCTs Reference 81	**Outcome measures** Pain scores, analgesic consumption, and side effects. **Patients included** Overall of 896 patients, 449 of them received GBP. **GBP dosages** from 300 to 1200 mg generally given as a single dose 1-2 h before surgery.	Oral GBP was associated with a statistically significant reduction in post-operative pain at 0 to 4 hours (WMD -1.57, 95% CI: -2.14, -0.99) and at 20 to 24 hours (WMD -0.74, 95% CI: -1.03, -0.45) compared with the placebo. GBP was also associated with a statistically significant reduction in post-operative analgesic use (WMD -17.84, 95% CI: -23.50, -12.18) and a significantly increased incidence of sedation OR 3.28; 95% CI: 1.21-8.87) compared with placebo. There was no statistically significant difference between GBP and control in nausea (WMD, 0.9; 95% CI, 0.43-1.89), vomiting (OR=0.71; 95% CI, 0.43-1.16), or dizziness/lightheadedness OR=1.27; 95% CI, 0.67-2.41).	Perioperative oral GBP appears to be a useful adjunct for the postoperative analgesia through a different mechanism than other available analgesic agents. As a part of a multimodal treatment plan, GBP may provide synergistic analgesic effects with other agents.

(Table 5). contd…..

Author, year, trials included, reference	Patients included, outcome measures, dosages	Main results	Conclusions
Tiippana, 2007 22 CRTs, Reference 79	**Outcome measures** Pain scores, analgesic consumption, and side effects. **Patients included** A total of 1909 patients, 786 received GBP, and 99 received PGL. **GBP dosages** from 300 to 1200 mg. In the PGL study the dose was 50 or 300 mg. Thirteen of the studies were single-dose trials and 9 with multiple dosing of GBP or PGL.	There was wide variation in pain at rest after different types of surgery. The overall VAS pain difference between GBP and control groups ranged from 5 mm to 35 mm during the first 12 h post surgery and from 0 mm to 28 mm during 12h-24 h post-surgery. The opioid-sparing effect during the first 24 h after a single preoperative dose of GBP 300–1200 mg, administered 1–2 h before surgery, ranged from 20% to 62%, (WMD -2.0, 95% CI: -2.5, -1.4). The combined effect of a single dose of GBP on opioid consumption was equivalent to reduction of 30 ± 4 mg of morphine consumed during the first 24 h after the surgery. Heterogeneity among the studies was significant (P<0.0001). The NNT to prevent nausea, vomiting, or urinary retention were 25, 6, and 7, respectively. The NNH for GBP to produce excessive sedation or dizziness were 35 and 12, respectively. There were no significant differences in any other adverse effects.	GBP is effective in reducing pain intensity, opioid consumption and opioid-related adverse effects after surgery. It has very few adverse effects. Because of the heterogeneous data of these studies, no conclusions about the optimal dose and duration of the treatment can be drawn.
McQuay, 2008 18 RCTs, Reference 82	**Outcome measures** Pain scores, analgesic consumption, and side effects. Trials with similar pain scores between the groups within a predetermined time interval were classified as category A and those reporting different pain scores between the groups within the same time period as category B. **Patients included** A total of 1217 patients. **GBP dosages** from 300 to 1200 mg. All trials used a placebo, except one using oxazepam. All trials, except one, administered one or more doses of GBP before operation, 5 of these continued GBP after operation.	In Category A trials, the pain scores in the placebo groups at 4 h were all 30/100 mm VAS or equivalent. This was achieved even though baseline pain scores were greater than 30/100 mm with one exception. This may reflect an effective analgesic delivery system, which a valid analgesic consumption outcome measure should have. Most Category B trials failed to achieve a similar reduction in pain score at 4 h. In some trials, it was not achieved even at later time points, and this may reflect a failing of analgesic delivery. This suggests that Category B trials were less robust than category A. Of the seven category A trials, four reported reduced analgesic consumption with GBP compared with placebo at one or more time points and three trials reported no difference between GBP and placebo. The weighted mean analgesic consumption for GBP compared with placebo (24 h where available, or longest time) was 71% in Category A trials. All 11 Category B trials reported a decrease in analgesic consumption with GBP at one or more time points. The weighted mean analgesic consumption of GBP compared with placebo was 59% for Category B trials. Combining all 18 trials, the weighted mean consumption was 62%, a reduction in analgesic consumption in the GBP group of 38%. There were a statistically significant increase in the incidence of sedation (RR, 2.2; 95%CI: 1.7–3.0) and dizziness (RR, 1.6; 95%CI: 1.1–2.2) and a statistically significant decrease in the incidence of vomiting (RR, 0.7; 95%CI: 0.5–0.9) but not nausea with GBP compared with control group.	The analgesic consumption outcome measure, comparing consumption in different treatment groups after test and control interventions, is valid only when the groups have achieved similar pain scores. It is not clear about whether or not perioperative GBP is a useful part of perioperative care. Where the pain scores in the treatment and control groups did not come down to similar levels, should make the reader sceptical.
Mathiesen 2007 23 RCTs Reference 85	**Outcome measures** Pain scores, analgesic consumption, side effects **Patients included** Overall of 1529 patients **GBP dosages** from 300 mg/day to 1.200 mg/day	The reported 24-hour opioid consumption was significantly reduced with gabapentin administration. Quantitative analysis of five trials in abdominal hysterectomy showed a significant reduction in morphine consumption (WMD, – 13 mg; 95% CI: -19, -8 mg), and in early pain scores, VAS at rest (WMD, – 11 mm; 95% CI: -12, -2 mm) and VAS during activity (WMD, -8 mm; 95% CI: -13, -3 mm), favouring gabapentin. In spinal surgery, (4 trials), analyses demonstrated a significant reduction in morphine consumption (WMD, -31 mg; 95% CI: -53, -10 mg) and pain scores, VAS early (WMD -17 mm; 95 % CI: - 31, -3 mm) and VAS late (WMD, -12 mm; 95% CI: - 23, -1 mm) also favouring gabapentin treatment. Nausea was improved with gabapentin in abdominal hysterectomy (RR, 0.7; 95 % CI: 0.5, 0.9). Other side-effects were unaffected.	perioperative use of gabapentin has a significant 24-hour opioid sparing effect for both abdominal hysterectomy and spinal surgery patients, whereas the reduction in pain score is more inconsistent. Nausea may be reduced in abdominal hysterectomy. All the other side effects were not significantly different between treatment groups.

(Table 5). contd…..

Author, year, trials included, reference	Patients included, outcome measures, dosages	Main results	Conclusions
Peng, 2007 18 RCTs reference 84	**Outcome measures** Pain scores, analgesic consumption, and side effects. **Patients included** Overall of 1181 patients. **GBP dosages** from 300 mg/day to 1,800 mg/day	Reduce of analgesic consumption in the first 24 h: (ratio of means 0.65, 95% CI: 0.59, 0.72, p<0.001) and delayed time to first analgesic by 7.9 minutes (WMD 7.9, 95% CI: 4.2, 11.6, p<0.001). GBP significantly reduced post-operative pain at rest by 27% (95% CI: 6.8 mm, 15.8 mm) at 2 h and by 39% (95% CI: 8.5 mm, 20.2 mm) at 4 h and maintain this reduction at 12 and 24 h. With the exception of 24 h after surgery, GBP use was also associated with a significant reduction in pain with movement, ranging from 18 to 28%. GBP was associated with more dizziness (RR 1.40, 95% CI: 1.06, 1.84, p<0.02) and less pruritus (RR 0.30, 95% CI: 0.13, 0.70, p<0.005) and vomiting (RR 0.73, 95% CI: 0.56, 0.95, p<0.02). Borderline increased risk of sedation with GBP (RR 1.65, 95% CI: 1.00, 2.74, p=0.05) and no significant impact on the occurrence of respiratory depression or nausea.	GBP improves the analgesic efficacy of opioids at rest and with movement, reduces analgesic consumption and reduces opioid-related adverse events. However, it is also associated with an increased risk of dizziness and sedation.

GBP – gabapentin; PGL – pregabalin; RCTs – randomised clinical trials; WMD – weighted mean difference; NNT - numbers-needed-to-treat; NNH - numbers-needed-to-harm**;** RR - relative risk; 95%CI - 95% confidence interval

[79-85] and the other systematic-narrative reviews [11, 28, 77, 78] demonstrated a large heterogeneity of the published double blind randomized clinical trials currently available. Due to this heterogeneity especially with respect to surgical procedure, patient population, trial design and quality, gabapentinoids dose and their combination with other analgesics and duration of treatment, it would be very cautious on expressing definitive conclusions on the specific clinical utility of gabapentin and PGL for postoperative pain. Furthermore, the critical point of view of McQuay *et al.* with respect to the use of post-operative opioid consumption as a major outcome for RCTs on post- surgery pain management, arise an important interrogative-point regarding an important methodological aspect of this kind of studies.

Nevertheless, a large number of published placebo-controlled, double-blind, randomized trials have demonstrated the postoperative analgesic efficacy with GBP and PGL, the RCTs that take in consideration gabapentinoids' analgesic and opioid-sparing efficacy with respect to other analgesic drugs are very heterogeneous [47, 51, 53, 55, 57, 62, 65, 66, 69, 70, 72, 74, 76]. Gabapentinoids are perhaps superior to celecoxib [69] and meloxicam [66] and border line with respect to lornoxicam [53]. Gilron *et al.* in a study published in 2005 described as GBP and rofecoxib provided better analgesia than either single agent and also PCA-morphine consumption is more reduced with GBP-rofecoxib treatment [41]. Studying GBP-rofecoxib association, Mikkelsen *et al.* found only opioid sparing effects in confront of rofecoxib alone [51] in discordance with Turan *et al.* results who did not report substantial differences between GBP-rofecoxib combination and rofecoxib or GBP alone with respect to VAS reduction and opioids sparing [47]. Meanwhile, in confront with clonidine, GBP is more efficacious as Mohammadi *et al.* [62] or similar as Ghafari *et al.* findings [65]. GBP-acetaminophen was more effective than GBP alone with respect to overall opioid consumption and on VAS reduction till 4 h post-surgery, however the groups were than similar for each other during the remaining follow up period [55]. No more data that tested this combination are available at the moment. The gabapentinoids-dexamethasone association did not offer further benefits on VAS reduction in confront of GBP [57], acetaminophen [74, 76], or dexamethasone alone [57] and a significant opioid sparing has been reached only in one of these three studies [57]. No other RCTs that studied this kind of combination are available in the literature at the best of our knowledge.

The optimal dose of the gabapentinoids for the post-operative pain management is not clear. Said-Ahmed reported that increasing the pre-emptive dose of gabapentin (300 to 1200 mg), significantly decrease the severity of post-myomectomy pain and total opioid consumption during the first 24 hours after surgery [60]. These findings are in discordance with Pandey *et al.* results after lumbar discectomy setting, published on 2005, that demonstrated pain reduction with 600mg was better than with 300 mg but no additional benefits were observed at doses of 900 or 1200mg [44]. However, further work is needed to better define the optimal GBP dose for specific surgical procedures.

The GBP Elimination half-life is 4.8-8.7 h [90, 91] and the PGL elimination half-life is 5.5-6.7h [92, 93]. The likely time during which the clinical effect of GBP/PGL should be maximally present is 4–12 h after surgery. Beyond 24 h, no residual effect of single dose GBP was expected. as confirmed by several authors who administered only pre-emptive GBP/PGL did not find analgesic or opioid sparing effects over than 24 h [47, 64, 65, 71]. However, Fassoulaki *et al.* in two different studies [48, 59] found analgesic benefits after peri-operative GBP administration 1 month after surgery. A possible answer could be that treating acute postoperative pain preoperatively may prevent or attenuate persistent postsurgical pain [94] but further investigation are needed to elucidate this aspect.

The mechanism of gabapentin in the prevention of PONV is unknown but it could possibly be due to the indirect effect of opioid sparing or a direct effect on tachykinin activity [95]. Two RCTs published in 2004 are discordant about GBP effects on PONV. Pandey *et al.* reported more sedation and nausea [34], whereas Turan *et al.* reported less nausea/vomiting and less urinary retention with gabapentin [39]. The majority of the RCTs that considered a direct gabapentinoids-placebo-confront (18 of 24) reported

opioid-sparing effects with GBP or PGL administration vs placebo. However, only two of these trials reported a concurrent reduction in opioid-related nausea or vomiting in GPB-alone group vs placebo group [57, 68]. Due to the well-known antiemetic effect of dexamethasone [104] [96] when it was administered in combination with GBP a significant PONV reduction has been reported [57, 74]. Turan *et al.* reported as the highest morphine sparing effect was achieved in GBP-rofecoxib group registering also the lowest PONV incidence in those patients after hysterectomy [47]. Two studies reported higher incidence of PONV with GBP [51] or PGL [71] administration. Generally our data on PONV incidence are in accordance with those of Seib *et al.* [83] and Hurley *et al.* [81] meta-analysis and in discordance with the other authors who described a significant reduction of nausea and vomiting [79, 80, 82, 84, 85]. Meanwhile, the information reported from the other systematic-narrative reviews regarding PONV are inconclusive [11, 28, 77, 78] Furthermore, it would be considered that RCTs included in the previous reviews and those included in the present one are partially different.

CONCLUSION

In conclusion, gabapentin and pregabalin are effective in reducing pain intensity and opioid consumption after surgery in confront with placebo. The analgesic potentials of gabapentinoids in comparison with other standard post-operative regimens are still not clear. There are not exhaustive evidences about the optimal dose and duration of the post-operative treatment with GBP/PGL. Since only a little number of RCTs has followed the patients for a long post-operative period, the efficacy of gabapentinoids in preventing chronic post-operative pain needs to be elucidated in future studies. Gabapentin and pregabalin seem not to have any influence on the prevention of post-operative nausea and vomiting.

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