Supplementary material

GABA DOSE Supplemental Digital Content

Supplemental Digital Content 1 Search strategies

Preliminary searches performed 13 November 2013

Total number of references identified: 16895 references
Number of duplicates removed: 3189 references
Number of references in final list: 13706 references

Batch name: 131113_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL)(Issue 10 of 12, 2013) in The Cochrane Library (2411 hits in CENTRAL)
#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP)(1946 to November 2013)(7072 hits)
1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to November 2013)(3653 hits)

1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (http://apps.webofknowledge.com)(1900 to November 2013)(3759 hits)
#3 3,759 #2 AND #1
#2 385,187 TS=(pain*)
#1 68,630 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Preliminary searches performed 30 June 2014

Total number of references identified: 16861 references
Number of duplicates removed: 3592 references
Number of references in final list: 13569 references
Number of new references: 789 references

Batch name: 140701_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL)(Issue 6 of 12, 2014) in The Cochrane Library (2619 hits in CENTRAL)
#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP)(1946 to July 2014)(6319 hits)
1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]

4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to July 2014)(3847 hits)
1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (http://apps.webofknowledge.com)(1900 to July 2014)(4076 hits)
#3 4,076 #2 AND #1
#2 417,945 TS=(pain*)
#1 72,059 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Preliminary searches performed 14 November 2014

Total number of references identified: 17315 references
Number of duplicates removed: 4105 references
Number of references in final list: 13210 references
Number of new references: 462 references

Batch name: 141114_J Wetterslev_GABA NEW

Cochrane Central Register of Controlled Trials (CENTRAL)(Issue 11 of 12, 2014) (2645 hits)
#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4

#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP)(1946 to November 2014)(6549 hits)
1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to November 2014)(3962 hits)
1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (1900 to November 2014)(4159 hits)
#3 4,159 #2 AND #1
#2 417,588 TS=(pain*)
#1 72,305 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Preliminary searches performed 9 April 2015

Total number of references identified: 17466 references
Number of duplicates removed: 4042 references
Number of references in final list: 13424 references
Number of new references: 126 references

Batch name: 150409_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 3 of 12, 2015) (2629 hits)
#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP)(1946 to April 2015) (6432 hits)
1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to April 2015) (4081 hits)
1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (1900 to April 2015) (4324 hits)

#3 4,324 #2 AND #1
#2 430,421 TS=(pain*)
#1 73,791 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Preliminary searches performed 23rd September 2015
Total number of references identified: 18200 references
Number of duplicates removed: 4184 references
Number of references in final list: 14016 references
Number of new references: 1188 references

Batch name: 150915_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 8 of 12, 2015) (2798 hits)
#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP) (1946 to September 2015) (6621 hits)
1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to September 2015) (4289 hits)
1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]

4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (1900 to September 2015) (4492 hits)
#3 4,492 #2 AND #1
#2 445,898 TS=(pain*)
#1 75,431 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Preliminary searches performed 12th April 2016

Total number of references identified:	references
Number of duplicates removed:	references
Number of references in final list:	references
Number of new references:	references

Batch name: 160412_J Wetterslev_GABA

Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 4 of 12, 2015) (2993 hits)
#1 MeSH descriptor: [Amines] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#2 MeSH descriptor: [gamma-Aminobutyric Acid] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#3 MeSH descriptor: [Cyclohexanecarboxylic Acids] explode all trees and with qualifiers: [Adverse effects - AE, Therapeutic use - TU]
#4 (gaba* or neurontin* or neurotonin* or horizant*)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Pain] explode all trees
#7 pain*
#8 #6 or #7
#9 #5 and #8
#10 adult* or middle age* or aged
#11 #9 and #10

MEDLINE (Ovid SP) (1946 to April 2016) (6625 hits)
1. exp Amines/ae, tu [Adverse Effects, Therapeutic Use]
2. exp gamma-Aminobutyric Acid/ae, tu [Adverse Effects, Therapeutic Use]
3. exp Cyclohexanecarboxylic Acids/ae, tu [Adverse Effects, Therapeutic Use]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5. 1 or 2 or 3 or 4
6. exp Pain/
7. pain*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]

8. 6 or 7
9. 5 and 8
10. limit 9 to (humans and ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)"))

EMBASE (1974 to April 2016) (4474 hits)
1. amine/ae, dt, th [Adverse Drug Reaction, Drug Therapy, Therapy]
2. 4 aminobutyric acid/ae, dt [Adverse Drug Reaction, Drug Therapy]
3. cyclohexanecarboxylic acid derivative/ae, dt [Adverse Drug Reaction, Drug Therapy]
4. (gaba* or neurontin* or neurotonin* or horizant*).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. 1 or 2 or 3 or 4
6. exp pain/
7. pain*.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. 6 or 7
9. 5 and 8
10. limit 9 to (human and (adult <18 to 64 years> or aged <65+ years>))

Science Citation Index Expanded (1900 to April 2016) (4717 hits)
#3 #2 AND #1
#2 TS=(pain*)
#1 TS=(gaba* or neurontin* or neurotonin* or horizant*)

Google Scholar search

After the 1st search, 13th November 2013
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

After the 2nd search, 30th June 2014
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

Limits: titles from 1st November 2013 and on

After the 3rd search, 14th November 2014
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

Limits: titles from 1st June 2014 and on

After the 4th search, 9th April 2015
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

Limits: titles from 1st November 2014 and on

<u>After the 5th search, 23rd September 2015</u>
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

Limits: titles from 1st April 2015 and on

<u>After the 6th search, 12th April 2016</u>
Gabapentin AND Postoperative pain
Gabapentin AND Acute pain management
Gabapentin AND Perioperative pain management

Limits: titles from 1st September 2015 and on

Supplemental Digital Content 2 Opioid conversion

Opioid	**Administration**	**Opioid: Intravenous morphine**
1 mg Fentanyl	i.v.	100 mg morphine
1 mg Hydromorphone	i.v.	5 mg morphine
1 mg Morphine oral	oral	0.33 mg morphine
1 mg Nalbuphine	i.v.	1 mg morphine
1 mg Pethidine/Meperidine	i.v.	0.13 mg morphine
1 mg Propoxyphene	i.v.	5 mg morphine
1 mg Tramadol oral	oral	0.07 mg morphine

Supplemental Digital Content 3 Trial characteristics

Trial	**No* of patients**	**Surgical Procedures**	**Dose** *mg/day (bolus mg)*	**Treatment** *Single / Multiple dose*	**Total 24-hour morphine consumption** *Intra venous morphine (mg)*	
					Intervention (mg) *(Mean SD)*	**Control (mg)** *(Mean SD)*
Amr 2009[32]	100	Radical or partial mastectomy	300 mg/day (300 mg)	Multiple dose	13.5 (0.5)	22.0 (2.1)
Bang 2009[36]	46	Arthroscopic shoulder surgery	300 mg/day	Single dose	32.1 (29.1)	30.1 (28.67)
Behdad 2012[39]	61	Hysterectomy	300 mg/day (100 mg)	Multiple dose	-	-
Chowdhury 2010[46]	200	Gynecological surgery	300 mg/day	Single dose	-	-
Clarke 2014[48]	179	Total knee arthroplasty	200 mg /day (600 mg)	Multiple dose	37 (1.5)	48 (1.3)
Ghafari 2009[60]	66	Abdominal hysterectomy and salphingooophrectomy	300 mg/day (300 mg)	Multiple dose	15.8 (1.2)	26.9 (2.3)
Hassani 2014[67]	60	Laparoscopic gastric by-pass	100 mg/day	Single dose	-	-
Khurana 2013[77]	60	Lumbar discectomy	300 mg/day (300 mg)	Multiple dose	-	-
Mohammadi 2008[95]	70	Assisted reproductive techniques	300 mg/day	Single dose	-	-
Mohammadi 2009[96]	80	Abdominal surgery/gynecological surgery	300 mg/day	Single dose	-	-
Lichtinger 2011[84]	40	Bilateral photorefractive keratectomy	300 mg/day (600 mg)	Multiple dose	-	-
Pandey 2004c[107]	56	Single level lumbar disc surgery	300 mg/day	Single dose	90.9 (34.1)	92.5 (41.8)
Ray 2015[118]	60	Abdominal hysterectomy	300 mg/day	Single dose	-	-
Sekhavet 2009[123]	98	Abdominal hysterectomy	300 mg /day (600 mg)	Multiple dose	40.1 (14.5)	52.7 (21.1)
Spence 2011[131]	57	Shoulder arthroscopy	300mg/day (300 mg)	Multiple dose	-	-
Vahedi 2011[140]	76	Lumbar laminectomy and discectomy	300 mg/day	Single dose	18.6 (9.0)	21.5 (11.3)

Vasigh 2016[141]	76	Laminectomy	300 mg/day (600 mg)	Multiple dose	-	-
Verma 2008[142]	50	Abdominal hysterectomy	300 mg/day	Single dose	-	-
Waikakul 2011[144]	48	Spine, major joint, tumor and major limb surgery	300 mg/day (400 mg)	Multiple dose	15.5 (9.3)	18 (15.5)
Yoon 2001[145]	32	Hysterectomy	300 mg/day (400 mg)	Multiple dose	24.1 (9.9)	32.7 (14.6)
Ajori 2011[30]	138	Abdominal hysterectomy	600 mg/day	Single dose	-	-
Azemati 2013[33]	100	Mastectomy or quandrandectomy and axillary node dissection	600 mg/day	Single dose	-	-
Bafna 2014[143]	60	Gynecological surgery	600 mg/day	Single dose	-	-
Bashir 2009[38]	100	Laparoscopic cholecystectomy	600 mg/day	Single dose	-	-
Bhandari 2014[41]	40	Laparoscopic cholecystectomy	600 mg/day (600 mg)	Multiple dose	-	-
Bharti 2012[42]	40	Total mastectomy with axillary node dissection	600 mg/day	Single dose	2.1 (2.2)	4.9 (3.4)
Celebi 2013[45]	60	Gynecological laparoscopy	600 mg/day	Single dose	-	-
Clarke 2009b[147]	115	Total hip arthroplasty	600 mg/day	Single dose	37.0 (1.5)	48 (1.3)
Ercan 2014[54]	34	Carotid Endartectomy	600 mg/day	Single dose	-	-
Gosai 2015[64]	60	Mastectomy	600 mg/day	Single dose	-	-
Grover 2009[66]	46	Total mastectomy with axillary node dissection	600 mg/day	Single dose	-	-
Hoseini 2015[68]	44	Cholecystectomy	600 mg/day	Single dose	-	-
Joseph 2014[71]	50	Abdominal hysterectomy	600 mg/day (600 mg)	Multiple dose	38.7 (18.0)	44.3 (16.0)
Kavitha 2013[72]	56	Intraocular surgery/cataract	600 mg/day	Single dose	-	-
Kazak 2009[73]	60	Nasal septal, nasal sinus surgery	600 mg/day	Single dose	-	-
Khademi 2009[74]	87	Open cholecystectomy	600 mg/day	Single dose	2.8 (1.3)	3.5 (1.5)
Khezri 2013[76]	80	Cataract surgery	600 mg/day	Single dose	-	-
Kinney 2011[79]	125	Thoratectomy; lobectomy; pneumonectomy; chest wall resection	600 mg/day	Single dose	-	-
Manhoori 2014[85]	50	Unilateral herniorrhaphy	400 mg/day	Single dose	-	-
Maleh 2013[86]	80	Laparoscopic surgery	600 mg/day	Single dose	2.5 (2.6)	2.7 (2.7)
Mardani-Kivi 2013[88]	108	Anterior Collateral Ligament reconstruction	600 mg/day	Single dose	2.5 (2.3)	3.7 (2.5)

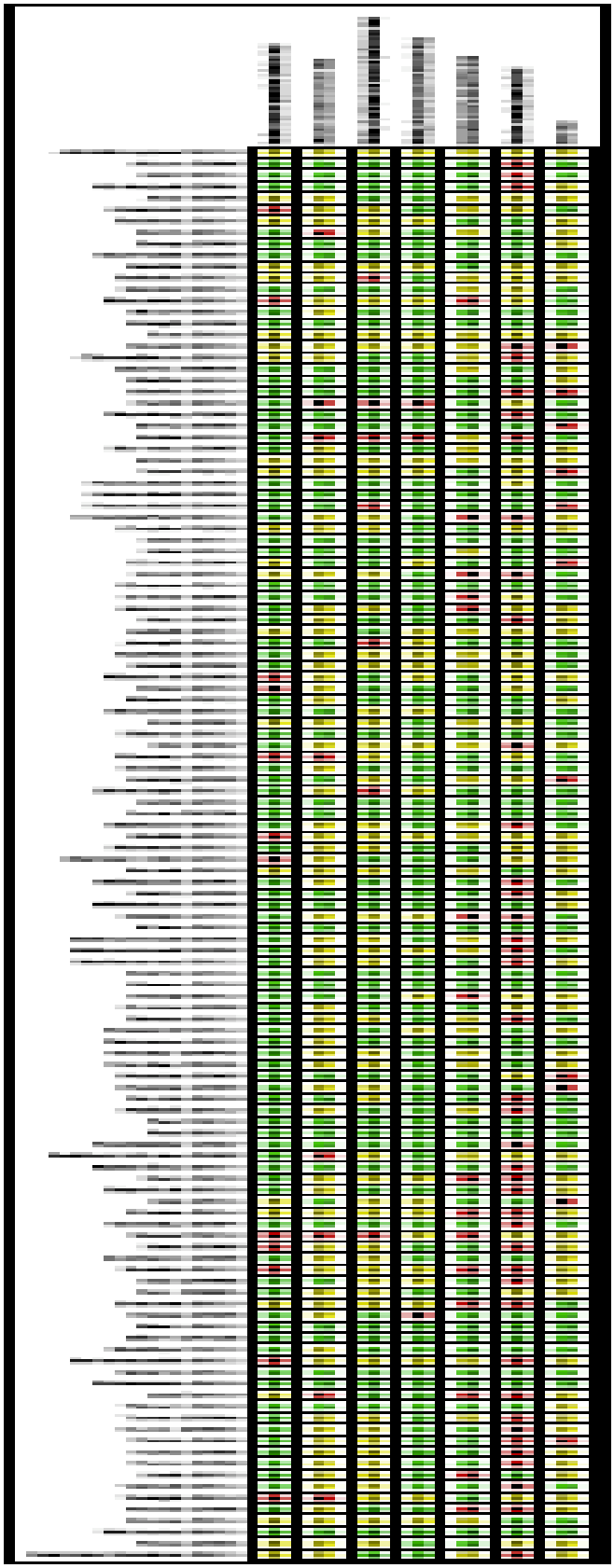
Menda 2010[89]	60	Coronary Artery Bypass Graft	600 mg/day	Single dose	6.0 (8.5)	15.1 (20)
Metry 2008[91]	68	Unilateral radical mastectomy and axillary dissection	600 mg/day (1200 mg)	Single dose	16.1 (7.7)	29.2 (9.6)
Misra 2013[94]	73	Craniotomy for intracranial tumor	600 mg/day	Single dose	24.6 (19.6)	29.2 (25.2)
Monks 2015[98]	197	Cesarean section	600 mg/day (600 mg)	Multiple dose	10.0 (11.9)	10.0 (7.4)
Moore 2010[99]	44	Cesarean section	600 mg/day	Single dose	3.0 (3.0)	4.0 (5.0)
Özcan 2011[102]	40	Supratentorial tumor surgery	600 mg/day	Single dose	15.0 (5.0)	19.0 (4.2)
Pandey 2005[108]	60	Open donor nephrectomy	600 mg/day	Single dose	59.4 (23.2)	92.5 (41.8)
Pandey 2006[105]	250	Laparoscopic cholecystectomy	600 mg/day	Single dose	39.2 (26.3)	67.7 (25.3)
Parikh 2010[109]	60	Elective surgery	600 mg/day	Single dose	31.7 (20.3)	31.9 (19.8)
Paul 2013[111]	101	Total knee arthroplasty	600 mg/day (200 mg)	Multiple dose	27.9 (23.0)	26.8 (19.0)
Paul 2015[112]	102	Total hip arthroplasty	600 mg/day (600 mg)	Multiple dose	19.7 (16.4)	25.1 (14.5)
Saeed 2013[121]	100	Laparoscopic cholecystectomy	600 mg/day	Single dose	-	-
Sava 2009[122]	50	Colorectal surgery	600 mg/day	Single dose	35.6 (14.1)	54.7 (13.0)
Semira 2013[124]	60	Laparoscopic cholecystectomy	600 mg/day	Single dose	-	-
Sharma 2015[127]	40	Laparoscopic cholecystectomy	600 mg/day (600 mg)	Multiple dose	-	-
Short 2012[9]	63	Cecaerean section	300 mg	Single dose	5.7 (5.3)	7.9 (3.8)
Siddiqui 2013[129]	72	Major bowel surgery	600 mg/day	Single dose	-	-
Soltanzadeh 2011[130]	60	Coronary Artery Bypass Grafting	400 mg/day (800 mg)	Multiple dose	2.5 (0.9)	4.0 (1.5)
Srivastava 2009[132]	120	Open cholecystectomy	600 mg/day	Single dose	25.4 (4.5)	37.6 (8.4)
Zaldivar-Ramirez 2011[146]	34	Nissen laparoscopic fund-operation	600 mg/day (300 mg)	Multiple dose	-	-
Adam 2006[29]	53	Arthroscopic shoulder surgery	800 mg/day	Single dose	-	-
Badawy 2014[34]	40	Abdominal hysterectomy	800 mg/day	Single dose	11.5 (2.3)	13.0 (2.9)
Deniz 2012[49]	51	Radical Retropubic Prostatectomy	900 mg/day	Single dose	22.2 (11.9)	25.6 (10.5)
Farzi 2015[55]	103	Septorhinoplasty	900 mg/day	Single dose	-	-
Ghai 2011[61]	60	Abdominal hysterectomy	900 mg/day	Single dose	5.4 (1.6)	4.3 (1.9)
Ghai 2012[62]	60	Abdominal hysterectomy	900 mg/day	Single dose	-	-

Kuhnle 2010[82]	82	PRK Myopia surgery	900 mg /day (300 mg)	Multiple dose	-	-
Kim 2004[78]	41	Mastectomy	900 mg/day	Single dose	35.8 (20.8)	33.5 (26.1)
Koc 2007[80]	40	Varicocele	800 mg/day	Single dose	-	-
Leung 2006[83]	21	Spine surgery	900 mg/day (900 mg)	Multiple dose	-	-
Lunn 2015[5]	140	Total knee arthroplasty	900 mg/day	Multiple dose	45.4 (35.7)	50.5 (41.4)
Marashi 2012[87]	44	Thyroidectomy	900 mg/day	Single dose	18.3 (15.6)	65.7 (31.0)
Mishra 2016[93]	60	Laparoscopic cholecystectomy	900 mg/day	Single dose	-	-
Neogi 2012[100]	60	Laparoscopic cholecystectomy	900 mg/day	Single dose	-	-
Pakravan 2012[104]	100	Post photorefractive keratectomy surgery	900 mg/day (300 mg)	Multiple dose	-	-
Prabhakar 2007[113]	20	Elective brachial plexus exploration	800 mg/day	Single dose	23.8 (5.0)	20.0 (2.1)
Radhakrishnan 2005[114]	30	Lumbar laminectomy or lumbar discectomy	800 mg/day (400 mg)	Multiple dose	-	-
Rajendran 2014[116]	60	Small gastrointestinal procedures	900 mg/day	Single dose	-	-
Ram 2015[115]	60	Abdominal hysterectomy	900 mg/day	Single dose	-	-
Rimaz 2014[119]	60	Dacryocystorhinostomy	900 mg/day	Single dose	-	-
Short 2012a[9]	63	Cesarean section	600 mg	Single dose	6.7 (3.6)	7.9 (3.8)
Abdelmageed 2010[28]	60	Tonsillectomy	1200 mg/day	Single dose	6.6 (1.3)	12.2 (1.1)
Al-Mujadi 2005[31]	72	Elective thyroid surgery	1200 mg/day	Single dose	15.2 (7.6)	29.5 (9)
Bartholdy 2006[37]	76	Sterilization laparoscopic with Filshie clips	1200 mg/day	Single dose	-	-
Bakry 2011[35]	60	Cataract surgery	1200 mg/day	Single dose	-	-
Bekawi 2014[40]	60	Laparoscopic cholecystectomy	1200 mg/day (1200 mg)	Multiple dose	0 (2.2)	7.5 (0.7)
Brogly 2008[43]	43	Total or partial thyroidectomy	1200 mg/day	Single dose	0 (1.48)	0 (4.4)
Butt 2010[44]	100	Mastectomy	1200 mg/day	Single dose	-	-
Clarke 2013[47]	44	General-, gynecological-, plastic and ENT surgery	1200 mg/day	Single dose	-	-
Dierking 2003[50]	80	Abdominal hysterectomy and salphingooophrectomy	2400 mg/day (600 mg)	Multiple dose	43.0 (23.7)	63.0 (25.9)
Dirks 2002[51]	65	Unilateral radical mastectomy with axillary dissection	1200 mg/day	Single dose	-	-

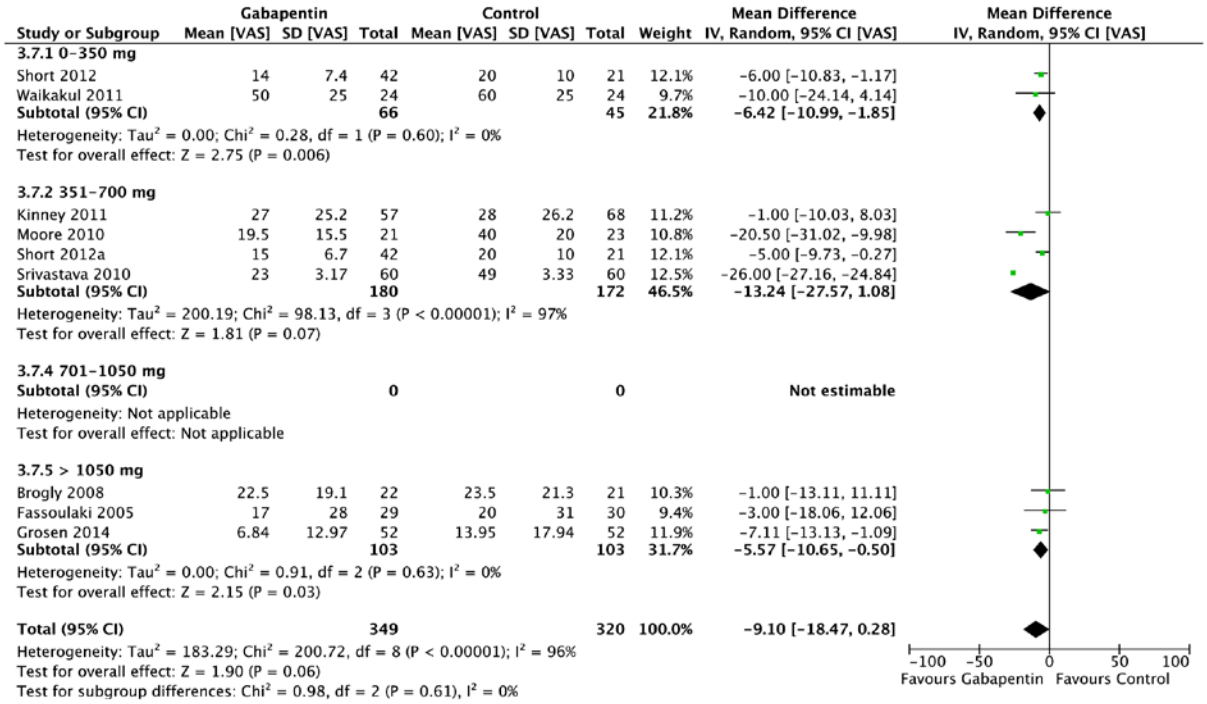
Doha 2010[52]	59	Radical Mastectomy	1200 mg/day	Single dose	39.9 (33.0)	42.7 (36.1)
Durmus 2006[53]	50	Total abdominal hysterectomy	1200 mg/day	Single dose	40.0 (10.0)	66.0 (10.0)
Fassoulaki 2002[57]	50	Radical mastectomy or lobectomy with axillary node dissection	1200 mg/day (1200 mg)	Multiple dose	23.8 (5.0)	23.2 (5.8)
Fassoulaki 2005[58]	59	Abdominal hysterectomy	1600 mg/day 400 mg	Multiple dose	20.3 (7.9)	25.7 (11.2)
Fassoulaki 2006[56]	60	Abdominal hysterectomy	1600 mg/day 800 mg	Multiple dose	22.0 (2.9)	35.0 (4.8)
Frouzanfard 2013[59]	50	Abdominal hysterectomy	1200 mg/day	Single dose	1.2 (0.2)	5.2 (2.8)
Gilron 2004[63]	47	Abdominal hysterectomy	1800 mg/day 600 mg	Multiple dose	56.8 (32.4)	82.1 (48.2)
Grosen 2014[65]	104	Thoracotomy for malignancy	1200 mg/day (1200 mg)	Multiple dose	11.2 (21.6)	17.9 (23.69)
Hout 2007[69]	51	Exploratory thoracotomy, pneumonectomy, lobectomy, segmentectomy, biopsy	1200 mg/day	Single dose	2.4 (2.5)	2.7 (3.2)
Jajeda 2014[70]	50	Upper abdominal surgery	1200 mg/day	Single dose	-	-
Khan 2013[75]	69	Abdominal hysterectomy	1200 mg/day	Single dose	13.1 (4.7)	24.3 (9.3)
Kosucu 2013[81]	60	Posterolateral or lateral thoracotomy	1200 mg/day	Single dose	25.9 (8.3)	44.0 (11.0)
Lunn 2015a[5]	141	Total knee arthroplasty	1300 mg/day	Multiple dose	46.2 (41.0)	50.5 (41.4)
Ménigaux 2004[90]	40	Arthroscopic anterior cruciate ligament	1200 mg/day	Single dose	21.0 (12.0)	20.0 (19.0)
Mikkelsen 2006[92]	51	Tonsillectomy	1800 mg/day (1200 mg)	Multiple dose	-	-
Mohammed 2012[97]	80	Functional endoscopic sinus surgery	1200 mg/day	Single dose	-	-
Omran 2005[101]	50	Posterolateral thoracotomy for lobectomy	1200 mg/day (1200 mg)	Multiple dose	23.9 (2.6)	31.5 (2.8)
Özgenzil 2011[103]	60	Decompressive lumbar laminectomy and discectomy	1800 mg/day 600 mg	Multiple dose	29.5 (9.6)	37.3 (9.5)
Pathak 2014[110]	80	Cholecystectomy	1200 mg/day	Single dose	-	-
Rapchuk 2009[117]	54	Cardiac surgery	1200 mg/day	Single dose	-	-
Rorarius 2004[102]	90	Vaginal hysterectomy	1200 mg/day	Single dose	-	-
Sen 2009a[125]	40	Abdominal hysterectomy and salphingooophrectomy	1200 mg/day	Single dose	31.0 (12.0)	48.0 (17.0)
Sen 2009b[126]	59	Unilateral inguinal herniotomy	1200 mg/day	Single dose	20.0 (11.5)	28.0 (11.5)

Sheen 2008[128]	80	Orthopedic surgeries	1200 mg/day	Single dose	-	-
Syal 2010[133]	60	Open cholecystectomy	1200 mg/day	Single dose	40.2 (35.2)	46.7 (35.8)
Tirault 2010[134]	135	Ear-nose and throat-, general-, orthopedic-, and gynecologic surgery	1200 mg/day	Single dose	-	-
Turan 2003a[12]	50	Abdominal hysterectomy and salphingooophrectomy	1200 mg/day	Single dose	27.0 (14.4)	42.0 (8.4)
Turan 2003b[135]	50	Discectomy spinal fusion surgery	1200 mg/day	Single dose	16.3 (8.9)	42.8 (10.9)
Turan 2004[137]	50	Ear Nose and Throat surgery	1200 mg/day	Single dose	-	-
Turan 2005[136]	40	Lower limb surgery	1200 mg/day (1200 mg)	Multiple dose	-	-
Turan 2006[138]	50	Abdominal hysterectomy and salphingooophrectomy	1200 mg/day (1200 mg)	Multiple dose	-	-
Ucak 2011[139]	40	Coronary Artery Bypass Graft	1200 mg/day (1200 mg)	Multiple dose	9.9 (5.4)	14.9 (7.3)

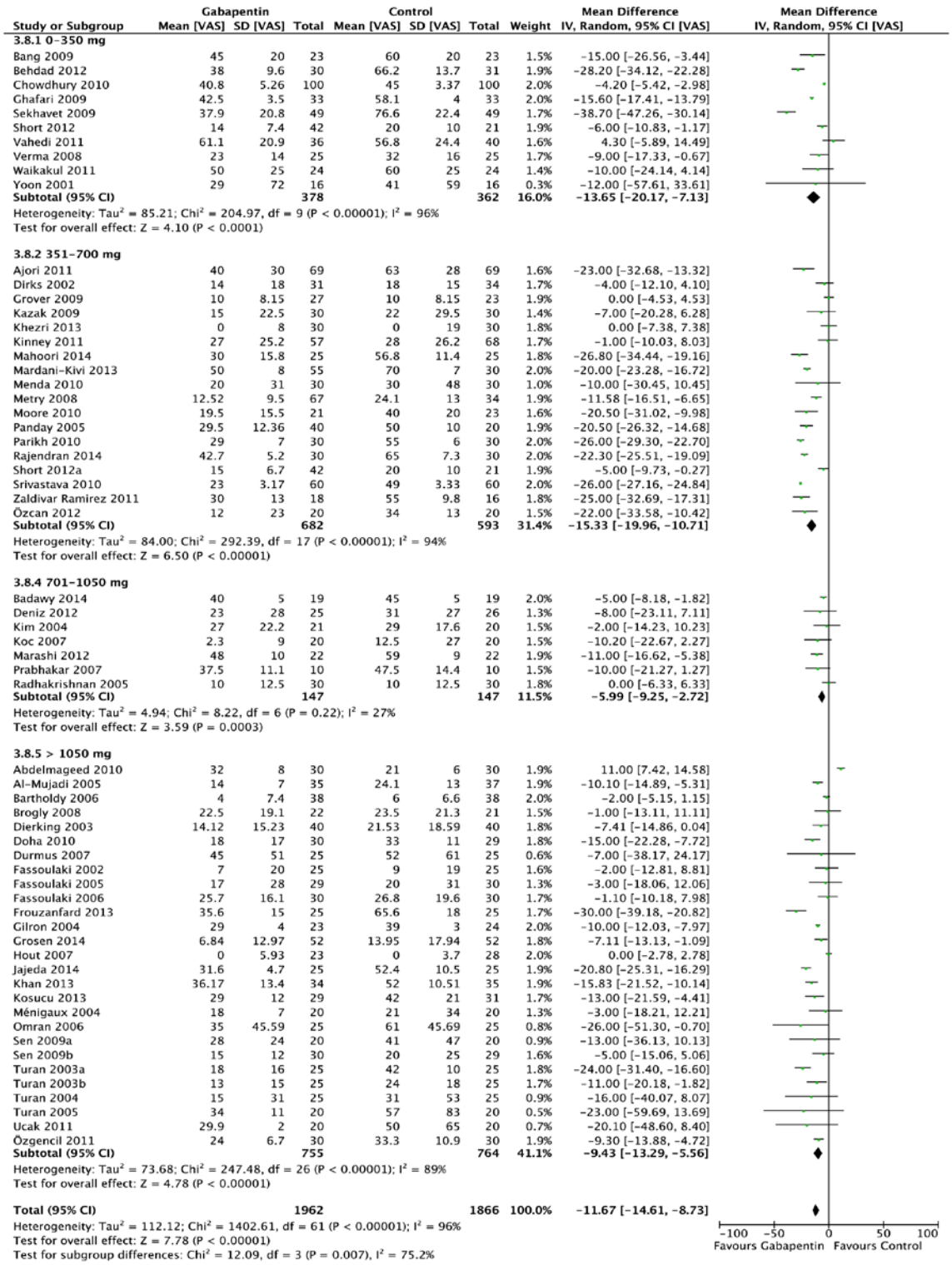
Supplemental Digital Content 4: Bias evaluations



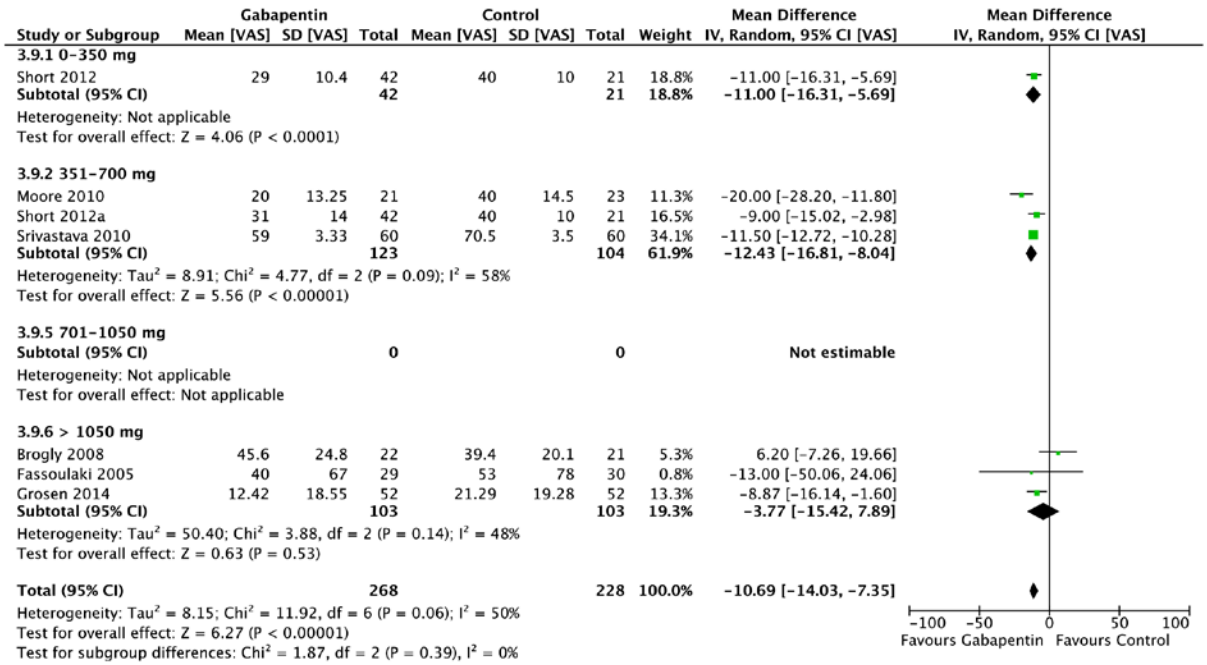
Supplemental Digital Content 5 Forest plot of VAS 6h rest from trials with low risk of bias



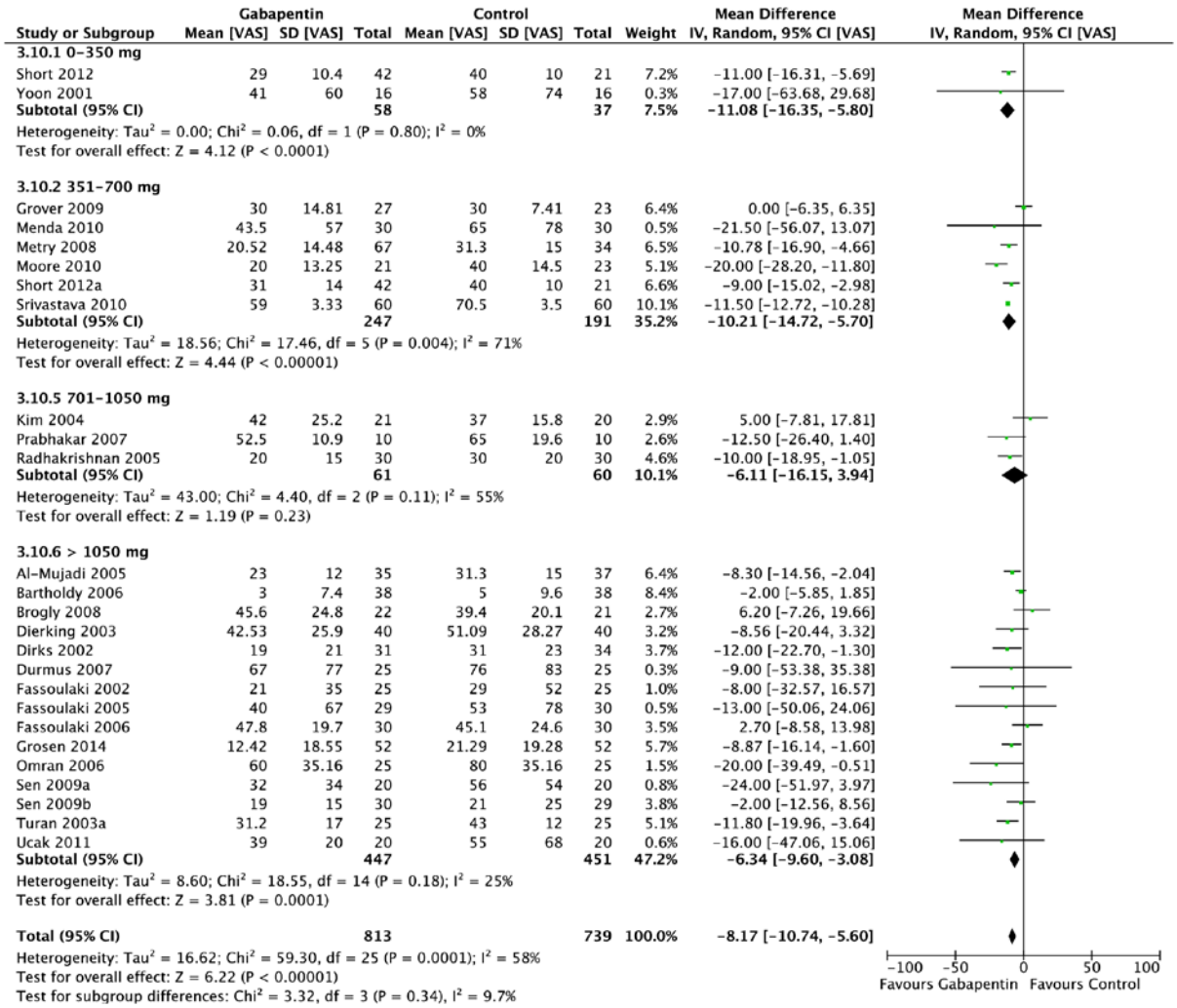
Supplemental Digital Content 6 Forest plot of VAS 6h rest from all trials estimates



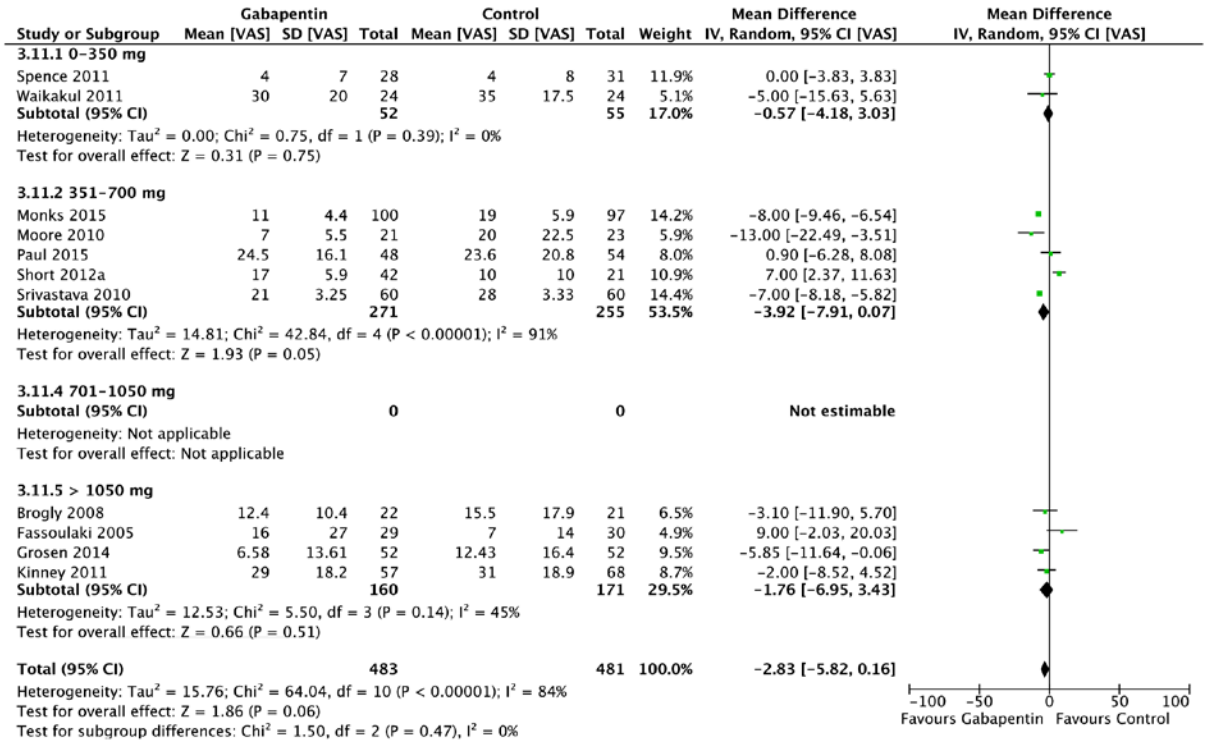
Supplemental Digital Content 7 Forest plot of VAS 6h mobilization from trials with low risk of bias



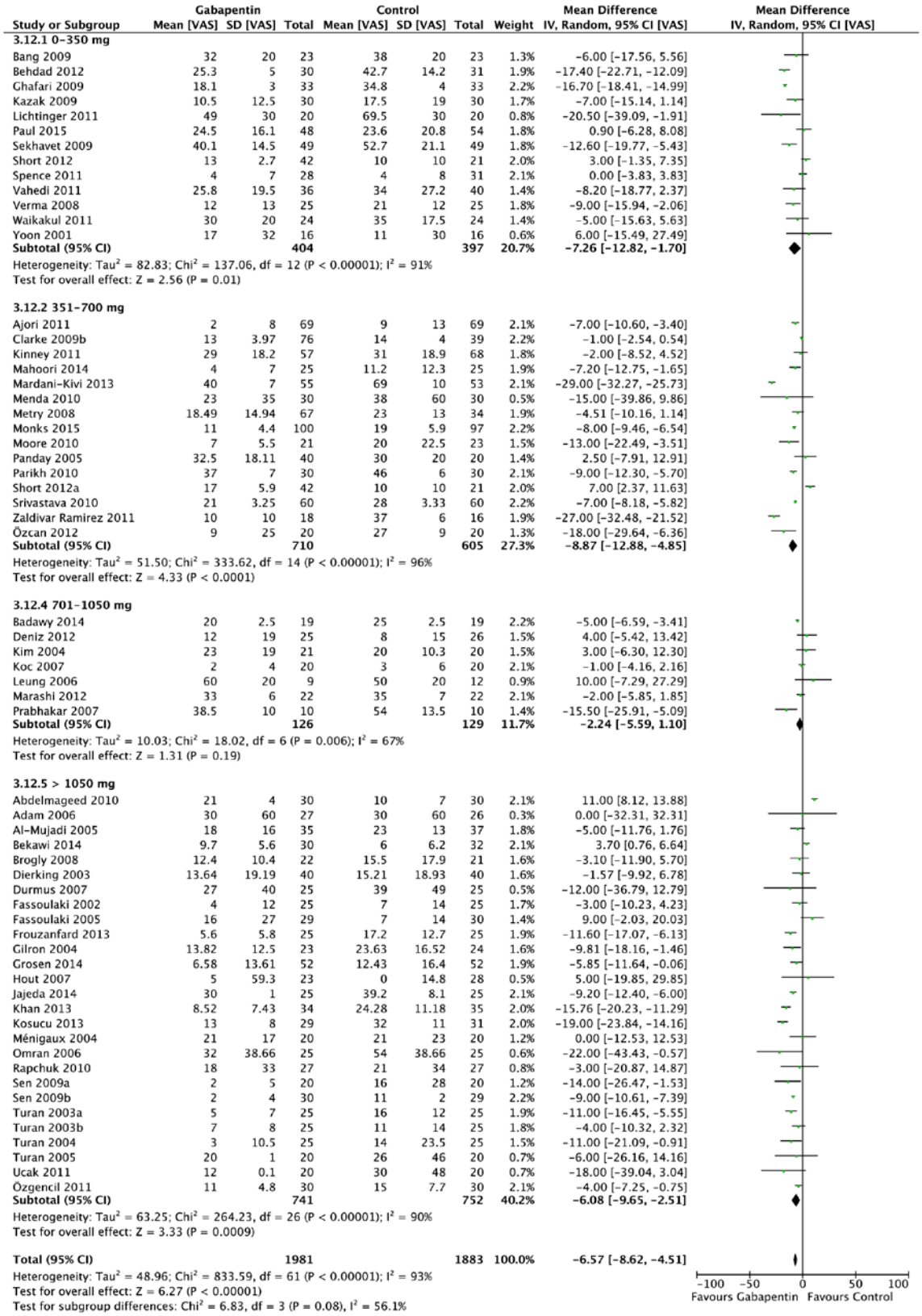
Supplemental Digital Content 8 Forest plot of VAS 6h mobilization from all trials estimates



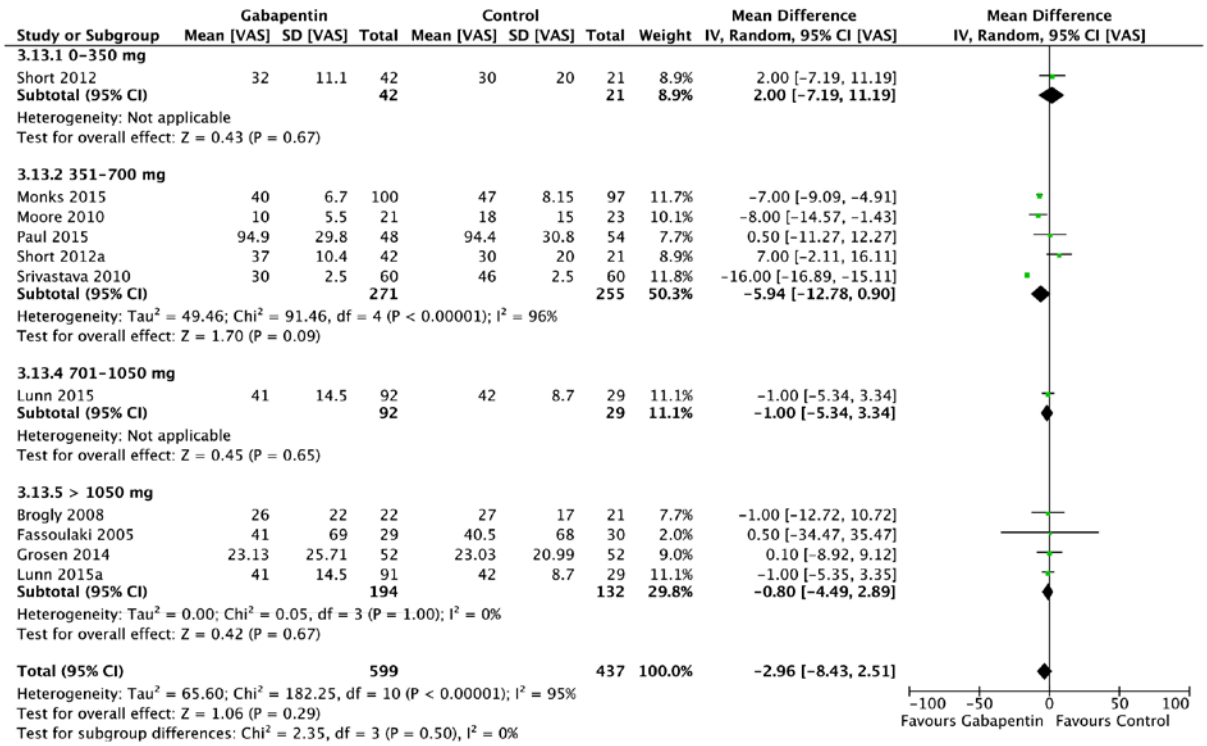
Supplemental Digital Content 9 Forest plot of VAS 24h rest from trials with low risk of bias



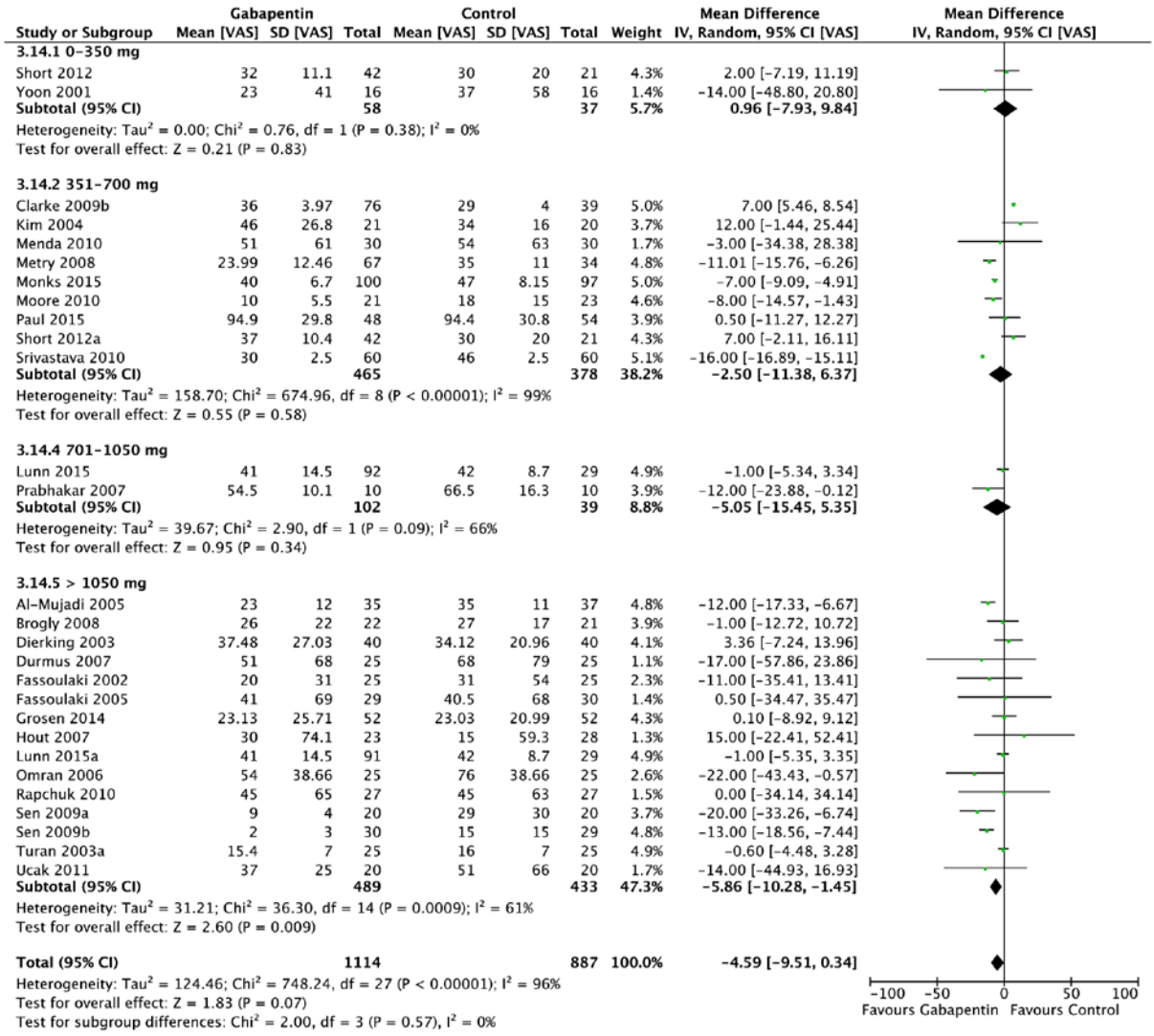
Supplemental Digital Content 10 Forest plot of VAS 24h rest from all trials estimates



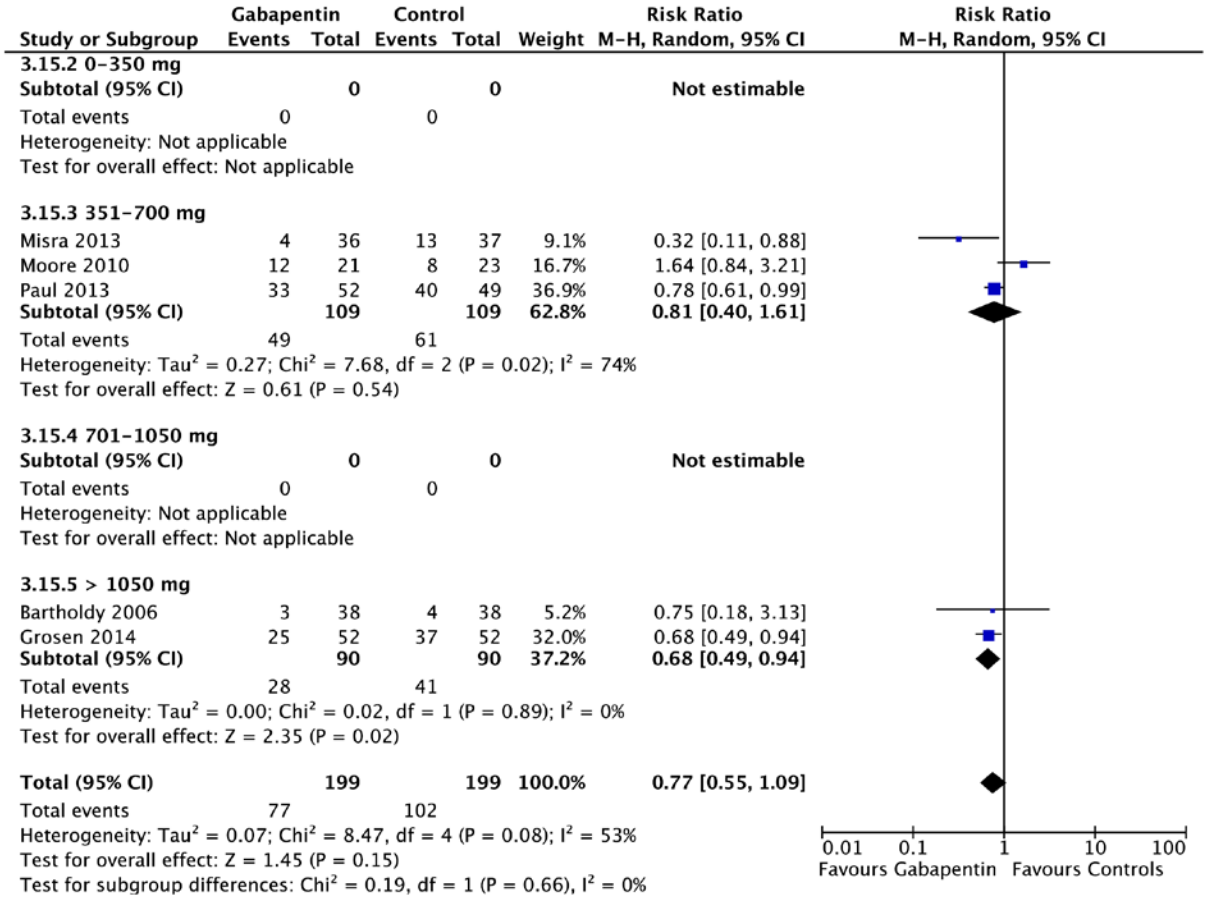
Supplemental Digital Content 11 Forest plot of VAS 24h mobilization from trials with low risk of bias



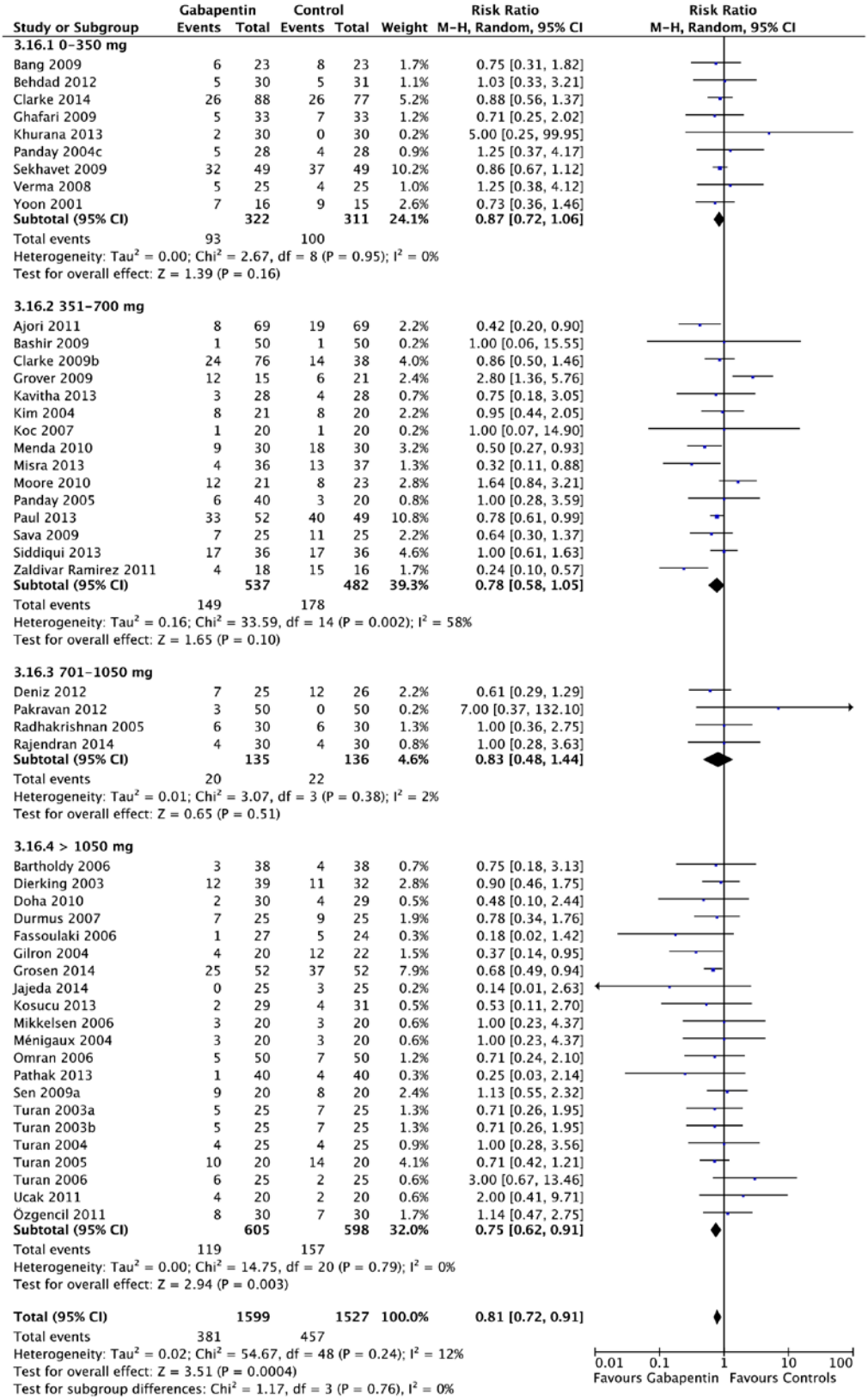
Supplemental Digital Content 12 Forest plot of VAS 24h mobilization from all trials estimates



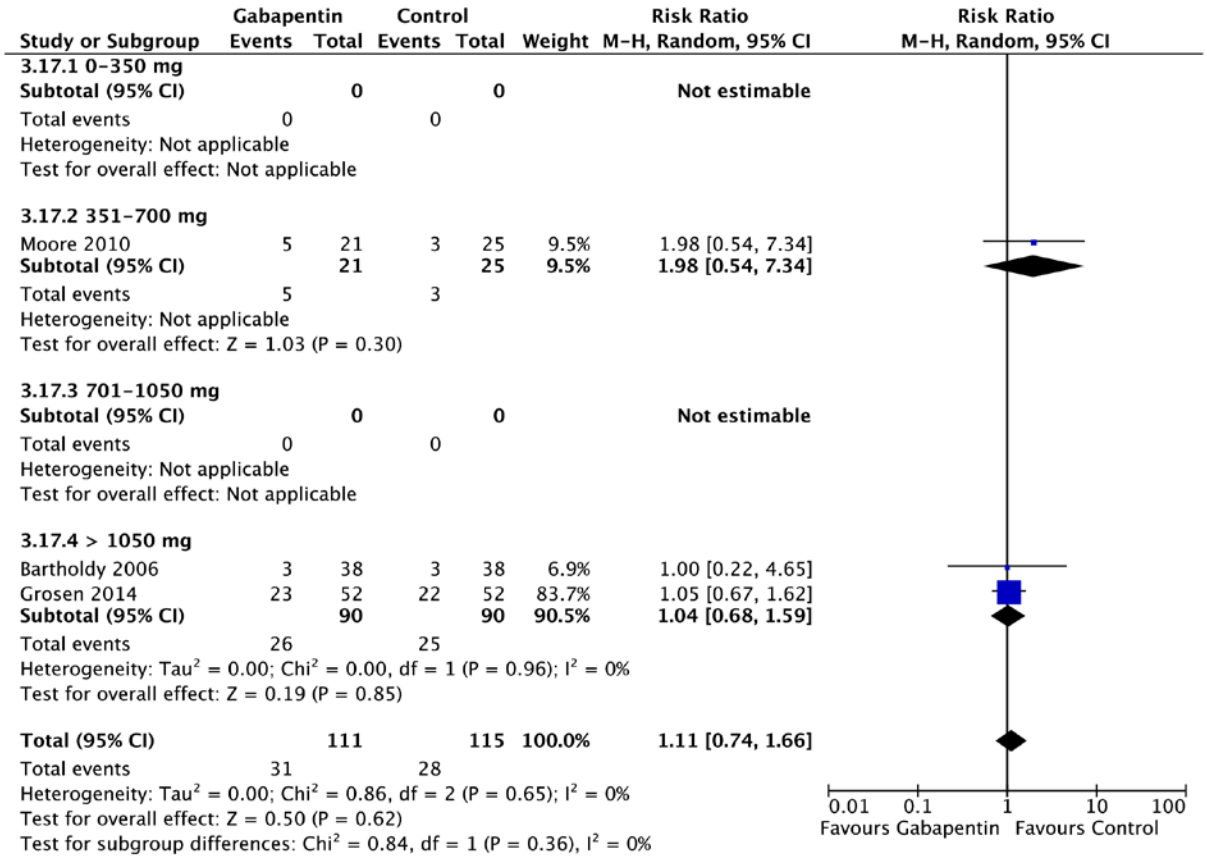
Supplemental Digital Content 13 Forest plot of nausea from trials with low risk of bias



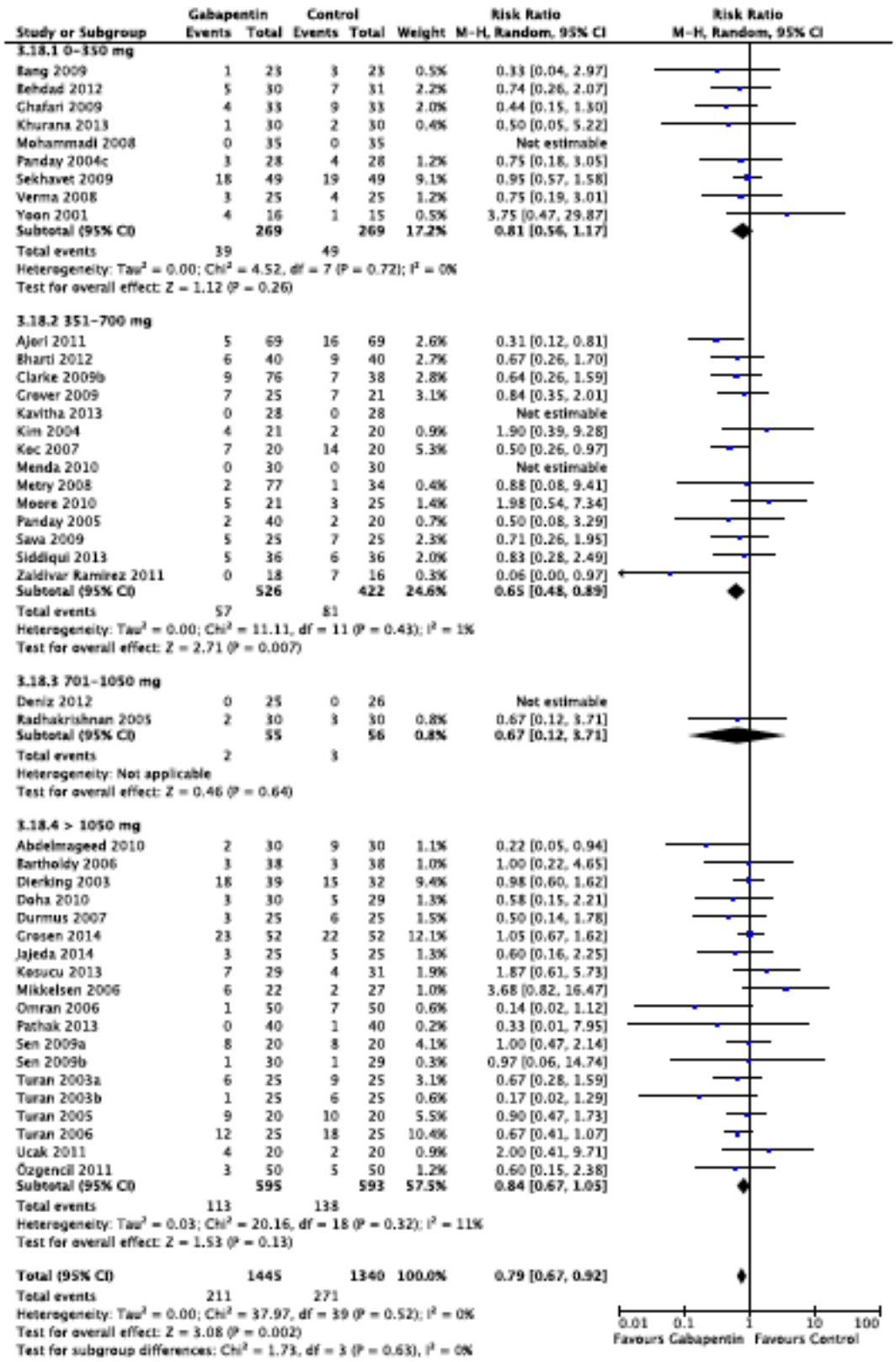
Supplemental Digital Content 14 Forest plot of nausea from all trials estimates



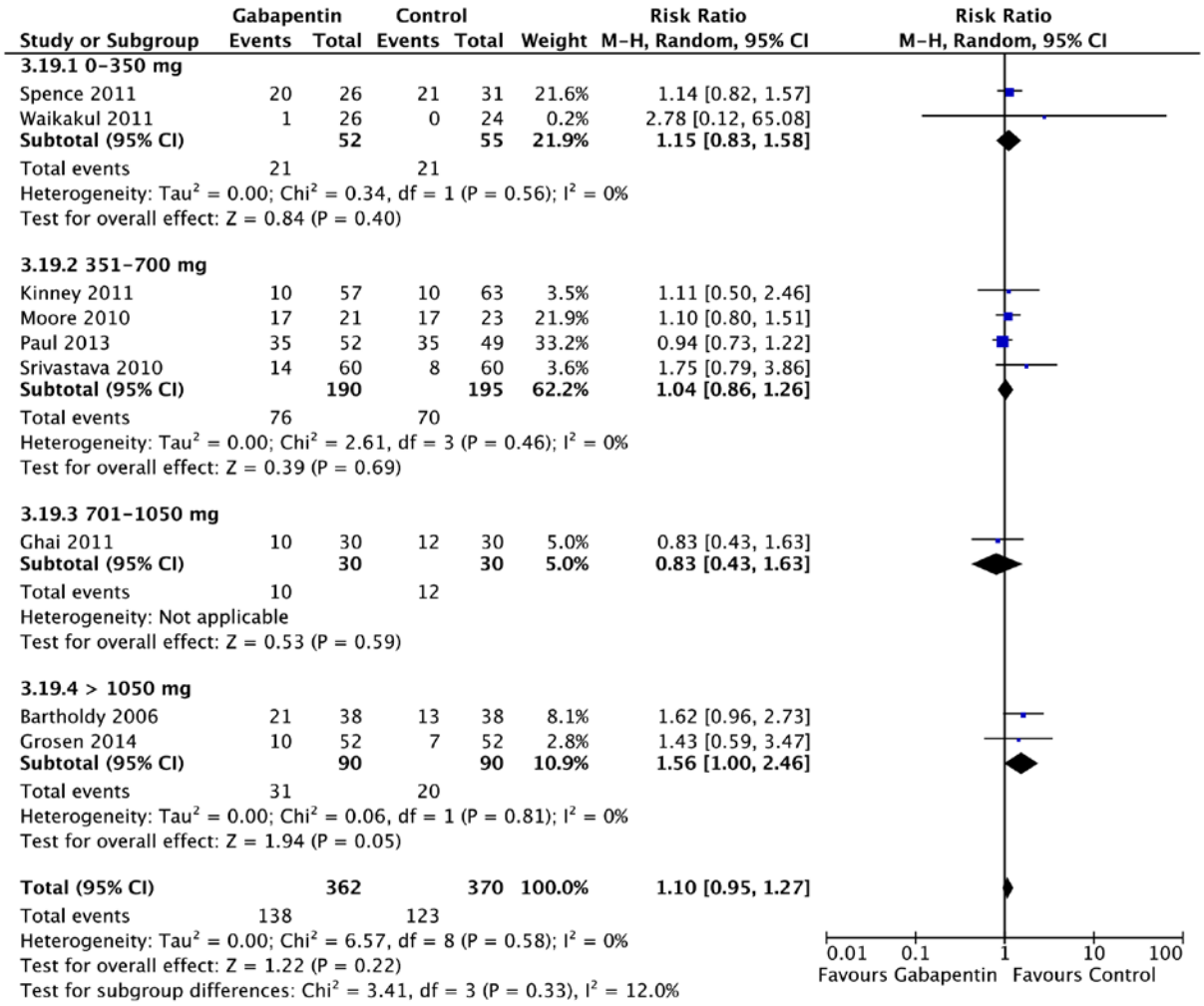
Supplemental Digital Content 15 Forest plot of vomiting from trials with low risk of bias



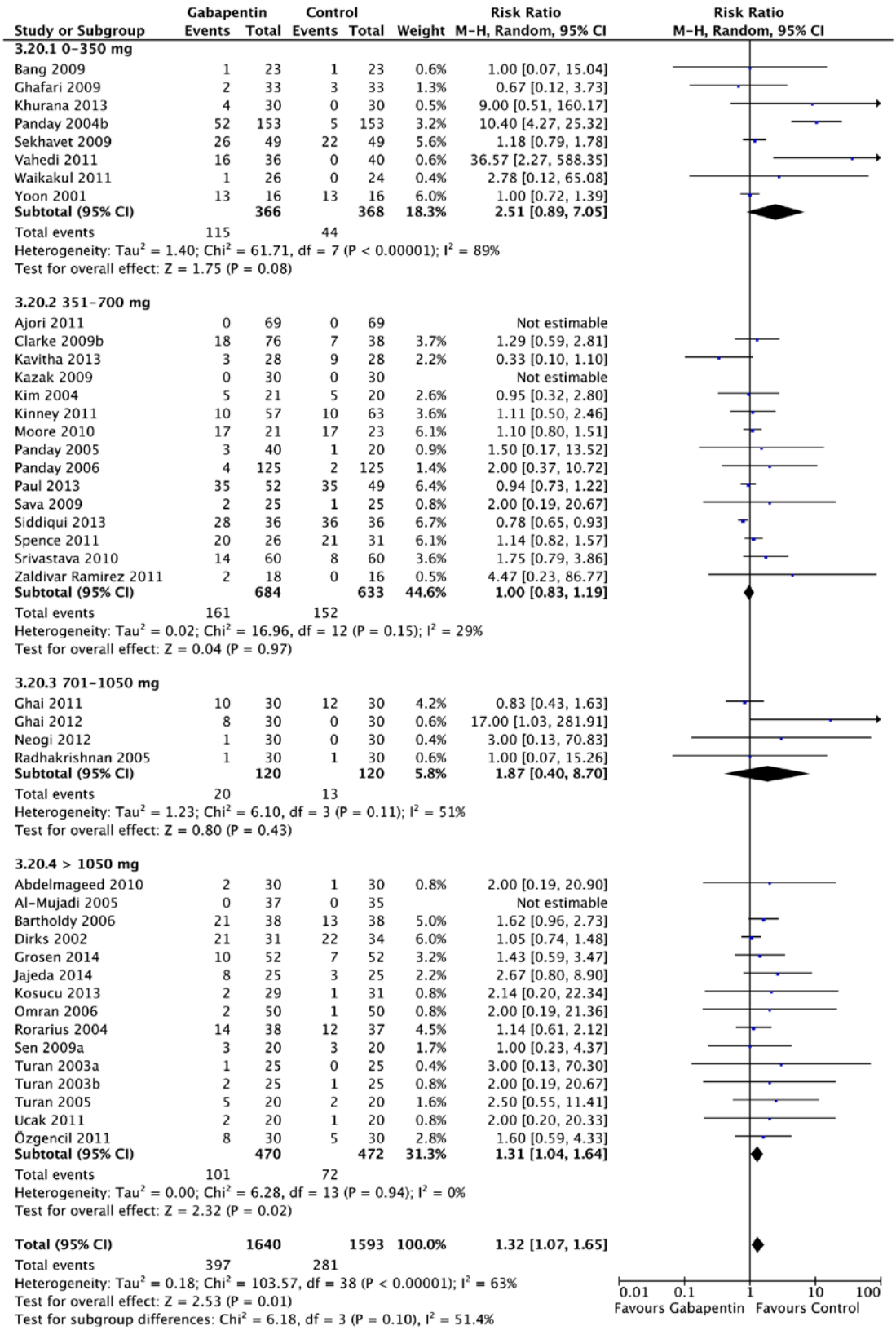
Supplemental Digital Content 16 Forest plot of vomiting from all trials estimates



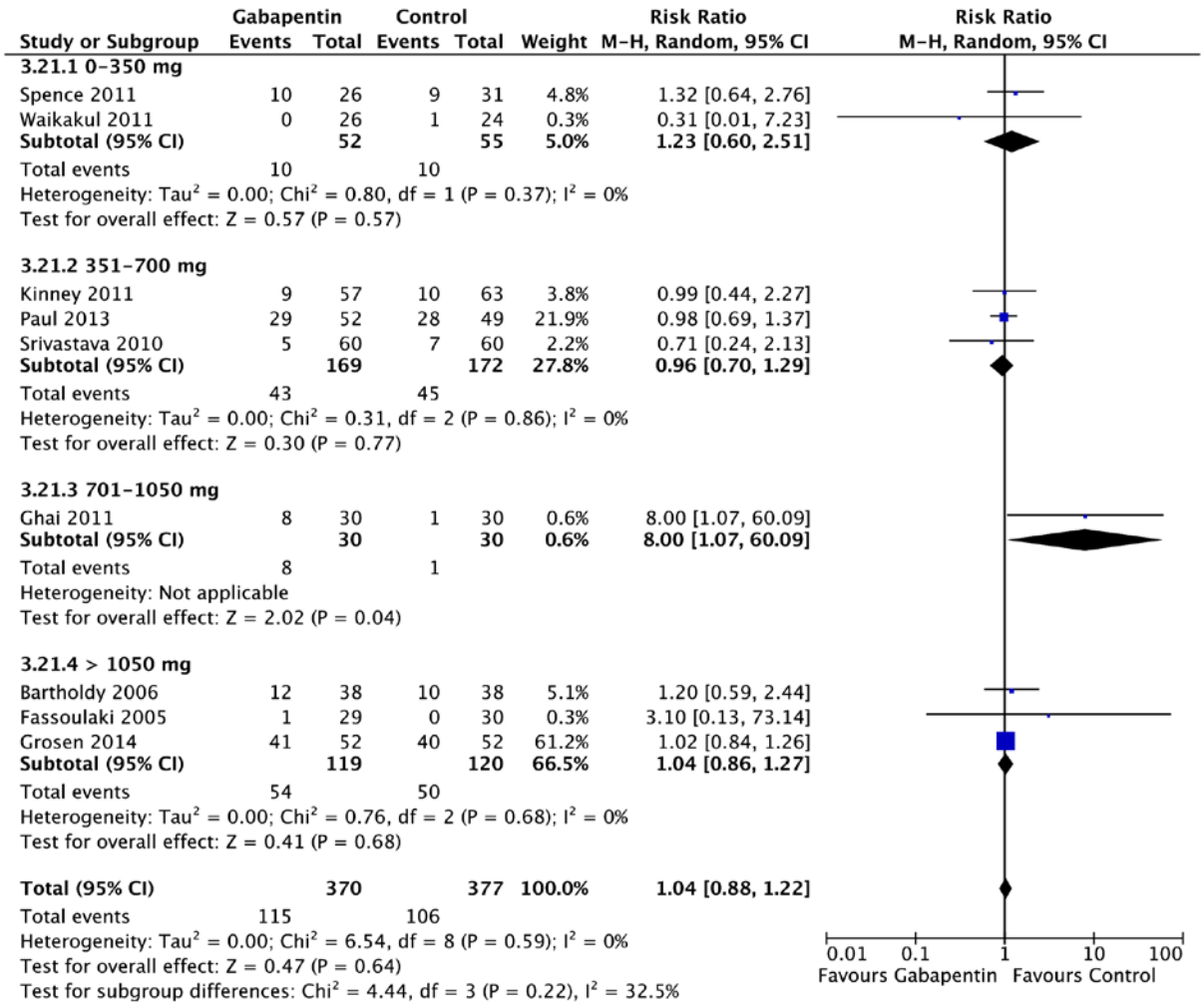
Supplemental Digital Content 17 Forest plot of sedation from trials with low risk of bias



Supplemental Digital Content 18 Forest plot of sedation from all trials estimates



Supplemental Digital Content 19 Forest plot of dizziness from trials with low risk of bias



Supplemental Digital Content 20 Forest plot of dizziness from all trials estimates