SUPPLEMENTARY MATERIALS

Literature search:

Search criteria were as follow:

- pain[Majr] AND chronic AND (tramadol OR tapentadol) AND placebo
- tramadol OR tapentadol AND ("Pain Measurement" OR "Pain"[Majr]) NOT neoplasms AND placebo AND drug therapy AND Humans
- tramadol OR tapentadol AND pain AND (publisher OR "in process") AND trial

These searches resulted in a list of sources of potential interest. This list was incorporated into Reference Manager® Version 11 (Thomson Reuters, Carlsbad, CA). Further review reduced the list to sources of primary interest. Each of these sources was individually examined to identify or rule out potential additional sources of information.

The sources of primary interest identified above were used to create a database in an Excel® spreadsheet format. Studies were included in the database if they reflected treatments, study conditions, and patient populations of interest, and were rejected if they contained information not of interest or if the reports were insufficiently detailed to be used to construct a model. In some cases, a study contained data of interest and additional data not deemed to be of interest. In these cases only the data of interest were extracted. The following inclusion criteria were used regarding studies to be entered into the database:

- Active treatment with tramadol or tapentadol
- Preferences for double-blind, randomized, controlled, parallel group study design, but may include cross-over and open-label design in some cases if other criteria are met
- Contained data reflective of pain, pain intensity, patient severity, patient's global assessment, physician's global assessment, adverse events (gastrointestinal) and dropouts.

Study results from tables, figures, or textual information in the individual reports were included. Relevant figures were digitized, and then converted into numeric values using Didger® Version 3 (Golden Software, Golden, CO). Information pertaining to the different study design settings and the patient characteristics were captured in the database to the extent possible.

In all cases where available relevant summary statistics (mean, median, geometric mean, harmonic mean) and the corresponding measurements of standard deviation (SD) or standard error (SE) were available, they were entered into the database. In some cases SD/SE values were either not provided or not able to be digitized with sufficient accuracy due to poor source document resolution

Included studies were randomized, placebo-controlled, with a parallel-group or cross-over design, published in 1985 or later, with at least 5 days of treatment exposure or follow-up that reported pain intensity.

Table S1: List of trials retained in the analysis, with key information

Author	Pub Year	Duration	N*	Pain intensity	Constipation	Nausea	Dizziness	Vomiting	Somnolence	DropOut for AE	DropOut for LoE	Dosing Method	Treatment arms retained in the current analysis
Adler	2002	4 weeks	202	✓						✓	✓	titration	tramadol
Affilalo	2010	15 weeks	681	✓	✓	✓	✓	✓	✓	✓	✓	titration to fixed	tapentadol / placebo
Babul	2004	12 weeks	246	✓	✓	✓	✓	✓	✓	✓	✓	titration	tramadol / placebo
Beaulieu	2007	4 weeks	122		✓	✓	✓	✓	✓	✓	✓	flexible	tramadol
Bennett	2003	91 days	313	✓	✓	✓	✓		✓	✓	✓	flexible	tramadol / placebo
Bianchi	2003	1 week	8	✓						✓		fixed	tramadol / placebo
Biovail Laboratories Inc	2005	12 weeks	246	✓						✓	✓	titration to fixed	tramadol
Boureau	2003	6 weeks	127	✓								flexible	tramadol / placebo
Burch	2007	12 weeks	589	✓	✓	✓	✓		✓	✓	✓	titration to fixed	tramadol / placebo
Buynak	2010	15 weeks	637	✓	✓	✓	✓	✓	✓	✓	✓	titration to fixed	tapentadol / placebo
Caldwell	1999	30 days	36	✓	✓	✓	✓	✓	✓	✓	✓	titration	placebo
Chindalore	2005	3 weeks	51	✓	✓	✓	✓	✓	✓	✓	✓	escalation	placebo
Choi	2007	2 weeks	189	✓	✓	✓	✓	✓	✓	✓		titration	tramadol
Dalgin	1997	39 days	146	✓	✓	✓						titration	tramadol
Elan	2002	4 weeks	67	✓								fixed	placebo
Emkey	2004	91 days	306	✓	✓	✓	✓	✓	✓	✓	✓	titration	tramadol / placebo
Fishman	2007	12 weeks	552		✓	✓	✓	✓	✓	✓	✓	titration to fixed	tramadol / placebo
Fleischmann	2001	91 days	129	✓	✓	✓	✓			✓	✓	titration	tramadol / placebo
Freeman	2007	9 weeks	312	✓	✓	✓	✓		✓	✓	✓	flexible	tramadol / placebo
Gana	2006	12 weeks	1011	✓	✓	✓	✓	✓	✓	✓	✓	titration to fixed	tramadol / placebo
Gimbel	2003	6 weeks	77	✓	✓	✓	✓	✓	✓	✓	✓	flexible	placebo
Hale	2005	18 days	75	✓	✓					✓	✓	flexible	placebo
Hale	2009	12 weeks	679	✓	✓	✓	✓	✓	✓	✓		flexible	tapentadol
Harati	1998	42 days	131	✓	✓	✓	✓	✓	✓	✓	✓	flexible	tramadol / placebo

Hartrick	2009	6 weeks	488		✓	✓	✓	✓	✓	✓	✓	flexible	tapentadol / placebo
Jensen	1994	2 weeks	81		✓	✓	✓	✓		✓		fixed	tramadol
Kelly	2009	15 weeks	681	✓	✓	✓	✓	✓	✓			flexible	tapentadol / placebo
Kelly	2010	15 weeks	344							✓		flexible	tapentadol
Kosinski	2007	12 weeks	1011	✓								fixed	tramadol / placebo
Lee	2006	1 week	267	✓						✓	✓	fixed	tramadol / placebo
Li	2008	7 days	48	✓	✓	✓		✓		✓	✓	fixed	tramadol
Ma	2008	4 weeks	58	✓	✓	✓	✓	✓	✓			flexible	placebo
Malonne	2004	14 days	230	✓	✓	✓	✓	✓	✓	✓		fixed	tramadol / placebo
Markenson	2005	90 days	51	✓	✓	✓	✓	✓	✓	✓	✓	flexible	placebo
Matsumoto	2005	4 weeks	124		✓	✓	✓	✓	✓	✓	✓	fixed	placebo
Mongin	2004	12 weeks	314		✓	✓		✓	✓	✓	✓	titration	tramadol
Mullican	2001	4 weeks	309		✓	✓	✓	✓	✓	✓		titration	tramadol
Norrbrink	2009	4 weeks	35		✓	✓	✓					flexible	tramadol / placebo
Pavelka	1998	4 weeks	54							✓		prn use	tramadol
Peloso	2000	4 weeks	35	✓								fixed	placebo
Peloso	2004	91days	336	✓	✓	✓	✓	✓	✓	✓	✓	titration	tramadol / placebo
Rauck	1994	4 weeks	234	✓	✓	✓	✓	✓	✓	✓	✓	titration	tramadol
Roth	2000	18 months	45	✓	✓	✓	✓	✓	✓	✓	✓	fixed	placebo
Ruoff	2003	91 days	318	✓						✓	✓	titration	tramadol / placebo
Schnitzer	2000	7 weeks	254			✓				✓	✓	flexible	tramadol / placebo
Schwartz	2011	12 weeks	389	✓	✓	✓	✓	✓		✓	✓	fixed	tapentadol / placebo
Silverfield	2002	10 days	212	✓	✓	✓	✓	✓	✓	✓	✓	flexible	tramadol / placebo
Sindrup	1999	4 weeks	90		✓	✓	✓					flexible	tramadol / placebo
Thorne	2008	8 weeks	154	✓	✓	✓	✓	✓	✓	✓	✓	titration	tramadol / placebo
Vidal	2005	6 weeks	132							✓	✓	titration to fixed	tramadol
Vorsanger	2008	12 weeks	384		✓	✓	✓			✓	✓	fixed	tramadol / placebo
Webster	2006	12 weeks	101	✓	✓	✓	✓	✓	✓	✓	✓	flexible	placebo
Wild	2010	52 weeks	894	✓	✓	✓	✓	✓	✓	✓	✓	flexible	tapentadol
Contributing articles				39	40	40	36	31	31	44	36		

N*: maximum between number of patients contributing to the efficacy (PI) analysis or safety analysis (AEs and DropOuts)

Table S2: Consistency between previous and current meta-analysis results concerning frequency of withdrawals and of specific adverse events

	Moore and McQuay (2005) – Table 3		**Current analysis**		
	placebo	oral opioids	placebo	tapentadol	tramadol
Withdrawals					
Due to adverse event	7.1	22	7.1	18.7	20.5
Due to lack of efficacy	20	6.5	18.5	6.1	7.8
Specific adverse events					
Constipation	5.0	15	5.3	15.1	18.0
Nausea	5.6	21	8.0	21.7	22.2
Vomiting	2.4	10	2.2	6.7	9.9
Somnolence	4.0	14	3.8	12.6	13.2
Dizziness	4.5	14	4.6	15.7	13.2

Table S3: Reference list

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