Supplementary materials

1. Additional information on methods

Eligibility criteria

Opioids like fentanyl, remifentanil, alfentanil and morphine were considered as analgesic drugs supporting the sedation protocol. No drug combinations (e.g. propofol+midazolam or propofol+remifentanil/fentanyl and midazolam+remifentanil/fentanyl) were taken into account in this study.

Search strategy

We searched the databases MedLine (via PubMed) and EMBASE (via Scopus) using the following keywords:

- PubMed database search string: ((("Dexmedetomidine[Mesh]" OR "Benzodiazepines[Mesh]") OR "Propofol[Mesh]") AND ("Conscious Sedation[Mesh]" OR "Deep Sedation[Mesh]")) AND ("Respiration, Artificial[Mesh]" OR "Intensive Care Units[Mesh]")
  PubMed eligibility limits: Article types: Clinical trial, species: Humans, patients: All adults (18+)
- Scopus database search string: (TITLE-ABS-KEY(propofol) OR TITLE-ABS-KEY(benzodiazepines) OR TITLE-ABS-KEY(dexmedetomidine)) AND TITLE-ABS-KEY(sedation) AND (TITLE-ABS-KEY(mechanical ventilation) AND TITLE-ABS-KEY(intensive care unit))
  Scopus eligibility limits: Search type: From journal sources, documents type: Classified as article

Data extraction

The following data were extracted:

Descriptive section: inclusion and exclusion criteria, design and setting of study, sample size of intent to treat patients, baseline characteristics (age, weight, intensive care unit (ICU) scoring system values, ICU admission reason, sedation level at enrolment).

Interventions section: treatments tested, sedative and analgesic doses, rescue medications.

Results section: Duration of study drug treatment, time at target sedation level, number of patients receiving analgesic drugs, duration of mechanical ventilation, duration of mechanical ventilator-free breathing, time to weaning, weaning time, time to extubation, ICU Length of Stay, hospital Length of Stay.

On-demand treatment: Doses of rescue medication, mean daily dose of on-demand treatment(s)

All the available data were made uniform in terms of mean and standard deviation (SD) by means of appropriate fitting processes (i.e., taking into account the right-skewedness of survival time distributions) whenever necessary. The estimates of summary statistics built as combination of reported outcomes are obtained by means of bootstrapping techniques.

Primary outcomes

In some cases, mean values of quantities not explicitly defined in the article but mentioned in published reviews citing the article, have been defined by means of summary statistics combining outcomes reported in the original article (for example, the duration of mechanical ventilation determined as sum of ICU admission time and time to extubation). Furthermore, for such quantities, standard deviations have been calculated through bootstrapping using the available information of the combined quantities.

Statistical analysis

For every outcome of interest (duration of mechanical ventilation (Dmv), weaning time (Tw), time to extubation (Tex) and length of ICU stay (Ticu), the overall effect size for each treatments comparison was determined as a weighted mean of effect size estimates obtained from extracted data. Pair wise treatment comparisons were calculated for pairs of strategies in direct comparison. The intervention effect estimate between two arbitrary treatments T_j & T_k, namely d_{jk}, was calculated as

$$d_{jk} = \frac{\sum_{i=1}^{n} w_{ijk} d_{ijk}}{\sum_{i=1}^{n} w_{ijk}}$$

where the sums run over the n available comparisons and d_{ijk} is the difference in means between outcomes values of T_j and T_k extracted from the i-th comparison; the weights w_{ijk} can be expressed as

$$w_{ijk} = \frac{1}{SE_{ijk}^2 + \tau^2}$$

taking into consideration the variability within study (through the standard error of the mean SE_{ijk}) and the estimate of heterogeneity between all the true effects of the studies contributing to the treatment comparison (through the between-studies variance τ^2 depending on T_j & T_k). The estimation of the parameter τ permits also to distinguish between "fixed" ($\tau = 0$) or "random" ($\tau \neq 0$) effect model. Further the estimation of heterogeneity (and τ) can be obtained by means of the statistic function Q_{ij} (or simply Q) defined as

$$Q_{jk} = \sum_{i=1}^{n} \frac{(d_{jk} - d_{ijk})^2}{SE_{ijk}^2}$$

Through the function Q heterogeneity can be tested mainly in two ways: (i) directly through a Q-test using the Q function (with $p(Q)<0.05$ the null hypothesis of homogeneity is rejected); (ii) defining an Higgins index I^2 to quantify the extent of heterogeneity. In the present work, the statistical analyses for direct comparisons and the heterogeneity tests have been calculated using both “R” statistical computing software with the “meta” package and Review Manager 5.2 software with the DerSimonian and Laird method used for the calculation of τ, which yielded the same results.

2. Detailed results of the literature search

Literature search

The literature search identified 346 publications (59 in PubMed, 287 in Scopus). 114 papers were excluded during title-based screening for the following reasons:

- 4 refer to experiments on animals
- 49 deal with non-target patients (paediatric, not intubated, non-invasive mechanical ventilation)
- 19 do not compare different therapeutic strategies (case study, only one sedative agent used)
- 6 do not compare target drugs
- 3 show only pharmacokinetic or pharmacodynamic results
- 13 are methodological studies
- 17 are duplicates (collected twice in the databases)
- 3 are based on non-original data

A further 99 were excluded during abstract-based screening for the following reasons:

- 3 do not study target patients
- 7 do not compare target drugs
- 1 does not compare different therapeutic strategies
- 1 does not consider target groups
- 5 show only pharmacokinetic or pharmacodynamic results
- 31 do not compare different therapeutic strategies or target medications
- 26 are methodological studies
- 2 are written in languages (Chinese, Japanese) not included in the eligibility criteria
- 3 do not present outcomes of interest
- 20 do not report original data

Of the 133 papers entering full text evaluation, another 94 were excluded:

- 2 do not compare target drugs
- 5 do not compare different therapeutic strategies or target medications
- 16 do not consider target groups
- 1 shows only pharmacokinetic/pharmacodynamic results
- 15 are methodological studies
- 2 unavailable
- 1 is written in language (Chinese) not included in the eligibility criteria
- 27 do not present outcomes of interest
- 5 show only partial results
- 20 do not report original data

From the 346 search results identified, 39 studies entered the list of eligible papers.

Additionally, a careful manual checking conducted on references included in reviews and retrospective articles resulted in a list of 83 papers and yielded the inclusion of another 17 articles on the list of eligible papers.

A final review excluded 10 studies involving propofol as comparator, 4 studies involving benzodiazepines (BDZ) and 2 studies using dexmedetomidine (Dx) because comparators are not target treatments. One reference was excluded because in the MIDEX trial the comparison was not in the scope of the present analysis (BDZ vs Dx), and in the PRODEX trial (Propofol vs Dx) Dx is administered for sedation times longer than 24h. Data from a retrospective paper were not extracted because Dx was administered for sedations time longer than 24h, while 3 papers were excluded because the comparison was not in the scope of the present analysis (BDZ vs Dx).

Table S1. Overview of included RCTs after full text-based selection for primary analyses

RCT selected papers							
Author (year)	**Design**	**N Pts**	**Pts Type**	**Tr 1**	**Tr 2**	**ST**	**Outcomes**
Aitkenhead (1989)	RCT	100	Mix	Pr-1%	Mz	STS	Tw
Barrientos (1997)	RCT	118	Mix	Mz	Pr-2%	LTS	Tw*
Carrasco (1993)	RCT	88	Med+Surg	Mz	Pr	STS, LTS	Tw*
Carrasco (1998)	RCT	50	Surg	Mz	Pr	STS	Tw*, Ticu
Carson (2006)	RCT	132	Med	Lz	Pr	LTS	Dmv, Ticu
Corbett (2005)	RCT	89	Surg	Dx	Pr-2%	STS	Dmv, Ticu
Costa (1994)	RCT	104	Mix	Pr	Mz	LTS	Dmv, Tw*, Ticu
Degauque (1991)	RCT	11	Mix	Pr	Mz	LTS	Ticu
Ghori (2007)	RCT	28	Trauma	Mz	Pr	LTS	Ticu
Grounds (1987)	RCT	60	Surg	Pr-1%	Mz	STS	Dmv, Tw
Hall (2001)	RCT	124	Med+Surg	Mz	Pr	STS, LTS	Tw, Ticu
Herr (2003)	RCT	295	Surg	Dx	Pr	STS	Dmv, Tw, Tex
Higgins (1994)	RCT	80	Surg	Pr	Mz	STS	Dmv, Tw, Tex
Huey-Ling (2008)	RCT	60	Surg	Pr	Mz	STS	Dmv, Tw, Tex, Ticu
Izquierdo-Riera (1998)	RCT	100	Trauma	Mz	Pr	LTS	Ticu
Kress (2001)	RCT	128	Med	Pr	Mz	LTS	Dmv, Ticu
Maldonado (2009)	RCT	60	Surg	Pr	Dx	STS, LTS	Tex, Ticu
		60	Surg	Pr	Mz	LTS	
McMurray (1990)	RCT	100	Surg	Pr-1%	Mz	STS	Dmv, Tw*

Mesnil (2011)	RCT	47	Mix	Pr-2%	Mz	LTS	Dmv, Tw, Ticu
Michalopulos (1998)	RCT	144	Surg	Pr	Mz	STS	Dmv, Ticu
Roekaerts (1993)	RCT	30	Surg	Pr	Mz	STS	Dmv, Tw
Ruokonen (2009)	RCT	44	Med+Surg	Mz	Pr-2%	LTS	Dmv, Tw, Ticu
Sandiumenge (2000)	RCT	63	Trauma	Mz	Pr-2%	LTS	Ticu
Searle (1997)	RCT	41	Surg	Mz	Pr	STS	Tw*, Ticu
Snellen (1990)	RCT	40	Surg	Mz	Pr	STS	Dmv, Tw
Venn (2001)	RCT	20	Surg	Dx	Pr	STS	Tw*
Weinbroum (1997)	RCT	67	Surg+Trauma	Mz	Pr-1%	LTS	Tw,Tex,Ticu

Dmv: Duration of mechanical ventilation (explicitly mentioned in paper), Dx: Dexmedetomidine, LTS: Long term sedation (>24h), Lz: Lorazepam, Med: Medical, Mix: Surg+Med+Trauma, Mz: Midazolam, Pr: Propofol, Pts: Patients, RCT: Randomized controlled trial, ST: Sedation type, STS: Short term sedation (≤24h), Surg: Surgical, Tex: Time to extubation, Ticu: ICU Length of stay, Tr= Treatment; Tw: Weaning time, Tw: Weaning time reported in the study as "extubation time".*

Table S2. Overview of non RCTs papers after full text-based selection included in the broad analysis

Non RCT selected papers							
Author (year)	**Design**	**N Pts**	**Pts Type**	**Tr 1**	**Tr 2**	**SG**	**Outcomes**
Anger (2010)	PS	56	Surg	Pr	Dx	STS	Dmv, Ticu
Barletta (2009)	RS	100	Surg	Dx	Pr	STS	Dmv
Barrientos (2001)	Ph IV	51	Mix	Pr-2%	Mz	LTS	Tw*
DeBellis (2002)	RS	40	Med	Pr	Mz	LTS	Tw*
Fong (2007)	RS	287	Med+Surg	Pr	Lz	LTS	Dmv, Ticu
Kuru (1999)	RS	17	Med	Pr	Lz	LTS	Dmv, Ticu
Park (2007)	PS	111	Mix	Pr	Mz	LTS	Dmv, Ticu
Reichert (2011)	RS	70	Surg	Dx	Pr	STS	Tex

Dmv: Duration of mechanical ventilation (explicitly mentioned in paper), Dx: Dexmedetomidine, LTS: Long term sedation (>24h), Lz: Lorazepam, Med: Medical, Mix: Surg+Med+Trauma, Mz: Midazolam, Ph IV: Phase IV, Pr: Propofol, PS: Prospective, Pts: Patients, RCT: Randomized controlled trial, RS: Retrospective, ST: Sedation type, STS: Short term sedation (≤24h), Surg: Surgical, Tex: Time to extubation, Ticu: ICU Length of stay, Tr= Treatment; Tw: Weaning time, Tw: Weaning time reported in the study as "extubation time".*

Comments on included articles

The following data and quantities are renamed or recalculated from paper indications:

- In Herr et al. (2003), mean weaning time is calculated as the difference between time to extubation and time to weaning.
- For the studies Higgins et al. 1994, Searle et al. 1997, Roekaerts (1993), McMurray et al. (1990) and Snellen et al. (1990) the duration of mechanical ventilation has been obtained as a combination of the original data (extubation time, time to ICU arrival, etc...) in agreement with the "Length of Ventilation" values reported in the review by Ostermann et al. (2000).
- By means of data extracted from Higgins et al. 1994 weaning time was calculated using the mean value and the percentage of patients weaned off

mechanical ventilation. For duration of mechanical ventilation and extubation time only the mean values can be obtained through the existing data; the standard deviations of these outcomes for each considered treatment were calculated through the mean of the coefficients of variation (ratio of the standard deviation to the mean) weighed for the number of patients.

- In the study by Huey-Ling et al. (2008) time to extubation corresponds to the duration of mechanical ventilation.
- In the study by Michalopoulos et al. (1998) time to extubation can be assumed as the same as duration of mechanical ventilation.
- Regarding the studies by Costa et al. (1994) and Degauque et al. (1997) the outcome values here reported are extracted by review studies Ho et al. (2008) and Ostermann et al. (2000) because of lacking access to original data. Besides, in study by Costa et al (1994) the standard deviation of weaning time was obtained with the coefficients of variation, as in the case of the study Higgins et al. (1994).
- In Degauque et al. (1997) to avoid division by zero in the analysis mean ICU LOS value was set to 0.01 since for this quantity only the first decimal number is shown.
- In DeBellis et al. (2002) time to extubation after stopping sedation for midazolam is two orders of magnitude longer (about 2,000±4,900 minutes) than those reported for other comparators (propofol or remifentanil, about 20-30 minutes). Considering this heterogeneity and the missing answer after the attempt to contact two of the authors the values were precautionary extracted and reported.

Finally we note that:

- In Carrasco et al. (1998) and Carrasco et al. (1993) inclusion criteria on age is > 16y but the reported age range values are larger than 18y. In Aitkenhead (1989) the patients' age is ≥ 17y but age mean and SD are representative of adult groups. We included all these studies in our analyses.
- In Ruokonen et al. (2009) only the propofol and midazolam comparison is considered; the duration of mechanical ventilation and weaning time values for the control groups, where either propofol or midazolam were administered, are not reported for single treatment but as unique Standard Care group value, and therefore outcomes values cannot be assigned to any treatment group in this analysis. Differently, length of ICU stay is indicated separately for each treatment group and has been included in the analysis.
- In Reichert (2011) only the median values of time to extubation are reported and then these data were not included as input in the meta-analyses.

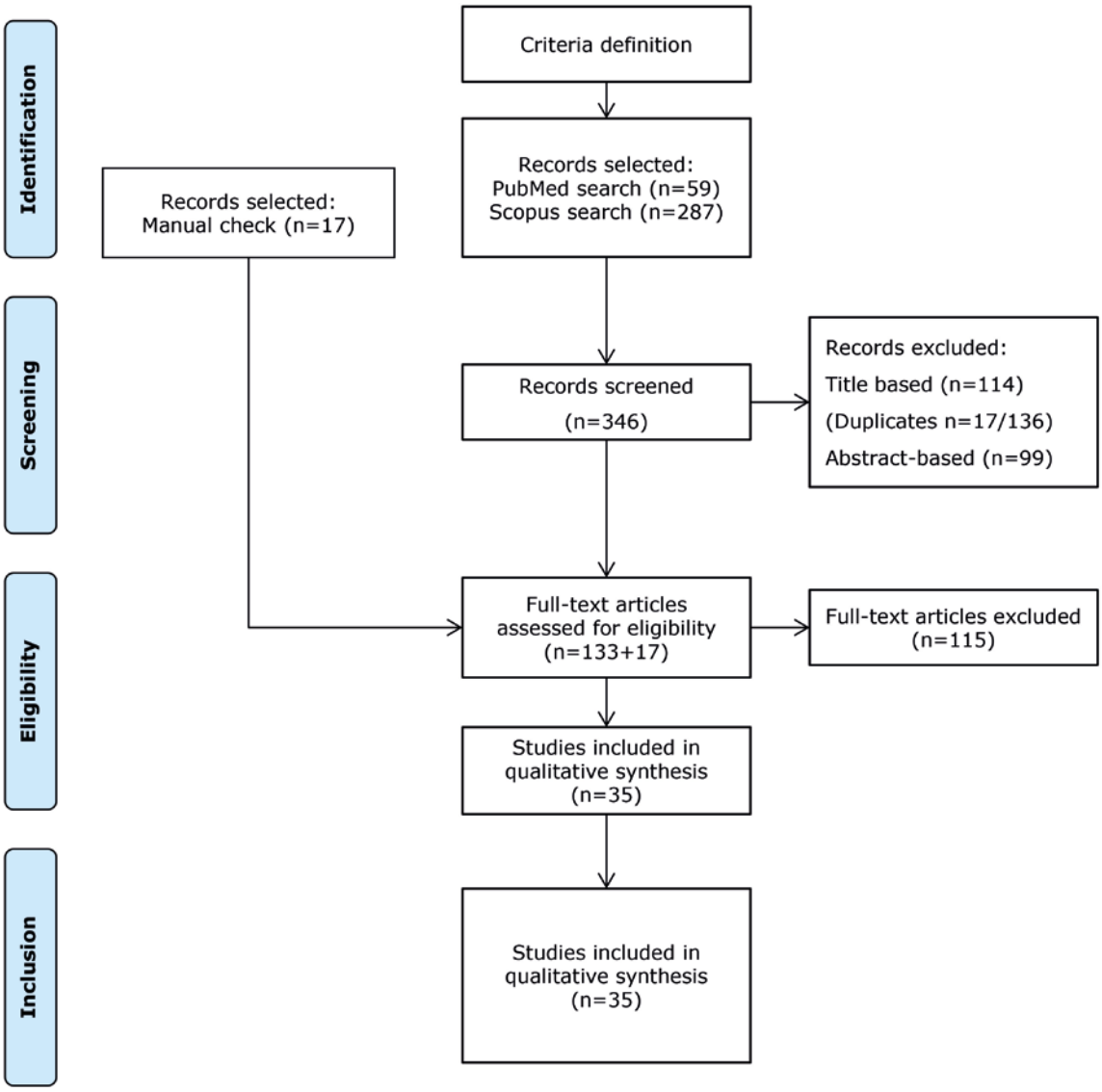


Figure S1. Flow diagram of article selection in the meta-analysis (PRISMA guideline).

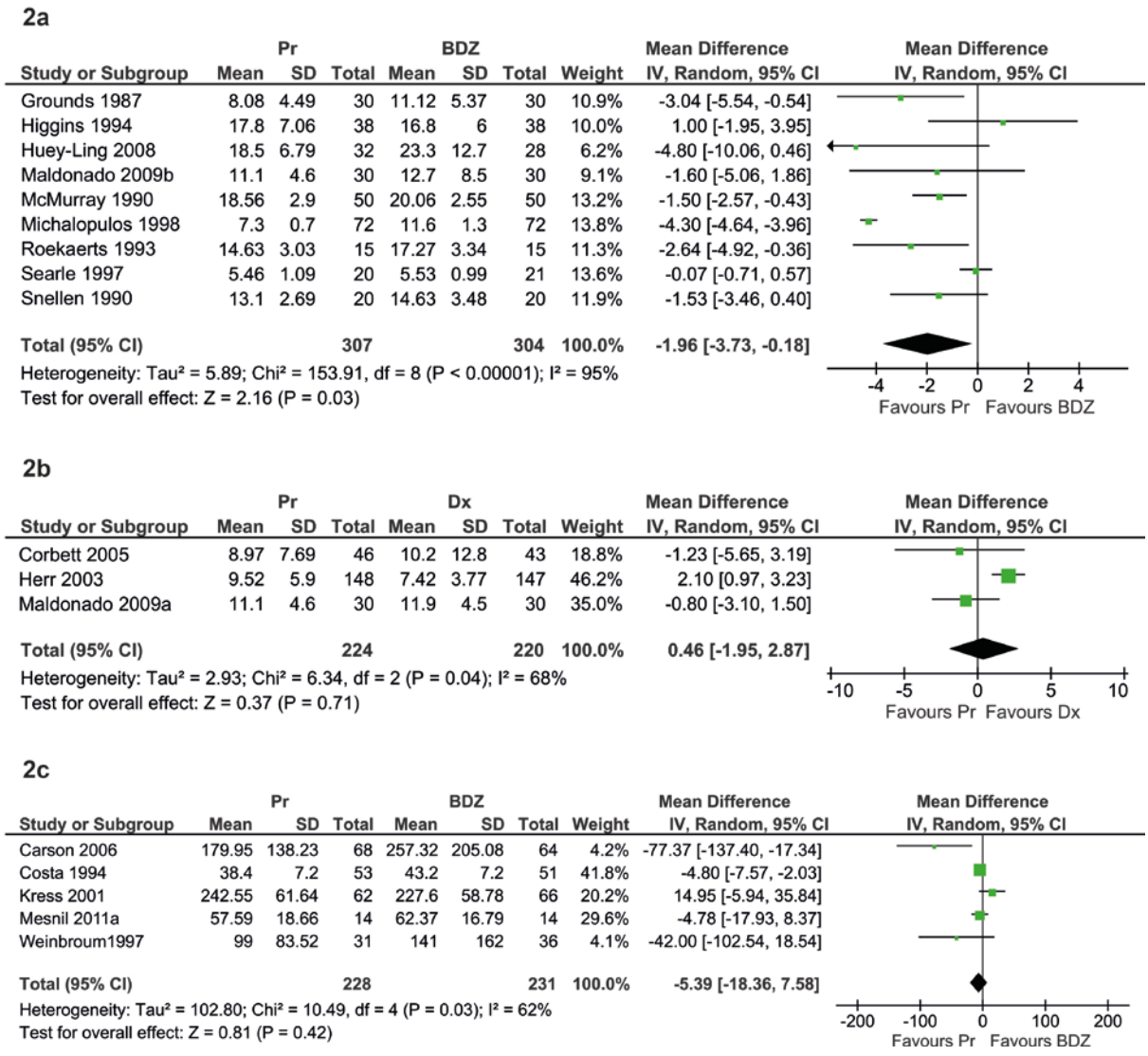
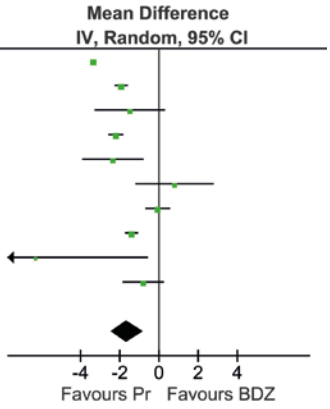


Figure S2: Duration of mechanical ventilation with propofol short-term sedation (a,b) and long-term sedation (c) vs. comparators. Mean values are shown in hours. Pr=propofol, BDZ=benzodiazepine, SD=standard deviation, CI=confidence interval

3a

Study or Subgroup	Pr Mean	Pr SD	Pr Total	BDZ Mean	BDZ SD	BDZ Total	Weight	Mean Difference IV, Random, 95% CI
Grounds 1987	0.42	0.05	30	3.77	0.38	30	12.8%	-3.35 [-3.49, -3.21]
McMurray 1990	0.2	0.29	50	2.13	1.17	50	12.6%	-1.93 [-2.26, -1.60]
Snellen 1990	2.57	2.46	20	4.05	3.28	20	8.2%	-1.48 [-3.28, 0.32]
Carrasco 1993a	0.3	0.01	20	2.5	0.9	20	12.5%	-2.20 [-2.59, -1.81]
Roekaerts 1993	4.17	2.25	15	6.52	2.13	15	9.0%	-2.35 [-3.92, -0.78]
Higgins 1994	4.3	5.57	42	3.5	3.36	38	7.6%	0.80 [-1.19, 2.79]
Searle 1997	1.46	1.09	21	1.53	0.99	20	12.0%	-0.07 [-0.71, 0.57]
Carrasco 1998a	0.9	0.3	25	2.3	0.8	25	12.6%	-1.40 [-1.73, -1.07]
Hall 2001a	5.6	7.01	21	11.9	12.75	26	1.9%	-6.30 [-12.05, -0.55]
Huey-Ling 2008	3.5	1.13	32	4.3	2.65	28	10.8%	-0.80 [-1.86, 0.26]
Total (95% CI)			**276**			**272**	**100.0%**	**-1.61 [-2.47, -0.76]**

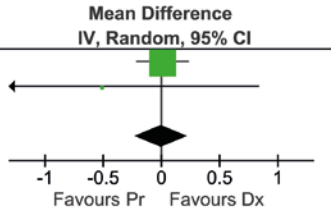
Heterogeneity: Tau² = 1.48; Chi² = 263.43, df = 9 (P < 0.00001); I² = 97%
Test for overall effect: Z = 3.69 (P = 0.0002)



3b

Study or Subgroup	Pr Mean	Pr SD	Pr Total	Dx Mean	Dx SD	Dx Total	Weight	Mean Difference IV, Random, 95% CI
Venn 2001	0.48	0.32	10	0.47	0.18	10	97.2%	0.01 [-0.22, 0.24]
Herr 2003	3.83	7.69	148	4.34	3.31	147	2.8%	-0.51 [-1.86, 0.84]
Total (95% CI)			**158**			**157**	**100.0%**	**-0.00 [-0.23, 0.22]**

Heterogeneity: Tau² = 0.00; Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)



3c

Study or Subgroup	Pr Mean	Pr SD	Pr Total	BDZ Mean	BDZ SD	BDZ Total	Weight	Mean Difference IV, Random, 95% CI
Aitkenhead 1989	0.08	0.05	53	2.47	1.77	47	16.5%	-2.39 [-2.90, -1.88]
Carrasco 1993c	0.4	0.1	16	13.5	4	12	16.0%	-13.10 [-15.36, -10.84]
Carrasco 1993b	0.8	0.3	10	36.6	6.8	10	14.6%	-35.80 [-40.02, -31.58]
Costa 1994	2	0.86	53	7.2	3.1	51	16.5%	-5.20 [-6.08, -4.32]
Weinbroum 1997	2	7.41	31	3.2	4.47	36	15.5%	-1.20 [-4.19, 1.79]
Barrientos-Vega 1997	34.8	29.4	27	97.9	54.6	25	3.2%	-63.10 [-87.21, -38.99]
Hall 2001b	8.4	6.47	4	46.8	52.44	10	1.8%	-38.40 [-71.51, -5.29]
Hall 2001c	7.4	10.05	21	31.3	54.06	17	2.8%	-23.90 [-49.96, 2.16]
Mesnil 2011a	5.44	6	14	9.99	9.78	14	13.1%	-4.55 [-10.56, 1.46]
Total (95% CI)			**229**			**222**	**100.0%**	**-12.73 [-17.50, -7.97]**

Heterogeneity: Tau² = 35.73; Chi² = 358.02, df = 8 (P < 0.00001); I² = 98%
Test for overall effect: Z = 5.24 (P < 0.00001)

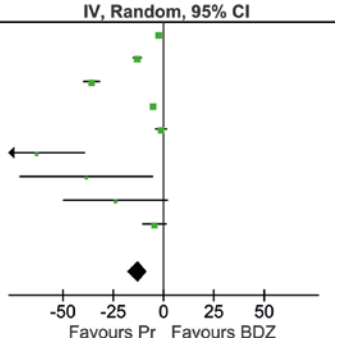
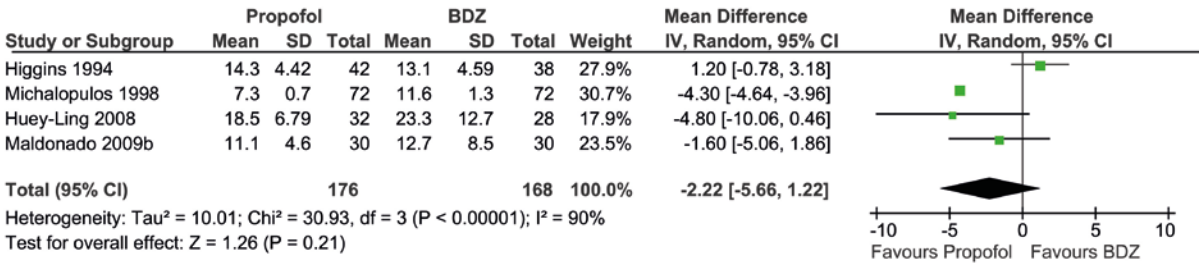
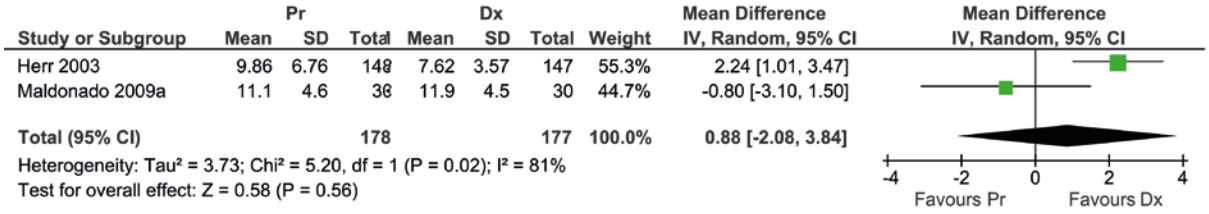


Figure S3: Weaning time with propofol short-term sedation (a,b) and long-term sedation (c) vs. comparators in RCTs. Mean values are shown in hours. Pr=propofol, BDZ=benzodiazepine, SD=standard deviation, CI=confidence interval

4a



4b



4c

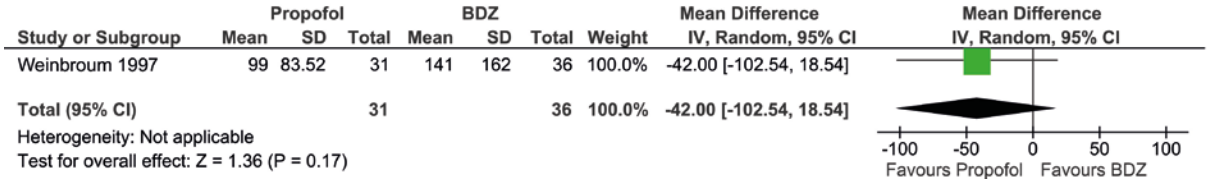
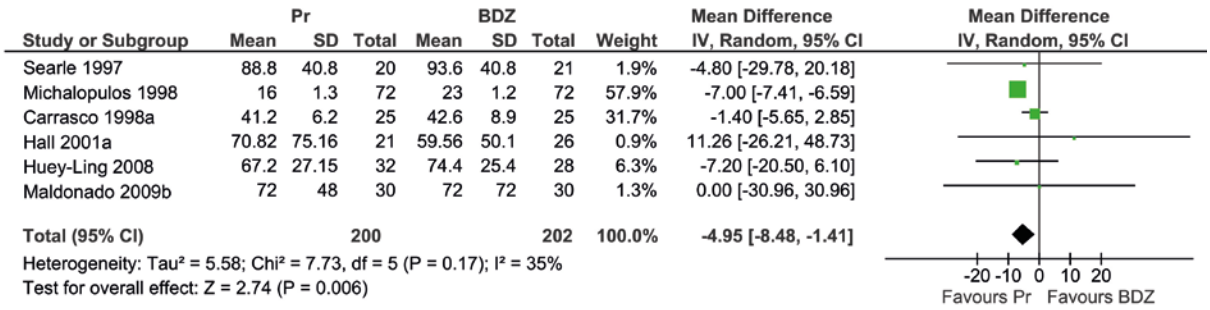
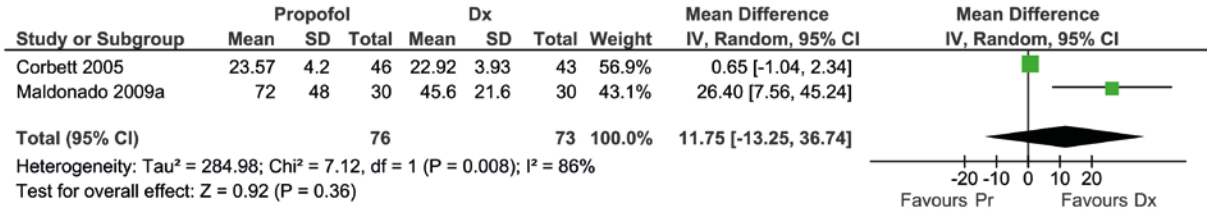


Figure S4: Time to extubation with propofol short-term sedation (a, b) and long-term sedation (c) vs. comparators in RCTs. Mean values are shown in hours. Pr=propofol, BDZ=benzodiazepine, SD=standard deviation, CI=confidence interval

5a



5b



5c

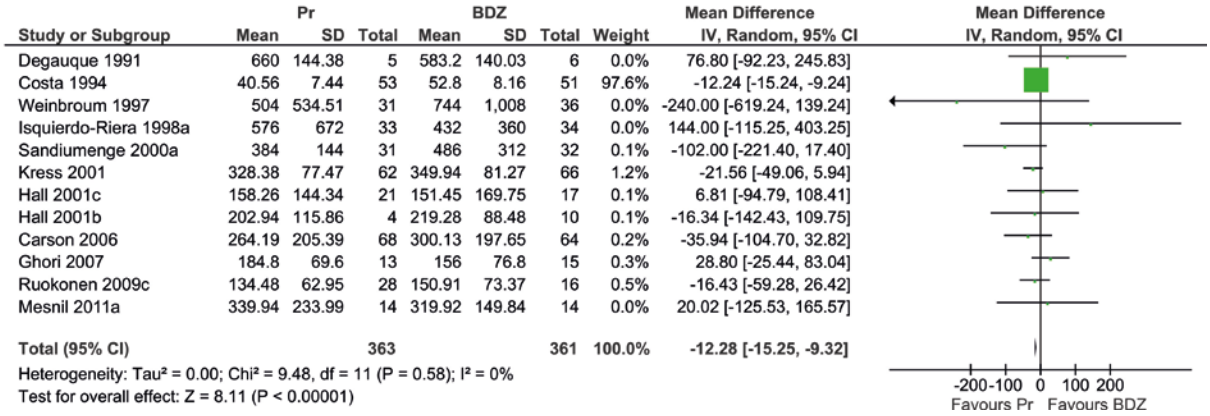


Figure S5: Length of stay in the ICU with propofol short-term sedation (a,b) and long-term sedation (c) vs. comparators. Mean values are shown in hours. Pr=propofol, BDZ=benzodiazepine, SD=standard deviation, CI=confidence interval