Supplementary Data

Comparison of modafinil and pitolisant in narcolepsy: a non-inferiority meta-analytical approach

CONTENTS

1 Tables and Figures of the manuscript

Table 1. Included publications following review of published RCTs on drug treatment for narcolepsy

Study	Tested drugs	Design	Treatment duration	Sample size	Endpoints of interest	Comments
Billiard et al. 1994	Modafinil 300 mg/d Placebo	RCT, 2-way4-wk, crossover	4 wks, 2 wk placebo washout (WO)	N=50	MWT, cataplexy, sleep attacks, inadvertent naps	No ESS. Safety not documented. Selected only for MWT and cataplexy.
Broughton et al. 1997	Modafinil 200 mg/d Modafinil 400 mg/d Placebo	Double-blind, crossover RCT 3 x 2 wks	3 x 2 wks No WO period	N=75	MWT (primary endpoint), ESS, sleep attacks, inadvertent naps. Safety = AE.	Safety data poorly documented.
US-MDF, 1998	Modafinil 200 mg/d Modafinil 400 mg/d Placebo	DB-RCT 3 parallel groups	9 wks	N=283 n=92 placebo n=96 MDF200 n=95 MDF400	20 min MWT and CGI (primary endpoint) ESS MSLT Sleep attacks on daily basis Safety AE	No data on cataplexy.
US-MDF, 2000	Modafinil 200 mg/d Modafinil 400 mg/d Placebo	DB–RCT 3 parallel groups	9 wks	N=271 n=89/MDF200 n=89/MDF400 n=93/placebo	- ESS - 20 min MWT, sleep attacks, inadvertent naps - CGI - Safety AE	No data on cataplexy
Moldofsky et al. 2000	Modafinil 300-500 mg/d Placebo.	DB, placebo-controlled, 2 wks after 16-wk MDF open label (OL).	16 wks OL. 2 wks DB.	N=63	40 min MWT ESS Daily number of cataplectic attacks Number of periods of severe sleepiness, voluntary sleep episodes (naps), and sleep attacks	Study assessing the treatment interruption and withdrawal symptoms after 16-wk OL. Safety not documented. Study selected only for efficacy.y
Harsh et al. 2006	Armodafinil 150 mg/d Armodafinil 250 mg/d Placebo	DB,RCT 3 parallel groups	12 wks	N=196 n=64/ADF 150 n=67/ADF 250 n=63/placebo	20 min MWT (primary endpoint) ESS Cataplexy CGI Cognitive tests (CDR) Fatigue inventory - Safety	Safety only most frequent AE (>5%)
Black & Houghton 2006	Placebo Modafinil 200-600 mg/d Sodium oxybate 6–9 g/d sodium oxybate 6–9 g/d + Modafinil 200-600 mg/d	DB, RCT 4 parallel groups	8 wks	N=222 n=55/placebo n=63/MDF n=50/X n=54/X +MDF	20 min MWT (primary endpoint) ESS CGI Sleep attacks Safety	No data on cataplexy
Saletu et al. 2005	Modafinil fixed titration at 3 wks (200 mg/dW1, 300 mg/d,W2, 400 mg/d W3) Placebo	DB, RCT Placebo-controlled crossover	3 wks 1 wk	N=16 matched with 16 control HV	- ESS - MSLT, EEG - AE	Safety data poorly documented
Dauvilliers et al. 2013 (HARMONY I)	Pitolisant up to 40 mg/d Modafinil up to 400 mg/d Placebo	DB, RCT 3 parallel groups	8 wks	N=94 n=31/pitolisant n=33/MDF n=30/placebo	ESS (primary endpoint), % of responders, 20 min MWT Cataplexy and Sleep attacks CGI, Safety AE	

Szakacs et al. 2017 (HARMONY CTP)	Pitolisant up to 40 mg/d Placebo	DB, RCT two parallel groups	7 wks	N=105 n=54/pitolisant n=51/placebo	Weekly rate of cataplexy (primary endpoint) ESS, % of responders 40 min MWT CGI, Patient Global Opinion, Safety AE	Patients included with at least 3 cataplexy per wk

Table 2. Comparison of treatments and studied endpoints within studies

Study	Placebo	MDF	PIT	ESS	MWT	CTP	AE
Billiard et al. 1994	*	*			+	+	
Broughton et al. 1997	*	*		+	+	+	+
US-MDF, 1998	*	*		+	+		+
US-MDF, 2000	*	*		+	+	+	+
Moldofsky et al. 2000	*	*		+	+		
Saletu et al. 2005	*	*		+	+		+
Harsh et al. 2006	*	*		+	+	+	+
Black & Houghton 2006	*	*		+	+		+
Dauvilliers et al. 2013	*	*	*	+	+	+	+
Szakacs et al.2017	*		*	+	+	+	+

Abbreviations: AE, adverse event; CTP, cataplexy; ESS, Epworth Sleepiness Scale; MDF, modafinil up to 400 mg/day; MWT, Maintenance Wakefulness Test; PIT, pitolisant up to 40 mg/day

Table 3. Publications excluded from the network meta-analysis

Study	Tested drugs	Design	Treatment duration	Sample size	Endpoints	Comments
Laffont et al.1988. (MOD 024)	Modafinil 200 mg/d Placebo	DB, RCT crossover 2 x 2wks	2 wks	N=10	No data on ESS, MWT, cataplexy No data on safety reported	Not published, only as an abstract. No data on ESS, MWT, or cataplexy. Safety not documented.
Boivin et al.1993	Modafinil 300 mg/d Placebo	DB, RCT 4-wk crossover	4 wks	N=10	PSG, EMG (Periodic Leg Movement index) EDS on 10 points VAS (no ESS) Cognitive test (FCRTT) Daily number of sleep attacks	No data on ESS, MWT or cataplexy Safety not documented
Besset et al.1993	Modafinil 300 mg/d Placebo	DB, RCT 4-wk crossover	4 wks	N=16	Stanford scale instead of ESS. Attention Safety (poor data) PSG (REM).	No data on ESS, MWT or cataplexy Safety data poorly documented
Kollb-Sielecka et al. 2017 (HARMONY Ibis)	Pitolisant up to 20 mg/d Modafinil up to 400 mg/d Placebo	DB-RCT 3 parallel groups	8 wks	N= 165 n=67/pitolisant n=65/MDF n=33/placebo	ESS (primary endpoint), % of responders 40 min MWT Cataplexy and Sleep attacks CGI Safety AE	

Table 4. Characteristics and tests for each analysis

	ESS	**MWT**	**Cataplexy[a]**	**NS1[b]**	**OSS[c]**	**BR1[d]**	**NS2[e]**	**BR2[f]**
Studies (n)	9	10	4	10	9	9	10	9
Pairwise computations (n)	11	12	6	12	11	11	12	11
$I^{2\,(\%)}$	45	0.0	0	0.01	0.01	0.01	0.01	0.01
Difference with Placebo[g]	MD	MD	MD	MD	RR	MD	MD	MD
Modafinil (MDF)	-2.7^{***}	2.7^{*}	-0^{ns}	0.41^{**}	1.59^{**}	0.35^{**}	0.38^{**}	0.30^{***}
Pitolisant (PIT)	-3.4^{***}	4.8^{***}	-5.9^{***}	0.87^{***}	1.38^{ns}	0.84^{***}	0.56^{***}	0.54^{***}
Tests								
-Within Q_h	0.05	0.76	0.89	0.08	0.01	0.03	0.04	0.06
-Between Q_i	0.41	0.27	0.34	0.72	0.32	0.62	0.51	0.5
P-scores:								
-MDF	0.59	0.54	0.32	0.59	0.17	0.58	0.39	0.4
- PIT	0.91	0.95	1	0.91	0.41	0.91	0.11	0.11
-Placebo	0.00	0.02	0.18	0	0.92	0.01	1	0.99
Difference PIT-MDF	−0.69	2.12	−0.49	0.46	0.86	0.49	0.15	0.24
- 95% CI	−2.18, 0.79	−0.95, 5.19	−0.86, −0.12	−0.11, 0.49	0.44, 1.24	0.08, 1.03	−0.15, 0.45	−0.19, 0.70
- P[h]	0.015 (0.36)	0.04 (0.18)	<0.001 (0.012)	0.004 (0.22)	0.66 (0.04)	0.021(<0.001)	0.32	0.25

Number of studies, number of pairwise computations, heterogeneity index (I^2), and tests of within-design (Q_h, measuring heterogeneity between studies), and between-designs (Q_i, measuring between design inconsistency) for the following endpoints: ESS, MWT, cataplexy, narcolepsy Z-Score, safety, and benefit/risk ratio.

*(a) weekly reduction of cataplexy rate (CTP); (b) NS1= Narcolepsy Score aggregating efficacy for EDS and cataplexy , thus appropriate for Type 1 Narcolepsy patients; (c) overall safety score (OSS); (d) BR1= benefit/risk ratio applicable for Narcolepsy type 1 patients combining EDS and Cataplexy, calculated as the residual of the linear fit of the NS1 by the OSS.; (e) NS2 = Narcolepsy score limited to efficacy on EDS and appropriate for Narcolepsy type 2 patients; (f) BR2= Benefit/Risk ratio based on efficacy limited to EDS, applicable to Narcolepsy type 2 patients and calculated as the residual of the linear fit of EDS Z score by OSS. (g) Differences between Modafinil or Pitolisant with placebo expressed as Mean differences (MD) or Risk Ratios (RR), significance abbreviated as ns (p>.05), * (p<.05), ** (0.001<p<.01), *** (p<.001). (h) The P value of the difference is associated with the non-inferiority test compared with the Null hypothesis that the difference is at least as large as the pre-specified NIM. The P-value enclosed within parentheses correspond to a superiority test of pitolisant on Modafinil.*

Figure 1. PRISMA flow diagram

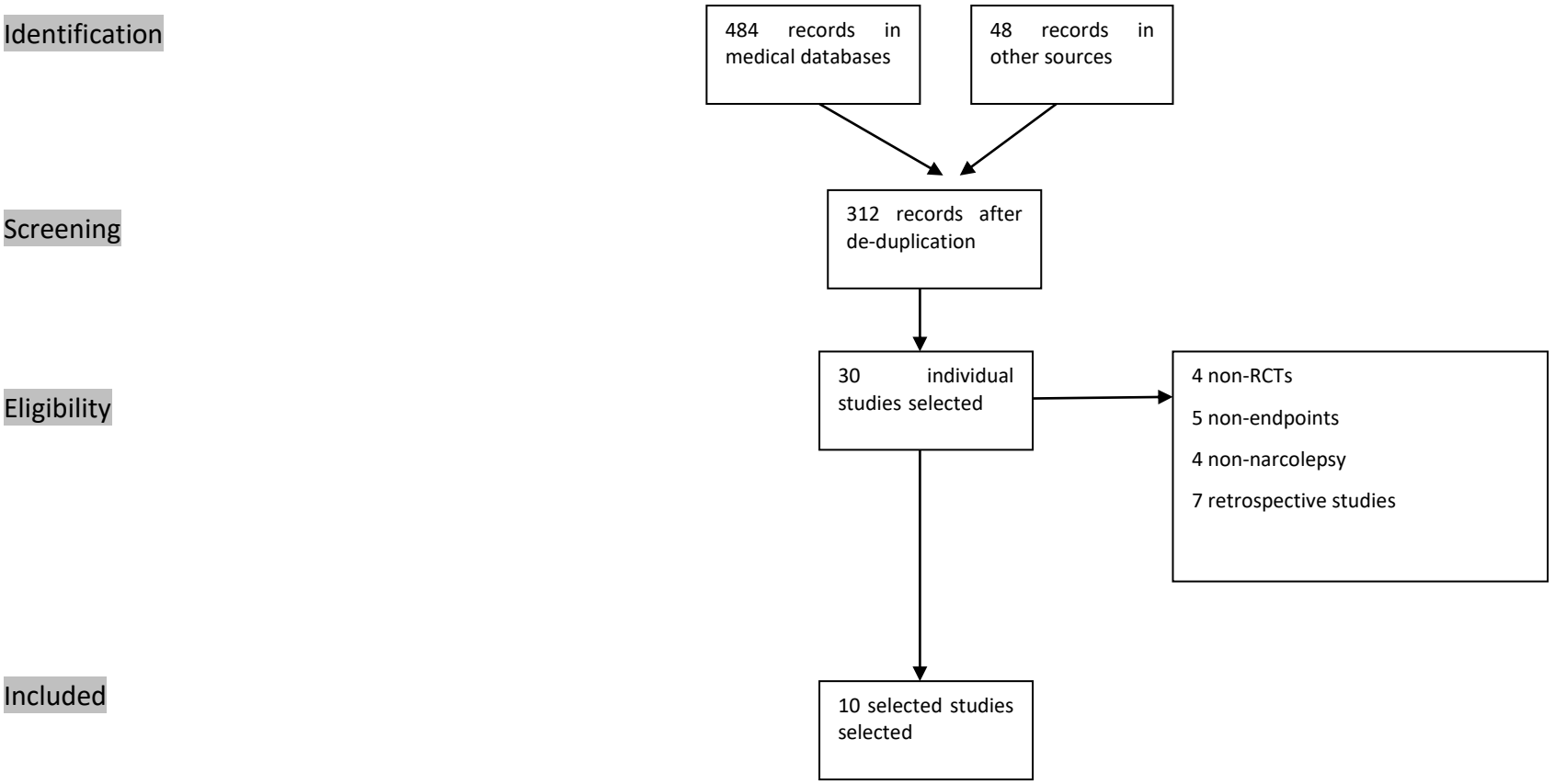


Figure 2: Network tree

A network meta-analysis was needed to account both for the direct comparisons, but also indirect comparisons between modafinil and pitolisant. In this network evidence graph, each node in the network is associated with a treatment (pcb=placebo, p40=pitolisant up to 40 mg, mdf: modafinil up to 400 mg). An overlap (edge) between any two treatments represents a direct comparison, the thickness of the overlap proportional to the inverse of the standard error of the treatment effect.

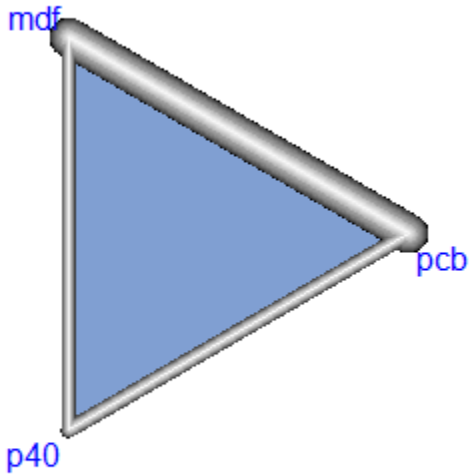
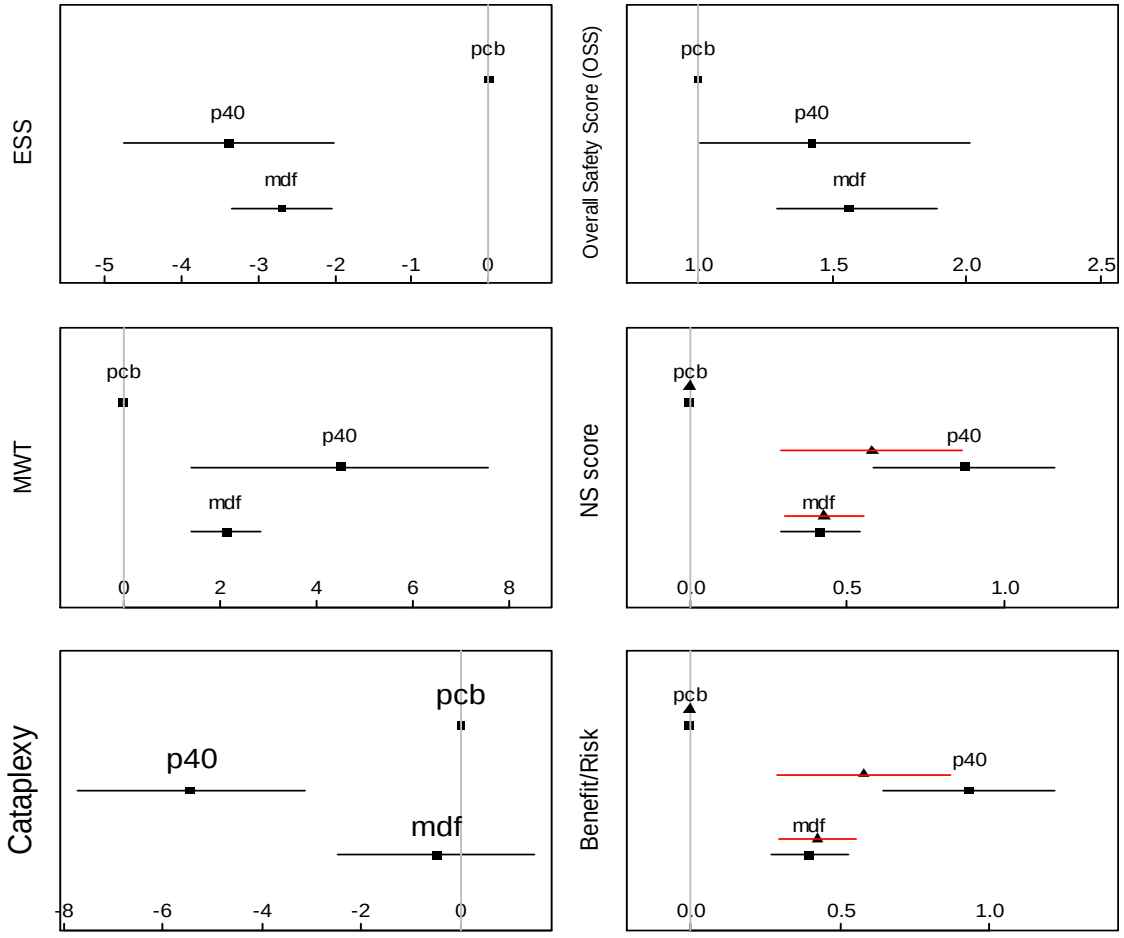


Figure 3 . Forest Plot for all the compared endpoints

Measures : ESS (mean change from baseline in ESS scores), MWT (mean change from baseline in minutes), Cataplexy (mean change from baseline in Weekly Rate of cataplexies), Overall Safety Score (Relative Risk defined as the ratio between the number of treatment emergent adverse events nTEAE on the considered drug on nTEAE on the placebo arm. For the NS scores and Risk benefits sub-graphics, Black square represent NS1 Score and corresponding benefit/risk adapted for Narcolepsy type 1 patients, whereas black triangles represent similar values for NS2 and corresponding Benefit/Risk for Narcolepsy type 2 patients.



2 Data

	id	year	ep	mean1	sd1	n1	mean2	sd2	n2	mean3	sd3	n3	trt1	trt2	trt3	type	keylabel	sortvar
1	Billard94	1994	2	10.09	6.48	21	8.19	6.48	21	NA	NA	NA	mdf	pcb		f	1	1
2	Billard94	1994	3	0.32	0.70	10	0.28	0.47	10	NA	NA	NA	mdf	pcb		f	2	2
3	Black06	2006	6	2.00	NA	56	7.00	NA	63	NA	NA	NA	pcb	mdf			3	3
4	Black06	2006	5	10.00	NA	56	8.00	NA	63	NA	NA	NA	pcb	mdf			4	4
5	Black06	2006	4	12.00	NA	56	7.00	NA	63	NA	NA	NA	pcb	mdf			5	5
6	Black06	2006	2	-2.72	4.36	56	-0.53	4.36	63	NA	NA	NA	pcb	mdf		mc	6	6
7	Black06	2006	1	13.00	8.00	56	13.00	8.00	56	NA	NA	NA	pcb	mdf		mc	7	7
8	Broughton97	1997	6	13.00	NA	75	7.00	NA	75	NA	NA	NA	mdf	pcb			8	9
9	Broughton97	1997	5	12.00	NA	75	6.00	NA	75	NA	NA	NA	mdf	pcb			9	10
10	Broughton97	1997	4	16.00	NA	75	5.00	NA	75	NA	NA	NA	mdf	pcb			10	11
11	Broughton97	1997	2	17.20	13.00	71	11.20	9.80	71	NA	NA	NA	mdf	pcb		f	11	12
12	Broughton97	1997	1	14.10	5.60	71	16.50	4.40	71	NA	NA	NA	mdf	pcb		f	12	73
13	Harm1	2015	6	13.00	NA	33	2.00	NA	30	11.00	NA	31	mdf	pcb	p40		13	14
14	Harm1	2015	5	7.00	NA	33	3.00	NA	30	5.00	NA	31	mdf	pcb	p40		14	15
15	Harm1	2015	4	11.00	NA	33	9.00	NA	30	11.00	NA	31	mdf	pcb	p40		15	16
16	Harm1	2015	3	0.22	0.33	28	0.23	0.43	24	0.14	0.22	25	mdf	pcb	p40	mr	16	17
17	Harm1	2015	2	12.40	6.60	33	7.11	9.00	30	13.00	8.30	32	mdf	pcb	p40	f	17	18
18	Harm1	2015	1	-6.90	6.20	33	-3.35	4.16	30	-5.80	6.20	31	mdf	pcb	p40	mc	18	8
19	Harsch06	2006	6	6.00	NA	67	0.00	NA	63	NA	NA	NA	mdf	pcb			19	26
20	Harsch06	2006	5	7.00	NA	67	2.00	NA	63	NA	NA	NA	mdf	pcb			20	27
21	Harsch06	2006	4	19.00	NA	67	7.00	NA	63	NA	NA	NA	mdf	pcb			21	28
22	Harsch06	2006	3	0.10	1.14	67	0.10	0.56	63	NA	NA	NA	mdf	pcb		mc	22	29
23	Harsch06	2006	2	9.50	6.10	67	12.50	6.60	63	NA	NA	NA	mdf	pcb		f	23	30
24	Harsch06	2006	1	15.70	4.70	67	17.50	3.90	63	NA	NA	NA	mdf	pcb		f	24	19
25	Hctp	2017	6	3.00	NA	54	1.00	NA	51	NA	NA	NA	p40	pcb			25	32
26	Hctp	2017	5	6.00	NA	54	6.00	NA	51	NA	NA	NA	p40	pcb			26	33
27	Hctp	2017	4	8.00	NA	54	9.00	NA	51	NA	NA	NA	p40	pcb			27	34
28	Hctp	2017	3	0.42	0.38	54	0.87	0.79	51	NA	NA	NA	p40	pcb		mr	28	35
29	Hctp	2017	2	12.00	15.90	54	4.60	19.50	51	NA	NA	NA	p40	pcb		f	29	36
30	Hctp	2017	1	-5.76	4.22	54	-1.85	4.30	51	NA	NA	NA	p40	pcb		mc	30	25
31	Moldfsky00	2000	6	1.00	NA	30	3.00	NA	30	NA	NA	NA	mdf	pcb			31	45
32	Moldfsky00	2000	5	2.00	NA	30	1.00	NA	30	NA	NA	NA	mdf	pcb			32	46
33	Moldfsky00	2000	4	3.00	NA	30	3.00	NA	28	NA	NA	NA	mdf	pcb			33	47
34	Moldfsky00	2000	2	9.70	7.90	30	16.40	13.70	28	NA	NA	NA	mdf	pcb		f	34	48
35	Moldfsky00	2000	1	13.20	5.70	28	15.40	5.80	33	NA	NA	NA	mdf	pcb		mc	35	43
36	Saletu05	2005	6	6.00	NA	16	11.00	NA	16	NA	NA	NA	mdf	pcb			36	50
37	Saletu05	2005	5	14.00	NA	16	2.00	NA	16	NA	NA	NA	mdf	pcb			37	51
38	Saletu05	2005	4	8.00	NA	16	3.00	NA	16	NA	NA	NA	mdf	pcb			38	52
39	Saletu05	2005	2	14.10	27.30	16	16.50	27.60	16	NA	NA	NA	mdf	pcb		f	39	53
40	Saletu05	2005	1	15.00	5.00	16	14.00	5.40	16	NA	NA	NA	mdf	pcb		f	40	44
41	US00	2000	6	40.00	NA	89	12.00	NA	93	NA	NA	NA	mdf	pcb		E	41	59
42	US00	2000	5	4.00	NA	89	1.00	NA	93	NA	NA	NA	mdf	pcb		E	42	60
43	US00	2000	4	25.00	NA	89	10.00	NA	93	NA	NA	NA	mdf	pcb		E	43	61
44	US00	2000	2	2.10	4.80	89	-0.70	4.20	88	NA	NA	NA	mdf	pcb		mc	44	62
45	US00	2000	1	-5.00	4.95	89	-1.70	3.60	88	NA	NA	NA	mdf	pcb		mc	45	54
46	US98	1998	6	32.00	NA	95	23.00	NA	92	NA	NA	NA	mdf	pcb		E	46	69
47	US98	1998	5	15.00	NA	95	11.00	NA	92	NA	NA	NA	mdf	pcb		E	47	70
48	US98	1998	4	25.00	NA	95	40.00	NA	92	NA	NA	NA	mdf	pcb		E	48	71
49	US98	1998	2	2.30	4.80	95	-0.70	4.80	92	NA	NA	NA	mdf	pcb		mc	49	72
50	US98	1998	1	13.00	5.70	95	17.10	5.00	92	NA	NA	NA	mdf	pcb		f	50	63

3 ESS values

3.1 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	0	1.51	1.51
mdf	pcb	-2.4	0.85	0.85
mdf	p40	-1.1	1.55	2.21
mdf	pcb	-3.55	1.32	1.51
p40	pcb	-2.45	1.35	1.56
mdf	pcb	-1.8	0.76	0.76
p40	pcb	-3.91	0.83	0.83
mdf	pcb	-2.2	1.48	1.48
mdf	pcb	1	1.84	1.84
mdf	pcb	-3.3	0.65	0.65
mdf	pcb	-4.1	0.78	0.78

3.2 Results of Fixed and Random Models

3.2.1.1 Fixed Model

```
Results (fixed effect model):
            treat1 treat2     MD           95%-CI    Q leverage
Black06        mdf    pcb -2.698 [-3.353; -2.042] 3.19     0.05
Broughton97    mdf    pcb -2.698 [-3.353; -2.042] 0.12     0.15
Harm1          mdf    p40  0.694 [-0.792;  2.180] 0.66     0.12
Harm1          mdf    pcb -2.698 [-3.353; -2.042] 0.32     0.05
Harm1          p40    pcb -3.392 [-4.757; -2.026] 0.36     0.20
Harsch06       mdf    pcb -2.698 [-3.353; -2.042] 1.40     0.19
Hctp           p40    pcb -3.392 [-4.757; -2.026] 0.39     0.70
Moldfsky00     mdf    pcb -2.698 [-3.353; -2.042] 0.11     0.05
Saletu05       mdf    pcb -2.698 [-3.353; -2.042] 4.04     0.03
US00           mdf    pcb -2.698 [-3.353; -2.042] 0.86     0.26
US98           mdf    pcb -2.698 [-3.353; -2.042] 3.23     0.18
```

3.2.1.2 Random Model

```
Results (random effects model):
            treat1 treat2     MD           95%-CI
Black06        mdf    pcb -2.514 [-3.473; -1.555]
Broughton97    mdf    pcb -2.514 [-3.473; -1.555]
Harm1          mdf    p40  0.650 [-1.386;  2.686]
Harm1          mdf    pcb -2.514 [-3.473; -1.555]
Harm1          p40    pcb -3.164 [-5.037; -1.291]
Harsch06       mdf    pcb -2.514 [-3.473; -1.555]
Hctp           p40    pcb -3.164 [-5.037; -1.291]
Moldfsky00     mdf    pcb -2.514 [-3.473; -1.555]
Saletu05       mdf    pcb -2.514 [-3.473; -1.555]
US00           mdf    pcb -2.514 [-3.473; -1.555]
US98           mdf    pcb -2.514 [-3.473; -1.555]
```

3.3 Tests

```
Number of studies: k = 9
Number of treatments: n = 3
Number of pairwise comparisons: m = 11
Number of designs: d = 3

Fixed effect model

Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):

        MD           95%-CI
mdf -2.698 [-3.353; -2.042]
p40 -3.392 [-4.757; -2.026]
pcb      .                .

Random effects model

Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):

        MD           95%-CI
mdf -2.514 [-3.473; -1.555]
p40 -3.164 [-5.037; -1.291]
pcb      .                .

Quantifying heterogeneity / inconsistency:
tau^2 = 0.8263; I^2 = 45.5%

Tests of heterogeneity (within designs) and inconsistency (between designs):

                    Q d.f. p-value
Total           14.68    8  0.0656
Within designs  12.89    6  0.0459
Between designs  1.80    2  0.4075
```

3.4 P-values

```
    P-score (fixed) P-score (random)
p40          0.9099           0.8669
mdf          0.5901           0.6328
pcb          0.0000           0.0002
```

3.5 Pairwise comparisons - Fixed model

```
      mdf   p40   pcb
mdf  0.00 -0.79 -3.35
p40 -2.18  0.00 -4.76
pcb  2.04  2.03  0.00
```

3.5.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

```
     mdf  p40   pcb
mdf 0.00 2.18 -2.04
p40 0.79 0.00 -2.03
pcb 3.35 4.76  0.00
```

3.5.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

```
     mdf  p40 pcb
mdf  NaN 0.36   0
p40 0.36  NaN   0
pcb 0.00 0.00 NaN
```

3.5.3 Pairwise comparison P values

3.6 Pairwise comparisons - Random model

	mdf	p40	pcb
mdf	0.00	-1.39	-3.47
p40	-2.69	0.00	-5.04
pcb	1.55	1.29	0.00

3.6.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

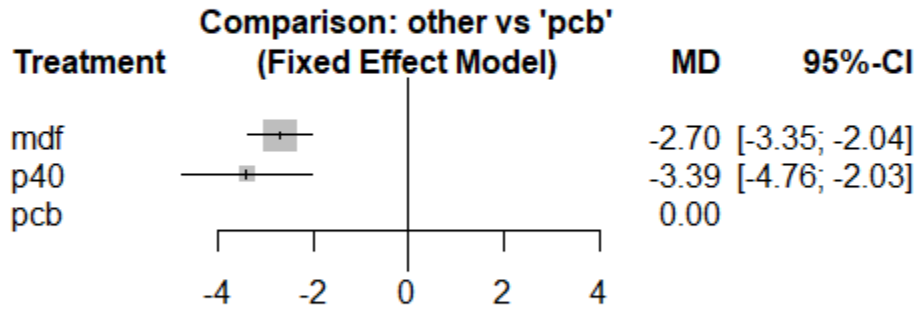
	mdf	p40	pcb
mdf	0.00	2.69	-1.55
p40	1.39	0.00	-1.29
pcb	3.47	5.04	0.00

3.6.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

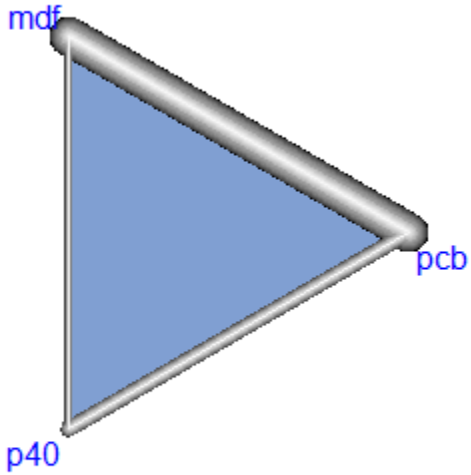
	mdf	p40	pcb
mdf	NaN	0.53	0
p40	0.53	NaN	0
pcb	0.00	0.00	NaN

3.6.3 Pairwise comparison P values

3.7 Forest Plot



3.8 Network Evidence Graph



4 MWT values

4.1 Main Treatment effect for each study

4.2 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	1.9	2	2
mdf	pcb	1.19	0.8	0.8
mdf	pcb	3.2	1.93	1.93
mdf	p40	-0.6	1.86	2.12
mdf	pcb	5.29	2	2.37
p40	pcb	5.89	2.2	3.04
mdf	pcb	3	1.12	1.12
p40	pcb	7.4	3.48	3.48
mdf	pcb	4.3	2.96	2.96
mdf	pcb	3	9.71	9.71
mdf	pcb	2.8	0.68	0.68
mdf	pcb	3	0.7	0.7

4.3 Results of Fixed and Random Models

4.3.1.1 Fixed Model

Results (fixed effect model):

	treat1	treat2	MD	95%-CI	Q	leverage
Billard94	mdf	pcb	2.649	[1.933; 3.366]	0.14	0.03
Black06	mdf	pcb	2.649	[1.933; 3.366]	3.33	0.21
Broughton97	mdf	pcb	2.649	[1.933; 3.366]	0.08	0.04
Harm1	mdf	p40	-2.122	[-5.192; 0.947]	0.51	0.54
Harm1	mdf	pcb	2.649	[1.933; 3.366]	1.24	0.02
Harm1	p40	pcb	4.772	[1.696; 7.848]	0.14	0.27
Harsch06	mdf	pcb	2.649	[1.933; 3.366]	0.10	0.11
Hctp	p40	pcb	4.772	[1.696; 7.848]	0.57	0.20
Moldfsky00	mdf	pcb	2.649	[1.933; 3.366]	0.31	0.02
Saletu05	mdf	pcb	2.649	[1.933; 3.366]	0.00	0.00
US00	mdf	pcb	2.649	[1.933; 3.366]	0.05	0.29
US98	mdf	pcb	2.649	[1.933; 3.366]	0.25	0.27

4.3.1.2 Random Model

Results (random effects model):

	treat1	treat2	MD	95%-CI
Billard94	mdf	pcb	2.649	[1.933; 3.366]
Black06	mdf	pcb	2.649	[1.933; 3.366]
Broughton97	mdf	pcb	2.649	[1.933; 3.366]
Harm1	mdf	p40	-2.122	[-5.192; 0.947]
Harm1	mdf	pcb	2.649	[1.933; 3.366]
Harm1	p40	pcb	4.772	[1.696; 7.848]
Harsch06	mdf	pcb	2.649	[1.933; 3.366]
Hctp	p40	pcb	4.772	[1.696; 7.848]
Moldfsky00	mdf	pcb	2.649	[1.933; 3.366]
Saletu05	mdf	pcb	2.649	[1.933; 3.366]
US00	mdf	pcb	2.649	[1.933; 3.366]
US98	mdf	pcb	2.649	[1.933; 3.366]

4.4 Tests

```
Number of studies: k = 10
Number of treatments: n = 3
Number of pairwise comparisons: m = 12
Number of designs: d = 3

Fixed effect model

Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):
       MD         95%-CI
mdf 2.649 [1.933; 3.366]
p40 4.772 [1.696; 7.848]
pcb     .              .

Random effects model

Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):
       MD         95%-CI
mdf 2.649 [1.933; 3.366]
p40 4.772 [1.696; 7.848]
pcb     .              .

Quantifying heterogeneity / inconsistency:
tau^2 = 0; I^2 = 0%

Tests of heterogeneity (within designs) and inconsistency (between designs):
                    Q d.f. p-value
Total            6.72    9  0.6666
Within designs   4.17    7  0.7601
Between designs  2.55    2  0.2799
                        Q df      pval
Total            6.716143  9 0.6666456
Within designs   4.169454  7 0.7600659
Between designs  2.546689  2 0.2798940
```

4.5 P-values

```
    P-score (fixed) P-score (random)
pcb          0.9994 =0.0           0.9994
mdf          0.4562 =0.54          0.4562
p40          0.0444 =0.95          0.0444
```

4.6 Pairwise comparisons - Fixed model

```
      mdf   p40  pcb
mdf  0.00 -5.19 1.93
p40 -0.95  0.00 1.70
pcb -3.37 -7.85 0.00
```

4.6.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

```
      mdf   p40  pcb
mdf  0.00  0.95 3.37
p40  5.19  0.00 7.85
pcb -1.93 -1.70 0.00
```

4.6.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

```
     mdf  p40 pcb
mdf  NaN 0.18   0
p40 0.18  NaN   0
pcb 0.00 0.00 NaN
```

4.6.3 Pairwise comparison P values

4.7 Pairwise comparisons - Random model

```
      mdf   p40  pcb
mdf  0.00 -5.19 1.93
p40 -0.95  0.00 1.70
pcb -3.37 -7.85 0.00
```

4.7.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

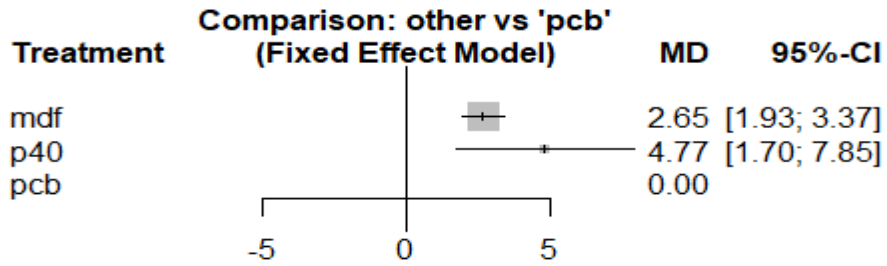
```
      mdf   p40  pcb
mdf  0.00  0.95 3.37
p40  5.19  0.00 7.85
pcb -1.93 -1.70 0.00
```

4.7.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

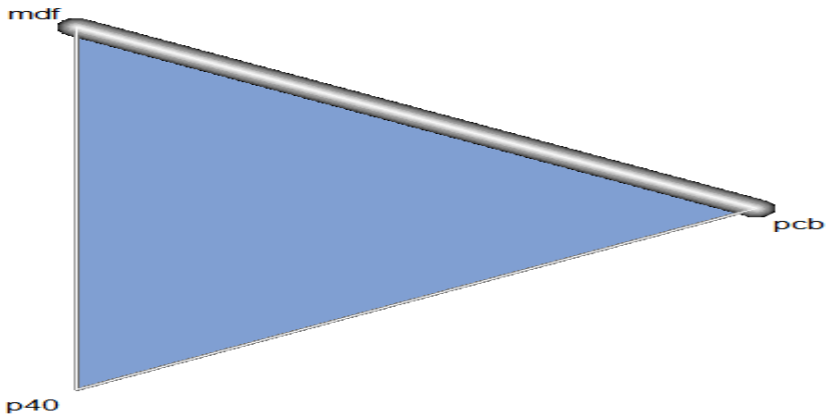
```
     mdf  p40 pcb
mdf  NaN 0.18   0
p40 0.18  NaN   0
pcb 0.00 0.00 NaN
```

4.7.3 Pairwise comparison P values

4.8 Forest Plot



4.9 *Network Evidence Graph*



5 Cataplexy Rates

5.1 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	0.06	0.45	0.45
mdf	p40	0.24	0.28	0.33
mdf	pcb	-0.03	0.28	0.34
p40	pcb	-0.26	0.29	0.36
mdf	pcb	0	0.18	0.18
p40	pcb	-0.73	0.2	0.2

5.2 Results of Fixed and Random Models

5.2.1.1 Fixed Model

Results (fixed effect model):

	treat1	treat2	SMD	95%-CI	Q	leverage
Billard94	mdf	pcb	-0.049	[-0.317; 0.219]	0.06	0.09
Harm1	mdf	p40	0.495	[0.124; 0.865]	0.61	0.32
Harm1	mdf	pcb	-0.049	[-0.317; 0.219]	0.00	0.16
Harm1	p40	pcb	-0.544	[-0.855; -0.233]	0.60	0.19
Harsch06	mdf	pcb	-0.049	[-0.317; 0.219]	0.08	0.61
Hctp	p40	pcb	-0.544	[-0.855; -0.233]	0.82	0.62

5.2.1.2 Random Model

Results (random effects model):

	treat1	treat2	SMD	95%-CI
Billard94	mdf	pcb	-0.049	[-0.317; 0.219]
Harm1	mdf	p40	0.495	[0.124; 0.865]
Harm1	mdf	pcb	-0.049	[-0.317; 0.219]
Harm1	p40	pcb	-0.544	[-0.855; -0.233]
Harsch06	mdf	pcb	-0.049	[-0.317; 0.219]
Hctp	p40	pcb	-0.544	[-0.855; -0.233]

5.3 Tests

```
Number of studies: k = 4
Number of treatments: n = 3
Number of pairwise comparisons: m = 6
Number of designs: d = 3
Fixed effect model
Treatment estimate (sm = 'SMD', comparison: other treatments vs 'pcb'):
       SMD           95%-CI
mdf -0.049 [-0.317;  0.219]
p40 -0.544 [-0.855; -0.233]
pcb      .                .
Random effects model
Treatment estimate (sm = 'SMD', comparison: other treatments vs 'pcb'):
       SMD           95%-CI
mdf -0.049 [-0.317;  0.219]
p40 -0.544 [-0.855; -0.233]
pcb      .                .
Quantifying heterogeneity / inconsistency:
tau^2 = 0; I^2 = 0%
Tests of heterogeneity (within designs) and inconsistency (between designs):
                   Q d.f. p-value
Total           2.18    3  0.5360
Within designs  0.02    1  0.8939
Between designs 2.16    2  0.3393
                         Q df      pval
Total           2.17948722  3 0.5360000
Within designs  0.01777515  1 0.8939375
Between designs 2.16171207  2 0.3393049
```

5.4 P-values

```
    P-score (fixed) P-score (random)
p40          0.9976           0.9976
mdf          0.3223           0.3223
pcb          0.1801           0.1801
```

5.5 Pairwise comparisons - Fixed model

```
      mdf  p40   pcb
mdf  0.00 0.12 -0.32
p40 -0.86 0.00 -0.85
pcb -0.22 0.23  0.00
```

5.5.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

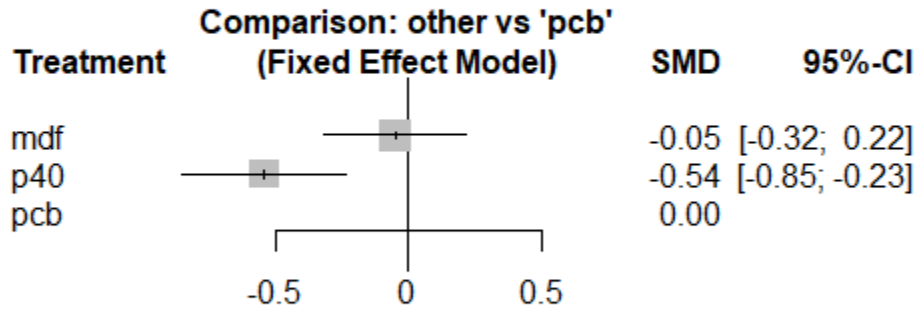
```
      mdf  p40   pcb
mdf  0.00 0.86  0.22
p40 -0.12 0.00 -0.23
pcb  0.32 0.85  0.00
```

5.5.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

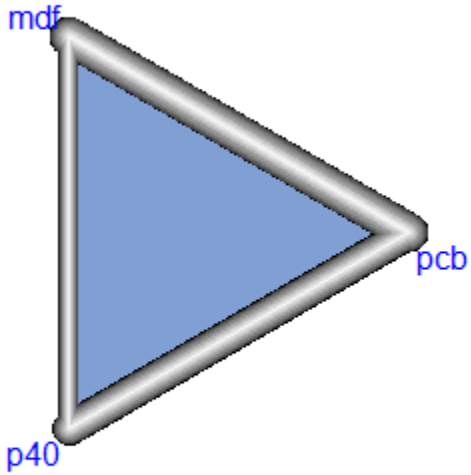
```
     mdf  p40  pcb
mdf  NaN 0.01 0.72
p40 0.01  NaN 0.00
pcb 0.72 0.00  NaN
```

5.5.3 Pairwise comparison P values

5.6 Forest Plot



5.7 Network Evidence Graph



6 Aggregate Narcolepsy Index

6.1 Main Treatment effect for each study

6.2 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	0.5	0.16	0.16
mdf	pcb	0.45	0.25	0.31
mdf	p40	-0.41	0.25	0.3
p40	pcb	0.86	0.26	0.32
mdf	pcb	0.7	0.15	0.15
p40	pcb	0.9	0.2	0.2
mdf	pcb	0.7	0.15	0.15
mdf	pcb	-0.02	0.18	0.18
mdf	pcb	-0.12	0.26	0.26
mdf	pcb	0.12	0.45	0.45
mdf	pcb	-0.14	0.35	0.35
mdf	pcb	0.26	0.18	0.18

6.3 Results of Fixed and Random Models

6.3.1.1 Fixed Model

Results (fixed effect model):

	treat1	treat2	MD	95%-CI	Q	leverage
Broughton97	mdf	pcb	0.406	[0.279; 0.532]	0.34	0.16
Harm1	mdf	pcb	0.406	[0.279; 0.532]	0.02	0.04
Harm1	mdf	p40	-0.466	[-0.768; -0.165]	0.03	0.26
Harm1	p40	pcb	0.872	[0.585; 1.159]	0.00	0.21
US00	mdf	pcb	0.406	[0.279; 0.532]	3.96	0.19
Hctp	p40	pcb	0.872	[0.585; 1.159]	0.02	0.56
US98	mdf	pcb	0.406	[0.279; 0.532]	4.06	0.20
Harsch06	mdf	pcb	0.406	[0.279; 0.532]	5.92	0.14
Moldfsky00	mdf	pcb	0.406	[0.279; 0.532]	4.15	0.06
Billard94	mdf	pcb	0.406	[0.279; 0.532]	0.41	0.02
Saletu05	mdf	pcb	0.406	[0.279; 0.532]	2.38	0.03
Black06	mdf	pcb	0.406	[0.279; 0.532]	0.63	0.12

6.3.1.2 Random Model

Results (random effects model):

	treat1	treat2	MD	95%-CI
Broughton97	mdf	pcb	0.340	[0.129; 0.551]
Harm1	mdf	pcb	0.340	[0.129; 0.551]
Harm1	mdf	p40	-0.511	[-0.963; -0.058]
Harm1	p40	pcb	0.851	[0.422; 1.279]
US00	mdf	pcb	0.340	[0.129; 0.551]
Hctp	p40	pcb	0.851	[0.422; 1.279]
US98	mdf	pcb	0.340	[0.129; 0.551]
Harsch06	mdf	pcb	0.340	[0.129; 0.551]
Moldfsky00	mdf	pcb	0.340	[0.129; 0.551]
Billard94	mdf	pcb	0.340	[0.129; 0.551]
Saletu05	mdf	pcb	0.340	[0.129; 0.551]
Black06	mdf	pcb	0.340	[0.129; 0.551]

6.4 Tests

```
Number of studies: k = 10
Number of treatments: n = 3
Number of pairwise comparisons: m = 12
Number of designs: d = 3

Fixed effects model

Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):
       MD         95%-CI
mdf 0.406 [0.279; 0.532]
p40 0.872 [0.585; 1.159]
pcb     .             .

Random effects model

Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):
       MD         95%-CI
mdf 0.340 [0.129; 0.551]
p40 0.851 [0.422; 1.279]
pcb     .             .

Quantifying heterogeneity / inconsistency:
tau^2 = 0.0582; I^2 = 58.9%

Tests of heterogeneity (within designs) and inconsistency (between designs):
                    Q d.f. p-value
Total           21.91    9  0.0092
Within designs  21.83    7  0.0027
Between designs  0.08    2  0.9595
                         Q df        pval
Total           21.91047320  9 0.009167085
Within designs  21.82774925  7 0.002720019
Between designs  0.08272395  2 0.959481760
```

6.5 P-values

```
    P-score (fixed) P-score (random)
pcb          1.0000           0.9996
mdf          0.4994           0.4937
p40          0.0006           0.0068
```

6.6 Pairwise comparisons - Fixed model

```
      mdf   p40  pcb
mdf  0.00 -0.77 0.28
p40  0.16  0.00 0.58
pcb -0.53 -1.16 0.00
```

6.6.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

```
      mdf   p40  pcb
mdf  0.00 -0.16 0.53
p40  0.77  0.00 1.16
pcb -0.28 -0.58 0.00
```

6.6.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

```
    mdf p40 pcb
mdf NaN   0   0
p40   0 NaN   0
pcb   0   0 NaN
```

6.6.3 Pairwise comparison P values

6.7 Pairwise comparisons - Random model

```
      mdf   p40  pcb
mdf  0.00 -0.96 0.13
p40  0.06  0.00 0.42
pcb -0.55 -1.28 0.00
```

6.7.1 Lower 95% CI of Effect size (R-C) [r=row,c=column]

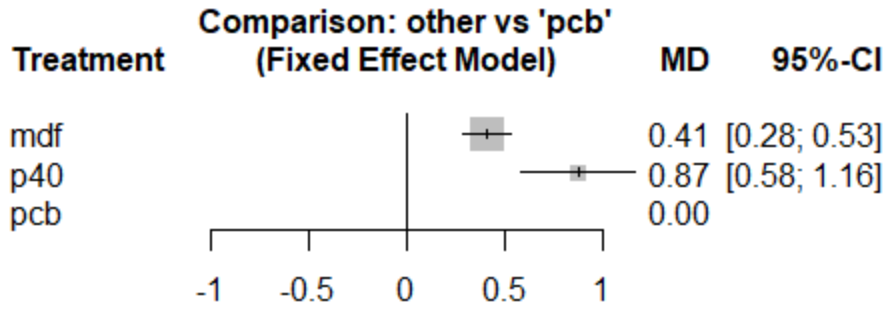
```
      mdf   p40  pcb
mdf  0.00 -0.06 0.55
p40  0.96  0.00 1.28
pcb -0.13 -0.42 0.00
```

6.7.2 Upper 95%CI of Effect size (R-C) [r=row,c=column]

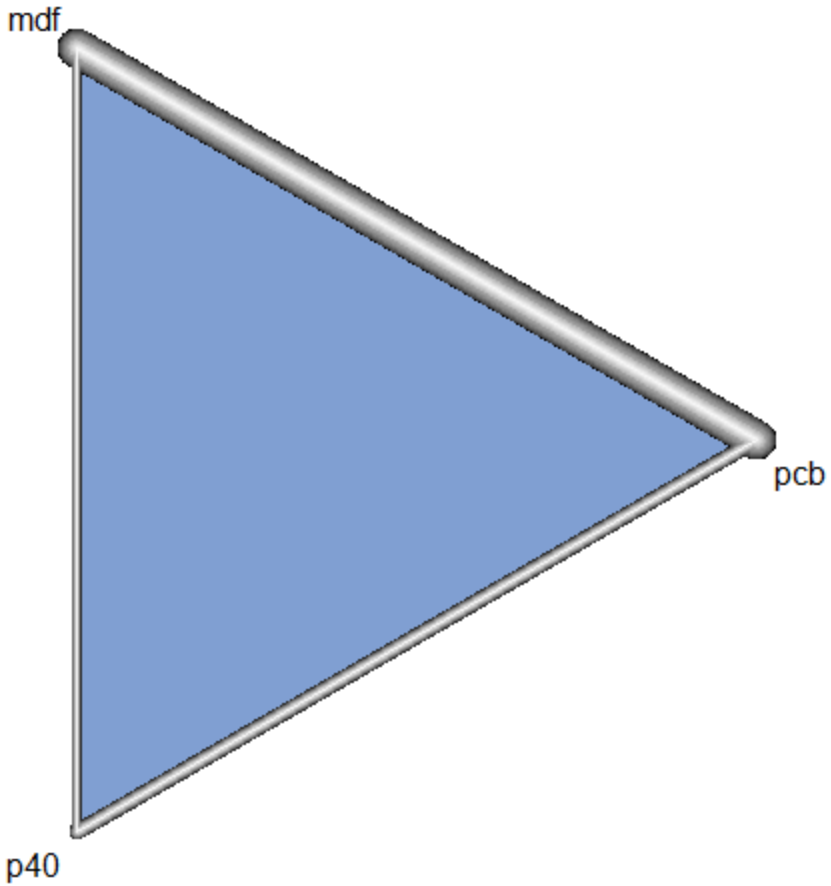
```
     mdf  p40 pcb
mdf  NaN 0.03   0
p40 0.03  NaN   0
pcb 0.00 0.00 NaN
```

6.7.3 Pairwise comparison P values

6.8 Forest Plot



6.9 Network Evidence Graph



7 Safety General including headaches

7.1 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	-0.66	0.44	0.44
mdf	pcb	1.16	0.49	0.49
mdf	p40	-0.06	0.34	0.41
mdf	pcb	0.1	0.37	0.47
p40	pcb	0.17	0.37	0.46
mdf	pcb	0.94	0.41	0.41
p40	pcb	-0.18	0.44	0.44
mdf	pcb	-0.07	0.77	0.77
mdf	pcb	0.98	0.58	0.58
mdf	pcb	0.96	0.34	0.34
mdf	pcb	-0.5	0.21	0.21

7.2 Results of Fixed and Random Models

7.2.1.1 Fixed Model

```
Results (fixed effect model):
            treat1 treat2    RR         95%-CI    Q leverage
Black06        mdf    pcb 1.122 [0.870; 1.445] 3.09     0.09
Broughton97    mdf    pcb 1.122 [0.870; 1.445] 4.65     0.07
Harm1          mdf    p40 1.054 [0.629; 1.766] 0.08     0.42
Harm1          mdf    pcb 1.122 [0.870; 1.445] 0.00     0.08
Harm1          p40    pcb 1.065 [0.645; 1.758] 0.05     0.31
Harsch06       mdf    pcb 1.122 [0.870; 1.445] 4.10     0.10
Hctp           p40    pcb 1.065 [0.645; 1.758] 0.28     0.33
Moldfsky00     mdf    pcb 1.122 [0.870; 1.445] 0.06     0.03
Saletu05       mdf    pcb 1.122 [0.870; 1.445] 2.25     0.05
US00           mdf    pcb 1.122 [0.870; 1.445] 6.04     0.14
US98           mdf    pcb 1.122 [0.870; 1.445] 8.71     0.38
```

7.2.1.2 Random Model

```
Results (random effects model):
            treat1 treat2    RR         95%-CI
Black06        mdf    pcb 1.381 [0.810; 2.353]
Broughton97    mdf    pcb 1.381 [0.810; 2.353]
Harm1          mdf    p40 1.250 [0.447; 3.498]
Harm1          mdf    pcb 1.381 [0.810; 2.353]
Harm1          p40    pcb 1.105 [0.416; 2.930]
Harsch06       mdf    pcb 1.381 [0.810; 2.353]
Hctp           p40    pcb 1.105 [0.416; 2.930]
Moldfsky00     mdf    pcb 1.381 [0.810; 2.353]
Saletu05       mdf    pcb 1.381 [0.810; 2.353]
US00           mdf    pcb 1.381 [0.810; 2.353]
US98           mdf    pcb 1.381 [0.810; 2.353]
```

7.3 Tests

```
Number of studies: k = 9
Number of treatments: n = 3
Number of pairwise comparisons: m = 11
Number of designs: d = 3
Fixed effect model
Treatment estimate (sm = 'RR', comparison: other treatments vs 'pcb'):
       RR         95%-CI
mdf 1.122 [0.870; 1.445]
p40 1.065 [0.645; 1.758]
pcb     .              .
Random effects model
Treatment estimate (sm = 'RR', comparison: other treatments vs 'pcb'):
       RR         95%-CI
mdf 1.381 [0.810; 2.353]
p40 1.105 [0.416; 2.930]
pcb     .              .
Quantifying heterogeneity / inconsistency:
tau^2 = 0.4081; I^2 = 72.7%
Tests of heterogeneity (within designs) and inconsistency (between designs):
                    Q d.f.  p-value
Total           29.32    8   0.0003
Within designs  28.89    6 < 0.0001
Between designs  0.43    2   0.8068
                         Q df          pval
Total           29.3190087  8 0.00027870530
Within designs  28.8896610  6 0.00006383266
Between designs  0.4293477  2 0.80680452737
```

7.4 P-values

```
    P-score (fixed) P-score (random)
pcb          0.7045           0.7307
p40          0.4910           0.5426
mdf          0.3046           0.2267
```

7.5 Pairwise comparisons - Fixed model

```
      mdf   p40   pcb
mdf  0.00 -0.46 -0.14
p40 -0.57  0.00 -0.44
pcb -0.37 -0.56  0.00
```

7.5.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

```
     mdf  p40  pcb
mdf 0.00 0.57 0.37
p40 0.46 0.00 0.56
pcb 0.14 0.44 0.00
```

7.5.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

```
     mdf  p40  pcb
mdf  NaN 0.84 0.38
p40 0.84  NaN 0.81
pcb 0.38 0.81  NaN
```

7.5.3 Pairwise comparison P values

7.6 Pairwise comparisons - Random model

```
      mdf   p40   pcb
mdf  0.00 -0.81 -0.21
p40 -1.25  0.00 -0.88
pcb -0.86 -1.08  0.00
```

7.6.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

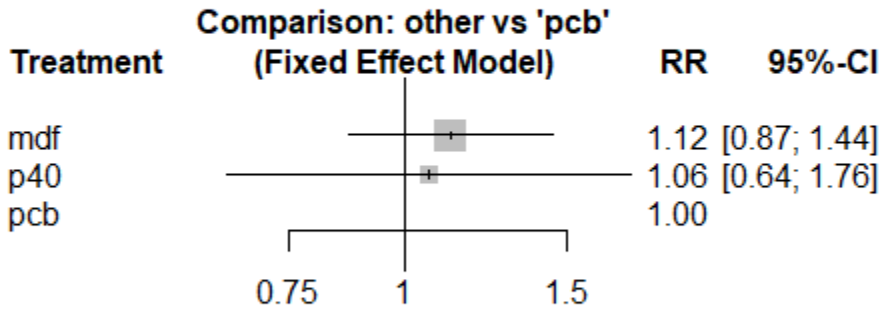
```
     mdf  p40  pcb
mdf 0.00 1.25 0.86
p40 0.81 0.00 1.08
pcb 0.21 0.88 0.00
```

7.6.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

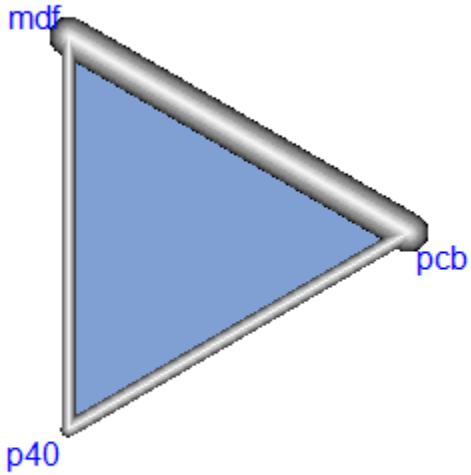
```
     mdf  p40  pcb
mdf  NaN 0.67 0.24
p40 0.67  NaN 0.84
pcb 0.24 0.84  NaN
```

7.6.3 Pairwise comparison P values

7.7 Forest Plot



7.8 Network Evidence Graph



8 Safety Central Nervous System

8.1 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	-0.34	0.44	0.44
mdf	pcb	0.69	0.47	0.47
mdf	p40	0.27	0.53	0.59
mdf	pcb	0.75	0.64	0.78
p40	pcb	0.48	0.68	0.96
mdf	pcb	1.19	0.78	0.78
p40	pcb	-0.06	0.54	0.54
mdf	pcb	0.69	1.2	1.2
mdf	pcb	1.95	0.67	0.67
mdf	pcb	1.43	1.11	1.11
mdf	pcb	0.28	0.37	0.37

8.2 Results of Fixed and Random Models

8.2.1.1 Fixed Model

```
Results (fixed effect model):
            treat1 treat2    RR         95%-CI    Q leverage
Black06        mdf    pcb 1.664 [1.131; 2.446] 3.78     0.20
Broughton97    mdf    pcb 1.664 [1.131; 2.446] 0.15     0.17
Harm1          mdf    p40 1.451 [0.680; 3.093] 0.03     0.44
Harm1          mdf    pcb 1.664 [1.131; 2.446] 0.10     0.06
Harm1          p40    pcb 1.147 [0.549; 2.395] 0.13     0.15
Harsch06       mdf    pcb 1.664 [1.131; 2.446] 0.76     0.06
Hctp           p40    pcb 1.147 [0.549; 2.395] 0.13     0.48
Moldfsky00     mdf    pcb 1.664 [1.131; 2.446] 0.02     0.03
Saletu05       mdf    pcb 1.664 [1.131; 2.446] 4.63     0.09
US00           mdf    pcb 1.664 [1.131; 2.446] 0.69     0.03
US98           mdf    pcb 1.664 [1.131; 2.446] 0.39     0.28
```

8.2.1.2 Random Model

```
Results (random effects model):
            treat1 treat2    RR         95%-CI
Black06        mdf    pcb 1.795 [1.117; 2.885]
Broughton97    mdf    pcb 1.795 [1.117; 2.885]
Harm1          mdf    p40 1.509 [0.613; 3.714]
Harm1          mdf    pcb 1.795 [1.117; 2.885]
Harm1          p40    pcb 1.190 [0.500; 2.832]
Harsch06       mdf    pcb 1.795 [1.117; 2.885]
Hctp           p40    pcb 1.190 [0.500; 2.832]
Moldfsky00     mdf    pcb 1.795 [1.117; 2.885]
Saletu05       mdf    pcb 1.795 [1.117; 2.885]
US00           mdf    pcb 1.795 [1.117; 2.885]
US98           mdf    pcb 1.795 [1.117; 2.885]
```

8.3 Tests

```
Number of studies: k = 9
Number of treatments: n = 3
Number of pairwise comparisons: m = 11
Number of designs: d = 3
Fixed effect model
Treatment estimate (sm = 'RR', comparison: other treatments vs 'pcb'):
       RR         95%-CI
mdf 1.664 [1.131; 2.446]
p40 1.147 [0.549; 2.395]
pcb     .              .
Random effects model
Treatment estimate (sm = 'RR', comparison: other treatments vs 'pcb'):
       RR         95%-CI
mdf 1.795 [1.117; 2.885]
p40 1.190 [0.500; 2.832]
pcb     .              .
Quantifying heterogeneity / inconsistency:
tau^2 = 0.1195; I^2 = 26%
Tests of heterogeneity (within designs) and inconsistency (between designs):
                    Q d.f. p-value
Total           10.81    8  0.2128
Within designs  10.43    6  0.1077
Between designs  0.38    2  0.8272
                         Q df      pval
Total           10.8082444  8 0.2128028
Within designs  10.4288286  6 0.1077163
Between designs  0.3794158  2 0.8272007
```

8.4 P-values

```
    P-score (fixed) P-score (random)
pcb          0.8187           0.8224
p40          0.5949           0.5811
mdf          0.0863           0.0966
```

8.5 Pairwise comparisons - Fixed model

```
      mdf   p40   pcb
mdf  0.00 -0.39  0.12
p40 -1.13  0.00 -0.60
pcb -0.89 -0.87  0.00
```

8.5.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

```
      mdf  p40  pcb
mdf  0.00 1.13 0.89
p40  0.39 0.00 0.87
pcb -0.12 0.60 0.00
```

8.5.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

```
     mdf  p40  pcb
mdf  NaN 0.34 0.01
p40 0.34  NaN 0.72
pcb 0.01 0.72  NaN
```

8.5.3 Pairwise comparison P values

8.6 Pairwise comparisons - Random model

```
      mdf   p40   pcb
mdf  0.00 -0.49  0.11
p40 -1.31  0.00 -0.69
pcb -1.06 -1.04  0.00
```

8.6.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

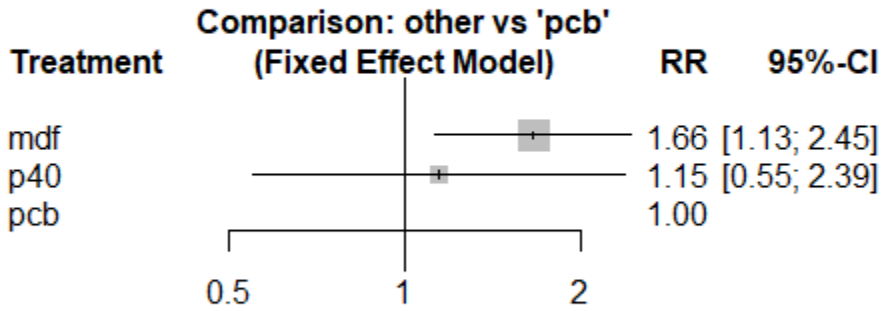
```
      mdf  p40  pcb
mdf  0.00 1.31 1.06
p40  0.49 0.00 1.04
pcb -0.11 0.69 0.00
```

8.6.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

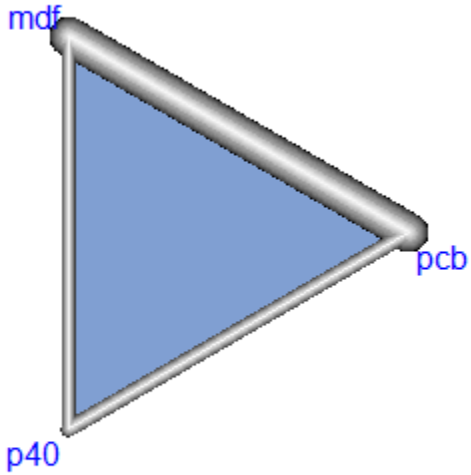
```
     mdf  p40  pcb
mdf  NaN 0.37 0.02
p40 0.37  NaN 0.69
pcb 0.02 0.69  NaN
```

8.6.3 Pairwise comparison P values

8.7 Forest Plot



8.8 Network Evidence Graph



9 Safety Gastro-Intestinal Events

9.1 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	1.14	0.78	0.78
mdf	pcb	0.62	0.44	0.44
mdf	p40	0.1	0.32	0.33
mdf	pcb	1.78	0.72	0.94
p40	pcb	1.67	0.72	1.06
mdf	pcb	2.5	1.46	1.46
p40	pcb	1.04	1.14	1.14
mdf	pcb	-1.1	1.12	1.12
mdf	pcb	-0.61	0.36	0.36
mdf	pcb	1.25	0.29	0.29
mdf	pcb	0.3	0.23	0.23

9.2 Results of Fixed and Random Models

9.2.1.1 Fixed Model

```
Results (fixed effect model):
            treat1 treat2    RR         95%-CI    Q leverage
Black06        mdf    pcb 1.673 [1.262; 2.216] 0.63     0.03
Broughton97    mdf    pcb 1.673 [1.262; 2.216] 0.06     0.11
Harm1          mdf    p40 0.955 [0.524; 1.743] 0.21     0.85
Harm1          mdf    pcb 1.673 [1.262; 2.216] 1.82     0.02
Harm1          p40    pcb 1.751 [0.919; 3.337] 1.10     0.10
Harsch06       mdf    pcb 1.673 [1.262; 2.216] 1.86     0.01
Hctp           p40    pcb 1.751 [0.919; 3.337] 0.18     0.08
Moldfsky00     mdf    pcb 1.673 [1.262; 2.216] 2.06     0.02
Saletu05       mdf    pcb 1.673 [1.262; 2.216] 9.47     0.16
US00           mdf    pcb 1.673 [1.262; 2.216] 6.23     0.24
US98           mdf    pcb 1.673 [1.262; 2.216] 0.88     0.39
```

9.2.1.2 Random Model

```
Results (random effects model):
            treat1 treat2    RR         95%-CI
Black06        mdf    pcb 1.841 [1.004; 3.376]
Broughton97    mdf    pcb 1.841 [1.004; 3.376]
Harm1          mdf    p40 0.766 [0.226; 2.602]
Harm1          mdf    pcb 1.841 [1.004; 3.376]
Harm1          p40    pcb 2.402 [0.693; 8.318]
Harsch06       mdf    pcb 1.841 [1.004; 3.376]
Hctp           p40    pcb 2.402 [0.693; 8.318]
Moldfsky00     mdf    pcb 1.841 [1.004; 3.376]
Saletu05       mdf    pcb 1.841 [1.004; 3.376]
US00           mdf    pcb 1.841 [1.004; 3.376]
US98           mdf    pcb 1.841 [1.004; 3.376]
```

9.3 Tests

```
Number of studies: k = 9
Number of treatments: n = 3
Number of pairwise comparisons: m = 11
Number of designs: d = 3
Fixed effect model
Treatment estimate (sm = 'RR', comparison: other treatments vs 'pcb'):
       RR         95%-CI
mdf 1.673 [1.262; 2.216]
p40 1.751 [0.919; 3.337]
pcb     .              .
Random effects model
Treatment estimate (sm = 'RR', comparison: other treatments vs 'pcb'):
       RR         95%-CI
mdf 1.841 [1.004; 3.376]
p40 2.402 [0.693; 8.318]
pcb     .              .
Quantifying heterogeneity / inconsistency:
tau^2 = 0.4414; I^2 = 67.3%
Tests of heterogeneity (within designs) and inconsistency (between designs):
                    Q d.f. p-value
Total           24.49    8  0.0019
Within designs  21.02    6  0.0018
Between designs  3.47    2  0.1767
                         Q df        pval
Total           24.485745  8 0.001898967
Within designs  21.018789  6 0.001820410
Between designs  3.466956  2 0.176668877
```

9.4 P-values

```
    P-score (fixed) P-score (random)
pcb          0.9777           0.9461
mdf          0.2797           0.3447
p40          0.2425           0.2092
```

9.5 Pairwise comparisons - Fixed model

```
      mdf   p40   pcb
mdf  0.00 -0.65  0.23
p40 -0.56  0.00 -0.08
pcb -0.80 -1.21  0.00
```

9.5.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

```
      mdf  p40  pcb
mdf  0.00 0.56 0.80
p40  0.65 0.00 1.21
pcb -0.23 0.08 0.00
```

9.5.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

```
     mdf  p40  pcb
mdf  NaN 0.88 0.00
p40 0.88  NaN 0.09
pcb 0.00 0.09  NaN
```

9.5.3 Pairwise comparison P values

9.6 Pairwise comparisons - Random model

	mdf	p40	pcb
mdf	0.00	-1.49	0.00
p40	-0.96	0.00	-0.37
pcb	-1.22	-2.12	0.00

9.6.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

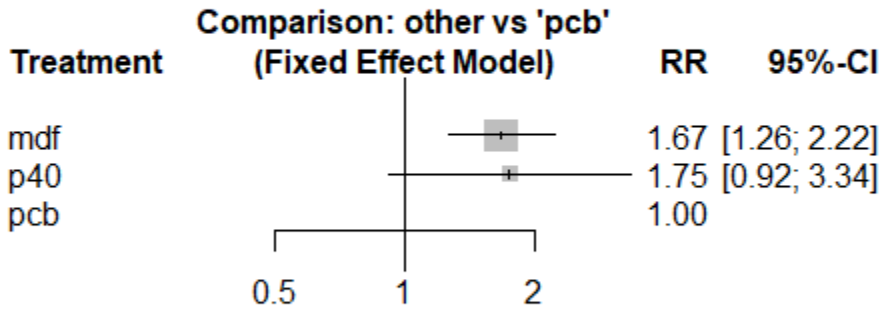
	mdf	p40	pcb
mdf	0.00	0.96	1.22
p40	1.49	0.00	2.12
pcb	0.00	0.37	0.00

9.6.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

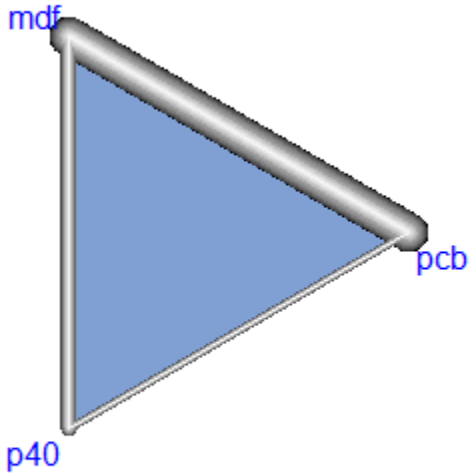
	mdf	p40	pcb
mdf	NaN	0.67	0.05
p40	0.67	NaN	0.17
pcb	0.05	0.17	NaN

9.6.3 Pairwise comparison P values

9.7 Forest Plot



9.8 Network Evidence Graph



10 Safety All events

10.1 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	0.82	0.35	0.35
mdf	p40	0.08	0.21	0.24
mdf	pcb	0.7	0.25	0.32
p40	pcb	0.62	0.26	0.34
mdf	pcb	1.14	0.33	0.33
p40	pcb	0	0.36	0.36
mdf	pcb	-0.06	0.23	0.23
mdf	pcb	1.21	0.43	0.43
mdf	pcb	-0.15	0.43	0.43
mdf	pcb	0.56	0.18	0.18
mdf	pcb	-0.2	0.32	0.32

10.2 Results of Fixed and Random Models

10.2.1.1 Fixed Model

```
Results (fixed effect model):
            treat1 treat2   IRR         95%-CI    Q leverage
Broughton97    mdf    pcb 1.565 [1.296; 1.889] 1.18     0.08
Harm1          mdf    p40 1.100 [0.779; 1.552] 0.01     0.56
Harm1          mdf    pcb 1.565 [1.296; 1.889] 0.62     0.09
Harm1          p40    pcb 1.423 [1.006; 2.012] 0.65     0.28
US00           mdf    pcb 1.565 [1.296; 1.889] 4.51     0.09
Hctp           p40    pcb 1.423 [1.006; 2.012] 0.96     0.25
US98           mdf    pcb 1.565 [1.296; 1.889] 5.05     0.18
Harsch06       mdf    pcb 1.565 [1.296; 1.889] 3.16     0.05
Moldfsky00     mdf    pcb 1.565 [1.296; 1.889] 1.95     0.05
Saletu05       mdf    pcb 1.565 [1.296; 1.889] 0.40     0.30
Black06        mdf    pcb 1.565 [1.296; 1.889] 4.11     0.09
```

10.2.1.2 Random Model

```
Results (random effects model):
            treat1 treat2   IRR         95%-CI
Broughton97    mdf    pcb 1.596 [1.138; 2.240]
Harm1          mdf    p40 1.156 [0.604; 2.215]
Harm1          mdf    pcb 1.596 [1.138; 2.240]
Harm1          p40    pcb 1.380 [0.739; 2.576]
US00           mdf    pcb 1.596 [1.138; 2.240]
Hctp           p40    pcb 1.380 [0.739; 2.576]
US98           mdf    pcb 1.596 [1.138; 2.240]
Harsch06       mdf    pcb 1.596 [1.138; 2.240]
Moldfsky00     mdf    pcb 1.596 [1.138; 2.240]
Saletu05       mdf    pcb 1.596 [1.138; 2.240]
Black06        mdf    pcb 1.596 [1.138; 2.240]
```

10.3 Tests

```
Number of studies: k = 9
Number of treatments: n = 3
Number of pairwise comparisons: m = 11
Number of designs: d = 3
Fixed effect model
Treatment estimate (sm = 'IRR', comparison: other treatments vs 'pcb'):
      IRR         95%-CI
mdf 1.565 [1.296; 1.889]
p40 1.423 [1.006; 2.012]
pcb     .              .

Random effects model
Treatment estimate (sm = 'IRR', comparison: other treatments vs 'pcb'):
      IRR         95%-CI
mdf 1.596 [1.138; 2.240]
p40 1.380 [0.739; 2.576]
pcb     .              .
Quantifying heterogeneity / inconsistency:
tau^2 = 0.1495; I^2 = 64.6%
Tests of heterogeneity (within designs) and inconsistency (between designs):
                    Q d.f. p-value
Total           22.59    8  0.0039
Within designs  20.30    6  0.0024
Between designs  2.28    2  0.3195
                         Q df        pval
Total           22.586814  8 0.003937277
Within designs  20.304632  6 0.002443899
Between designs  2.282182  2 0.319470247
```

10.4 P-values

```
    P-score (fixed) P-score (random)
pcb          0.9884           0.9204
p40          0.3644           0.4126
mdf          0.1471           0.1669
```

10.5 Pairwise comparisons - Fixed model

	mdf	p40	pcb
mdf	0.00	-0.25	0.26
p40	-0.44	0.00	0.01
pcb	-0.64	-0.70	0.00

10.5.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

	mdf	p40	pcb
mdf	0.00	0.44	0.64
p40	0.25	0.00	0.70
pcb	-0.26	-0.01	0.00

10.5.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

	mdf	p40	pcb
mdf	NaN	0.59	0.00
p40	0.59	NaN	0.05
pcb	0.00	0.05	NaN

10.5.3 Pairwise comparison P values

10.6 Pairwise comparisons - Random model

```
      mdf   p40   pcb
mdf  0.00 -0.50  0.13
p40 -0.80  0.00 -0.30
pcb -0.81 -0.95  0.00
```

10.6.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

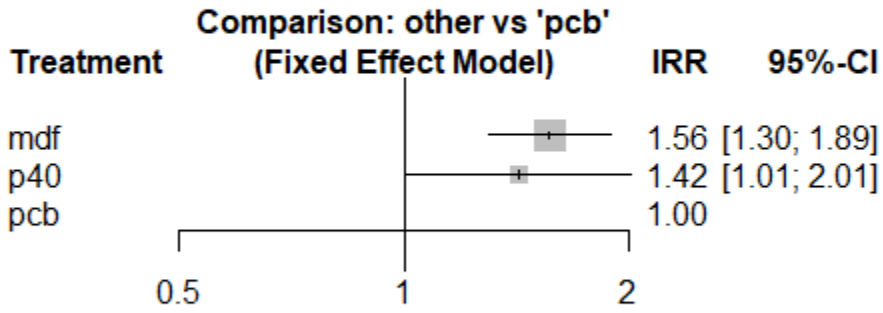
```
      mdf p40  pcb
mdf  0.00 0.8 0.81
p40  0.50 0.0 0.95
pcb -0.13 0.3 0.00
```

10.6.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

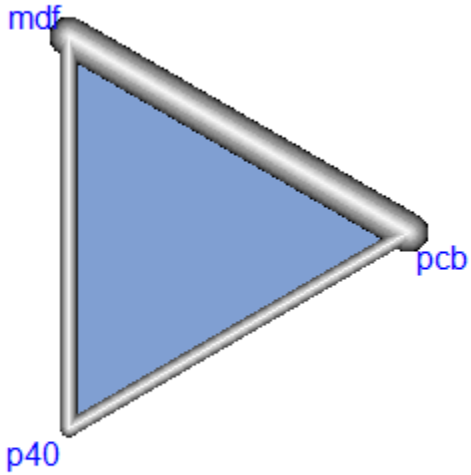
```
     mdf  p40  pcb
mdf  NaN 0.66 0.01
p40 0.66  NaN 0.31
pcb 0.01 0.31  NaN
```

10.6.3 Pairwise comparison P values

10.7 Forest Plot



10.8 Network Evidence Graph



11 Overall Benefit / Risk endpoint

11.1 Main treatment effect for each study

```
Comparison not considered in network meta-analysis:
   studlab treat1 treat2 TE seTE
 Billard94    mdf    pcb NA   NA
```

11.2 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	0.44	0.16	0.16
mdf	pcb	0.36	0.25	0.31
mdf	p40	-0.65	0.25	0.3
p40	pcb	1.01	0.26	0.32
mdf	pcb	0.6	0.15	0.15
p40	pcb	0.7	0.2	0.2
mdf	pcb	0.7	0.15	0.15
mdf	pcb	-0.07	0.18	0.18
mdf	pcb	-0.12	0.26	0.26
mdf	pcb	-0.27	0.35	0.35
mdf	pcb	0.26	0.18	0.18

11.3 Results of Fixed and Random Models

11.3.1.1 Fixed Model

```
Results (fixed effect model):

            treat1 treat2     MD           95%-CI    Q leverage
Broughton97    mdf    pcb  0.355 [ 0.227;  0.483] 0.27     0.16
Harm1          mdf    pcb  0.355 [ 0.227;  0.483] 0.00     0.05
Harm1          mdf    p40 -0.481 [-0.783; -0.179] 0.31     0.26
Harm1          p40    pcb  0.836 [ 0.549;  1.123] 0.30     0.21
US00           mdf    pcb  0.355 [ 0.227;  0.483] 2.74     0.19
Hctp           p40    pcb  0.836 [ 0.549;  1.123] 0.48     0.56
US98           mdf    pcb  0.355 [ 0.227;  0.483] 5.59     0.20
Harsch06       mdf    pcb  0.355 [ 0.227;  0.483] 5.89     0.14
Moldfsky00     mdf    pcb  0.355 [ 0.227;  0.483] 3.39     0.06
Saletu05       mdf    pcb  0.355 [ 0.227;  0.483] 3.12     0.03
Black06        mdf    pcb  0.355 [ 0.227;  0.483] 0.27     0.13
```

11.3.1.2 Random Model

```
Results (random effects model):

            treat1 treat2     MD           95%-CI
Broughton97    mdf    pcb  0.285 [ 0.059;  0.511]
Harm1          mdf    pcb  0.285 [ 0.059;  0.511]
Harm1          mdf    p40 -0.555 [-1.026; -0.084]
Harm1          p40    pcb  0.840 [ 0.396;  1.285]
US00           mdf    pcb  0.285 [ 0.059;  0.511]
Hctp           p40    pcb  0.840 [ 0.396;  1.285]
US98           mdf    pcb  0.285 [ 0.059;  0.511]
Harsch06       mdf    pcb  0.285 [ 0.059;  0.511]
Moldfsky00     mdf    pcb  0.285 [ 0.059;  0.511]
Saletu05       mdf    pcb  0.285 [ 0.059;  0.511]
Black06        mdf    pcb  0.285 [ 0.059;  0.511]
```

11.4 Tests

```
Number of studies: k = 9
Number of treatments: n = 3
Number of pairwise comparisons: m = 11
Number of designs: d = 3

Fixed effects model

Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):
       MD         95%-CI
mdf 0.355 [0.227; 0.483]
p40 0.836 [0.549; 1.123]
pcb     .              .

Random effects model

Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):
       MD         95%-CI
mdf 0.285 [0.059; 0.511]
p40 0.840 [0.396; 1.285]
pcb     .              .

Quantifying heterogeneity / inconsistency:
tau^2 = 0.0664; I^2 = 64.2%

Tests of heterogeneity (within designs) and inconsistency (between designs):
                     Q d.f. p-value
Total            22.36    8  0.0043
Within designs   21.25    6  0.0017
Between designs   1.11    2  0.5736
                         Q df        pval
Total            22.364738  8 0.004283165
Within designs   21.252957  6 0.001652138
Between designs   1.111781  2 0.573561265
```

11.5 P-values

```
    P-score (fixed) P-score (random)
pcb          1.0000           0.9966
mdf          0.4995           0.4981
p40          0.0005           0.0053
```

11.6 Pairwise comparisons - Fixed model

```
      mdf   p40  pcb
mdf  0.00 -0.78 0.23
p40  0.18  0.00 0.55
pcb -0.48 -1.12 0.00
```

11.6.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

```
      mdf   p40  pcb
mdf  0.00 -0.18 0.48
p40  0.78  0.00 1.12
pcb -0.23 -0.55 0.00
```

11.6.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

```
    mdf p40 pcb
mdf NaN   0   0
p40   0 NaN   0
pcb   0   0 NaN
```

11.6.3 Pairwise comparison P values

11.7 Pairwise comparisons - Random model

```
      mdf   p40  pcb
mdf  0.00 -1.03 0.06
p40  0.08  0.00 0.40
pcb -0.51 -1.28 0.00
```

11.7.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

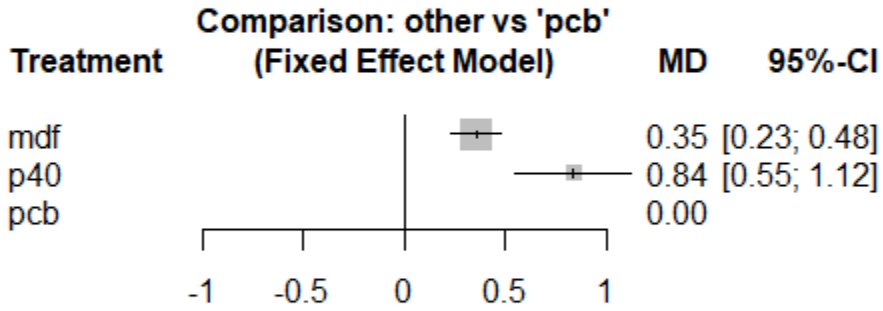
```
      mdf   p40  pcb
mdf  0.00 -0.08 0.51
p40  1.03  0.00 1.28
pcb -0.06 -0.40 0.00
```

11.7.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

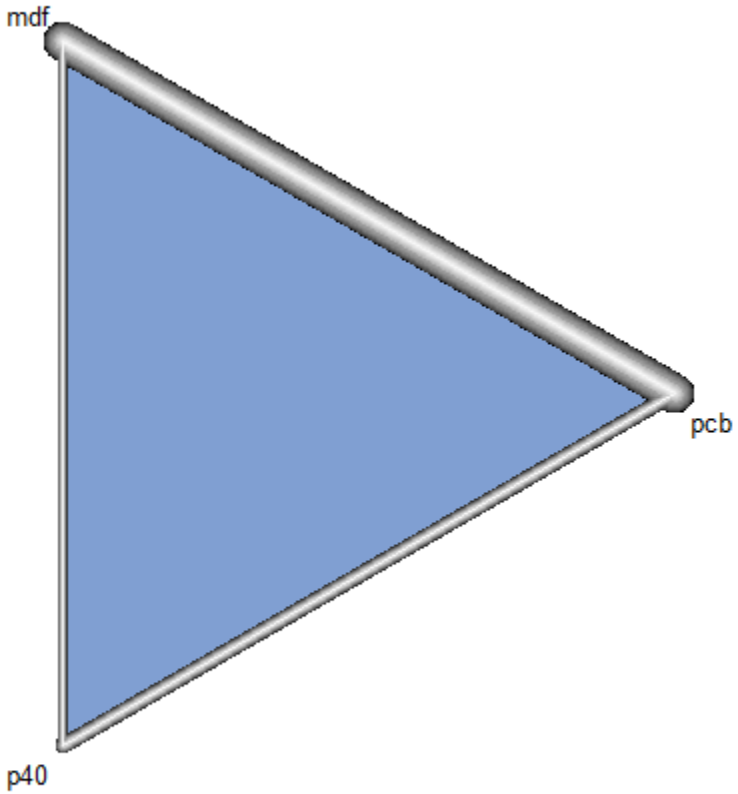
```
     mdf  p40  pcb
mdf  NaN 0.02 0.01
p40 0.02  NaN 0.00
pcb 0.01 0.00  NaN
```

11.7.3 Pairwise comparison P values

11.8 Forest Plot



11.9 Network Evidence Graph



12 Aggregate EDS Index

12.1 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	0.5	0.16	0.16
mdf	p40	0.06	0.25	0.3
mdf	pcb	0.66	0.25	0.31
p40	pcb	0.6	0.26	0.32
mdf	pcb	0.7	0.15	0.15
p40	pcb	0.66	0.2	0.2
mdf	pcb	0.7	0.15	0.15
mdf	pcb	-0.02	0.18	0.18
mdf	pcb	-0.12	0.26	0.26
mdf	pcb	0.3	0.45	0.45
mdf	pcb	-0.14	0.35	0.35
mdf	pcb	0.26	0.18	0.18

12.2 Results of Fixed and Random Models

12.2.1.1 Fixed Model

```
Results (fixed effect model):
            treat1 treat2     MD          95%-CI    Q leverage
Broughton97    mdf    pcb  0.427 [ 0.300; 0.553] 0.20     0.16
Harm1          mdf    p40 -0.153 [-0.455; 0.149] 0.49     0.26
Harm1          mdf    pcb  0.427 [ 0.300; 0.553] 0.58     0.04
Harm1          p40    pcb  0.580 [ 0.292; 0.867] 0.00     0.21
US00           mdf    pcb  0.427 [ 0.300; 0.553] 3.41     0.19
Hctp           p40    pcb  0.580 [ 0.292; 0.867] 0.17     0.56
US98           mdf    pcb  0.427 [ 0.300; 0.553] 3.51     0.20
Harsch06       mdf    pcb  0.427 [ 0.300; 0.553] 6.51     0.14
Moldfsky00     mdf    pcb  0.427 [ 0.300; 0.553] 4.49     0.06
Billard94      mdf    pcb  0.427 [ 0.300; 0.553] 0.08     0.02
Saletu05       mdf    pcb  0.427 [ 0.300; 0.553] 2.56     0.03
Black06        mdf    pcb  0.427 [ 0.300; 0.553] 0.82     0.12
```

12.2.1.2 Random Model

```
Results (random effects model):
            treat1 treat2     MD          95%-CI
Broughton97    mdf    pcb  0.371 [ 0.155; 0.586]
Harm1          mdf    p40 -0.182 [-0.643; 0.279]
Harm1          mdf    pcb  0.371 [ 0.155; 0.586]
Harm1          p40    pcb  0.553 [ 0.116; 0.990]
US00           mdf    pcb  0.371 [ 0.155; 0.586]
Hctp           p40    pcb  0.553 [ 0.116; 0.990]
US98           mdf    pcb  0.371 [ 0.155; 0.586]
Harsch06       mdf    pcb  0.371 [ 0.155; 0.586]
Moldfsky00     mdf    pcb  0.371 [ 0.155; 0.586]
Billard94      mdf    pcb  0.371 [ 0.155; 0.586]
Saletu05       mdf    pcb  0.371 [ 0.155; 0.586]
Black06        mdf    pcb  0.371 [ 0.155; 0.586]
```

12.3 Tests

```
Number of studies: k = 10
Number of treatments: n = 3
Number of pairwise comparisons: m = 12
Number of designs: d = 3
Fixed effect model
Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):
       MD         95%-CI
mdf 0.427 [0.300; 0.553]
p40 0.580 [0.292; 0.867]
pcb     .              .
Random effects model
Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):
       MD         95%-CI
mdf 0.371 [0.155; 0.586]
p40 0.553 [0.116; 0.990]
pcb     .              .
Quantifying heterogeneity / inconsistency:
tau^2 = 0.0623; I^2 = 60.6%
Tests of heterogeneity (within designs) and inconsistency (between designs):
                     Q d.f. p-value
Total            22.83    9  0.0066
Within designs   21.48    7  0.0031
Between designs   1.35    2  0.5096
                         Q df        pval
Total            22.828536  9 0.006593103
Within designs   21.480417  7 0.003120517
Between designs   1.348119  2 0.509635438
```

12.4 P-values

```
    P-score (fixed) P-score (random)
pcb          1.0000           0.9966
mdf          0.4199           0.3906
p40          0.0801           0.1128
```

12.5 Pairwise comparisons - Fixed model

```
      mdf   p40  pcb
mdf  0.00 -0.45 0.30
p40 -0.15  0.00 0.29
pcb -0.55 -0.87 0.00
```

12.5.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

```
      mdf   p40  pcb
mdf  0.00  0.15 0.55
p40  0.45  0.00 0.87
pcb -0.30 -0.29 0.00
```

12.5.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

```
     mdf  p40 pcb
mdf  NaN 0.32   0
p40 0.32  NaN   0
pcb 0.00 0.00 NaN
```

12.5.3 Pairwise comparison P values

12.6 Pairwise comparisons - Random model

	mdf	p40	pcb
mdf	0.00	-0.64	0.15
p40	-0.28	0.00	0.12
pcb	-0.59	-0.99	0.00

12.6.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

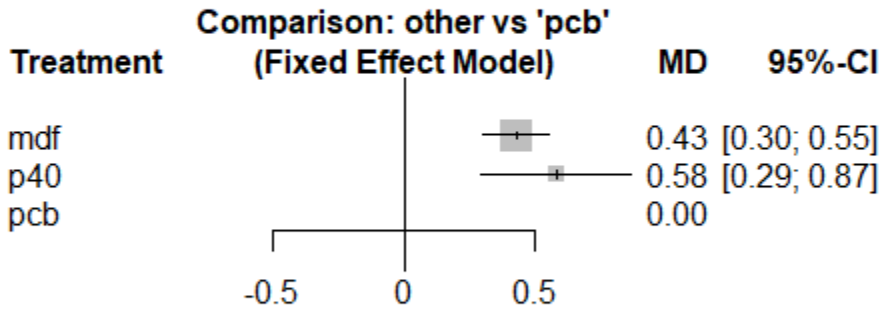
	mdf	p40	pcb
mdf	0.00	0.28	0.59
p40	0.64	0.00	0.99
pcb	-0.15	-0.12	0.00

12.6.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

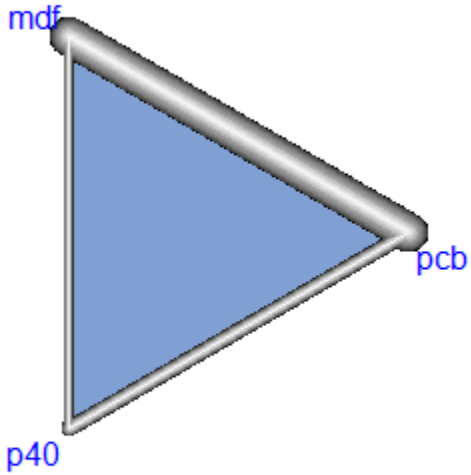
	mdf	p40	pcb
mdf	NaN	0.44	0.00
p40	0.44	NaN	0.01
pcb	0.00	0.01	NaN

12.6.3 Pairwise comparison P values

12.7 Forest Plot



12.8 Network Evidence Graph



13 Overall EDS Benefit / Risk endpoint

13.1 Pairwise effect size and adjusted standard deviation

Trt1	Trt2	TE	SE(TE)	AdjSE(TE)
mdf	pcb	0.44	0.16	0.16
mdf	p40	0.05	0.25	0.3
mdf	pcb	0.57	0.25	0.31
p40	pcb	0.52	0.26	0.32
mdf	pcb	0.6	0.15	0.15
p40	pcb	0.67	0.2	0.2
mdf	pcb	0.7	0.15	0.15
mdf	pcb	-0.09	0.18	0.18
mdf	pcb	-0.12	0.26	0.26
mdf	pcb	-0.27	0.35	0.35
mdf	pcb	0.26	0.18	0.18

13.2 Results of Fixed and Random Models

13.2.1.1 Fixed Model

```
Results (fixed effect model):
            treat1 treat2     MD          95%-CI    Q leverage
Broughton97    mdf    pcb  0.381 [ 0.253; 0.509] 0.13     0.16
Harm1          mdf    p40 -0.179 [-0.481; 0.123] 0.57     0.26
Harm1          mdf    pcb  0.381 [ 0.253; 0.509] 0.38     0.05
Harm1          p40    pcb  0.560 [ 0.273; 0.847] 0.02     0.21
US00           mdf    pcb  0.381 [ 0.253; 0.509] 2.19     0.19
Hctp           p40    pcb  0.560 [ 0.273; 0.847] 0.32     0.56
US98           mdf    pcb  0.381 [ 0.253; 0.509] 4.77     0.20
Harsch06       mdf    pcb  0.381 [ 0.253; 0.509] 7.24     0.14
Moldfsky00     mdf    pcb  0.381 [ 0.253; 0.509] 3.77     0.06
Saletu05       mdf    pcb  0.381 [ 0.253; 0.509] 3.38     0.03
Black06        mdf    pcb  0.381 [ 0.253; 0.509] 0.43     0.13
```

13.2.1.2 Random Model

```
Results (random effects model):
            treat1 treat2     MD          95%-CI
Broughton97    mdf    pcb  0.321 [ 0.092; 0.551]
Harm1          mdf    p40 -0.205 [-0.684; 0.274]
Harm1          mdf    pcb  0.321 [ 0.092; 0.551]
Harm1          p40    pcb  0.526 [ 0.074; 0.979]
US00           mdf    pcb  0.321 [ 0.092; 0.551]
Hctp           p40    pcb  0.526 [ 0.074; 0.979]
US98           mdf    pcb  0.321 [ 0.092; 0.551]
Harsch06       mdf    pcb  0.321 [ 0.092; 0.551]
Moldfsky00     mdf    pcb  0.321 [ 0.092; 0.551]
Saletu05       mdf    pcb  0.321 [ 0.092; 0.551]
Black06        mdf    pcb  0.321 [ 0.092; 0.551]
```

13.3 Tests

```
Number of studies: k = 9
Number of treatments: n = 3
Number of pairwise comparisons: m = 11
Number of designs: d = 3
Fixed effect model
Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):
       MD         95%-CI
mdf 0.381 [0.253; 0.509]
p40 0.560 [0.273; 0.847]
pcb     .              .
Random effects model
Treatment estimate (sm = 'MD', comparison: other treatments vs 'pcb'):
       MD         95%-CI
mdf 0.321 [0.092; 0.551]
p40 0.526 [0.074; 0.979]
pcb     .              .
Quantifying heterogeneity / inconsistency:
tau^2 = 0.0703; I^2 = 65.5%
Tests of heterogeneity (within designs) and inconsistency (between designs):
                     Q d.f. p-value
Total            23.21    8  0.0031
Within designs   21.83    6  0.0013
Between designs   1.38    2  0.5026
                         Q df        pval
Total            23.205912  8 0.003109698
Within designs   21.829828  6 0.001299910
Between designs   1.376084  2 0.502559082
```

13.4 P-values

```
    P-score (fixed) P-score (random)
pcb          1.0000           0.9929
mdf          0.4387           0.4013
p40          0.0614           0.1059
```

13.5 Pairwise comparisons - Fixed model

```
      mdf   p40  pcb
mdf  0.00 -0.48 0.25
p40 -0.12  0.00 0.27
pcb -0.51 -0.85 0.00
```

13.5.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

```
      mdf   p40  pcb
mdf  0.00  0.12 0.51
p40  0.48  0.00 0.85
pcb -0.25 -0.27 0.00
```

13.5.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

```
     mdf  p40 pcb
mdf  NaN 0.25   0
p40 0.25  NaN   0
pcb 0.00 0.00 NaN
```

13.5.3 Pairwise comparison P values

13.6 Pairwise comparisons - Random model

	mdf	p40	pcb
mdf	0.00	-0.68	0.09
p40	-0.27	0.00	0.07
pcb	-0.55	-0.98	0.00

13.6.1 Lower 95% CI of Effect size (R-C) [r=row, c=column]

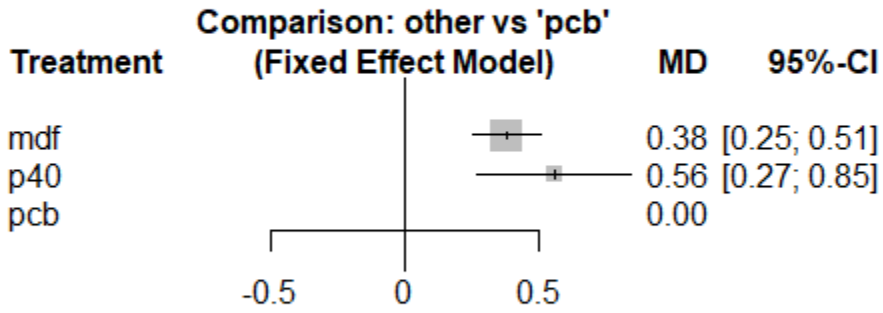
	mdf	p40	pcb
mdf	0.00	0.27	0.55
p40	0.68	0.00	0.98
pcb	-0.09	-0.07	0.00

13.6.2 Upper 95% CI of Effect size (R-C) [r=row, c=column]

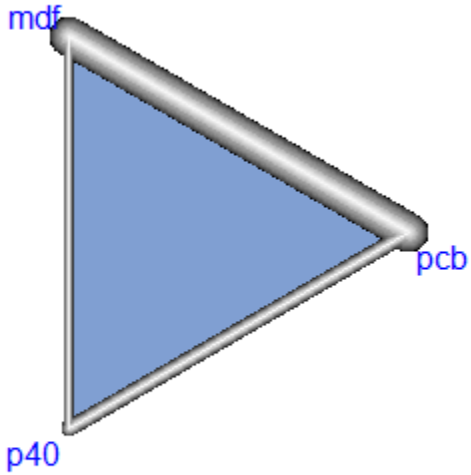
	mdf	p40	pcb
mdf	NaN	0.40	0.01
p40	0.40	NaN	0.02
pcb	0.01	0.02	NaN

13.6.3 Pairwise comparison P values

13.7 Forest Plot

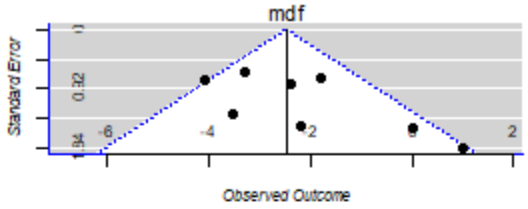


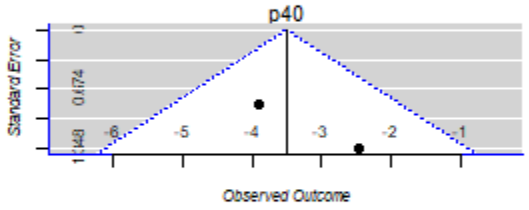
13.8 Network Evidence Graph



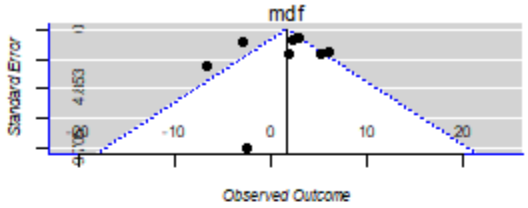
14 Funnel Plot

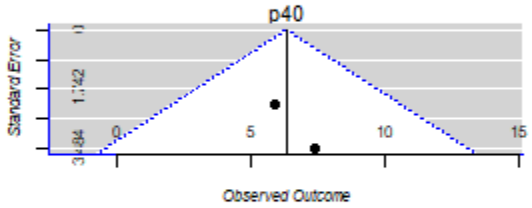
14.1 Funnel Plot Endpoint: 1



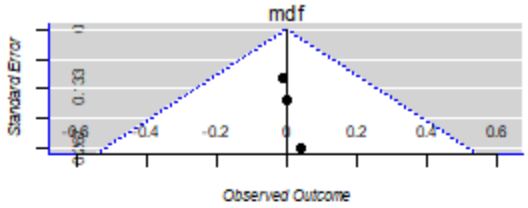


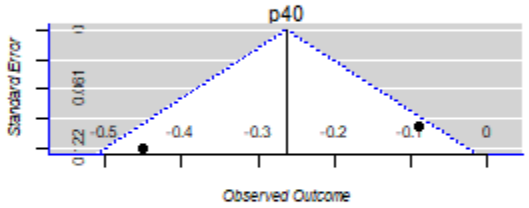
14.2 Funnel Plot Endpoint: 2





14.3 Funnel Plot Endpoint: 3





15 Risk of Bias within studies: Methodological Quality Index

	Internal Validity Questions								External Validity Questions						Statistical Validity Questions						
Author	X1	X2	X3	X4	X5	X6	X7	Mean IVS	X8	X9	X10	X11	X12	Mean EVS	X13	X14	X15	X16	X17	Mean SVS	MQS
Billard 1994	2	0	2	2	2	2	2	8.57	2	2	2	2	2	10.00	1	0	2	2	2	7.00	8.52
Broughton 1997	2	2	2	2	2	2	2	10.00	2	2	2	0	2	8.00	1	2	2	2	2	9.00	9.00
US-MDF 1998	2	2	2	2	2	2	2	10.00	2	2	2	2	2	10.00	2	2	2	2	2	10.00	10.00
US-MDF-2000	2	1	2	2	2	2	2	9.29	2	2	2	2	2	10.00	2	2	2	2	2	10.00	9.76
Moldofsky 2000	2	2	2	2	2	2	2	10.00	2	2	2	2	2	10.00	2	0	2	2	2	8.00	9.33
Harsch 2007	2	2	2	2	0	2	0	7.14	2	2	2	2	1	9.00	0	0	0	2	0	2.00	6.05
Saletu 2005	0	0	1	1	1	2	1	4.29	2	2	2	1	0	7.00	1	0	2	2	2	7.00	6.10
Black 2006	1	2	0	0	2	0	1	4.29	2	2	1	2	1	8.00	2	1	2	2	2	9.00	7.10
Dauvilliers 2013	2	2	2	2	2	2	0	8.57	2	2	2	2	2	10.00	2	2	2	2	2	10.00	9.52
Szakacs 2015	2	2	2	2	2	2	2	10.00	2	2	2	2	2	10.00	2	2	2	2	2	10.00	10.00

Methodological quality of the trials was assessed for internal, external and statistical validity. For each item, the scoring was 2 = appropriate; 1 = unclear; 0 = inadequate; blank space = undocumented. Assessments X1-7 (internal validity) were (1) assigned treatment adequately concealed prior to allocation; (2) outcomes of patients who withdrew or were excluded after allocation described and included in an “intention to treat” analysis; (3) outcome assessors blind to assignment status; (4) participants blind to assignment status following allocation; (5) treatment providers blind to assignment status; (6) identical care programs other than the trial options; (7) withdrawals <10% of the trial population. Items X8-12 (external validity) were: (8) inclusion and exclusion criteria for entry clearly defined; (9) outcome measures used clearly defined; (10) accuracy, precision, and observer variation of the outcome measures adequate; (11) timing of the outcome measures appropriate; (12) quality of allocation concealment was graded. Items X13-17 (validity) were: (13) power calculation; (14) existence of baseline comparison; (15) mention of primary endpoints (with necessary type 1 correction); (16) use of appropriate statistical technique; (17) publication is a full paper, an abstract, an unpublished report with clear table and graphical results. EVS = external validity score; IVS = internal validity score; SVS = statistical validity score

16 STATISTICAL PLAN

16.1 Summary

Study Objectives: Narcolepsy is a rare, disabling neurological disease. A limited number of symptomatic treatment options are available, including a recently approved one, not compared as yet on their efficacy and safety.

Methods: Randomised controlled trials (RCTs) comparing approved treatments for narcolepsy in adults were searched, following PRISMA guidelines. Excessive daytime sleepiness (EDS) was measured by the Epworth Sleepiness Scale (ESS), and the Maintenance of Wakefulness Test (MWT), and cataplexy by the weekly rate of cataplexy attacks during the treatment period. The safety endpoint was the incidence of treatment-emergent adverse events (TEAE). A network meta-analysis was needed for multiple treatment comparison, multi-arm studies and multi-criteria decision, based on a random model assuming heterogeneity between studies, and correcting standard error for multi-arm studies.

Results: 14 RCTs, 3 interventions and 6 dosages were found: sodium oxybate (6g and 9 g/day), modafinil (200-400 mg/day), and pitolisant (20 mg and 40 mg/day maximal doses). Significant heterogeneity between studies was found for almost all the endpoints (I^2>50%), but between-design consistency was demonstrated. For ESS and MWT, sodium oxybate 9 mg/day, modafinil and pitolisant 40 mg/day differed significantly from placebo, with similar efficacy. Pitolisant 40 mg/day and sodium oxybate 9 g in two nightly intakes, provided similar and significant anti-cataplectic effect. A good safety profile characterized by a TEAE Incidence Risk Ratio (IRR) <1.5 was found for all the compared treatments except for sodium oxybate 9 mg/day (IRR=2.24 ([1.11, 4.51], p<.001).

Conclusions: Three interventions at specific dosages (modafinil, sodium oxybate 9g, and pitolisant 40 mg) provide evidence of similar overall efficacy. Pitolisant had a slightly better safety profile and optimal Benefit/Risk ratio.

16.2 Introduction

Narcolepsy is a chronic and disabling neurological disorder mainly characterized by excessive daytime sleepiness (EDS), cataplexy, and REM sleep disorders. As a consequence of marked EDS, patients may exhibit psychosocial distress, as many aspects of working, home and social life are impacted. In addition, narcolepsy is associated with a high risk of co-morbidities. The International Classification of Sleep Disorders (ICSD-3) distinguishes ype-1 (with cataplexy) from type-2 (without cataplexy) narcolepsy.

Current guidelines do not provide unequivocal recommendations on how to choose first-line treatment based on the patient's primary phenotype and the compared medical benefit of existing interventions.

A Level 1 evidence base (Randomized Controlled Trials [RCTs] and meta-analysis) was reached for some interventions: modafinil on EDS and sodium oxybate on EDS and cataplexy. Pitolisant, the first compound of a new histamine H3R pharmacological class, was recently granted European Marketing Authorization in the treatment of narcolepsy with or without cataplexy. Other psychostimulants (methylphenidate, amphetamines) [Mitler et al. 1994], or antidepressants, which are used empirically to treat cataplexy did not provide any evidence through RCTs and were eliminated.

Although these active treatments were compared with placebo, their comparison was not conducted so far. This constitutes the objective of the present study.

16.3 Materials & Methods

16.3.1 Protocol and registration

The protocol, in conformity with PRISMA guidelines, was locked before data extraction and statistical analysis and pre-specified in the PROSPERO database.

16.3.2 Eligibility criteria

Eligibility was generally defined by the selection of Patients, Intervention, Comparison and Outcomes (PICO): *Patients* were adults with narcolepsy irrespective of gender and age. *Intervention* was any treatment with results in at least one RCT and available on the drug market. *Comparison* was conducted between the identified treatments and placebo (considered as control treatment), however, comparison between any pair of treatments was also sought. *Outcomes* were efficacy on EDS and cataplexy symptoms, and safety.

16.3.3 Information sources and search

All articles, books, and abstracts related to the efficacy and safety of drugs in narcolepsy were searched in the literature, irrespective of language, and cited references were checked manually. Electronic searches were performed in the following electronic databases: PubMed/MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library), Database of Abstracts of Reviews of Effects (DARE, Cochrane Library), Cochrane Database of Systematic Reviews (CDSR, The Cochrane Library), World Health Organization (WHO) International Trials Registry Platform (ICTRP) search portal, ClinicalTrials.gov, FDA website, and the EMA website. We also used public information that was collected for sodium oxybate on the EMA website (scientific discussion March 2007).

Search queries comprised a conjunctive/disjunctive list of the following key words: (modafinil or armodafinil) and narcolepsy, sodium oxybate or GHB and narcolepsy, methylphenidate and narcolepsy, amphetamines and narcolepsy, with selection of randomized controlled trials, controlled trials and adults. Once a first list of abstracts was retrieved and reviewed, each study appearing to meet inclusion criteria was independently reviewed in full by two reviewers.

16.3.4 Study selection

We selected RCTs providing data on at least one of the following selected outcomes in both efficacy and safety: Epworth Excessive Sleepiness Score (ESS), Maintenance of Wakefulness Test (MWT), number of cataplexy attacks during treatment exposure, and safety reporting at least existing AEs during the treatment exposure.

16.3.5 Data collection process

All data from publications were systematically reviewed. All tables mentioned in the Statistical Analysis Plan were organized in a Publication Report Form. Each publication was evaluated by the two authors.

16.3.6 Data items

For each study, we collected the publication year, description of the design (randomization and concealment procedures), sample size, patient disposition, intent-to-treat selection, endpoints, ESS, MWT, cataplexy, and safety data reported. Observed heterogeneities among trials were discussed.

16.3.7 Geometry of the network

The network evidence graph is a specific tool for network meta-analyses [Rücker & Schwarzer 2015]. For each endpoint, each node is associated with a treatment. An edge joining any two treatments represents a direct comparison, with the thickness of the edge weighted by the inverse of the standard error of the treatment effect.

16.3.8 Risk of bias in individual studies

The methodological quality of selected studies was evaluated on three validity domains (internal, external, and statistical validity). Domain-based evaluations (17 items) were performed by two raters, any discordance between reviewers discussed and resolved via consensus, and summarized by internal validity score (IVS, 7 items), external validity score (EVS, 5 items) and statistical validity score (SVS, 5 items). For studies with at

least four inadequate items, sensitivity analyses were conducted with and without them, results considered reliable when the two selections provide the same conclusions.

16.3.9 Endpoints

EDS was measured by ESS and MWT. Cataplexy was reported as the weekly rate of cataplexy (WRC). To provide a unique main endpoint and to reduce type-1 multiplicity in the analysis, we first combine ESS and MWT into the EDS mean Z-score, then we define the Narcolepsy Score (NS) as the mean of the EDS and WRC Z-scores (ESS and WRC used minus their values such that larger values indicate patient improvement). NS was our main endpoint; however, each endpoint was analyzed separately.

Safety was estimated by the incidence of reported TEAEs and divided into three categories: (A) *central nervous*: nervousness, anxiety, confusion, dizziness, sleep disorders, psychiatric disorders; (B) *gastrointestinal:* nausea, dyspepsia, dry mouth, vomiting, diarrhea, anorexia, abdominal pain, gastro-intestinal pain, constipation; and (C) *others*: weakness, fatigue, headaches, infection, pain, pyrexia, asthenia, and hypothermia. The main safety endpoint was the Overall Safety Score (OSS), defined as the TEAE incidence rate during the exposure period.

The Benefit/Risk (BR) ratio was used as a measure of the overall medical benefit or patient utility and attempts to combine efficacy (NS score) and safety (OSS score). Depending on a linear correlation observed between NS and OSS, the unit-less BR ratio was defined as the residual value of the linear fit between NS and OSS, or the simple ratio NS/OSS.

16.3.10 Summary measures

Continuous variables (ESS, MWT, and Z-scores) were compared using the weighted mean difference, except for endpoints with heterogeneous non-combinable units (e.g. cataplexy was reported in the studies as various non-convertible statistics) for which the standardized mean difference was used. For safety assessment, TEAE rates were compared using the Incidence Risk Ratio (IRR).

16.3.11 Synthesis of results

We assumed a random-effects model as the most likely assumption where differences might be expected among studies, but we performed the fixed model for sensitivity purposes. A network meta-analysis constitutes an appropriate technique for multiple comparisons. For the expected multi-arm corrections, correlated pairwise comparisons in multi-arm studies were corrected by the weight reduction approach, equivalent to the standard regression approach (dimension of the design matrix reduced until it is invertible). For the assessment of model fit, the Generalized Cochran Q_t, was split into Qd measuring the inconsistency between the net estimates Dt (based on a full design-by-treatment interaction random-effects model) and the direct differences Dd, and Qh evaluating the heterogeneity across studies. Treatment ranking by P-scores measured the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments, equivalently with the Surface Under the Cumulative RAnking curve (SUCRA) defined as the rank of treatment *i* within the range of treatments. Finally, all results were compared with an alternative statistical model assuming different assumptions [Salanti et al. 2011]. The statistical analyses were performed using R statistical packages (release version 3.2.4) and the meta-library Netmeta.

Before optimization, the heterogeneity of reports required conversion; median values and quartiles were converted into mean values using heuristic approximation. The estimate of non-reported SDs was based on the knowledge of the mean changes and the observed t-values or p-value. Final values were assimilated to mean changes by assuming that the correlation between baseline and final values was $R \cong 0.5$. Values not reported in tables were estimated from graphics. Crossover and parallel results were appropriately mixed and corrected under considerations of carryover effect.

16.3.12 Risk of bias across studies

The assessment of publication bias was assessed by funnel plots constructed for each endpoint and for all studied treatments, compared with placebo.

16.4 Mathematical aspects and computations

16.4.1 Model used in this analysis

$Y(n,1) \sim X(n,p)\ b(p,1) + E(n,1)$

Where Y= estimated between treatment differences, b=parameter vector (bi= each treatment effect), X= design matrix, and Residual E a multivariate normal N(0,D) with D diagonal with variances known from the literature.

Contrary to OLS, E is not unity needs Aitken estimation (Weighted LS regression), where $b=(X'D^{-1}X)^{-1}(X'D^{-1}Y)$ and the $SE(b)= s(X'D^{-1}X')^{-1}$. The simple case (2 treatments) simplifies to $Yi= 1_{(n,1).}$ D, Aitken providing b= mean of Y weighted by $1/s^2_i$.

However the general case is when D contains correlation (needing General Least square), in particular k treatments in the same trial provide k(k-1)/2 correlated contrasts, and X becomes more complex.

16.4.2 Design matrix:

X(n studies, p treatments): for 2 treatments $Yi= 1x_i – 1x_j +Eij$. Thus the ith row of X is 0 except column i=1 and j=-1. We must arbitrarily fix one treatment (for instance T1 often placebo) to 0. This is done using the model $Yijk= 0 + t_2+...+t_k$, thus estimates y2,… are relative to placebo.

16.4.3 Use of Hat Matrix Property:

$b=[(X'D^{-1}X)^{-1}(X'D^{-1})]Y$, [] is the H hat matrix, each observed (direct) difference is estimated by HY, a linear combination of the n observed contrasts, including the diagonal (leverage) which is the contribution of the corresponding observed difference.

16.4.4 Network meta-analysis

Network meta-analysis synthesizes information from randomized trials comparing two or more treatments for a given medical condition. Several techniques are available. Frequentist approaches are Lumley and Rücker.

Lumley

For each study, pairwise contrasts are repeated. A random factor is the trtpair (categories of treatment pair) capturing the incoherence within the same design. The variance is modeled as $a(b+s)^2$, where s is the constant known variance, b is sensed to estimate the random contribution, and a is a multiplicative overdispersion. For five treatments: zz<- lme(y1 ~ 0+t2+t3+t4+t5, random=~1|trtpair, weight= varConstPower (form=~sigma,fixed=list(power=1))). Approximate correction for multi-arms comparison in one trial is done by multiplying variances by 2 for comparisons within a 3-armed trial (each person being double-counted).

Rücker

Principle: retrieves Aitken model from Network theory ($X'D^{-1}X$) being the laplacian or admittance matrix and shows that for non-inversible D, aitken can be calculated by using the Penrose Pseudo-Inverse technique. Lumley resolves this question through a linear-mixed model, but avoids the correlation induced by multiple treatment comparisons in the same trial.

Network inconsistency and heterogeneity: (a) for each estimate of a product, the H Matrix diagonal provides the contribution of each known direct difference (before, all the studies with the same design (the same compared treatments have been previously aggregated by separate meta-analyses), and the diagonal (leverage)= proportion of contribution of its OWN direct difference, (b) The Cochrane generalized statistic: for each difference yi, let be Dt_i= the overall Net estimate and Dd_i the estimate based on direct differences only (if only one contrast for two treatments, Dti=yi). $Qt= \Sigma\ (y_i-Dt_i)^2$ measures the overall difference between the observed values and the Net estimates. However, Qt is a mix of heterogeneity between studies and inconsistencies between designs. For separating these effects, Qt is decomposed into Qh+Qi where $Qh = \Sigma\ (Y_i-$

$Dd_i)^2$ (heterogeneity between studies) and $Qi=\Sigma\ (Dd_i-Dt_i)^2$ (inconsistency between designs). Qt,Qi and Qh are tested with a χ^2 tests.

P scores: Ranks treatment [Rücker & Schwarzer 2015]. Pi is the mean of all 1 - Pj (Pj=one-sided P-value of accepting the alternative hypothesis that ti>tj). Pi can be interpreted as the mean extent of certainty that treatment *i* is better than another treatment and comparable to that of the Surface Under the Cumulative RAnking curve (SUCRA) which is the rank of treatment *i* within the range of treatments, measured on a scale from 0 (worst) to 1 (best) [Salanti et al. 2011].

Network Graph: planar graph, nodes corresponding to the treatments and edges corresponding to the observed treatment comparisons, with thickness proportional to the inverse standard error of random effect model comparing two treatments. Nodes are placed on a circle or optimized by Factor analysis.

NetMeta Library: implements Rücker technique.

(1) *Input data*: The user preferred format is Arm-Based format: each row is a study describing the k arms: either Mean, N, SD, or event, N). The command *Pairwise* will convert into contrast-Based format: each row describes each possible pair with TE (Treatment effect), seTE, Trt1 and Trt2 (two string denoting treatment), and studyLabel.contrast and corrects for multiplicity. With Pairwise you also choose your statistic (MD, OR, etc…):

nmaData <- pairwise(list(trt1,trt2,trt3), n=list(n1,n2,n3), mean=list(mean1, mean2,mean3), sd=list(sd1, sd2,sd3), data <myfile>, studlab=id, sm="MD")

if more than one endpoint is used, add an EP endpoint variable, a TYPE (designating which type : continuous with SD, continuous with SE, Median with IQ, Proportion, ..) and a DIR variable providing the direction of this variable. This is useful if Z-scores of endpoints are needed.

(2) netmeta constructs the net on the basis of contrast-based format: nma <- netmeta(TE, seTE, trt1, trt2, studlab, data=nmaData, reference="pcb")

(3) *forest* draws the forest tree plot of the nmares: forest(nma,reference="pcb")

(4) Meta-Regression can be done

16.4.5 References

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