Research Square

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Transvenous Phrenic Nerve Stimulation and Positive Airway Pressure devices for Central Sleep Apnea in Patients with Heart Failure with Reduced Ejection Fraction: A Network Meta-analysis

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Abstract

Purpose: Adaptive servo-ventilation (ASV) is contraindicated for central sleep apnea (CSA) treatment in patients with heart failure with reduced ejection fraction (HFrEF) limiting treatment options. Though, continuous positive airway pressure (CPAP), bi-level PAP with back-up rate (BPAP-BUR) and transvenous phrenic nerve stimulation (TPNS) are alternatives, not much is known about their comparative efficacies, which formed the basis of this network meta-analysis, in which their effects on apnea hypopnea index (AHI) and subjective daytime sleepiness (based on Epworth sleepiness score (ESS)), were analyzed.

Methods: PubMed was searched for potentially includable randomized controlled trials and network meta-analysis was conducted in R program using package *netmeta*.

Results: Network meta-analysis showed no statistically significant differences between interventions in AHI reduction. In exploring heterogeneity, sensitivity analysis elicited statistically significant differences in AHI reduction between ASV and TPNS (-18.30 [-27.8; -8.79]), with BPAP-BUR (-21.90 [-30.79; -13.01]) and CPAP (-23.10 [-29.22; -16.98]), favoring ASV. Of all the interventions, only TPNS showed a statistically significant decrease in ESS (-3.70 (-5.58; -1.82)) when compared to guideline directed medical therapy (used as a common comparator across trials), while also showing significant differences when compared with ASV (-3.20 (-5.86; -0.54)), BPAP-BUR (-4.00 (-7.33; -0.68)), and CPAP (-4.45 (-7.75; -1.14)). *Hasse* diagram, accounting for both AHI and ESS as outcomes for relative hierarchy showed relative superiority of both ASV and TPNS over BPAP-BUR and CPAP.

Conclusions: Results indicate relative superiority of TPNS and ASV to BPAP-BUR and CPAP in their effects on AHI and ESS reduction in patients with CSA and HFrEF.

Introduction

Central sleep apnea (CSA) is characterized by temporary withdrawal of central (brainstem-driven) respiratory drive that results in the cessation of respiratory muscle activity and airflow. Patients with heart failure (HF) commonly have a form of CSA, called Cheyne-Stokes respiration (CSR) in which ventilatory instability produces a distinctive form of periodic breathing with recurring cycles of crescendo-decrescendo ventilation with prolonged central apneas or hypopneas in between.[1] CSA-CSR occurs in up to 40% of patients with HF.[1,2] HF produces ventilatory control instability via several pathways that include pulmonary interstitial congestion, impaired cerebrovascular reactivity, caudal fluid shifts and prolonged circulation time and it is believed that the oscillation of the blood carbon dioxide levels around the apneic threshold appears to be the key factor in starting CSA and in perpetuating the ventilatory instability during sleep.[3] The repeated episodes of apnea in CSA, similar to OSA, are associated with hypoxemia, followed by reoxygenation and arousal in a cycle throughout the night, leading to frequent intermittent surges and upregulation of the sympathetic nervous system. In patients with HF sympathetic stimulation leads to further downstream effects such as tachycardia, peripheral vasoconstriction, sodium retention, and renin angiotensin-aldosterone system activation, all of which are associated with poor

prognosis in patients with HF.[4,5] Optimization of HF therapy is the cornerstone in the management of CSA in HF patients,[6] as studies have shown that when HF is clinically improved, CSA too generally improves more or less [7,8]. Because CSA often persists despite aggressive treatment of HF, targeted treatment for CSA must be considered. Treatment options for CSA have included positive airway pressure (PAP) based devices including, adaptive servo ventilation (ASV), bi-level PAP with back-up respiratory rate (BPAP-BUR), continuous PAP (CPAP) and supplemental nocturnal oxygen, or medications like theophylline or acetazolamide. Studies evaluating oxygen and medications have been limited by their small sample sizes, thus limiting strong, evidence-based clinical recommendations.[9,10] Transvenous phrenic nerve stimulation (TPNS) is the newest of the treatment options approved by the Food and Drug Administration for the treatment of moderate to severe CSA. TPNS primarily involves a neurostimulator with stimulation and sensing leads, implanted typically in the right pectoral region with the stimulation lead advanced into the right brachiocephalic vein to stimulate the phrenic nerve and a sensing lead which is typically placed in the azygos vein to sense respiration by thoracic impedance. The system is typically activated 1 month after implant and the device is further automatically programmed gradually over ~12 weeks to allow full diaphragmatic capture and resultant contraction during central apneas in sleep.[11] Since ASV is no longer indicated in CSA patients with left ventricular ejection fraction (LVEF) < 45%,[12] TPNS maybe a reasonable alternative to consider in these patients. Since TPNS has not been compared head-to-head with other PAP devices for CSA specifically in HF patients with reduced ejection fraction (HFrEF), we sought to determine their comparative efficacy using a network meta-analysis methodology. A network meta-analysis allows for comparisons of interventions that may not have been directly compared in head-to-head trials by simultaneously analyzing both direct comparisons of interventions within randomized controlled trials (RCTs) and indirect comparisons across multiple trials based on a common comparator.

Methods

The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) extension statement for network meta-analysis [13] as reported in Table E1.

Search Strategy and Study Eligibility Criteria

PubMed database was searched for RCTs from inception to November 20th, 2020. Inclusion and exclusion criteria for studies was similar to an already published direct pairwise meta-analysis.[14] Specifically, studies were considered for inclusion if they studied adult participants, aged $\geq$ 18 years, diagnosed with primary CSA (with or without CSR) with an overall mean (or -1 standard deviation (SD) from mean) apnea hypopnea index (AHI) cut-off of > 10 events/hour, with central apneas comprising > 50% of all respiratory events, and participants' mean (or +2 SDs from mean) EF was $\leq$ 50%. Additionally, studies were considered for inclusion only if they studied CPAP, ASV, BPAP-BUR or TPNS as interventions. Studies where data (of interest) was reported in median and inter-quartile range or presented in a way where mean and standard deviation or corresponding confidence intervals could not be ascertained were excluded from main analyses. From the included RCTs, those in the usual care or untreated control group

were designated in this network meta-analysis as under 'guideline directed medical therapy' akin to the same methodology used in a previously published direct pairwise meta-analysis.[14]

Data Extraction and Synthesis

The studies were assessed for 'study quality' based on modified Cochrane methods. Data extracted from studies included first author's name, publication year, study design, population characteristics, AHI, Epworth sleepiness score (ESS). Data were first extracted on Microsoft Excel sheets and then on the working sheets of '*Comprehensive Meta-Analysis*' (CMA version 2.2.064; Biostat, Englewood, N.J. U.S.A) software, to get uniform measures of changes as change scores computed as mean difference, corresponding 95% confidence intervals (CI) and standard errors (SE) between one intervention and control/active comparator. The R Foundation for Statistical Computing, Vienna, Austria) '*netmeta*' package was used for performing all network meta-analysis functions within the '*frequentist*' framework. This approach has been used in other network meta-analyses.[15,16] Results of network meta-analysis were presented as *netgraphs* or evidence plots (geometry of evidence), forest plots and *network league* tables, a square matrix showing all pairwise comparisons in a network meta-analysis. Inconsistency between direct and indirect/network meta-analysis was checked by '*netsplit*' tables. The rankings for different PAP interventions was performed by '*P-scores*'. *P-scores* are based solely on the point estimates and standard errors of the network estimates. They measure the extent of certainty that a treatment is better than another treatment, averaged over all competing treatments. This interpretation is comparable to that of the Surface Under the Cumulative RAnking curve (SUCRA).[17] Furthermore, '*Hasse*' diagram was constructed using R, which illustrates relations of different interventions in a partially ordered set with superior objects (interventions) located above inferior ones. Interventions not connected by arrows are considered incomparable, as individual rankings may go in opposite directions.[18] A 'comparison-adjusted' funnel plot to assess funnel plot asymmetry in network meta-analysis was constructed (for Eggers test of intercept, Begg and Mazumdar rank correlation test, and the Thompson-Sharp tests).[19]

Results

Figure 1 shows the study selection process. A total of 9 RCTs were included in this network meta-analysis.[20-28] Table 1 lists the baseline characteristics of this study population. Risk of bias assessment is presented in table E2 in online resource/supplement.

The *netgraphs* or network evidence plots for the geometry of the evidence/studies (number of studies, participants and trials between comparisons) for AHI and ESS analyses are presented in figure 2. In the network meta-analysis for AHI change, data from 8 studies[20-27] with a total of 648 participants was analyzed. Compared to GDMT, all interventions, ASV (-26.05 [-38.80; -13.31]), TPNS (-24.90 [-42.88; -6.92]), BPAP-BUR (-20.36 [-36.47; -4.25]) and CPAP (-16.01 [-25.42; -6.60]) showed statistically significant changes in AHI in their favor based on indirect (network) estimates (table 2 and figure 3a). There was no statistically significant difference between the interventions based on indirect (network)

estimates. Statistical heterogeneity was detected in the AHI network meta-analysis (tau^2 = 72.6; I^2 = 88.5%), as shown in table 2. Sensitivity analysis by selectively excluding one study at a time from the overall analysis did not result in reduction of heterogeneity. Only when both the studies by O'Connor et al[27] and Fietze et al[22] were selectively excluded from the overall analysis, did the heterogeneity drop- tau^2 dropped to 0.01 and I^2 value to 0.2%. Results are shown in table 2 and figure 3b. With this sensitivity analysis a statistically significant difference was found between ASV and all other active comparators- with TPNS the difference was -18.30 [-27.8; -8.79], with BPAP-BUR -21.90 [-30.79; -13.01] and with CPAP -23.10 [-29.22; -16.98], as shown in table 2. While TPNS ranked higher than BPAP-BUR and CPAP (based on P-scores, as explained below), there were no statistically significant inter-treatment differences between TPNS and the latter.

In the analysis for change in ESS among all interventions, data from 6 RCTs[21,22,24,25,27,28] was analyzed comprising a total of 374 participants. Only TPNS showed a statistically significant decrease in ESS when compared to GDMT (-3.70 (-5.58; -1.82)), based on both direct and indirect estimates. Results are shown in table 3 and figure 4. Because no direct evidence existed between TPNS and other interventions, the difference between TPNS and other interventions is based solely on indirect (network) meta-analysis estimate, showing statistically significant reduction in ESS when compared with ASV (-3.20 (-5.86; -0.54)), BPAP-BUR (-4.00 (-7.33; -0.68)), and CPAP (-4.45 (-7.75; -1.14)). There was no statistical heterogeneity detected in the ESS network meta-analysis ESS analysis (tau^2 = 0; I^2 = 0%).

Based on the *netsplit* table there was no statistical inconsistency detected between the network meta-analysis indirect estimates and direct meta-analysis estimates for AHI or ESS outcomes (*netsplit* tables in online resource/supplement).

P-score ranking, which is based solely on the point estimates and standard errors of the network estimates ranks ASV as first, TPNS as second, followed by BPAP-BUR and CPAP for the AHI network meta-analysis (the overall network ranking did not change with AHI sensitivity analysis) and ranks TPNS as first, ASV as second, followed by GDMT and then BPAP-BUR and CPAP coming last in the ESS network meta-analysis (figure 5). *Hasse* diagram accounting for both AHI and ESS as outcomes for relative hierarchy showed relative superiority of both ASV and TPNS over BPAP-BUR and CPAP (figure 5). When accounting for AHI sensitivity analysis the order in *Hasse* diagram did not change.

Publication bias for primary outcomes was assessed using *funnel* plots, which on visual inspection showed no evidence of plot asymmetry (figure 6).

Discussion

The results of this network meta-analysis based on the *Hasse* diagram and *P-scores* suggests ASV and TPNS as the most effective treatment for CSA in patients with HFrEF, in terms of their effects on AHI and ESS. This conclusion is based on ranking from *P-scores* and *Hasse* diagrams which are based solely on effect size and SEs. It is also noteworthy to mention that in AHI reduction all treatments were superior to

GDMT and in the overall analysis no inter-treatment differences were found. This analysis, however, showed high heterogeneity and upon exploring this heterogeneity with sensitivity analysis, two studies (22, 27) were found to be contributing to the overall heterogeneity. The sensitivity analysis showed a statistically significant difference between ASV and all others. In this sensitivity analysis, the study by O'Connor et al[27] stood out as one of the outliers and was excluded. This study had low statistical power primarily because after the results of the SERV-HF trial[12] became available further recruitment of participants was stopped. The other outlier was the study by Fietze et al[22] and while the study was similar to most other PAP intervention studies, in that the participants showed significant reductions in sleep-disordered breathing with PAP intervention along with an improvement in LVEF, the only difference between this study and others was that it reported respiratory disturbance index as opposed to AHI (which was reported in all the others) and this was defined by the authors as the sum of the Cheyne-Stokes Apnea index, periodic breathing index, obstructive apnea index and mixed apnea index. With the sensitivity analysis, although the ranking of studies did not change, the differences between ASV and TPNS as well as its difference with BPAP-BUR and CPAP did become significant. It is important to note here that TPNS unlike its other active comparators (in this network meta-analysis) does not treat any obstructive apneas or obstructive hypopneas.[29] Despite this limitation of TPNS, it is remarkable that in the overall AHI reduction, TPNS out-performed BPAP-BUR and all other interventions in ESS improvement, actually meeting the minimal clinically important difference threshold with GDMT (based on both direct and indirect estimates) and also when compared with ASV, BPAP-BUR and CPAP (based on indirect estimates). It was not possible to separately analyze the data on central apnea index in addition to the overall AHI, and this is because not many studies included in this network meta-analysis reported this index separately.

This network meta-analysis evaluated the comparative efficacy of only four selected treatment comparisons and while it shows superior efficacy of ASV in AHI reduction in patients with HFrEF with CSA with LVEF < 50%, use of ASV especially in those with LVEF < 45% is currently contraindicated due to the findings of SERV-HF trial that showed an absolute annual risk of cardiovascular death of 10% in patients with HFrEF-CSA who were randomized to ASV vs. 7.5% in those who were in the control group.[12] The results of the much-awaited ADVENT-HF trial may provide more clarity on future use of ASV in this particular population.[30] Two meta-analyses have shown conflicting results on the effects of ASV on LVEF- one showing that while ASV significantly reduced AHI, the effects on LVEF improvement were not significant[31] and the other showing significant improvement in LVEF with ASV as compared to control.[32] This network meta-analysis did not evaluate the comparative efficacy of treatments on LVEF improvement primarily because no such data was available from the included study on TPNS[21] and hence impossible to form a 'network' with other interventions in a network meta-analysis. Additionally, given the different follow-up durations of the various interventions in this network meta-analysis, a 6-month data of LVEF changes from TPNS would conceivably not have been a fair assessment when compared to others in the network meta-analysis, primarily because a period of approximately 3 months is needed to optimally titrate nerve 'stimulation'[29] and therefore one would not expect LV remodeling to be evident until after 6 months of maximum active therapy or in other words after 9–12 months of

randomization. Furthermore, while ASV, BPAP-BUR and CPAP interventions in this network meta-analysis treated both central and obstructive apneas and hypopneas, given that TPNS only addresses central apneas, an assessment of LVEF function in a network meta-analysis would not be reasonable. Even so, while the 'remedē System' pivotal trial[21] did not report the 6-month data on LVEF changes, it is reassuring to know that the 12-month [29] and 36-month [33] data did show small but significant improvements in LVEF compared to baseline. Furthermore, while there are issues of some sort with other interventions, like device safety issues with ASV in CSA patients with low LVEF[12], and in general poor adherence with any PAP (CPAP or BPAP), the overall safety profile of TPNS as shown in the 36 months follow-up is quite promising.[33] While the debate continues- whether CSA-CSR is a friend or foe in HF patients and that perhaps the hyperventilation during CSR may actually be protective in these patients[34-36], one theory on the possible physiological links between ASV and the noted cardiovascular adverse outcomes in SERV-HF trial, that has gained much attention relates to the possible effects of high PAP on intrathoracic pressure and downstream effects. Accordingly, high PAP leads to high intrathoracic pressure, in turn leading to decrease in venous return, decreasing thereby the right ventricular stroke volume and consequently decreasing LV filling and cardiac output and eventually tipping the sympatho-vagal balance in these HF patients to the sympathetic side, which can be deleterious to HF patients.[37] A recent proof-of-concept study showed that neither nocturnal CPAP nor ASV favorably altered the sympathetic tone at night in CSA patients with systolic HF and patients on ASV had a significantly lower CI as compared to those on CPAP.[38] Not only that, but another recent study [39] showed that use of ASV in these patients significantly decreased N3 sleep (during which vagal tone predominates) and significantly increased REM (during which sympathetic nervous activity is known to be highest or close to wakefulness activity) and N2 sleep (during which burst of sympathetic activity have been known to occur). In this context, the mechanism of action of phrenic nerve stimulation is different and opposite to that of ASV, in that while ASV increases intrathoracic pressure by PAP, TPNS via neurostimulation triggers normal breathing via diaphragmatic contraction and thus generates negative intrathoracic pressure, thereby favoring venous return to the heart.[29]

There are several limitations to this network meta-analysis. This network meta-analysis was limited in that it could not evaluate other outcomes of interest such quality-of-life metrics, or changes in LVEF, or mortality with each intervention. However as explained earlier, without having all included studies report data in similar units, one cannot create a 'network' in a network meta-analysis to analyze comparative efficacies or effectiveness of interventions specifically with regards to quality-of-life outcomes and LVEF. Analysis of mortality or other long term adverse outcomes was outside the scope of this network meta-analysis which primarily aimed at analyzing the efficacy of interventions and included studies with follow up data not long enough to be able to compute any meaningful data on such outcomes. Furthermore, the control groups in the included RCTs, which were used as common comparator or reference in the network meta-analysis, were regarded as 'GDMT', however, it is possible that the medical therapy may have varied in its composition in different studies over time as the guidelines evolved. Lastly, and most importantly a strict inclusion criteria in this network meta-analysis limited the number of studies in each intervention category and the efficacy data on TPNS is derived from

only one RCT.[21] Nevertheless, this is the first network meta-analysis to our knowledge assessing the comparative efficacy of all interventions in CSA patients with HFrEF.

In conclusion, this network meta-analysis suggests that both TPNS and ASV are superior to other interventions in managing sleep-disordered breathing in CSA patients with HFrEF and that TPNS therapy as opposed to other interventions can also improve subjective daytime sleepiness in these patients. This network meta-analysis may have to be updated when the results of ADVENT-HF trial[30] are published.

Declarations

Funding: This study was not sponsored by any funding agency or pharmaceutical company.

Conflicts of interests: IHI reports no conflicts of interest. RNK has received consulting fees in 2018 from Respicardia Inc, a company that manufactures a transvenous phrenic nerve stimulator; and consulting fees in 2020 from Philips Respironics, a company that manufactures positive airway pressure devices.

Availability of data and material: not applicable

Code availability: not applicable

Author contributions: IHI had full access to all extracted data in the network meta-analysis and takes responsibility for the integrity of the data and the accuracy of the data analysis. IHI and RNK contributed to assessment of study quality, the interpretation of analyses and in revisions of manuscript.

Ethics approval: not applicable

Consent to participate: not applicable

Consent for publication: not applicable

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Tables

TABLE 1:

	Age	Gender (male%)	BMI	Follow up duration (*for network meta-analysis*)	AHI	LVEF	PAP adherence (hours/night)
PAP = 128 DMT = 130	CPAP = 63.2±9.1 GDMT = 63.5±9.8	CPAP = 98% GDMT = 95%	CPAP = 28.8±5.5 GDMT = 29.3±6.5	24 months	CPAP = 40±15 GDMT = 40±17	CPAP = 24.8±7.9 GDMT = 24.2±7.6	3.6 to 4.3
PNS = 73 DMT = 78	TPNS = 65±12 GDMT = 65±13	TPNS = 86% GDMT = 92%	TPNS = 30.8±5.3 GDMT = 31.3±6.6	6 months	TPNS = 48.8±19.3 GDMT = 43.7±16.8	TPNS = 39.7±12.1 GDMT = 39.4±12.2	N/A
SV =17 PAP-ST = 20	ASV = 61.9 ± 9.1 BPAP-ST = 56.4 ± 10.9	ASV = 88% BPAP-ST = 95%	ASV = 26.9 ± 2.4 BPAP-ST = 28.9 ± 4.8	6 weeks	ASV = 31.7 ± 9.8* BPAP-ST = 34.9 ± 20.4*	ASV = 24.6 ± 7.9 BPAP-ST = 25.5 ± 9.2	N.R
PAP = 9 DMT = 8	CPAP = 58.3 ± 2.2 GDMT = 58.0 ± 2.0	N.R	CPAP = 28.9 ± 1.9 GDMT = 25.4 ± 1.8	3 months	CPAP = 49±11 GDMT = 35±11	CPAP = 24.0 ± 4.0 GDMT = 20.6 ± 3.2	5.6 ± 0.7
SV = 12 PAP = 11	ASV = 64.3± 8.8 CPAP = 65.8 ± 8.7	N.R	ASV = 26.3±4.2 CPAP = 26.9±5.2	3 months	ASV = 25.0±6.9 CPAP = 23.0±7.9	ASV = 32.0±7.9% CPAP = 32.9±5.9%	ASV = 4.7±0.6 CPAP =3.3±1.2
6 patients randomized in a cross-over design to each intervention	62.0±7.4	81%	27.3±3.2	14 days on each intervention	26.7±10.7	23.8±6.5	BPAP-BUR =5.1±1.5 CPAP = 5.6±1.5
PAP = 12 DMT = 12	CPAP = 61.0 ± 3.2 GDMT = 56.6 ± 3.2	N.R	CPAP = 26.0 ± 1.5 GDMT = 27.1 ± 1.5	3 months	CPAP = 43.2±4.9 GDMT = 33.1±7.1	CPAP = 21.2 ± 3.8 GDMT = 19.7 ± 2.7	CPAP = 5.9±0.6
SV = 65 DMT = 61	ASV = 61±14 GDMT = 63±13	ASV = 75% GDMT = 72%	ASV = 32.3±9.0 GDMT = 31.4±8.6	6 months	ASV = 35.7±17.1 GDMT = 35.1±16.7	ASV = 30.5±15.4 GDMT = 33.7±15.7	2.7 average
SV = 12 PAP = 13	ASV = 64.2±15.5 CPAP = 60.3±11.5	ASV = 100% CPAP = 100%	ASV = 25.2±3.3 CPAP = 28.8±6.3	6 months	ASV = 47±18.6 CPAP = 40.5±13.9	ASV = 29±9 CPAP = 30±9	4.3 3.1 (averaged in both ASV and CPAP)

N indicates total participants, BMI indicates body mass index, AHI indicates apnea-hypopnea index, LVEF indicates baseline left ventricular function, PAP indicates positive airway pressure device, ASV indicates adaptive servo-ventilator, BPAP-BUR indicates bi-level positive airway pressure with back-up rate, TPNS indicates transvenous phrenic nerve stimulation, CPAP indicates continuous positive airway pressure, GDMT indicates guidelines directed medical therapy,*indicates RDI defined in this study as sum of the Cheyne-Stokes Apnea index, periodic breathing index, obstructive apnea index and mixed apnea index; N/A indicates not applicable; N.R indicates data was not reported

Table 2: *Net League* table for AHI analysis:

NET LEAGUE TABLE FOR AHI ANALYSIS				
ASV	-	-2.00 [-21.37; 17.37]	-23.10 [-40.89; -5.31]	-15.80 [-33.86; 2.26]
-1.15 [-23.19; 20.89]	**TPNS**	-	-	-24.90 [-42.88; -6.92]
-5.69 [-20.36; 8.97]	-4.54 [-28.68; 19.60]	**BPAP-BUR**	-1.20 [-19.10; 16.70]	-
-10.05 [-22.07; 1.98]	-8.89 [-29.19; 11.40]	-4.35 [-18.62; 9.91]	**CPAP**	-19.33 [-29.62; -9.05]
-26.05 [-38.80; -13.31]	-24.90 [-42.88; -6.92]	-20.36 [-36.47; -4.25]	-16.01 [-25.42; -6.60]	**GDMT**
Studies in direct pairwise meta-analysis comparisons: ASV vs BPAP-BUR = Fietze 2008[22] ASV vs CPAP = Kasai 2013[24] ASV vs GDMT = O'Connor 2017[27] BPAP-BUR vs CPAP = Kohnlein 2002[25] CPAP vs GDMT = Bradley 2005[20], Granton 1996[23], Naughton 1995[26] TPNS vs GDMT = Costanzo 2016[21]				
Quantifying heterogeneity / inconsistency: tau^2 = 72.6; I^2 = 88.5%				
Tests of heterogeneity (within designs) and inconsistency (between designs):				
	Q	p value		
Total	34.84	<0.0001		
Within designs	2.00	0.36		
Between designs	32.84	< 0.0001		
NET LEAGUE TABLE FOR AHI SENSITIVITY ANALYSIS				
ASV	-	-	-23.10 [-29.22; -16.98]	-
-18.30 [-27.81; -8.79]	**TPNS**	-	-	-24.90 [-31.57; -18.23]
-21.90 [-30.79; -13.01]	-3.60 [-13.33; 6.12]	**BPAP-BUR**	-1.20 [-7.65; 5.25]	-
-23.10 [-29.22; -16.98]	-4.80 [-12.08; 2.48]	-1.20 [-7.65; 5.25]	**CPAP**	-20.10 [-23.01; -17.18]
-43.20 [-49.98; -36.42]	-24.90 [-31.57; -18.23]	-21.30 [-28.38; -14.22]	-20.10 [-23.01; -17.18]	**GDMT**
Studies in direct pairwise meta-analysis comparisons: ASV vs CPAP = Kasai 2013[24] BPAP-BUR vs CPAP = Kohnlein 2002[25] CPAP vs GDMT = Bradley 2005[20], Granton 1996[23], Naughton 1995[26] TPNS vs GDMT = Costanzo 2016[21]				
Quantifying heterogeneity / inconsistency: tau^2 = 0.01; I^2 = 0.2%				
Tests of heterogeneity (within designs) and inconsistency (between designs):				
	Q	p value		
Total	2	0.36		
Within designs	2	0.36		
Between designs	0	--		

League table for random effects model with network estimates in lower triangle and direct estimates in upper triangle; Example how to interpret this table: indirect (network meta-analysis) difference between ASV and TPNS is -1.15 [-23.19; 20.89], and between TPNS and BPAP-BUR is -4.54 [-28.68; 19.60]; cells marked with " – " means no direct pairwise meta-analysis existed in that comparison, ASV indicates adaptive servo-ventilator, BPAP-BUR indicates bi-level positive airway pressure with back-up rate, TPNS

indicates transvenous phrenic nerve stimulation, CPAP indicates continuous positive airway pressure, GDMT indicates guidelines directed medical therapy; ; Q, tau^2 and I^2 are heterogeneity tests

TPNS	-	-3.70 [-5.58; -1.82]	-	-
-3.20 [-5.86; -0.54]	**ASV**	-0.50 [-2.38; 1.38]	-0.70 [-3.33; 1.93]	-1.34 [-3.85; 1.17]
-3.70 [-5.58; -1.82]	-0.50 [-2.38; 1.38]	**GDMT**	-	-
-4.00 [-7.33; -0.68]	-0.80 [-2.79; 1.19]	-0.30 [-3.04; 2.44]	**BPAP-BUR**	-0.40 [-2.14; 1.34]
-4.45 [-7.75; -1.14]	-1.25 [-3.21; 0.71]	-0.75 [-3.47; 1.97]	-0.45 [-2.02; 1.13]	**CPAP**
Studies in direct pairwise meta-analysis comparisons: ASV vs BPAP-BUR = Fietze 2008[22] ASV vs CPAP = Kasai 2013[24], Philippe 2006[28] ASV vs GDMT = O'Connor 2017[27] BPAP-BUR vs CPAP = Kohnlein 2002[25] TPNS vs GDMT = Costanzo 2016[21]				
Quantifying heterogeneity / inconsistency: $tau^2 = 0$; $I^2 = 0\%$				
Tests of heterogeneity (within designs) and inconsistency (between designs):				
	Q	p value		
Total	0.09	0.95		
Within designs	0.07	0.78		
Between designs	0.01	0.90		

Table 3: Net League table for ESS analysis

Figures

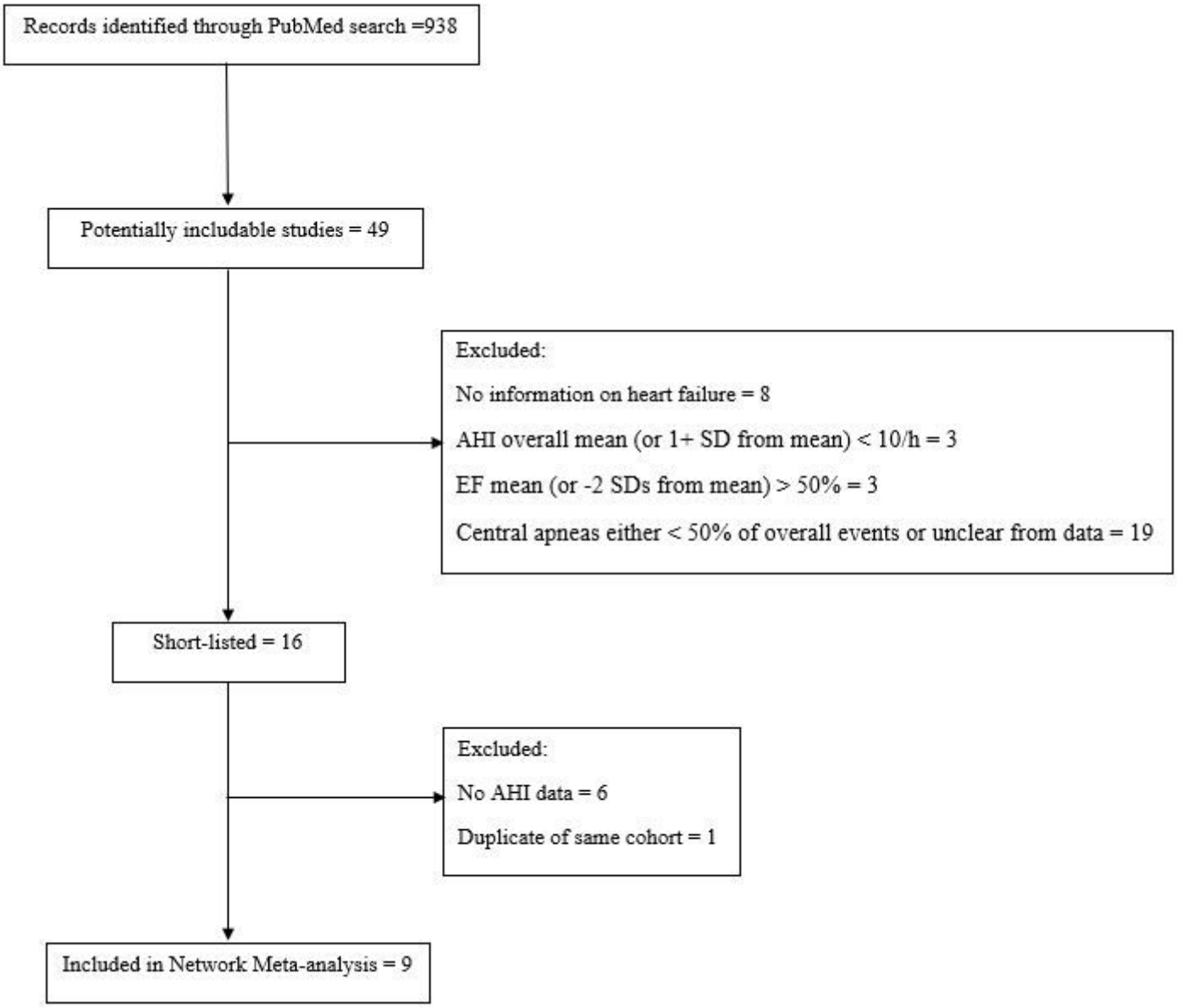


Figure 1

Search strategy and selection process

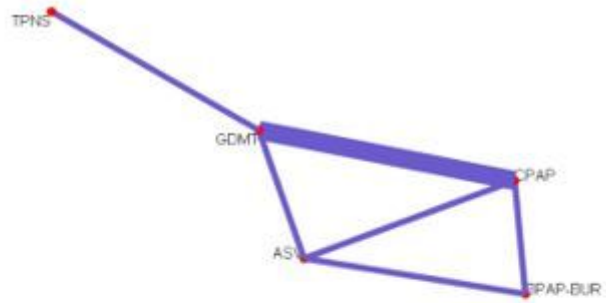


Figure 2b: AHI sensitivity analysis

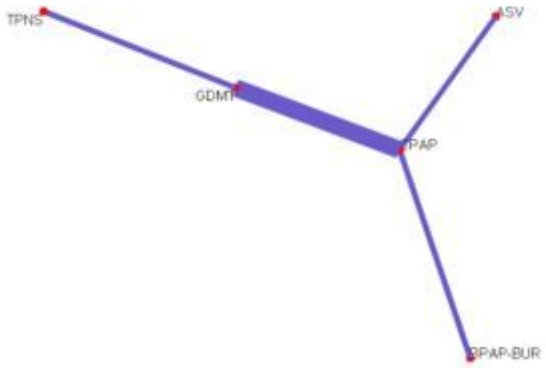


Figure 2c: ESS analysis

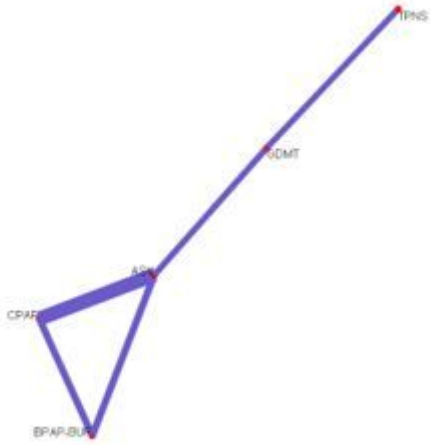


Figure 2

Network evidence plots for primary outcomes Graph plotted on a 3-dimensional plane, in which the nodes in the graph layout corresponded to the ventilatory mode and connecting lines displaying the treatment comparisons (thickness of lines indicating number of studies in each comparison). ASV indicates adaptive servo-ventilator, BPAP-BUR indicates bi-level positive airway pressure with back-up rate, TPNS indicates transvenous phrenic nerve stimulation, CPAP indicates continuous positive airway pressure, GDMT indicates guidelines directed medical therapy

Figure 3a: Forest plot for AHI analysis

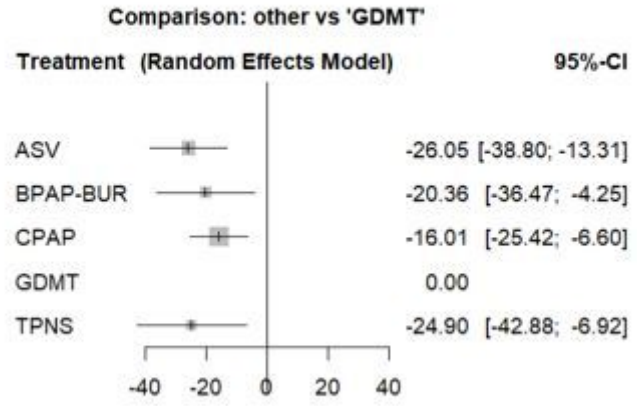


Figure 3b: Forest plot for AHI sensitivity analysis

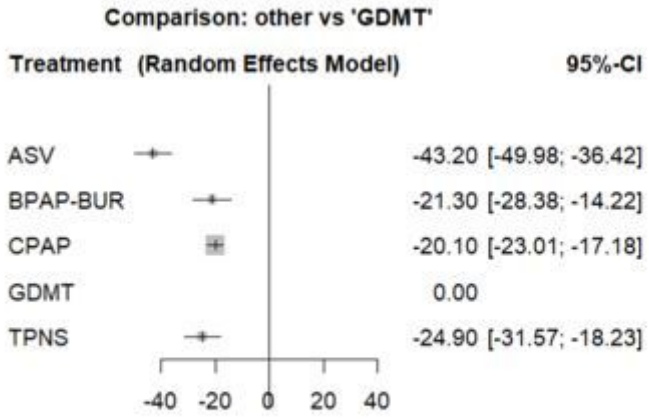


Figure 3

Network meta-analysis forest plot for AHI analysis The size of the square indicates the weight of the effect size as determined by the number of studies and participants. CI, confidence interval, AHI indicates apnea-hypopnea index

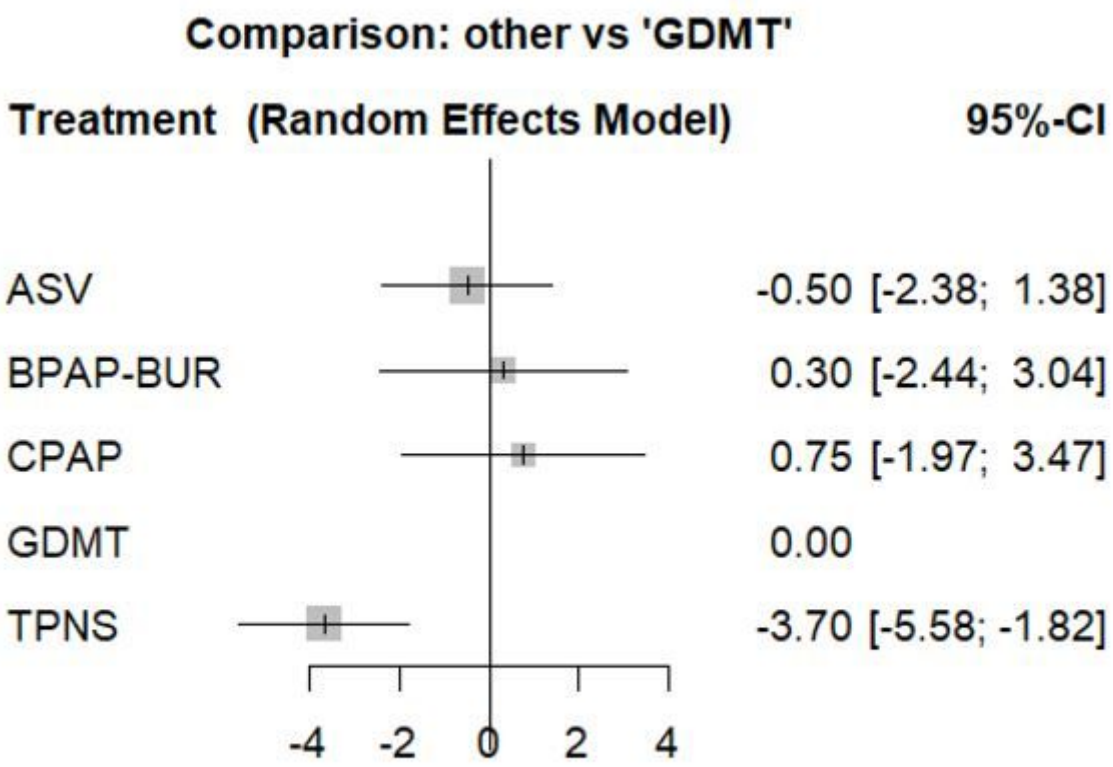
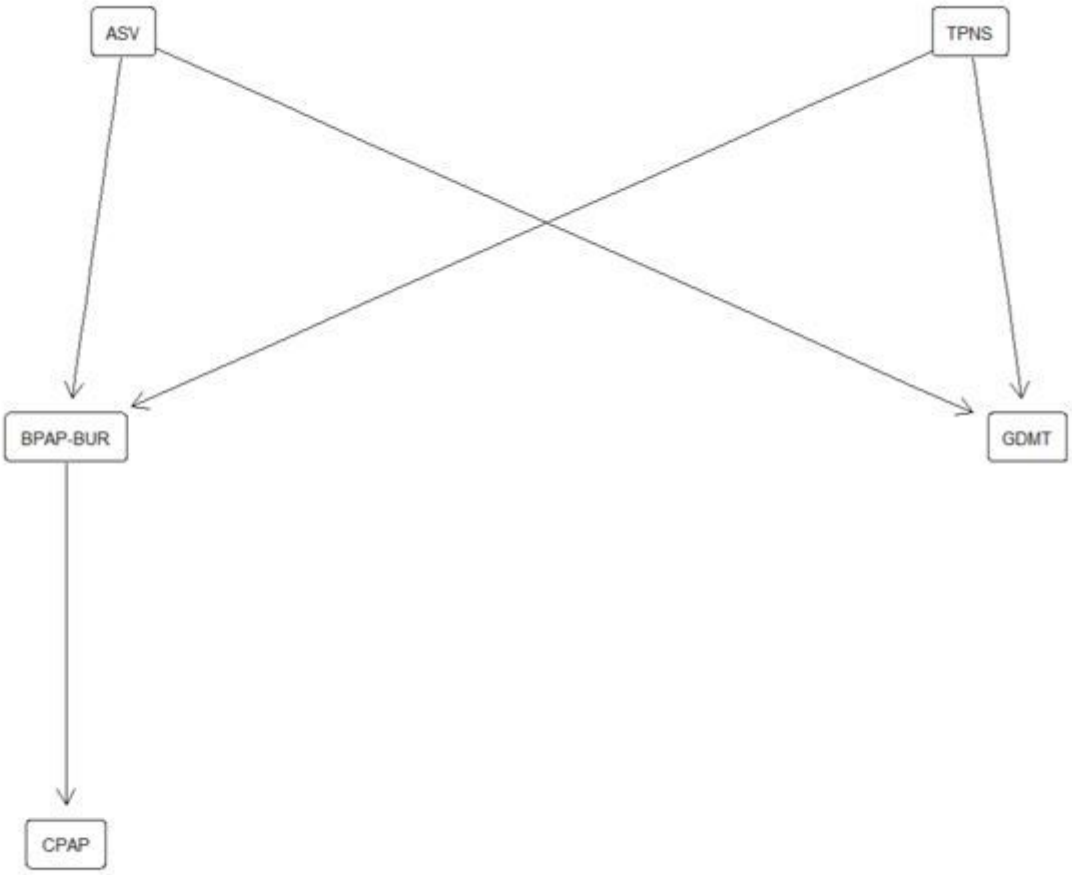


Figure 4

Network meta-analysis forest plot for ESS analysis The size of the square indicates the weight of the effect size as determined by the number of studies and participants. CI, confidence interval, ESS indicates Epworth sleepiness scale score



AHI analysis	P-scores (random effects model)	Rank
ASV	0.81 (1.00*)	1st
TPNS	0.72 (0.66*)	2nd
BPAP-BUR	0.57 (0.46*)	3rd
CPAP	0.38 (0.36*)	4th
GDMT	0.00 (0.00*)	5th
ESS analysis	**P-scores (random effects model)**	**Rank**
TPNS	0.99	1st
ASV	0.59	2nd
GDMT	0.39	3rd
BPAP-BUR	0.33	4th
CPAP	0.17	5th

Figure 5

Ranking of treatments for primary outcomes The Hasse diagram illustrates treatment relations in a partially ordered set with superior objects located above inferior ones. The treatments on the top of the diagram have a higher overall rank than the treatments below them, with arrows pointing to the inferior treatments. The P score (B) represents the probability that one treatment is better than the others, with higher values (ranging from 0 to 100) corresponding to a higher ranking. *P scores in brackets are from

AHI sensitivity analysis, the hierarchy of treatments as depicted in this figure was identical to that computed for AHI sensitivity analysis.

Figure 6a: Publication bias assessment for AHI analysis

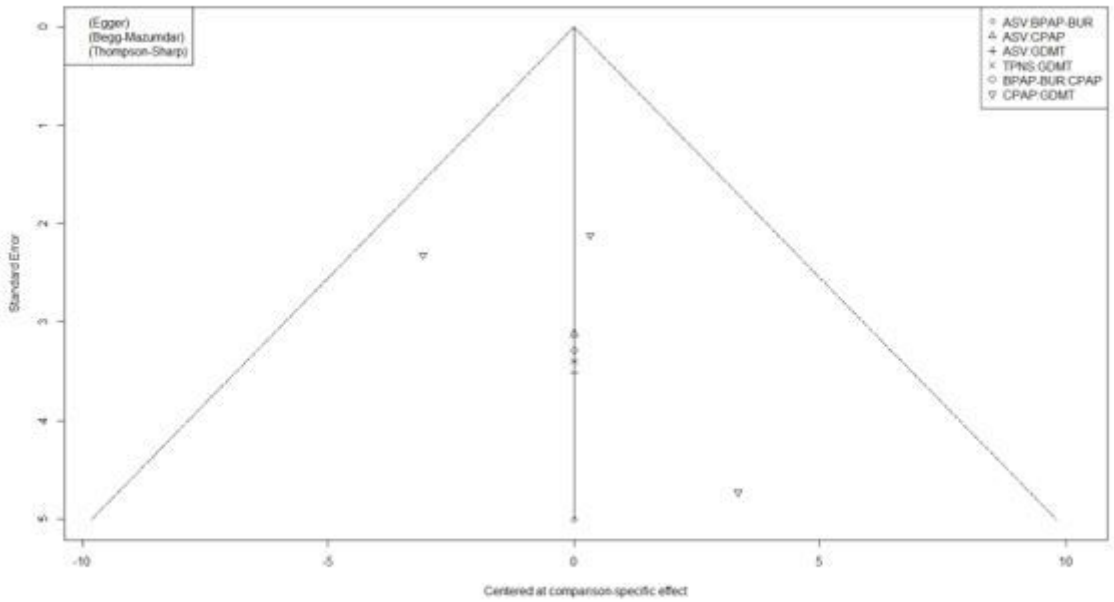


Figure 6b: Publication bias assessment for ESS analysis

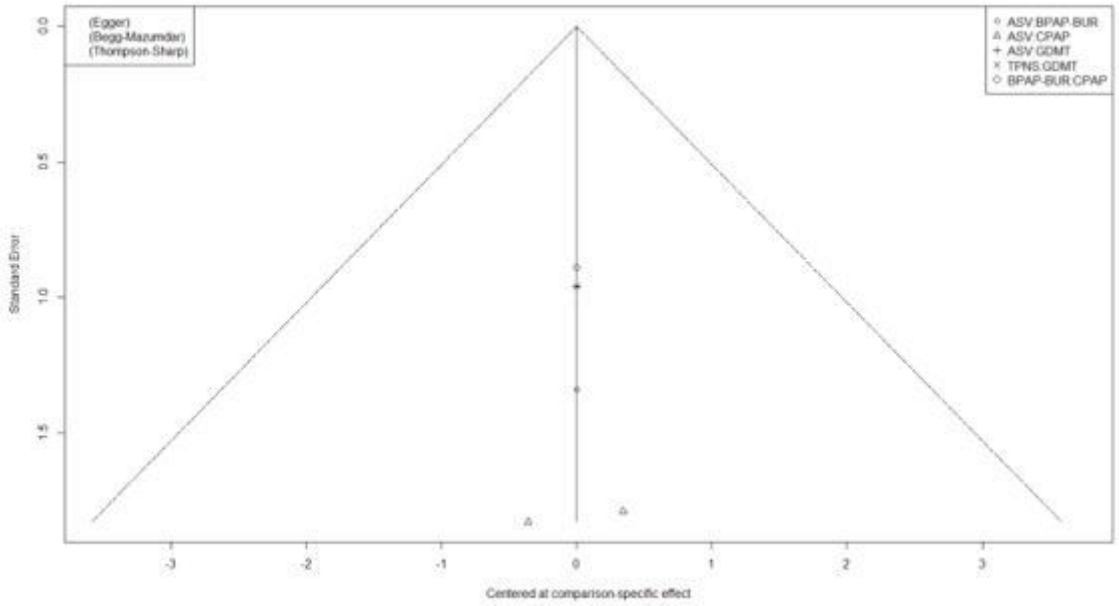


Figure 6

Comparison-adjusted funnel plots

Supplementary Files

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- APPENDIX.docx