Network meta-analysis of the efficacy and safety of seven oral phosphodiesterase 5 inhibitors for erectile dysfunction

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OBJECTIVES
To evaluate the overall efficacy and main reported adverse events (AE) of phosphodiesterase 5 inhibitors - PDE5i (sildenafil, vardenafil, tadalafil, avanafil, udenafil, mirodenafil and lodenafil) in men with erectile dysfunction (ED).

METHODS
A systematic review with network meta-analysis (NMA) was performed (CRD42017079308). Searches were conducted in Pubmed, Scopus and Web of Science. Randomized controlled trials (RCT) evaluating any PDE5i compared to placebo or other PDE5i were included. Evaluated outcomes were: efficacy measured through IIEF score and major AE. NMAs were built for each outcome of interest with effects sizes (mean difference – MD; odds ratio – OR) reported with 95% credibility intervals (CrI). The surface under the cumulative ranking curve analyses (SUCRA) were conducted.

RESULTS
Overall 179 RCT (50,620 patients) were included (see main networks in Figure 1). All PDE5i were significantly more effective than placebo, with sildenafil (25 mg and 50 mg) presenting the best profile for enhancing IIEF (98% and 80% probability in SUCRA, respectively) with MD compared to placebo of 13.08 [95% CrI: 10.06; 16.02]. Taladafil 10 mg and 20 mg also presented good efficacy profiles (73% and 76%, respectively). Avanafil and lodenafil presented poor efficacy results. Mirodenafil 150 mg caused more serious AE and medication related-AEs (95% in SUCRA), especially flushing and headache. Sildenafil at higher doses (100 mg) was more related to visual disorders (89%), while vardenafil and udenafil were more prone to cause nasal congestion (see Table 1 and Figure 2).

CONCLUSIONS
For patients requiring immediate stronger efficacy sildenafil at low doses (25 or 50 mg) should be the first-line therapy. Tadalafil (10 or 20 mg) should be indicated in men wishing to optimize tolerability and prolonged erection. The use of avanafil, lodenafil and mirodenafil are hardly justified given the lack of efficacy or high rates of AEs.

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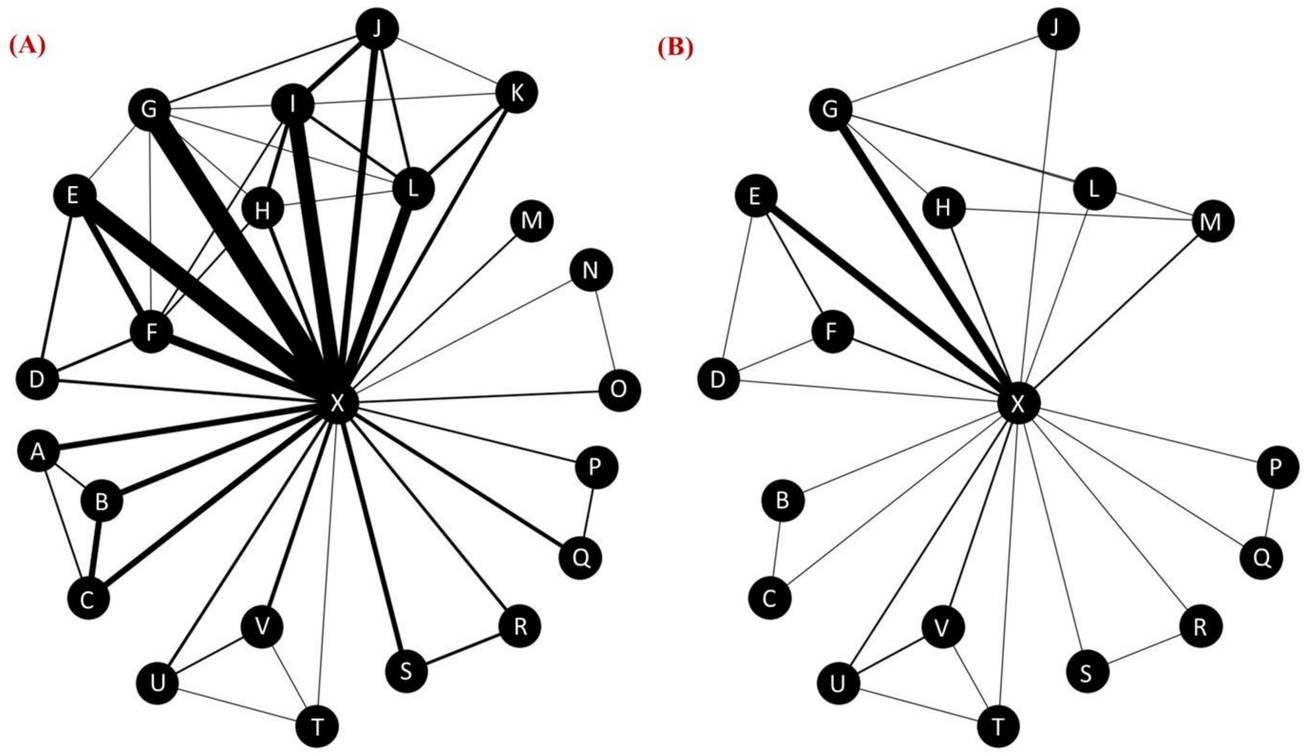

Figure 1. Network diagrams: IIEF (A) and medication related-AE (B)
Each node represents an intervention. The thickness of the lines is proportional to the number of studies for each pair of comparison. A: Avanafil 50 mg; B: Avanafil 100 mg; C: Avanafil 200 mg; D: Vardenafil 5 mg; E: Vardenafil 10 mg; F: Vardenafil 20 mg; G: Sildenafil 50 mg; H: Sildenafil 100 mg; I: Tadalafil 20 mg; J: Tadalafil 10 mg; K: Tadalafil 2.5 mg; L: Tadalafil 5 mg; M: Sildenafil 25 mg; N: Lodenafil 40 mg; O: Lodenafil 80 mg; P: Udenafil 75 mg; Q: Udenafil 50 mg; R: Udenafil 200 mg; S: Udenafil 100 mg; T: Mirodenafil 150 mg; U: Mirodenafil 50 mg; V: Mirodenafil 100 mg; X: Placebo

Table 1. SUCRA values for the evaluated outcomes

Interventions	IIEF	Medication related-AE	AE serious	Flushing	Headache	Nasal congestion	Visual disorders
Avanafil 50 mg	7.14%	-	24.67%	41.19%	49.91%	8.19%	20.00%
Avanafil 100 mg	20.45%	16.53%	75.07%	44.43%	48.59%	42.44%	36.50%
Avanafil 200 mg	40.27%	54.65%	71.47%	57.33%	87.41%	51.63%	31.13%
Lodenafil 40 mg	30.77%	-	-	52.38%	37.27%	-	61.56%
Lodenafil 80 mg	40.00%	-	-	76.81%	69.64%	-	83.44%
Mirodenafil 100 mg	83.00%	73.94%	-	55.90%	75.41%	-	28.19%
Mirodenafil 150 mg	46.05%	95.24%	-	90.50%	95.14%	-	-
Mirodenafil 50 mg	39.05%	59.24%	-	44.24	51.14%	42.88%	-
Sildenafil 25 mg	99.95%	38.65%	57.60%	54.33%	29.68%	-	36.13%
Sildenafil 50 mg	80.32%	48.47%	24.07%	67.86%	57.32%	40.81%	55.19%
Sildenafil 100 mg	62.73%	86.29%	55.00%	75.57%	64.23%	72.44%	89.13%
Tadalafil 2.5 mg	27.23%	-	39.80%	-	12.73%	29.69%	-
Tadalafil 5 mg	43.86%	36.00%	34.07%	17.05%	22.27%	70.25%	-
Tadalafil 10 mg	72.77%	32.47%	49.00%	17.57%	35.32%	39.63%	-
Tadalafil 20 mg	76.32%	-	31.27%	36.38%	51.05%	59.88%	62.44%
Udenafil 25 mg	-	-	-	-	-	-	-
Udenafil 50 mg	22.82%	25.00%	55.73%	28.24%	48.14%	30.31%	41.44%
Udenafil 75 mg	47.14%	42.00%	29.47%	28.86%	70.91%	58.00%	66.94%
Udenafil 100 mg	49.55%	67.82%	-	36.19%	16.68%	42.56%	47.88%
Udenafil 200 mg	80.14%	80.18%	-	69.14%	62.59%	69.50%	65.56%
Vardenafil 5 mg	38.55%	22.06%	89.80%	48.86%	22.50%	-	-
Vardenafil 10 mg	58.59%	53.82%	57.33%	75.76%	58.86%	87.88%	41.25%
Vardenafil 20 mg	80.41%	61.76%	66.80%	90.24%	74.45%	83.00%	68.19%
Placebo	0.55%	1.29%	39.47%	1.48%	3.09%	16.00%	18.31%

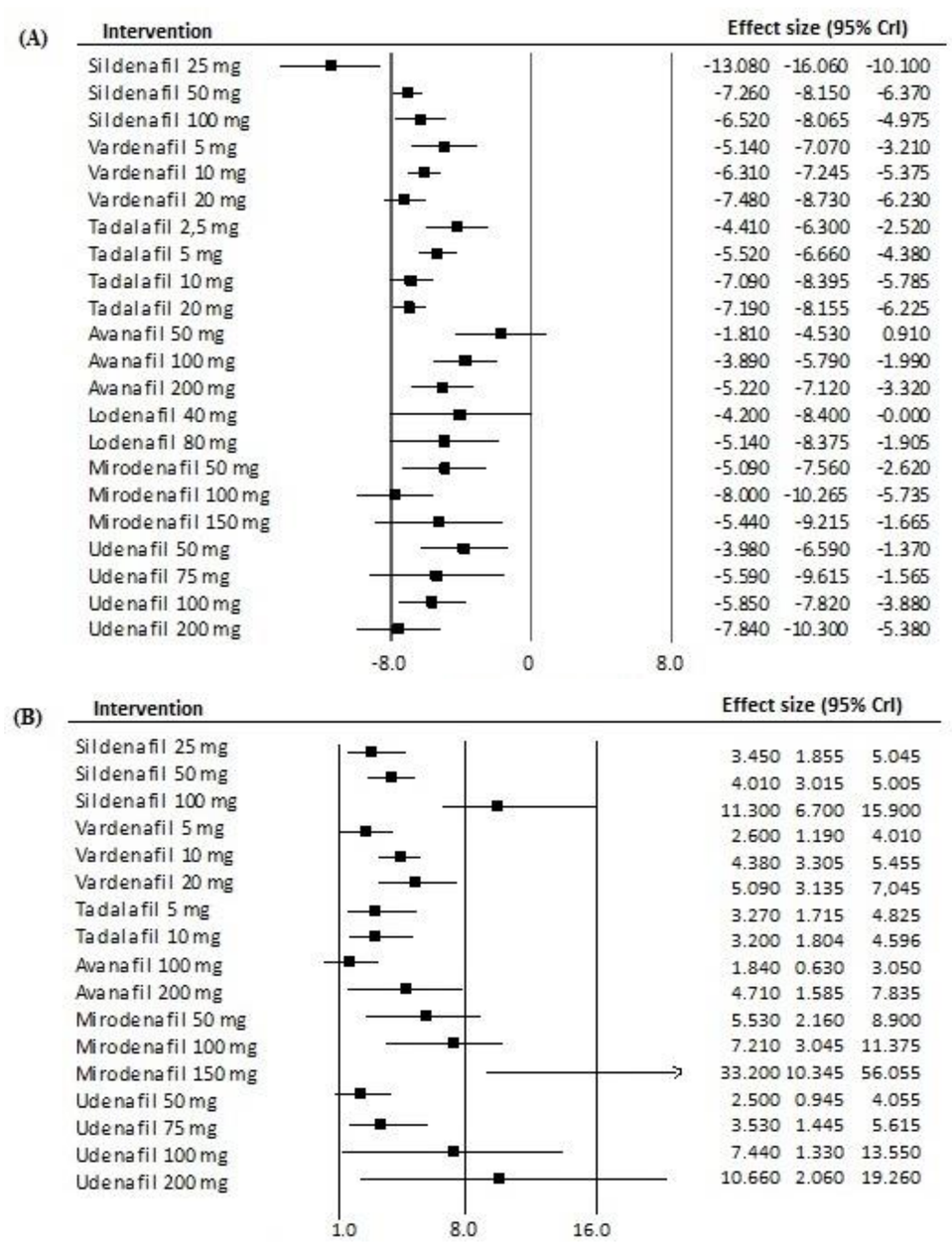

Figure 2. Meta-analyses comparing interventions *vs.* placebo
IIEF (A) and medication related-AE (B)