CONSIDERATIONS FOR INCLUDING DIFFERENT ROUTES OF ADMINISTRATION IN NETWORK META-ANALYSIS

A COMPREHENSIVE REVIEW

Powell L[1], Friesen M[1], O'Sullivan F[1], Popoff E[1]

[1]Broadstreet HEOR, 203 – 343 Railway St, Vancouver BC Canada

BACKGROUND

- Network meta-analysis (NMA) is a statistical technique used to compare multiple interventions simultaneously, including those not directly compared in head-to-head trials. NMA assumes homogeneity in the reference arm (e.g., placebo) across trials.
- However, pooling reference arms of varying routes of administration (ROA; e.g., oral, subcutaneous, intravenous) may challenge this assumption.
- For example, there are several factors that can affect the placebo response in drug trials, including frequency of drug administration and the invasiveness of the treatment (e.g., intravenous vs. oral route of administration).[1-3]

OBJECTIVE

- To review recently published NMAs that compared drugs with varying ROAs, to understand the frequency at which these analyses are conducted, and to identify the methods and considerations used to address this potential source of bias.

METHODS

- A search strategy using MESH terms and keywords was implemented in MEDLINE on May 9th, 2023, to capture published NMAs from January 2022 to the present **(Table 1).**

Table 1. MEDLINE search strategy

Line #	Search term	Number of hits
1	network meta-analysis/	4839
2	protocol.mp.	432823
3	1 not 2	4197
4	limit 3 to yr="2022-Current"	1308

- Studies of interest were NMAs that indirectly assessed pharmacological therapies with ≥1 ROA **(Table 2).**
- For studies that met these criteria, information was extracted on the disease area, ROAs, methodological adjustments, and any discussion of multiple ROAs as a study limitation.

Table 2. PICOS criteria for targeted literature review

PICOS	Criteria
Population	Any
Intervention	Pharmacologic treatments, any route of administration
Comparator	Other pharmacologic treatments or placebo
Outcome	Any
Study design	Network meta-analysis with >1 route of administration, with common comparator node (e.g., placebo)
Language	English
Publication date	2022-current

RESULTS

- The search strategy was run on May 9th, 2023, in MEDLINE.
- 1308 abstracts were identified, 427 full text articles were reviewed, and 140 studies met final inclusion criteria.
- The included studies (n=140) were NMAs conducted in a range of disease areas (rheumatology, neurology, cardiology, endocrinology, and others) that analyzed evidence for various ROA combinations, **(Figure 1).**
- Of these studies, only 17% (n=23) discuss multiple ROAs as a study limitation, potential source of bias, or as a consideration in their results interpretation **(Figure 2).**
- An even smaller number of published NMA adjusted for differing ROAs in their analysis (n=6, 4.3%; **Figure 2,Table 3**).
- Of the studies that adjusted for ROA, two different scenarios were identified:
  1. Networks evidence where one intervention had multiple ROAs
  2. Networks of evidence where interventions with various ROAs were incorporated
- Adjustment methods included meta-regression, subgroup analysis, analyzing nodes separately, and separate networks by ROA (**Table 3, Figure 3).**

Figure 1. Frequency of different route of administration combinations analyzed in the published network meta-analyses (n=140)

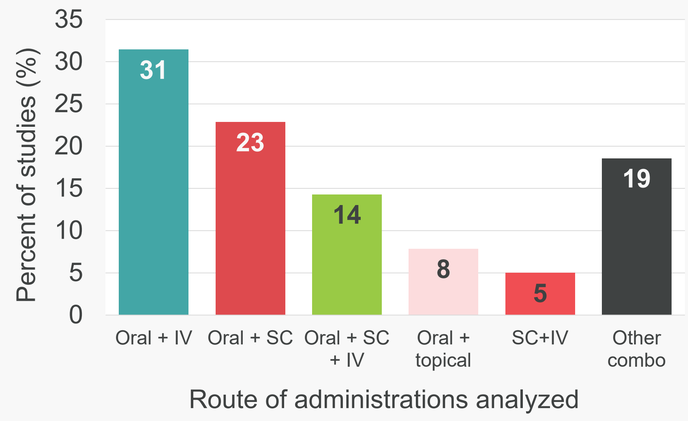


Figure 2. Route of administration was rarely adjusted for in published network meta-analysis

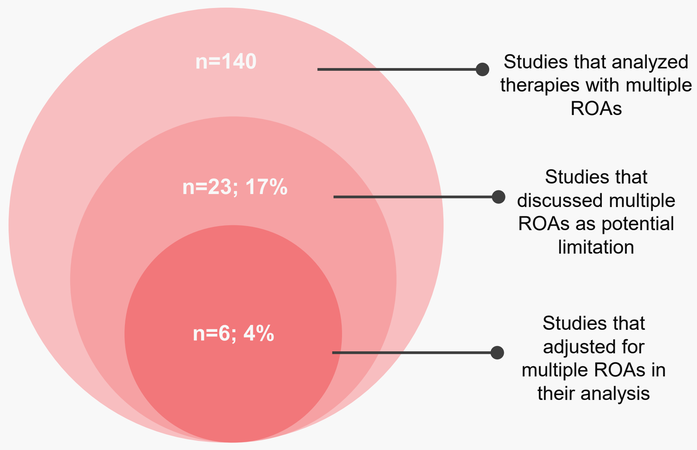
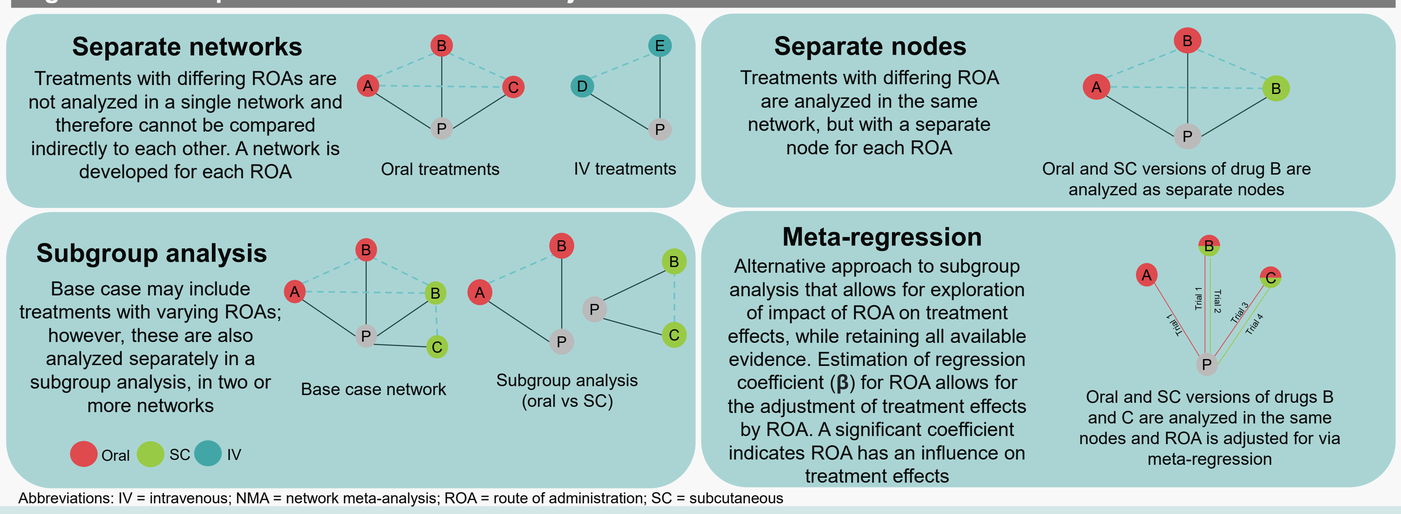


Table 3. Studies that included route of administration adjustment

Author, year	Disease area	ROA combination	Meta-regression	Subgroup analysis	Separate vs pooled nodes	Separate networks by ROA	Findings of the adjustment
Bastounis, 2022[4]	Fragility fractures	Oral + IV	■				Meta-regression results were not significant meaning mode of administration did not have significant impact on the NMA results.
Bo, 2022[5]	Stroke	Oral + IV		■			Subgroup analysis had no impact on the NMA outcome, as no individual drug in the network had multiple ROAs, and network was star shaped.
Chen, 2023[6]	Idiopathic membranous nephropathy	Oral + IV			■		Concluded that IV route was associated with a higher total remission rate and lower relapse than oral.
Zeng, 2022[9]	Adverse prostate events	Oral + transdermal + IM			■		Concluded that intramuscular injection was the most likely to rank first in decreasing prostate cancer cases.
Dayyani, 2022[7]	Aneurysmal subarachnoid hemorrhage	Oral + IV			■		Considered routes of administration as separate nodes in the model; based on clinical feedback.
Haghdoost, 2023[8]	Migraine	Oral + IV + SC				■	With this method, they did not compare drugs with differing ROAs into a single network, so could only draw conclusions vs placebo.

Abbreviations: IM = intramuscular; IV = intravenous; NMA = network meta-analysis; ROA = route of administration; SC = subcutaneous

Figure 3. Description of methods for ROA adjustment



Abbreviations: IV = intravenous; NMA = network meta-analysis; ROA = route of administration; SC = subcutaneous

DISCUSSION

- Commonly, when new treatments emerge, they are investigated in double-blind placebo-controlled trials, rather than in head-to-head studies with all relevant comparators.
- However, HTA bodies require indirect evidence, such as an NMA, when deciding on reimbursement strategies for novel therapies. Differing ROAs are a potential source of bias in an indirect treatment comparison (ITC) when the common comparator is placebo.
- Network geography and the number of studies for each comparator may reduce the ability to perform subgroup analyses and/or meta-regression for ROA.
- In these situations, this potential source of bias should be taken into consideration when interpreting the findings.

STRENGTHS AND LIMITATIONS

- This was a rigorously conducted targeted literature review capturing all NMAs published since 2022. However, this is just a snapshot of evidence, trends in analyses approaches over time cannot be ascertained.
- Published NMAs will differ from the analyses informing HTA submission; further review is required to see if the current findings are applicable to ITCs informing reimbursement decisions.

CONCLUSION

- In the recent literature, comparing drugs of differing ROAs using NMA is common, however the vast majority of studies do not account for this as a possible source of bias.
- The few studies that do adjust for ROA use meta-regression, subgroup analysis, separate nodes by ROA, or create different networks for each ROA.
- Future work will aim to quantify the impact of pooling reference arms of varying ROAs on the validity and interpretation of NMA results.

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CONTACT: lpowell@broadstreetheor.com