RESEARCH NOTE

A simple formula for enumerating comparisons in trials and network meta-analysis [version 1; referees: 2 approved]

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Abstract

We present use of a simple formula to calculate the number of pairwise comparisons of interventions within a single trial or network meta-analyses. We used the data from our previous network meta-analysis to build a study-based register and enumerated the direct pairwise comparisons from the trials therein. We then compared this with the number of comparisons predicted by use of the formula and finally with the reported number of comparisons (indirect or direct) within the network meta-analysis. A total of 133 trials included in the network generated 163 comparisons (16 unique direct comparisons for 8 interventions). The formula predicted an expected 28 indirect or direct comparisons and this is the number that were indeed reported. The formula produces an accurate enumeration of the potential comparisons within a single trial or network meta-analysis. Its use could help transparency of reporting should a shortfall occur between comparisons actually used and the potential total.

Keywords

Pairwise Comparisons, Study-Based Registers, Clinical Trials, Randomised Controlled Trials, Network Meta-Analysis, Systematic Reviews

Open Peer Review

Invited Referees

1

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2

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Any reports and responses or comments on the article can be found at the end of the article.
Introduction
The pairwise comparisons reported within each randomized controlled trial are being documented in study-based registers\(^1\). This lends itself to accurate indexing and enumeration of these comparisons within the studies and then subsequent supply of immediate, highly sensitive and highly specific search results to those wishing to investigate one or more particular comparisons within systematic reviews and meta-analyses or overviews and network meta-analysis\(^1,2\).

To gain a perspective on the absolute effectiveness of a treatment it is ideal to compare all the existing medications with placebo and for relative effects with each other in pairwise comparison trials. However, some of pairwise comparisons of the medications have not been tested within trials at all. Finally, even if some of the possible pairwise comparisons have been directly tested within trials not all may be eligible for inclusion in a network meta-analysis\(^1\). This leaves a gap between the research that has been done and the research that should or could have been undertaken and finding this highlights gaps in the fair testing of treatments\(^3\).

A two-arm trial will generate one pairwise comparison. A three-arm trial, however, will generate three, and a six-arm study, 15 pairwise comparisons. It is easy to lose track of how many comparisons one study can generate. This is more likely when it comes to the many direct, indirect or mixed comparisons within a network. This paper describes a simple formula for enumerating the possible number of comparisons within a single trial or planned network meta-analysis in advance.

Methods
The formula

The formula below solves this where \(n\) is the number of arms in a single study or network and \(N\) is the number of pairwise comparisons:

\[
N = \frac{n(n-1)}{2}
\]

Where \(n > 0\);

\(n\) is a natural number;

Then every intervention is compared to every other intervention except itself so: \(n^2(n-1)\);

Because \(N\) is a bidirectional comparison (\(X\) vs. \(Y\) = \(Y\) vs. \(X\)) so: \(n^2(n-1)/2\);

\(N\) is a triangular number.

A visual proof of a network of five interventions and \((5^2(5-1))/2=10\) pairwise comparisons is presented in Figure 1.

Adding any new intervention to the trial or network will create \(n-1\) new pairwise comparisons. For example, where there are 6 arms in a trial—or 6 nodes in network meta-analysis—there will be \((6^2(6-1))/2=15\) comparisons; adding a new intervention \((6+1=7)\) will create \(7-1=6\) new pairwise direct comparisons in

Figure 1. Network of five interventions and \((5^2(5-1))/2=10\) pairwise comparisons.
an individual trial and 6 direct or indirect comparisons in a network meta-analysis. Although this formula has been used for other purposes such as Metcalfe’s law in telecommunication, its use in the current context is novel.

Testing the formula: working back from existing network meta-analyses
We used the open data from our previously published network meta-analysis to re-create and enumerate the comparisons within the network. Using the direct comparisons reported in the trials within the network, we applied the formula and then compared the number of potential or expected comparisons (formula-derived) and the actual or observed number reported within the network analysis.

Results
Number of direct and indirect comparisons
We built a small study-based register based—thus avoiding the pitfall of multiple counting—containing all 133 included studies in our previous network meta-analysis. These trials reported comparisons from 8 interventions. Using our formula, 8 interventions should create 28 unique comparisons: \( \frac{8 \times (8-1)}{2} = 28 \) (Figure 2).

Reported comparisons within the trials
We extracted the separate intervention arms from the open data to re-create the direct comparisons from within trials. There trials had either two or three arms so each study could create either two or three comparisons. As a result the 133 studies had 163 comparisons, the majority of which were duplicated. After removing these duplicates, this created 16 unique direct comparisons with between 1 and 47 studies per comparison for 8 interventions (Table 1). These 16 observed comparisons are 57% of the 28 expected by use of the formula above.

Direct comparisons eligible for network meta-analysis
Among five networks reported in the final paper, the number of comparisons in these five network meta-analyses, however, varies from 6 (for 3 networks) to 11 (for 1 network) and 13 (for 1 network) (Figure 3). As visualized in Figure 3, only 21.42% to 46.42% of comparisons were eligible for pairwise meta-analysis (Table 2).

Comparisons in network meta-analysis plots
From Figure 3 we can calculate that about 42% of comparisons expected though use of the formula have not been tested directly in trials. This is a direct evidence-gap. The number of missing comparisons varies between nine out of 15 in three networks with six interventions, 17 out of 28 in one network with eight interventions, and 15 out of 28 in another network with eight interventions (Figure 3). However, all 28 comparisons expected by use of the formula were utilized and reported within the network meta-analysis. It is possible that some of the comparisons predicted by the formula would have been deemed ineligible—either by adherence to a network review protocol or though post hoc exclusions—but this was not the case in this particular review (Figure 4).

Discussion
This formula can be employed when estimating the total number of comparisons (direct and indirect combined) theoretically possible within a proposed network meta-analysis. It would be possible that there would sometimes be a discrepancy between...
| Comparison                              | Number of studies | Study tag                                                                 |
|----------------------------------------|------------------|---------------------------------------------------------------------------|
| Amphetamines vs. Atomoxetine           | 1                | Wigal 2005 (SLI381-404, NCT00506727)                                       |
| Amphetamines vs. Guanfacine            | 1                | Taylor 2001                                                               |
| Amphetamines* vs. Methylphenidate      | 6                | Coghil 2013 (SP489-325); Efron 1997; Plizka 2000; SPD489-405 (NCT0152915); SPD489-406 (NCT01552902); Stein 2011 (NCT00393042) |
| Amphetamines vs. Modafinil             | 1                | Taylor 2000                                                               |
| Amphetamines vs. Placebo               | 21               | Adler 2008b (NRP104.303, NCT00334880); Adler 2013 (SP489-403, NCT01101022); Biederman 2002 (SLI 381-301); Biederman 2007 (NRP104-301, NCT00248092); Biederman 2012 (2008P00971, NCT00801229); Coghil 2013 (SP489-325); Findling 2011 (SP489-305, NCT00735371); Frick 2017 (SP485-303, NCT01520222); Kay 2008a; Paterson 1999; Plizka 2000; Spencer 2001; SPD489-405 (NCT01552915); SPD489-406 (NCT0152902); Spencer 2006 (SLI381-314, NCT00507065); Spencer 2008 (SP486-301, NCT00150579); Stein 2011 (NCT00930042); Taylor 2000; Taylor 2001; Weisler 2006 (SLI381-303); Winhusen 2010 (NCT00253747) |
| Atropine vs. Guanfacine                | 1                | Hervas 2014 (SPD503-316, NCT01244490, EudraCT: 2010-018579-12)             |
| Atropine vs. Methylphenidate           | 8                | Bedard 2015 (NCT00183391); Newcorn 2008 (B4Z-MC-LYBI); Sangal 2006 (B4Z-US-LYAV); Schulz 2012; Spencer 2002a (B4Z-MC-HFBD); Spencer 2002b (B4Z-MC-HFBK); Wang 2007 (NCT00468083, B4Z-MC-LYBR (6834)); Weisler 2012 (NCT00880217) |
| Atropine vs. Placebo                   | 41               | Adler 2008a (B4Z-MC-LYBV, NCT0190931); Adler 2009a (B4Z-US-LYDQ, NCT0190979); Adler 2009b (B4Z-US-LYC); Adler 2013 (NRP10429091); Biederman 2002 (SLI381-301); Biederman 2007 (NRP104-301, NCT00248092); Biederman 2012 (2008P00971, NCT00801229); Coghil 2013 (SP489-325); Findling 2011 (SP489-305, NCT00735371); Frick 2017 (SP485-303, NCT01520222); Kay 2008a; Paterson 1999; Plizka 2000; Spencer 2001; SPD489-405 (NCT01552915); SPD489-406 (NCT0152902); Spencer 2006 (SLI381-314, NCT00507065); Spencer 2008 (SP486-301, NCT00150579); Stein 2011 (NCT00930042); Taylor 2000; Taylor 2001; Weisler 2006 (SLI381-303); Winhusen 2010 (NCT00253747) |
| Bupropion vs. Methylphenidate          | 2                | Jafarinia 2012; Moharari 2012 (IRCT201012295500N1)                         |
| Bupropion vs. Placebo                  | 4                | Casat 1989; Reimherr 2005; Wilens 2001; Wilens 2005 (NCT0048360)           |
| Clonidine vs. Methylphenidate          | 4                | Connor 2000; Kurlan 2002; Palumbo 2008 (NCT00031395); van der Meere 1999 |
| Clonidine vs. Placebo                  | 5                | Jain 2011 (NCT00565995); Kurlan 2002; Palumbo 2008 (NCT00031395); Singh 1995; van der Meere 1999 |
| Guanfacine vs. Placebo                 | 12               | Biederman 2008 (SPD503-301, NCT0152099); Connor 2010 (SPD503-307, NCT00367835); Hervas 2014 (SPD503-316, NCT01244440, EudraCT: 2010-018579-12); Kollins 2011 (SPD503-206, NCT00150592); McCracken 2016; NCT01069523; Newcorn 2013 (SPD503-304, NCT00150618); Palumbo 2008 (NCT00031395); van der Meere 1999 |
| Methyldopa vs. Modafinil               | 1                | Amir 2008                                                                 |
| Methyldopa vs. Placebo                 | 47               | Abikoff 2009; Adler 2009c (CR011560, NCT00326391); Biederman 2006a (subsample of NCT00181571); Biederman 2008 (EudraCT: 2010-018579-12); Kollins 2011 (SPD503-206, NCT00150592); McCracken 2016; NCT01069523; Newcorn 2013 (SPD503-314, NCT0097984); Ruginu 2014 (NCT0156051); Salee 2009 (SPD503-304, NCT00150618); Schahill 2001 (NCT0004376); Taylor 2001; Wilens 2015 (SPD503-312, EUDRACT2011-002221-21, NCT01081132) |
| Modafinil vs. Placebo                  | 8                | Arnold 2014 (C1538/2027/AD/US, NCT00315276); Biederman 2005 (Study 311 Cephalon); Biederman 2006b; Greenhill 2006a (Study 309 Cephalon); Kahbazi 2009; Ruginu 2003; Swanson 2006; Taylor 2000 |

* Amphetamines include Lisdexamfetamine.
Figure 3. Direct and indirect comparisons in the network meta-analysis of 8 interventions for primary outcome. (Dark lines are eligible comparisons for pairwise meta-analysis, added dotted blue lines show indirect comparisons). This image has been modified from Cotes et al. 2018 under Creative Commons Attribution License (CC BY).
Table 2. Comparisons from the body of evidence.

| Source of comparisons | Type of comparisons | Eligibility for analyses | # of comparisons | % of comparisons |
|-----------------------|---------------------|--------------------------|------------------|------------------|
| Formula               | √                   | √                        | 28               | 100.00           |
| Randomised trials     | √                   | ×                        | 16 (Table 1)     | 57.14            |
| Pairwise meta-analysis| √                   | ×                        | 6-13 (Figure 3)* | 21.42 to 46.42   |
| Network meta-analysis | √                   | √                        | 28 (Figure 2)    | 100.00           |

* There are five networks in Figure 3 and each has 6, 11, or 13 eligible comparisons. Three out of 16 comparisons from trials have not been included in any of five network plots.

The number of comparisons theoretically possible and those actually employed within any given network meta-analysis. The formula would highlight this for researchers and readers, before and after analyses, facilitate descriptions of why particular comparisons have not been included.

**Conclusion**

The formula produces an accurate enumeration of the potential comparisons within a single trial or network meta-analysis.

Any shortfall between the full potential of the data and the actual number of comparisons within a network meta-analysis should be possible to explain through reference to pre-stipulated eligibility criteria or post hoc exclusions.

**Data availability**

The data analyzed in the present study have been published previously.

**Grant information**

The authors declared that no grants were involved in funding this work.

**References**

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   PubMed Abstract | Publisher Full Text | Free Full Text
This is a useful paper for demonstrating and discussing how an established formula could be used for calculating all possible pairs of comparisons for interventions in a network meta-analysis. Thus, reviewers would be able to find out how many potential comparisons have not been carried out.

I have some minor suggestions numbered from 1) to 4):
1. In the abstract the following sentence should be amended for clarity perhaps as follows: “A total of 133 trials included in the network generated 163 comparisons (16 unique direct comparisons for 8 interventions)” Amendment: “A total of 133 trials of 8 interventions were selected which included 163 comparisons. The network of these showed 16 unique direct comparisons.”.
2. On page 2, it says that N is a triangular number. Either this point is not relevant, or why being a triangular number is important should be described.
3. I think they should say that the formula they have used is an established formula from combinatorics for calculating number of pairs for a number of items in a set.
4. On page 3 under “Comparisons in network meta-analysis plots”, line 2 and line 11 “though” should be changed to “through”.

Is the work clearly and accurately presented and does it cite the current literature? Yes

Is the study design appropriate and is the work technically sound? Yes

Are sufficient details of methods and analysis provided to allow replication by others? Yes

If applicable, is the statistical analysis and its interpretation appropriate? Yes

Are all the source data underlying the results available to ensure full reproducibility? No source data required

Are the conclusions drawn adequately supported by the results? Yes
Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Systematic reviews and meta-analysis and secondary data analysis.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Julie Broderick  
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In my opinion, this is a novel approach which allows the quantification of comparators in trials and network meta-analyses. Following on from this, the comparators which are possible versus how many were reported can be discussed in further depth. This formula has great applicability in terms of network meta-analysis methodology which is still very much a developing area.

Some very minor points;

1. Please add a table which demonstrates the use of the formula to quantify how many comparators are possible for trials from 2 interventions up to 10.
2. Pg 3, paragraph with the heading 'Reported comparisons within the trials' - line 2 change 'there to 'the'.
3. Explanation of Figure 4 in text is not clear.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Yes

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Systematic reviews, overview methodology, physical activity in chronic disease
I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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