Number needed to treat: enigmatic results for exacerbations in COPD

Samy Suissa[1,2]

Affiliations: [1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, Montreal, QC, Canada. [2]Dept of Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada.

Correspondence: Samy Suissa, Centre for Clinical Epidemiology, Jewish General Hospital, 3755 Cote Ste-Catherine, H-461, Montreal, QC, H3T 1E2, Canada. E-mail: samy.suissa@mcgill.ca

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NNT to prevent COPD exacerbations: why published values for tiotropium and fluticasone/salmeterol are inaccurate http://ow.ly/FEW9W

The number needed to treat (NNT), a simple tool to quantify the effectiveness or harm of a treatment, has been used in several studies of treatment for chronic obstructive pulmonary disease (COPD) [1, 2]. It provides the number of patients that need to be treated with the study drug for a given period of time, relative to the comparator, to prevent one patient from having the outcome event, *e.g.* a COPD exacerbation. It thus becomes an attractive tool for indirectly comparing different treatments with respect to the same outcome.

Some puzzling values of the NNT have been reported for two popular inhaled treatments of COPD, the long-acting anticholinergic tiotropium and the fluticasone/salmeterol combination. A meta-analysis of 22 tiotropium trials involving over 23 000 COPD patients reported, in comparison with placebo, an NNT of 16 patients over 1 year with tiotropium to prevent one exacerbation [3]. Conversely, the TORCH (Towards a Revolution in COPD Health) trial of 6000 COPD patients reported an NNT of four patients over 1 year with the fluticasone/salmeterol combination in comparison with placebo, to prevent one exacerbation [4]. This remarkable four-fold difference in the NNT is particularly baffling in view of the largely comparable effectiveness of these two treatments in preventing exacerbations.

In this article, I will describe some methodological issues regarding the calculation of NNT that led to this puzzling inconsistency. I will also provide advice for the calculation of the NNT in the context of outcomes such as exacerbations.

The NNT measure

The NNT is calculated using the difference in the proportion of patients with an outcome event over a desired period of time when comparing treated with untreated. This difference represents the proportion of patients for whom the outcome was prevented due to the treatment. The inverse of this difference produces the NNT, namely the number of patients that need to be treated to prevent one patient with the outcome [1]. For example, a randomised trial that finds, after 1 year of treatment, an incidence of COPD exacerbation of 40% in the drug-treated group compared with 45% in the placebo group implies that the drug prevents 5% of treated patients from having an exacerbation that they would have had otherwise. This corresponds to an NNT of 20 (1/5% or 1/0.05), *i.e.* 20 patients need to be treated continuously for 1 year to prevent one patient from incurring an exacerbation.

The NNT has been shown to be highly informative in evaluating the balance between the risk and benefit of a drug. For example, the NNT was illuminating in weighing up the benefit of inhaled corticosteroids in

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preventing COPD exacerbations against their risk of inducing pneumonia [5, 6]. It was instrumental in illustrating that the NNT, by accounting for the net differences due to the effect of inhaled corticosteroids, can reveal that the risk may outweigh the benefit [5]. This was observed even if pneumonias are much less frequent than COPD exacerbations, and particularly so with longer-term usage [7]. The NNT measure to assess the risk–benefit of a drug is also used in other areas of medicine, such as the effect of low-dose aspirin use in preventing cardiovascular events *versus* causing gastrointestinal bleeding [8].

Thus, in view of the simplicity in calculating the NNT and its widespread use in medicine, it is puzzling that such major discrepancies in the computed NNT were reported when comparing drugs of generally similar effectiveness in the treatment of COPD, such as tiotropium and fluticasone/salmeterol.

The treatment period

The meta-analysis of the 22 tiotropium trials reported an NNT of 16 patients "over 1 year" with tiotropium [3]. However, the duration of follow-up in these trials varied from 3 to 48 months. The calculation of the NNT involved all 22 trials, using the proportion of patients with an exacerbation over the pooled data, irrespective of the study duration. Thus, the proportion of patients with an exacerbation was based on a mix of short (3-month) and long-term (48-month) trials. Yet, the reported NNT of 16 specified the time period as "1 year".

This meta-analysis could have restricted its analysis exclusively to the 1-year trials. Table 1 displays the calculated NNT after stratifying the 22 trials according to their duration of follow-up. It shows clearly the wide variability in the NNT for the different durations, with the NNT varying from 15 (for 9 and 12 months) to 250 (for 48 months). In particular, it shows that for the six 1-year studies, the proportion of patients with at least one COPD exacerbation is 37.4% under tiotropium compared with 44.2% under placebo, leading to an NNT over 1 year of 15 (*i.e.* 1/6.8%). Coincidentally, this estimate of 15 turns out to be practically equal to the reported value of 16 based on all 22 trials of variable duration.

Moreover, even for the so-called "1-year" trials, it is likely that the follow-up times varied between patients, so that the simple proportion of patients with the event can be inaccurate when computing the NNT. In this case, the Kaplan–Meier approach, which accounts for variable follow-up times, produces the more accurate incidence as a function of follow-up time, from which the desired time-point is taken for the calculation of the NNT [9]. Nevertheless, in the absence of access to the individual patient data to use the Kaplan–Meier approach in the meta-analysis, the proportion can be used as an approximation.

Repeated events

Rather than using the proportion of patients with at least one exacerbation, the TORCH trial computed the NNT using the mean number of exacerbations per year [4]. It is interpreted as the number of patients that need to be treated to prevent one "event" over a given time period, considering that patients can have multiple events during follow-up [2]. This variation of the NNT does not quantify the reduction in the number of patients with exacerbations, but rather in the number of exacerbations.

This alternative formula, called the event-based NNT, has been criticised primarily because the original formulation of the NNT was aiming at the prevention of one patient with the event rather than the prevention of one event, with the latter leading to oddities such as 0.5 subjects need to be treated for 1 year to prevent one exacerbation [10–12].

TABLE 1 NNT to prevent a COPD exacerbation, from different length trials of tiotropium compared with placebo

Trial duration months	Patients with ⩾1 COPD exacerbation %		NNT
	Tiotropium	Placebo	
3	11.4	12.8	72
6	25.4	31.0	18
9	38.0	45.1	15
12	37.4	44.2	15
24	43.0	39.4	Negative
48	67.8	68.2	250
Pooled data	37.7	44.2	16

NNT: number needed to treat; COPD: chronic obstructive pulmonary disease.

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TABLE 2 NNT to prevent a COPD exacerbation over 1 year of treatment with fluticasone/salmeterol compared with placebo, for each of the 3 years of follow-up in the TORCH trial [4]

Year of follow-up	COPD exacerbations per patient per year		NNT
	Fluticasone/salmeterol	Placebo	
1	2.4	4.5	0.5
2	1.3	1.6	3
3	1.0	1.2	5

NNT: number needed to treat; COPD: chronic obstructive pulmonary disease; TORCH: Towards a Revolution in COPD Health.

Nevertheless, this NNT measure can be used, although with some important assumptions. Foremost is that the rate of the outcome event must be constant over the study follow-up. Table 2 displays the annualised rates of exacerbation in the TORCH trial for each of the 3 years of follow-up [4]. It shows that the rates of COPD exacerbation vary substantially over the 3 years of the study, being higher in the first year and decreasing thereafter. As a result, the NNT values differ significantly, from 0.5 patients in the first year to five patients in the third year of the trial who need to be treated for 1 year to prevent one exacerbation.

Table 3 shows that the rate of COPD exacerbation can even vary further within each year of follow-up. The resulting NNT values range from 0.5 for the first 6 months of the trial to 20 for the last 6 months of this 3-year trial, with wide variation within each of the 3 years.

Tiotropium *versus* fluticasone/salmeterol

Although the studies reporting the NNT values of 16 patients for tiotropium and four patients for fluticasone/salmeterol both use the terminology to "prevent one exacerbation in 1 year", it is evident that the two NNT values are not comparable. Indeed, one is based on a proportion of patients with at least one exacerbation while the other is based on the number of exacerbations. Since the TORCH trial does not provide the proportion of patients with an exacerbation after 1 year of treatment, so not does allow a legitimate comparison with the tiotropium data, we can use the TRISTAN (TRial of Inhaled STeroids ANd long-acting β_2 agonists) trial of fluticasone/salmeterol, which provides the Kaplan–Meier curves for the time to the first exacerbation [13]. It shows that, at 1 year, the proportion of patients with an exacerbation is around 38% with fluticasone/salmeterol compared with 43% with placebo. Thus, the NNT to prevent one patient from incurring an exacerbation with fluticasone/salmeterol treatment over 1 year is 20 (1/5%).

Conclusion

The NNT is a useful measure to quantify treatment effectiveness and safety, and it is natural to compare the NNT values of two treatments used for the same indication. Here I have shown that the NNT values of 16 and four patients, to prevent one COPD exacerbation in 1 year with tiotropium and fluticasone/

TABLE 3 NNT to prevent a COPD exacerbation over different 6-month periods during follow-up from the TORCH trial of fluticasone/salmeterol compared with placebo [4]

Period of follow-up	COPD exacerbations per patient per 6-month period		NNT
	Fluticasone/salmeterol	Placebo	
First year			
First 6 months	3.4	1.5	0.5
Second 6 months	1.1	0.85	4
Second year			
First 6 months	0.85	0.65	5
Second 6 months	0.75	0.65	10
Third year			
First 6 months	0.75	0.55	5
Second 6 months	0.45	0.40	20

NNT: number needed to treat; COPD: chronic obstructive pulmonary disease; TORCH: Towards a Revolution in COPD Health.

salmeterol, respectively, are so discordant simply because they were incorrectly calculated. With the proper calculation, the NNT values were 15 and 20, to prevent one COPD exacerbation in 1 year with tiotropium and fluticasone/salmeterol, respectively, compared with placebo.

The reported four-fold difference in the NNT for the two treatments was rather startling in view of the many randomised trials that have shown largely similar effectiveness in terms of exacerbations. The first reason for this discrepancy is that the two were actually based on very different measures, one on the proportion of patients with an exacerbation, while the other on the number of exacerbations. The second reason is that trials of different durations, such as 3-month trials in the tiotropium meta-analysis, were used to estimate the NNT for "1 year" of treatment. Such extrapolation from 3-month trials to 1-year NNT is problematic.

The third reason is the variation in the rate of exacerbation over time with the "event-based" NNT. Indeed, the measure assumes that the rate of exacerbation is the same for each time period of the study. We showed that this was not the case in the 3-year TORCH trial, resulting in the NNT being as low as 0.5 for the first 6 months of the trial and as high as 20 in the last 6 months of the trial. Such variations in the results over time suggest that this "event-based" NNT measure, based on the number of exacerbations, should be used with great caution.

In conclusion, the NNT is a valuable measure that can be used to compare different treatments. However, in doing so, it is important to ensure that the measures permit a comparison of like with like and are correctly calculated.

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