



TAGNET BULLETIN

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EVIDENCED-BASED MEDICINE Part 3 Applying Research Evidence to Decision Making

Introduction

In the August 1998 issue of the TAGNet Bulletin we looked at "What is Evidenced Based Medicine" and "Appraising the Evidence". In this article we will look at applying the research evidence to decision making.

Evidenced Based Medicine (EBM) involves incorporating the best available research information in clinical decision making. The EBM process involves a number of steps:-

individual patient will be affected one needs to know the average effect of treatment and whether the effect varies according to patient and disease factors.

The estimation approach to statistical analysis aims to quantify the variable of interest and also the uncertainty in this estimate, by means of a **Confidence Interval (CI)**. This is usually a range of values that are on either side of the point estimate, and it is within this interval that we can be 95% sure that the

Welcome to the sixth edition of the TAGNet Bulletin. In this issue we continue our series on Evidence Based Medicine and how to apply the research evidence to clinical decision making.

- **IDENTIFY THE PROBLEM** - formulate a focused clinical question based on the patient's problem
- **FIND**- search the literature for the best research information addressing your question.
- **APPRAISE** -evaluate the evidence for validity (is it true) and relevance (how important is it)
- **ACT**- applying the information to patient care

The strength of the evidence (ascertained from the appraisal step) incorporates appropriateness of study design, quality of study design and reporting, and the statistical precision of the results. It is important to note that an acceptable level of **statistical** significance does not necessarily mean that the result is also **clinically** significant. The actual **size** of the observed treatment effect needs to be interpreted with respect to its clinical importance before deciding whether a particular treatment should be applied to patient care.

In applying the research evidence to decision making, all outcomes (both adverse and beneficial) that are influenced by an intervention and apply to a patient need to be taken into account. To estimate whether an

"true" value lies. The CI is based on the idea that if the same study were done with a different sample of patients, the results would not be identical, but would fall somewhere within that interval; the CI reflects this sampling variation and gives an idea of how "confident" we are about where the "true" value lies. The CI provides a measure of both the **precision** of study results (for making inferences about the population of all such patients) and also an indication of the size of the observed effect. In contrast, p values are not as informative because they do not provide any information on the **size** or even the direction of an observed effect.

The benefits or harms of interventions can be expressed in a number of ways. To compare risks associated with an intervention, there are several measures of association between exposure and disease that are commonly used:

- **Attributable risk (AR) or risk difference** is the incidence of disease in exposed persons, minus the incidence in nonexposed persons. It is the additional incidence of disease related to exposure, taking into account the background incidence of disease.

- **Relative risk (RR) or risk ratio is the ratio** of incidence in exposed persons to

incidence in nonexposed persons. If the **ratio is > 1** there is an **increased risk** associated with the exposure; if the **ratio is <1** there is **decreased risk** associated with exposure.

However, RR does not give an indication of the actual magnitude of absolute risk, and hence is not very helpful in deciding about the clinical importance of an observed association. Even with large RRs the absolute risk may be quite small if the disease or outcome of interest is uncommon. The attributable risk (AR) is a more meaningful expression of risk in most clinical situations.

• Odds Ratio (OR)

The odds ratio originated in case control studies (such as those of drug side effects and exposures to harmful agents). In these cases it is not possible to estimate relative risks directly, because the prevalence of the adverse outcome (required for calculating the relative risk) is not usually known. However the ratio of odds can be used when the prevalence of the event is unknown, either by

- comparing the odds of incurring an adverse event in the exposed group (a/b) and the control group (c/d);
- or by comparing the odds of exposure in the event (a/c) and nonevent groups (b/d)

Both lead to the same result- ad/bc- which will be >1 when the exposure is harmful.

Epidemiological studies generally try to identify factors that cause harm: those with odds ratios greater than 1. Clinical trials typically look for treatments which reduce event rates and which have odds ratios of less than one. Note that a percentage reduction in the odds ratios may be quoted instead of the odds ratio eg the ISIS-4 trials reported a 7% reduction in the odds of mortality with captopril rather than reporting an odds ratio of 0.93 .

Odds ratios have a number of advantages and disadvantages in their clinical application. Advantages are:

- 1.Odds ratios can always take values between zero and infinity, which is not the case for relative risk (the range that relative risk can take depends on the baseline event rate). Odds ratios continue to be used, mostly due to superior mathematical properties.
- 2.Odds ratios possess a symmetrical

property: if one reverses the outcomes in the analysis and looks at good rather than bad, the relationships will have reciprocal odds ratios.

3. If one needs to make adjustments for confounding factors using multiple regression, the correct approach when measuring event rates is to use logistic regression models which work in terms of odds and report effects as odds ratios.

The disadvantages are:

1. Few people (including clinicians) are adept at interpreting event rates which are reported in terms of odds.
2. In many trials, odds ratios are not similar to relative risks; when the outcome of interest is rare in the population (often the reason for case-control studies) the odds ratio closely approximates the relative risk. The difference between the two values increases as the event rate rises.
3. Odds ratios cannot be used in the same simple way as relative risk reduction to calculate the corresponding NNTs (see below) for the treatments of interest. The clinician must employ standard formulae¹ or adopt a nomogram for conversion of ORs to RRs.²

Note that the relative risk and odds ratios do not tell us how frequently an event occurs, only that the event occurs more or less often in the experimental versus the control group.

• Relative Risk Reduction (RRR)

The most commonly reported measure of treatment effect in clinical trials is the Relative Risk Reduction (RRR). It is a measure of the proportional reduction in rates of bad outcomes between experimental and control subjects; where EER is the experimental event rate and CER is the control event rate, RRR is calculated as (EER – CER) / CER. The greater the RRR the more effective the therapy.

However it should be noted that relative risk reduction does not reflect the magnitude of the observed effect well and thus does not provide the best guidance about the clinical relevance of the result.

• Absolute Risk Reduction (ARR)

ARR is another means of expressing the impact of treatment. It is the absolute arithmetic difference between the experimental event rate (EER) and the

control event rate (CER), ie ARR= EER- CER (ignoring any minus sign that arises from this subtraction) .

The advantage of the ARR is that it does give an indication of clinical relevance. For example, an ARR of 1% in incidence of nausea with a new drug would not be clinically significant, even if in terms of RRR there is a 50% reduction (eg 2% to 1%).

• Absolute Risk Increase

ARI is the absolute arithmetic difference in rates of bad outcomes between experimental and control patients in a trial ie ARI= EER-CER.

• Number Needed to Treat (NNT)

This is a another way of describing the benefit a treatment may confer. It may be defined as the number of patients who need to be treated to achieve one additional favourable outcome, and is the reciprocal of the absolute risk reduction ie

$$NNT = \frac{1}{ARR}$$

• Number Needed to Harm (NNH)

The number of patients who, if they received the experimental treatment, would lead to one additional patient being harmed, compared with patients who received control treatment. It is the reciprocal of the ARI

$$NNH = \frac{1}{ARI}$$

In making a decision about the overall merits of any therapy, information about both NNT and NNH need to be taken into account. Even if these results are not reported in the published trial, they can be calculated from a knowledge of the EER (incidence of an outcome in the intervention group) and CER (incidence of an outcome in the placebo group) which are usually reported.

Example

To illustrate these points we can look at a therapeutic example, “do the more selective COX 2 inhibitors cause less serious GI toxicity?”, using data from the recently published head to head RCTs - CLASS and VIGOR. These trials evaluated the clinical outcomes of symptomatic ulcers, upper GI perforations and bleeding in patients with rheumatoid arthritis and osteoarthritis. (See Table 1)

Table 1: Major outcomes in order of most to least serious from CLASS¹ and VIGOR² trials

Outcome	Celecoxib %	Other* %	RR 95%CI	ARR %	NNT 4 mo	Rofecoxib %	Naproxen %	RR 95%CI	ARR ARI %	NNT NNH 9 mo
Myocardial infarction	0.3	0.3	0.9 0.4-2.1	NS	NS	0.4	0.1	4.0 1.3-12	0.3	333
Complicated ulcers	0.3	0.6	0.6 0.3-1.2	NS	NS	0.4	0.9	0.4 0.2-0.8	0.5	200
Serious adverse events	4.3	4.2	1.02 0.8-1.3	NS	NS	NR	NR			
Symptomatic ulcers	0.5	0.7	0.65 0.4-1.2	NS	NS	1.0	2.1	0.5 0.3-0.7	1.1	91
Withdrawals due to adverse events	18.4	20.6	0.89 0.8-0.97	2.2	44	16.4	16.1	1.02 0.9-1.1	NS	NS

This table is reproduced with kind permission from the Therapeutics Letter Issue 39, Jan/Feb 2001

* Half ibuprofen and half diclofenac

RR=Risk Reduction

CI=confidence Interval

ARR=Absolute Risk Reduction

NNT=Number Needed to Treat to prevent one event

ARI=Absolute Risk Increase

NNH=Number Needed to cause one Harmful event

NS=Non-Significant

NR=Not Reported

¹ Silverstein FE, Faich G, Goldstein JL. Gastrointestinal toxicity with celecoxib versus nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. JAMA 2000; 284:1247-1255.

² Bombardier C, Laine L, Reicin A, for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; 343:1520-8

For complicated ulcers, the relative risk for rofecoxib was 0.4% as compared with naproxen 0.9%. The absolute risk reduction is 0.5%, corresponding to *NNT of 200 ie for every 200 patients treated, there would be one prevented from suffering a complicated ulcer*. However, it can be seen that 0.4 % of patients taking rofecoxib had myocardial infarctions as compared to 0.1% patients on naproxen, which equates to a relative risk of 4 for rofecoxib- one is four times more likely to suffer a myocardial infarction with rofecoxib than naproxen. The absolute risk increase is 0.3%, which translates to *NNH of 333, ie for every 333 patients treated one additional patient would suffer a myocardial infarction*.

References

1. McQuay HJ, Moore RA. Using numerical results from systematic reviews in clinical practice. Ann Intern Med 1997; 126: 712-720.
2. Zhang J, Yu KF. What's the relative risk? JAMA 1998; 280: 1690-91.

Internet resources on Evidence Based Medicine

General
McMaster University Site (Canada)
<http://hiru.mcmaster.ca>

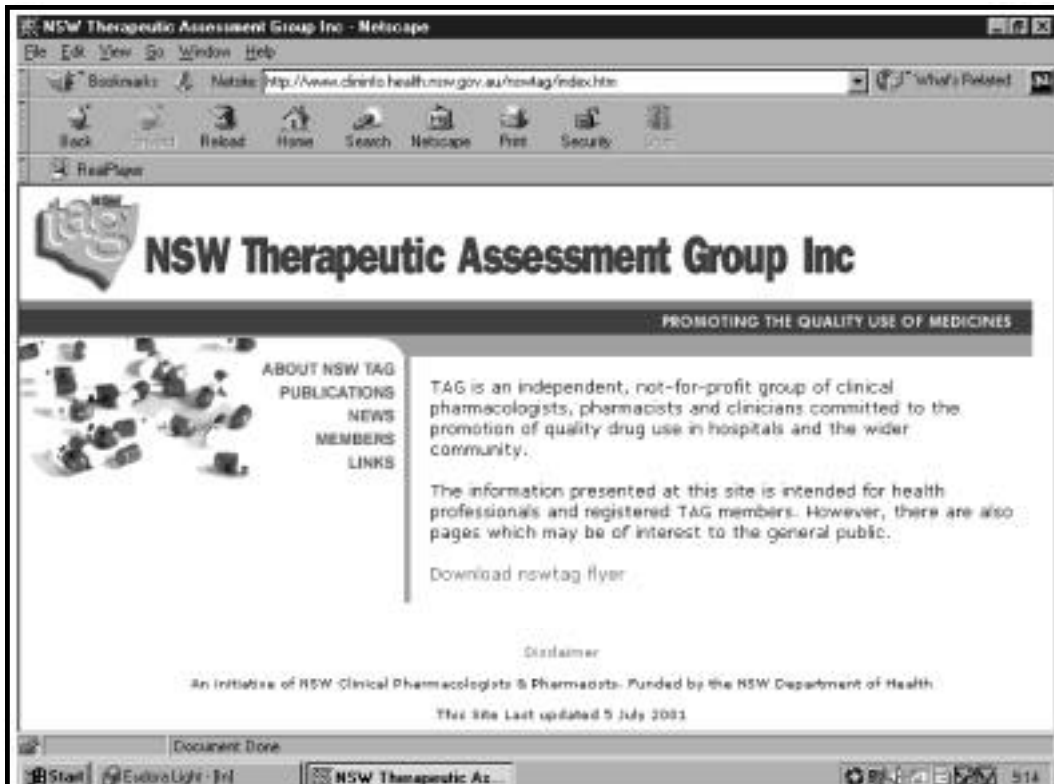
Users guides to the medical literature etc
Centre for Evidence based Medicine (Oxford)
<http://cebm.jr2.ox.ac.uk>

Scharr Netting the Evidence
A comprehensive bibliography of EBM resources
<http://www.shef.ac.uk/~scharr/ir/netting>

Guidelines National Health and Medical Research Council. (Australia)
www.health.gov.au/nhmrc/publicat/contents.htm

Other resources

User's guides to the medical literature: a series of articles published in JAMA. For details please contact the TAG office.



The NSW TAG Website

The NSW TAG Website is hosted within the Clinical Information Access Project (CIAP) Site of NSW Health.

The site may be accessed either by entering the URL for NSW TAG: www.nswtag.org.au

or through the Clinical Information Access Project (CIAP) site of NSW Health: www.clininfo.health.nsw.gov.au

Resource Documents

Since the publication of the 5th TAGNet Bulletin (August 2000) a number of new resource documents have been released.

They are:

- sevoflurane
- antiplatelet therapies
- COX-2 Inhibitors
- mycophenolate
- thrombolysis following acute myocardial infarction

The full documents, including an executive summary can be found at the TAG website



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