

The evidence-relevance gap – the example of hormone replacement therapy

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SYNOPSIS

Bridging the gap between scientific evidence and what is relevant for each patient is challenging. The ‘evidence-relevance’ gap is particularly apparent with the plethora of public information available about hormone replacement therapy, and where the patient expects concise and practical advice from a professional she knows and trusts. We need to recognise the limitations of clinical trials and consider the outcomes in absolute terms, then interpret the relevance to the patient. The relief of symptoms should be pursued on its own merits. The long-term benefits still need clarification with more research evidence.

Index words: evidence-based medicine, consumers, drug information.

(*Aust Prescr* 2002;25:60–2)

Introduction

‘Should I take HRT?’ is a common question in general practice. What we actually tell our patients about hormone replacement therapy (HRT) is dependent upon many factors. A key factor is the evidence about benefits and harm, but equally important are the patient’s symptoms, current knowledge, expectations and attitude to medical interventions. The challenge for the clinician is to bridge the gap between scientific evidence and what is relevant to the individual seeking advice.

There are two key perspectives when considering HRT:

- relief of menopausal symptoms
- long-term benefits.

Symptom relief

The advice about HRT should be relatively simple. A trial for 2–3 months will ascertain whether the flushes, vaginal dryness, fatigue or other symptoms are relieved. The patient can decide herself if she feels better or worse, and whether the effort and any adverse effects are acceptable or not. Having reflected on the phenomena of coincidence and placebos, the clinician can decide with the patient whether or not to continue. The duration of further treatment can be decided over the course of time, with some consideration of the long-term benefits and adverse effects.

Long-term benefits

A totally different approach is needed when considering the long-term benefits. An *Australian Prescriber* editorial said, ‘With all the caveats about the weaknesses of observational data, these data are all we can use when advising a woman about the potential risks and benefits of long-term HRT. Until the results of [further trials] are available it is not possible to make general recommendations for the duration of treatment’.¹ I would suggest that even when these major trials are completed the challenge of turning the evidence into relevant advice would remain.

Interpreting the relevance of clinical trials

The word ‘significant’

Statistical significance refers to a mathematical variable, a ‘p’ number, e.g. $p < 0.05$. This is a measure of the unlikelihood of an observation being due to co-incidence or wishful thinking. There is a frequent double play on this word in medical literature. A ‘highly significant’ result from a research trial should not be used to imply clinical significance.

Clinical relevance

Real-life outcomes determine relevance, not surrogate end-points such as bone mineral density or serum cholesterol. What is important to the patient is the reasonable likelihood of relieving or preventing some suffering. Surrogate end-points may have some relationship to morbidity in other contexts, but it is important for any medical intervention to be justified on the basis of human suffering prevented or relieved.

The dilution to irrelevance effect

Researchers have the habit of looking to a bigger trial for answers to difficult or previously unanswered questions. To seek statistical significance with larger sample sizes is in fact an implication of irrelevance for each individual. If you cannot show an effect in 1000 people, how relevant is a trial that needs 20 000 to achieve statistical significance? The pooling of data from multiple trials by meta-analysis has a similar goal, and therefore a similar weakness.

Consumer factors

When advising our patient about HRT we have to consider their views as well as the evidence.

Consumer effort

The ‘effort and bother of it all’ is largely unmeasured in clinical trials, where individuals are enrolled for the cause of research, and ongoing participation is encouraged and supported by the whole process of a trial. General practitioners who know their patients well, will understand the ‘effort and bother’ of starting any long-term medical intervention. The daily consumption of medication, the monthly visit to the pharmacy, and the six-monthly visit to the doctor are all burdens which can be substantial for some patients. Similarly, the so-called minor adverse effects such as weight gain and breast soreness are quite real for the sufferer. Furthermore, concern can arise that any new symptom might be related to the treatment, and this leads to further monitoring or investigation. The effort involved is well illustrated by the not infrequent plea, ‘Do I really have to take these tablets, Doctor?’ Finally, a general practitioner can sometimes anticipate that the compliance required is beyond the likely effort of the patient, especially when the goal is prevention rather than symptom relief.

Consumer attitude to risk

It is presumed that the consumer wants to worry about risk. Some will and some will not. An Australian study which assessed patients’ attitudes to HRT, thrombolysis and coronary artery bypass surgery concluded, ‘Patients do not view favourably the risk:benefit ratio of three surveyed medical interventions’.² This conclusion shows a difference between evidence-based medicine and consumer attitude. Similarly consumer attitude is often related to fear and preconceptions and every clinician knows how easy it is to induce anxiety.

Facts of life

Cancer, heart attack, or dementia will get us all one day. How hard should we try to avoid one to score another? Similarly with significant comorbidity or reduced life expectancy (e.g. multiple sclerosis or dementia), how relevant is long-term drug therapy that simply changes the odds of an unlikely event?

What advice can we give about long-term HRT?

I believe it is fruitful to examine data from the perspective of actual outcomes. Although the data may change a little when future trials are completed, the question will remain – how relevant will the change in outcome be to the patient?

While every woman is different, there are two main answers to questions about HRT.



Patient: ‘Should I take HRT, Doctor?’
 Doctor: ‘Do you have symptoms?’
 Patient: ‘Yes.’
 Doctor: ‘You will probably feel better. Give it a go.’

Patient: ‘Should I take HRT, Doctor?’
 Doctor: ‘Do you have symptoms?’
 Patient: ‘No.’
 Doctor: ‘Do you want to be as well as possible in 20 years, and do not mind 20 years of medication, and understand there may be both benefits and harms?’
 If yes: ‘Give it a go.’
 If no: ‘Leave well alone.’



Table 1

The outcome for 100 60-year-old women over 10 years

New event	No treatment	With HRT	Events per 100 treated		Notes
			Prevented	Caused	
Heart disease (angina, acute myocardial infarction, cardiovascular death)	10	7	3		Cholesterol 6.0, HDL 1.1, blood pressure 130/80, non-smoker, no pre-existing ischaemic heart disease ³ If pre-existing ischaemic heart disease – no benefit at all ⁴
Symptomatic fracture	3.2	1.6	1.6		Bone density loss is slowed by HRT, but is only a modest predictor of fracture ⁵ Many trials measure vertebral fracture, ² / ₃ of which are radiographic and asymptomatic ⁶
Breast cancer	2.5	3.2		0.7	Incidence not mortality ⁷
Venous thromboembolism	2.3	6.2		3.9	The impact on deep vein thrombosis/pulmonary embolism is very certain ⁸

Notes

- The improved outcome in heart disease and fracture are optimistic estimates of relative risk reduction.
- To extrapolate beyond 10 years may show more benefit, but equally plausible is more harm.

In Table 1 I have collated some data from major clinical trials. It presents the approximate outcome data for 100 60-year-old women over a period of 10 years.

The pertinent observation here is that the actual number of patients whose outcome is changed is actually rather small. The pertinent question is how relevant are these harms and benefits, considering the effort involved, to the patient seeking my advice?

There is a case to dismiss the long-term benefits of HRT, not because of lack of evidence, but because they might just be irrelevant. If a woman seeks advice about the benefits and risks of long-term HRT, the absolute long-term outcome data should be considered. Some women wanting detailed information about HRT could be presented with the absolute data; many others will trust their doctor explicitly. What we tell them will depend on our understanding of the evidence and our knowledge of the patient. Unfortunately it is not as simple as saying, ‘There is significant (statistical) evidence of benefit’, or worse, ‘All women should take HRT’.

Conclusion

The advice to patients about hormone replacement therapy needs to be carefully considered. As discussed in the previous *Australian Prescriber* editorial, the clinical trials have limitations.¹ There are also limitations in translating the evidence from trials to advice given and the ‘real world’. The benefit of relieving symptoms speaks for itself. The change in long-term outcome, both beneficial and harmful, is relatively small, and considering consumer factors, may well be irrelevant for many.

REFERENCES

1. MacLennan AH. Long-term hormone replacement therapy. *Aust Prescr* 2000;23:90-2.
2. Fitzgerald SP, Phillipov G. Patient attitudes to commonly promoted medical interventions. *Med J Aust* 2000;172:9-12.

3. Anderson KM, Wilson PW, Odell PM, Kannel WB. An updated coronary risk profile. A statement for health professionals. *Circulation* 1991;83:356-62.
4. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. HERS Research Group. *JAMA* 1998;280:605-13.
5. National Prescribing Service. Hormone replacement therapy – is the evidence in? *NPS News* Oct 2000;12:1-2.
6. Jones G, Nguyen T, Sambrook PN, Kelly PJ, Gilbert C, Eisman JA. Symptomatic fracture incidence in elderly men and women: the Dubbo Osteoporosis Epidemiology Study (DOES). *Osteoporos Int* 1994;4:277-82.
7. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;350:1047-59.
8. Grady D, Wenger N, Herrington D, Khan S, Furberg C, Hunninghake D, et al. Postmenopausal hormone therapy increases risk for venous thromboembolic disease: the Heart and Estrogen/progestin Replacement Study. *Ann Intern Med* 2000;132:689-96.

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