therapeutics letter
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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

Twenty-Five Pearls from 25 years (part 1)

The Therapeutics Initiative is celebrating its 25th anniversary this year, in part by highlighting key conclusions from the 120 issues of the Therapeutics Letter published so far. In this first of a 2-part series we present 13 "clinical pearls" found in Letters published between 1994 and 2005.

1 Thiazides are clearly the drug of first choice for the treatment of uncomplicated hypertension

Drugs of choice in the treatment of hypertension [Jun 1995, issue 7]. This conclusion was based on a hierarchy of outcomes, which 24 years ago we defined as effectiveness (morbidity and mortality outcomes), blood pressure lowering efficacy, tolerability (adverse effects), convenience and cost. It is fascinating to appreciate that our conclusions have not changed since 1995. In ***Using best evidence in the management of hypertension*** [May-Jun 2017, issue 106] we concluded **"Low-dose thiazide diuretics are the best drug class for starting therapy."**

2 In many clinical settings start with a dose that is ¼ to ½ the manufacturer's recommended starting dose

Dose titration: minimize to maximize [Oct 1995, issue 10]. Introductory doses are frequently too high, therefore, it is often prudent to titrate doses, which can reduce the chance of adverse effects as well as cost.

3 Until randomized trials testing menopausal hormone therapy are completed, long-term therapy decisions have to be made in the face of uncertainty, balancing the potential benefits and risks in individual patients

Menopausal hormone therapy [May-Jul 1996, issue 14]. Subsequent randomised trials in 2002 (WHI/ HERS2) resulted in our follow-up Letter, ***Menopausal combined hormone therapy update*** [Oct-Dec 2002, issue 46]. We concluded that **"long-term combined hormone therapy leads to more harm than good in menopausal women, whether they are healthy or have coronary artery disease."**

4 Fewer physicians and patients will choose a therapy when the data is presented as absolute risk reduction (ARR) and number needed to treat (NNT) than if it is presented as relative risk (RR) or relative risk reduction (RRR)

Evidence based drug therapy. What do the numbers mean? [Aug-Oct 1996, issue 15]. In this Letter we explained how clinicians and patients should use RCT data to make the most informed decisions. We also discussed the processes we use to compile the evidence that is presented in the Therapeutics Letters.

5 Patients with "mild" symptoms of benign prostatic hyperplasia (BPH) should be reassured and do not need any treatment

Medical management of benign prostatic hyperplasia [May-Jun 1997, issue 19]. This Letter concluded that "watchful waiting" is the best initial strategy rather than drug therapy and that before using any drug, it's important to develop a clear treatment goal with the patient. Subsequently, ***Benign prostatic hypertrophy: An update on drug therapy*** [Jan-Mar 2006, issue 58] provided more detailed information about the magnitude of the benefits and harms of alpha blockers and 5-alpha reductase inhibitors.

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6 Exercise and weight loss are effective in preventing and treating type 2 diabetes

Management of type 2 diabetes [Jan-Mar 1998, issue 23]. Nothing has changed the strong recommendations for exercise and weight loss made back in 1998 and while we have published a number of other Letters on type 2 diabetes, and more are planned in the near future, evidence for optimal drug management remains elusive.

7 For primary prevention the likelihood of benefit is considerably less than for secondary prevention

Lipid lowering therapy [Apr-May 1998, issue 24]. In this Letter, the first of many on statins, we demonstrated why it's important to distinguish between trials of patients who have established coronary artery disease (secondary prevention) where therapy shows some benefit versus trials involving patients with no evidence of such disease (primary prevention) where treatment has minimal effect in most populations.

8 Since almost all clinical data about celecoxib remain unpublished and is therefore unavailable for critical appraisal and assessment, it is impossible for the TI to provide timely unbiased information to you and other health professionals

Celecoxib (Celebrex): Is it a breakthrough drug? [Aug-Sep 1999, issue 31]. When celecoxib was launched as the first Cox-2 selective inhibitor, we were concerned that the clinical trials, leading to the regulator's decision to approve the drug, were not published and not available for scrutiny by independent assessors.

9 COX-2 selective NSAIDS were associated with the same incidence of serious adverse events as non-selective NSAIDS

Selective COX-2 inhibitors: Are they safer NSAIDs? [Jan-Feb 2001, issue 39]. In this Letter we reiterated the importance of using a hierarchy of outcomes to assess the net health effect of an intervention. **"The best measure of overall safety, serious adverse events, is a required outcome of all clinical trials. This category includes death, life-threatening events, events leading to or prolonging hospitalization, and cancers."**

10 Esomeprazole at equivalent doses offers no therapeutic advantage over other PPIs (including omeprazole)

Do single stereoisomer drugs provide value? [Jun-Sep 2002, issue 45]. We also concluded "The concept that a single enantiomer of a chiral drug may be preferable to a racemic mixture is intellectually appealing. However, in most instances this strategy has not been demonstrated to confer any clinical advantage."

11 Because of the unfavourable harm to benefit balance for antidepressants in individuals less than 19 years of age, first line therapy is multiple supportive interventions: sleep hygiene, exercise, regular dietary patterns, consistent parenting and practical problem-solving regarding schooling and life stressors

Antidepressant medications in children and adolescents [Apr-Jun 2004, issue 52]. At that time no antidepressants were approved in Canada for individuals less than 19 years of age.

12 Product monographs do not adequately inform clinicians

Rofecoxib (Vioxx) withdrawal generates uncertainty about "COX-2s". Do product monographs adequately inform? [Jul-Oct 2004, issue 53]. The rofecoxib monograph did not provide a complete picture of the risk of myocardial infarction and total serious adverse events for rofecoxib. On the positive side we noted that sometimes product monographs provide harm data including serious adverse events that are not published elsewhere.

13 Donepezil has not been demonstrated to improve outcomes of importance to patients and caregivers (e.g. institutionalization or disability)

Drugs for Alzheimer's Disease [Apr-Aug 2005, issue 56]. Similarly, rivastigmine, galantamine and memantine have not been studied in terms of these important outcomes. It also concludes that acetylcholinesterase inhibitors cause gastrointestinal, muscular and other adverse effects and likely increase serious adverse events.

The draft of this Therapeutics Letter was submitted for review to 130 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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