GP Research Review™

Making Education Easy

Issue 141 – 2019

In this issue:

Abbreviations used in this issue
ACE = angiotensin-converting enzyme
AE = adverse event
AKI = acute kidney injury
ARB = angiotensin receptor blocker
BP = blood pressure
CKD = chronic kidney disease
COPD = chronic obstructive pulmonary disease
CVD = cardiovascular disease
HR = hazard ratio
ICS = inhaled corticosteroid
ICD-10 = International Classification of Diseases, 10th revision
LABA = long-acting β-agonist
LABA = long-acting muscarinic antagonist
NSAID = nonsteroidal anti-inflammatory drug
OR = odds ratio
RCT = randomised controlled trial
RR = relative risk
SNRI = serotonin-norepinephrine reuptake inhibitor
SSRI = selective serotonin reuptake inhibitor
UTI = urinary tract infection
VAS = visual analogue scale

Welcome to issue 141 of GP Research Review.

In one of the papers in this issue, long-term data from the large, multinational Prospective Urban Rural Epidemiology (PURE) study appear to contradict globally accepted dietary guidelines recommending restriction of whole-fat dairy products. The saturated fats in these products are believed to adversely affect lipid levels and increase the risk of CVD. Interestingly, the evidence from the PURE study is from low- and middle-income countries, whereas almost all previous research has been from developed Western countries. PURE found lower rates of CVD and mortality amongst people who consumed >2 daily servings of dairy products compared with people with lower intakes, leading the study researchers to suggest that CVD rates might improve in countries with low milk intake if they consume dairy products.

Our Natural Health section describes encouraging research findings from a large cohort of French adults in whom a higher organic food score, reflecting a higher frequency of organic food consumption, was associated with a reduced risk of cancer. Organic food consumption therefore appears to have very important benefits, although it is unfortunate that for many people, the high prices of such foods make them unaffordable in comparison to corresponding conventional products.

I hope you enjoy this issue and I welcome your comments and feedback.

Kind regards,
Jim

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Goodfellow Gems

Depression in the elderly

While depression is more common in young people, in older people it is associated with more functional and cognitive impairment and carries significant costs for the family and health system.[1] People over 70 years of age experience greater symptom severity than younger people and are more likely to have a diagnosis of depression after 2 years.

Persistent severe depression is associated with the onset of dementia.

There is a paucity of trials on medication or talk therapy in those over 75 years. Medication has increased risk of falls and seizures.

Carers are important therapeutically and in terms of progress and relapse but risk getting stressed.

The authors recommend focussing on physical functioning, sustained support, psychosocial functioning and greater community support. Suicide is an issue in the infirm elderly and removing lethal means such as medication, gardening poisons and guns is worth considering.

Reference: Depression in older adults BMJ 2018. Click here

Gems are chosen by the Goodfellow director Dr. Bruce Arroll to be either practice changing or practice maintaining. The information is educational and not clinical advice. www.goodfellowunit.org/gems

Mirtazapine added to SSRIs or SNRIs for treatment resistant depression in primary care: phase III randomised placebo controlled trial

Authors: Kessler DS et al.

Summary: This UK study recruited 480 adults aged ≥18 years diagnosed with treatment-resistant depression after using an SSRI or SNRI for ≥6 weeks in primary care. At study entry, all participants had scores of ≥14 on the Beck Depression Inventory, second revision (BDI II) and satisfied ICD-10 criteria for depression. As well as their usual SSRI or SNRI treatment, the patients were randomised to mirtazapine (n=241) or placebo (239) and were followed-up at 12, 24, and 52 weeks. At the primary 12-week follow-up, evaluable data from 431 (89.8%) study participants revealed a lower mean BDI II score among mirtazapine recipients than among placebo recipients (18.0 vs 19.7), with an adjusted difference between means of −1.83 (p=0.09). However, the study researchers point out that as the confidence interval includes the null and the most likely (mean) effect is small, clinical benefit is unlikely. Moreover, mirtazapine was associated with a higher rate of AEs and a lower rate of treatment adherence compared with placebo.

Comment: I certainly agree with the author's concern about the "what next" option in a number of conditions that demonstrate no improvement with treatment and where evidence of further effective treatment options is limited. The treatment of non-responding depression is certainly one of these. This paper looked at the addition of mirtazapine to the regime of non-responsive depressed patients already on an SSRI (e.g. fluoxetine) or an SNRI (e.g. venlafaxine). There was no evidence of benefit from the addition of mirtazapine.

Reference: BMJ. 2018;363:k4691
Abstract

Triple therapy in the management of chronic obstructive pulmonary disease: systematic review and meta-analysis

Authors: Zheng Y et al.

Summary: These researchers identified 21 RCTs published up to April 2018 comparing the rate of moderate-to-severe exacerbations between triple therapy (a LAMA, LABA and ICS) and dual therapy or monotherapy in patients with COPD. Patients administered triple therapy had a significantly reduced rate of moderate or severe exacerbations compared with those on LAMA monotherapy (RR 0.71; 95% CI, 0.60 to 0.85), LAMA and LABA (RR 0.78; 95% CI, 0.70 to 0.88), or ICS and LABA regimens (RR 0.77; 95% CI, 0.66 to 0.91). Triple therapy was also associated with significant improvements in trough FEV_1 and health-related quality of life as compared with either dual therapy or monotherapy. According to the researchers, triple therapy had a reassuring overall safety profile, although it was associated with an increased risk of pneumonia compared with dual LAMA and LABA therapy (RR 1.53; 95% CI, 1.25 to 1.87).

Comment: It seems that triple therapy is becoming more established in the treatment of moderate-to-severe COPD. While the jury is still out, this meta-analysis comes down on the side of triple therapy (LAMA, LABA and ICS) as compared with LAMA monotherapy, dual LAMA and LABA, or dual ICS and LABA. While the objective gains were modest, there was a reduction in exacerbation rate at the expense of an increase in incidence of pneumonia as compared with the dual LABA and LAMA group. There was, however, no evidence of an increase in mortality with triple therapy as a result of the pneumonia.

Reference: BMJ. 2018;363:k4388
Abstract

Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study

Authors: Dehghan M et al.

Summary: The multinational Prospective Urban Rural Epidemiology (PURE) study examined the associations between total dairy and specific types of dairy products (milk, yoghurt and cheese; grouped by whole- and low-fat dairy) with mortality and major CVD for 136,384 individuals aged 35–70 years from low- and middle-income countries. The study period was from 1 January 2003 through 14 July 2018. The primary outcome was the composite of mortality or major CV events (defined as death from CV causes, non-fatal myocardial infarction, stroke, or heart failure). Over a mean 9.1 years of follow-up, 10,567 composite events (deaths [n=6,796] or major CV events [n=5,855]) were recorded. Compared with no dairy intake, a higher intake of total dairy (>2 servings/day) significantly lowered the risk of the composite outcome (HR 0.84; 95% CI, 0.75 to 0.94; p=0.0004), total mortality (HR 0.83; 95% CI, 0.72 to 0.96; p=0.0052), non-CV mortality (HR 0.86; 95% CI, 0.72 to 1.02; p=0.046), CV mortality (HR 0.77; 95% CI, 0.58 to 1.01; p=0.029), major CVD (HR 0.78; 95% CI, 0.67 to 0.90; p=0.0001) and stroke (HR 0.66; 95% CI, 0.53 to 0.82; p=0.0003); no such significant association was seen with myocardial infarction (HR 0.89; 95% CI, 0.71 to 1.11; p=0.163). Higher intakes (>1 serving vs no intake) of milk (HR 0.90; 95% CI, 0.82 to 0.99; p=0.0529) and yogurt (HR 0.86; 95% CI, 0.75 to 0.99; p=0.0051) also lowered the risk of the composite outcome, whereas no association was seen between cheese intake and the composite outcome (HR 0.88; 95% CI, 0.76 to 1.02; p=0.1399). Butter intake was low and not significantly associated with clinical outcomes (HR 1.09; 95% CI, 0.90 to 1.33; p=0.4113).

Comment: Difficult to comment on this one, as the study outcome flies in opposition of "accepted" doctrine. The authors of this study were numerous and included Uncle Tom Cobley and all. I was unable to access the funding source, but noted that the countries involved were low- to middle-income, so overall nutritional status needs to be taken into account. Nonetheless, it raises the question as to whether "accepted" doctrine is yet another sacred cow (no pun intended with the title of this paper) and clearly we need some more and extended research.

Reference: Lancet. 392(10161):2288-97
Abstract

Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

Benefits and harms of antihypertensive treatment in low-risk patients with mild hypertension

Authors: Sheppard JP et al.

Summary: These researchers analysed data from the UK Clinical Practice Research Datalink for the period from 1 January 1998 through 30 September 2015 involving 19,143 patients aged 18–74 years with low-risk mild hypertension (untreated BP of 140/90 to 159/99 mm Hg) and no previous treatment who were administered antihypertensives within 12 months of diagnosis. They were matched 1:1 by propensity score with patients who were not prescribed such treatment. A Cox proportional hazards regression analysis of data from a median 5.8 years of follow-up failed to show any association between antihypertensives and mortality (HR 1.02; 95% CI, 0.88 to 1.17) or between antihypertensives and CVD (HR 1.09; 95% CI, 0.95 to 1.25). Antihypertensives increased the risk of AEs, including hypotension (HR 1.69; 95% CI, 1.30 to 2.20; number needed to harm at 10 years [NNH10], 41), syncope (HR 1.28; 95% CI, 1.10 to 1.50; NNH10, 35), electrolyte abnormalities (HR 1.72; 95% CI, 1.12 to 2.65; NNH10, 111) and acute kidney injury (HR 1.37; 95% CI, 1.00 to 1.88; NNH10, 91).

Comment: The diagnosis of hypertension is a very important one. If incorrect, it may doom the patient with unnecessary treatment, which can be lifelong. The decision to treat does not entirely rest on the absolute BP but is multifactorial, including – among other things – smoking history, family history, lipid levels, of course BP, and patient preferences, after being given an understanding of the risk. This study showed that treatment of mild hypertension provided no benefit over a relatively short timeframe (5.8 years) and in fact the treatment itself markedly increased the risk of AEs.

Reference: JAMA Intern Med. 2018;178(12):1626-34
Abstract

Association of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use with outcomes after acute kidney injury

Authors: Brar S et al.

Summary: This retrospective analysis obtained data from Canada's Alberta Kidney Disease Network population database to assess whether use of an ACE inhibitor or ARBs within 6 months after hospital discharge improves outcomes for patients with AKI. The analysis included 46,253 hospitalised adults aged ≥18 years with an AKI episode (defined as a 50% increase between prehospital and peak in-hospital serum creatinine concentrations) between 1 July 2008 and 31 March 2015. Around half (n=22,193) of the patients were prescribed an ACE inhibitor or ARB within 6 months of hospital discharge. In analyses adjusted for comorbidities, preadmission use of ACE inhibitors or ARBs, demographics, baseline kidney function, other factors related to index hospitalisation, and use of health care services before hospitalisation, mortality was lower after 2 years amongst the patients who received an ACE inhibitor or ARB compared with those who did not (adjusted HR 0.85; 95% CI, 0.81 to 0.89). However, ACE inhibitors and ARBs were associated with a higher risk of hospitalisation for a renal cause (adjusted HR 1.28; 95% CI, 1.12 to 1.46). There was no association between ACE inhibitors or ARBs and progression to end-stage renal disease.

Comment: One could say that the outcome of this study was a draw! After AKI, those prescribed either ACE inhibitors or ARBs had a marginally reduced mortality over 2 years (HR 0.85), but they had a higher risk of hospitalisation from a renal cause (HR 1.28). Probably a win to active treatment with one or the other agent, providing a close eye is kept on the renal function.

Reference: JAMA Intern Med. 2018;178(12):1681-90
Abstract

Efficacy of low-dose amitriptyline for chronic low back pain: a randomized clinical trial

Authors: Urquhart DM et al.

Summary: This Australian trial randomised 146 adults (mean age, 54.8 years) with chronic, nonspecific, low back pain to receive low-dose amitriptyline (25 mg/day) or benztropine mesylate (1 mg/day) for 6 months. Four-fifths (81%) of the cohort completed 6 months of follow-up. Pain intensity was assessed at 3 and 6 months using VAS and Descriptor Differential Scale scores. Low-dose amitriptyline was not associated with greater pain reductions over benztropine mesylate at either 3 months (adjusted difference, –1.05) or at 6 months (adjusted difference, –7.81). Although low-back disability (as assessed by the Roland Morris Disability Questionnaire) was significantly improved with low-dose amitriptyline compared with benztropine mesylate at 3 months (adjusted difference, –1.62; p=0.01), this significant difference did not persist at 6 months (adjusted difference, –0.98; p=0.18). An assessment of work absence and hindrance with the Short Form Health and Labour Questionnaire found no between-group differences in outcomes at 3 months (ORs for work absence, 0.86 and work hindrance, 0.78), or at 6 months (ORs for work absence, 1.51 and for work hindrance, 0.53). Nine patients in each group discontinued the study because of treatment-related AEs ($\chi^2 = 0.004$; p=0.95).

Comment: A mixed result for the use of amitriptyline in low back pain – reduction of disability at 3 months, but no significant pain improvement at 3 months and an insignificant one at 6 months. This was a small study, and the daily dose was modest (25 mg). The authors are correct in stating that based on this study, amitriptyline may be an effective treatment for chronic low back pain.

Reference: JAMA Intern Med. 2018;178(11): 1474-81
Abstract

Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections: a randomized clinical trial

Authors: Hooton TM et al.

Summary: This single-centre, open-label trial randomised 140 healthy women (mean age, 35.7 years) with recurrent cystitis (≥3 episodes in the previous year) drinking <1.5 L of fluid/day to drink, in addition to their daily fluid intake, 1.5 L of water daily (water group) or no additional fluids (controls) for 12 months. During the study period, 111 cystitis episodes were reported by women in the water group compared with 216 episodes in the control group (mean, 1.7 vs 3.2, respectively; p<0.001). Fewer antimicrobial regimens were used to treat cystitis episodes in the water group compared with the control group (mean, 1.9 vs 3.6; p<0.001); corresponding mean time intervals between cystitis episodes were 142.8 and 84.4 days, respectively (p<0.001). At 12 months, the water group had higher mean urine volume measurements (1.4 vs 0.1 L; p<0.001), more frequent voids (2.4 vs –0.1; p<0.001) and lower urine osmolality (–402.8 vs –24.0 mOsm/kg, respectively; p<0.001), compared with controls.

Comment: Recurrent "urinary tract infections" or symptoms of cystitis are not an uncommon presentation in my practice. On most occasions, (when I do them), cultures are negative. This study demonstrates a dramatic reduction in episodes of this unpleasant condition, which is also verified by the reduction in antimicrobials prescribed. Increased water intake – way to go!

Reference: JAMA Intern Med. 2018;178(11):1509-15
Abstract

Frequency and associations of prescription nonsteroidal anti-inflammatory drug use among patients with a musculoskeletal disorder and hypertension, heart failure, or chronic kidney disease

Authors: Bouck Z et al.

Summary: Using data from a population-based Ontario healthcare claims database, this Canadian research group identified 2,415,291 musculoskeletal-related primary care consultations made between 1 April 2012 and 31 March 2016 by 814,049 older adults (mean age, 75.3 years) with hypertension, heart failure, or CKD. NSAIDs were prescribed in 224,825 (9.3%) of the consultations. Among the 7,365 primary care physicians in this analysis, the median physician-level prescribing rate was 11.0%. When the researchers examined the association of prescription NSAID use with safety-related outcomes between 8 and 37 days after each consultation in a sample of 35,552 matched patient pairs, each consisting of an exposed and nonexposed patient matched on the logit of their propensity score for prescription NSAID use (exposure), they found similar rates of cardiac complications (any emergency department visit or hospitalisation for CVD; 0.8% vs 0.8%), renal complications (any hospitalisation for hyperkalaemia, AKI, or dialysis; 0.1% vs 0.1%) and death (0.1% vs 0.1%), respectively. Rates of CV and renal safety-related outcomes did not differ between exposed and nonexposed patients (0.9% vs 0.8%; absolute risk difference, 0.0003; 95% CI, –0.001 to 0.002; p=0.74).

Comment: This is a large study that challenges yet another sacred cow, at least with short-term NSAID use. NSAIDs have long been contraindicated in elderly patients with cardiac conditions including heart failure, and CKD. In this study, after receiving a script for a NSAID, patients were observed for 1 month after use, and there was no difference seen in cardiovascular and renal safety-related outcomes as compared with patients who did not have such a prescription. This flies against current recommendations and is somewhat reassuring at least in the short-term, when one just has to prescribe an NSAID, as there is little in the way of alternatives.

Reference: JAMA Intern Med. 2018;178(11):1516-25
Abstract

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Independent commentary by Associate Professor Jim Reid.

Jim Reid has a private family medicine practice at the Caversham Medical Centre, Dunedin, New Zealand. He is a Distinguished Fellow of the Royal New Zealand College of General Practitioners and is also a Fellow of the American College of Chest Physicians.
For full bio CLICK HERE.

EVIDENCE-BASED NATURAL HEALTH
by Dr Chris Tofield

Lactobacillus rhamnosus GG versus placebo for acute gastroenteritis in children

Authors: Schnadower D et al.

Summary: In this study, 971 children aged 3 months to 4 years (median age, 1.4 years) presenting with acute gastroenteritis to one of 10 US paediatric emergency departments were randomly assigned to receive a 5-day course of *Lactobacillus rhamnosus* GG at a dose of 1×10^{10} colony-forming units twice daily or matching placebo. The primary outcome of moderate-to-severe gastroenteritis (defined as an illness episode with a total score of ≥9 on the modified Vesikari scale within 14 days after enrolment) was reported in 11.8% of the *L. rhamnosus* GG group and in 12.6% of the placebo group (RR 0.96; 95% CI, 0.68 to 1.35; p=0.83). Similarly, outcomes did not differ significantly between *L. rhamnosus* GG-treated children and placebo recipients in regard to the duration of diarrhoea (median, 49.7 h vs 50.9 h; p=0.26), duration of vomiting (median, 0 h in each group; p=0.17), daycare absenteeism (median, 2 days in each group; p=0.67), or the rate of household transmission (defined as the development of symptoms of gastroenteritis in previously asymptomatic household contacts; 10.6% vs 14.1%, respectively; p=0.16).

Comment: Probiotics are one of the most commonly studied natural supplements and intuitively it makes sense that they may help in acute gastroenteritis. However, apparently not so for *L. rhamnosus* GG, which was found to be ineffective in treating acute gastroenteritis in preschool children in this study. However, with over 800 published research papers on *L. rhamnosus* GG, this shouldn't detract from other potential benefits of this probiotic.

Reference: N Engl J Med. 2018;379:2002-14
Abstract

Association of frequency of organic food consumption with cancer risk: findings from the NutriNet-Santé Prospective Cohort Study

Authors: Baudry J et al.

Summary: This French investigation explored the association between organic food consumption and the risk of cancer amongst 68,946 adults (mean age at baseline, 44.2 years) with available information on the consumption frequency (never, occasionally, or most of the time) of 16 labelled organic food products and dietary intake between 2009 and 2016. The 16 components were summed to provide an organic food score (ranging from 0 to 32 points), modelled as quartiles. During a mean 4.56 years of follow-up, 1,340 first incident cancer cases were identified; these were most often breast cancers (n=459), prostate cancers (n=180), skin cancers (n=135), colorectal cancers (n=99), non-Hodgkin lymphomas (n=47) and other lymphomas (n=15). In Cox proportional hazards regression analysis adjusted for potential cancer risk factors, high organic food scores were inversely and significantly associated with the overall risk of cancer (HR for quartile 4 vs quartile 1, 0.75; 95% CI, 0.63 to 0.88; p=0.001; absolute RR, 0.6%; HR for a 5-point increase, 0.92; 95% CI, 0.88 to 0.96).

Comment: Have you sometimes wondered whether paying extra for organic food results in proven health benefits? Well, this is the first study I've come across that looked at this issue and it found in favour of eating organically. Eating organic food resulted in a small reduction in the incidence of cancer in the nearly 70,000 French participants followed. While this study is a good start, there are doubtless other advantages of eating food grown or made without pesticides, preservatives, artificial flavours, colourings, etc., but this will have to be addressed in future research.

Reference: JAMA Intern Med. 2018;178(12):1597-606
Abstract

Dr Christopher Tofield
Dr Tofield completed his medical training at St Bartholomew's and the Royal London Hospital in London. He now works part time in general practice in Tauranga, is involved with clinical research, has published several medical papers and a textbook on pharmacology, and is clinical advisor to Bay of Plenty District Health Board. **For full bio CLICK HERE.**