Welcome to issue 100 of GP Research Review.

Shaun Holt propositioned me in the Koru Club in Auckland about a concept he had, called Research Review, some eight years ago; I had no idea that it would still be running – I had no idea that it would now have over 5500 subscribers and would be something I still thoroughly enjoy doing. Although it is supported by industry advertising never once in the 100 editions has there been any editorial compromise, or editorial requirements. My comments are completely my own.

So where to from here? That Research Review for General Practice has 5688 subscribers as it is, is a disincentive to make radical change. Nonetheless, lack of change can mean lack of progress. From this issue we are including Goodfellow Gems, practice changing or maintaining information selected by Dr Bruce Arroll, Director of the Goodfellow Foundation. And from next month, another new feature called “Trips, Traps and Tricks” will be added. This will be a short section that basically can include anything, including, but not necessarily to do with, medicine. It could include travel, medicine of course, wine, food – anything that could be of general interest. I would request you to send me anything relevant.

So, onwards and upwards for the next 100!!!!

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

Kind Regards
Jim

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Independent commentary by Associate Professor Jim Reid.

Jim Reid graduated in medicine at the University of Otago Medical School in Dunedin New Zealand. He had previously trained as a pharmacist. He undertook his postgraduate work at the University of Miami in Florida. Currently he is Head of Rural Health and Deputy Dean of the School at the Dunedin School of Medicine. He has a private family medicine practice at the Caversham Medical Centre, Dunedin, New Zealand. For full bio CLICK HERE.

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Sore throat in primary care project: a clinical score to diagnose viral sore throat

Authors: Mistik S et al.

Summary: These investigators from Turkey describe their new scoring system for diagnosing viral sore throat in primary care patients. The study aimed to determine the rate of bacterial and viral causes and to demonstrate seasonal variations. Over a 52-week period, 624 throat cultures for group A β-haemolytic streptococci (GABHS) and nasopharyngeal swabs were obtained from patients who presented to primary care. Almost half of the patients (n=277; 44.3%) had a viral infection and GABHS infection was diagnosed in 116 patients (18.5%). An infectious cause was identified in 356 patients (57.1%). Rhinovirus was the most commonly detected infectious agent overall (highest in November, 34.5%) and the highest GABHS rate was in November (32.7%). Analysis of data provided a scoring system, termed the Mistik Score, for the diagnosis of viral sore throat. The predictive model for positive viral analysis included the following variables: absence of headache, stuffy nose, sneezing, temperature of ≥37.5°C on physical examination, and the absence of tonsillar exudate and/or swelling.

Reference: Fam Pract. 2015;32(3):263-8

Abstract

Adherence and medication utilisation patterns of fixed-dose and free combination of angiotensin receptor blocker/thiazide diuretics among newly diagnosed hypertensive patients: a population-based cohort study

Authors: Hsu CI et al.

Summary: This study analysed data from Taiwan’s National Health Insurance Research Database to determine rates of adherence and persistence among newly diagnosed hypertensive patients using fixed-dose (FDC) and free combinations (FC) of angiotensin receptor blocker (ARB)/thiazide diuretics. Adherence was measured by medication possession ratio (MPR) and persistence by time from day of initiation to treatment discontinuation. The adjusted MPRs were all significantly higher among the FDC cohort compared with the FC cohort (6 months: 66.55% vs 63.86%, respectively; 1 year: 52.58% vs 46.73%, respectively; 2 years: 42.66% vs 32.45%, respectively; p<0.001 for all comparisons). Patients receiving FDC therapy were less likely to discontinue their therapy. The adjusted MPRs were all significantly higher among the FDC cohort compared with the FC cohort (6 months: 66.55% vs 63.86%, respectively; 1 year: 52.58% vs 46.73%, respectively; 2 years: 42.66% vs 32.45%, respectively; p<0.001 for all comparisons). Patients receiving FDC therapy were less likely to discontinue their therapy (adjusted HR 0.79; 95% CI, 0.74 to 0.85).

Comment: For New Zealand, the conclusion should read: “The Mistik Score MAY be useful to diagnose viral sore throat in some parts of New Zealand”. While in many places, the most common cause of sore throat is viral, in others, strep throat is common, and the consequences of missing it are much greater. The probability of positive viral analysis on a Mistik score of 5 was 82%. In this study, approximately 17% of participants were shown to have group A strep infection and the risk of missing this on score alone is high. Swab is still the gold standard in this country. As an aside, for someone who has practiced in the south of NZ for over 30 years, I have only seen one case of rheumatic fever, and have never seen a strep-induced glomerulonephritis.


Abstract
Comparative safety of testosterone dosage forms

Authors: Layton JB et al.

Summary: In order to determine the comparative cardiovascular safety of testosterone injections, patches, and gels, these researchers retrospectively analyzed data from 3 cohorts: administrative claims from a US cohort of commercially insured men (1 January 2000 to 31 December 2012), a random sample of Medicare claimants (1 January 2007 to 31 December 2010) and general practitioner records from the UK (1 January 2000 to 30 June 2012). The entire analysis comprised 544,115 men aged ≥18 years who had initiated use of testosterone patches (6.9%), gels (55.8%), or injections (37.4%) following 180 days with no testosterone use. The men were followed for up to 1 year for cardiovascular and cerebrovascular events including myocardial infarction (MI), unstable angina, stroke, and composite acute event (MI, unstable angina, or stroke), venous thromboembolism (VTE), mortality, and all-cause hospitalisation. The majority of men in the Medicare cohort were injection initiators (51.2%), most in the US commercially insured population were gel initiators (56.5%), while the UK database included equal proportions of injections and gel users (approximately 41%). Compared with men using gels, injection initiators had a greater risk of cardiovascular events (i.e. MI, unstable angina, and stroke) (hazard ratio [HR] 1.26; 95% CI, 1.18 to 1.35), hospitalisation (1.16; 1.13 to 1.19), and death (1.34; 1.15 to 1.56) but not VTE (0.92; 0.76 to 1.11). Compared with gels, patches were not associated with any increased risk for cardiovascular events (HR 1.10; 0.94 to 1.29), hospitalisation (1.04; 1.00 to 1.08), death (1.02; 0.77 to 1.33), or VTE (1.08; 0.79 to 1.47).

Comment: Testosterone is one of the agents “in the gun” at present with high interest from a number of patients eager to treat perceived “andropause”. Google is full of sites on the subject and when a man is seeking the prescription of such. Put simply, gels and patches are much safer than injection, and in contrast with the latter did not confer increased hazards of cardiovascular events, hospitalisation, or death. Neither agent increased VTE.

Reference: JAMA Intern Med. 2015;175(7):1187-96

The new lipid guidelines: What do primary care clinicians think?

Authors: Jamé S et al.

Summary: Outcomes are reported from an Internet-based pilot survey of practicing primary care clinicians within the San Francisco Bay Area Collaborative Research Network in March 2014, who were questioned on their awareness, attitudes, and practices relating to the newly released 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Prevention of Primary and Secondary Atherosclerotic Disease. The survey also explored obstacles to implementation and suggestions for improving shared decision-making. Of 600 clinicians who were invited to participate, 183 responded to the survey. Of those respondents, 176 (96%) were aware of the guidelines. The majority (64%) reported implementing the new guidelines with at least some of their patients; a quarter (25%) reported adopting the guidelines for many of their patients. Disagreeing with the guidelines was the main obstacle to adoption.

Comment: Development of guidelines is easy, and a guideline in one developed country, with minor limitations, is like all the others. What is difficult is their uptake and implementation, especially in primary care. The cost of development is considerable and most funding is spent in this direction, the result being a complicated and detailed document, comprising many pages. GPs find these interesting and place them on the must-read-sometime pile. They remain there indefinitely – sometime for most never comes! What is needed for GPs is a two-A4-page clear, concise summary, preferably laminated! What I want to know is what is being recommended, why is it being recommended (brief authoritative evidence), and how I implement the recommendations. If guidelines were presented in such a way, uptake in primary care would be much higher.

Reference: Am J Med. 2015;128(8):914.e5-914

Erectile dysfunction and undiagnosed diabetes, hypertension, and hypercholesterolemia

Authors: Skeldon SC et al.

Summary: This US investigation examined data from men aged ≥20 years who participated in the National Health and Nutrition Examination Survey during 2001–2004. Erectile dysfunction was determined by a single, validated survey question. Logistic regression analyses investigated the relationship between erectile dysfunction and undiagnosed cardiometabolic risk factors. In multivariate adjusted analyses, men with erectile dysfunction had more than double the odds of having undiagnosed diabetes (odds ratio [OR] 2.20; 95% CI, 1.10 to 4.37); no such association was found for undiagnosed hypertension or undiagnosed hypercholesterolaemia. For the average man aged 40–59 years, the predicted probability of having undiagnosed diabetes increased from 1 in 50 in the absence of erectile dysfunction to 1 in 10 in the presence of erectile dysfunction.

Comment: Erectile dysfunction (which as readers will realise is not uncommon) is 5 times more common in men with undiagnosed diabetes than those without. I do hope that with this information, pharmacy (to which erectile dysfunction medication has been released) will undertake routine HbA1C assessment on all new patients requesting such medication. Knowing the outcome of this study, I certainly will be doing so on patients who consult me.


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REF: 1. Pharmaceutical Schedule. 2. Seebri Breezhaler Data Sheet. 3. Onbrez Breezhaler Data Sheet. ONB0715-015 SEED715-016 10PCH4461 BGA150011

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Beta-blocker use and 30-day all-cause readmission in Medicare beneficiaries with systolic heart failure

Authors: Bhatia V et al.

Summary: Until this study, it was unknown whether the initial negative inotropic effect of beta-blocker medications would lead to early hospital readmission in patients with systolic heart failure and reduced ejection fraction. This analysis identified 3067 Medicare beneficiaries discharged alive from 106 Alabama hospitals between 1998 and 2001 with a diagnosis of heart failure and ejection fraction <45%. 2202 of these patients had not been receiving beta-blocker therapy when they were admitted to hospital; 383 were subsequently discharged with a prescription for a beta-blocker. Propensity scores were used to assemble a matched cohort of 380 pairs of patients receiving and not receiving beta-blockers who were balanced on 36 baseline characteristics. The matched patients had a mean age of 73 years and mean ejection fraction of 27%; 45% were women and 33% were African American. Beta-blocker use was not associated with 30-day all-cause readmission (HR 0.87; 95% CI, 0.64 to 1.18) or heart failure readmission (HR 0.95; 95% CI, 0.57 to 1.58), but was significantly associated with lower 30-day all-cause mortality (HR 0.29; 95% CI, 0.12 to 0.73). Over a 4-year post-discharge period, discharge prescription of beta-blockers was associated with lower mortality (HR 0.81; 95% CI, 0.67 to 0.98) and with the combined outcome of all-cause mortality or all-cause readmission (HR 0.87; 95% CI, 0.74 to 0.97), without higher 30-day readmission (HR 0.89; 95% CI, 0.76 to 1.04).

Comment: This paper reinforces the appropriate use of beta-blockers with systolic heart failure — those discharged on these agents had lower mortality at 30 days, and this extended to 4 years, with respect to mortality and readmission. Beta-blockers seem now to be the way to go — consult the guidelines!!!


Abstract

An audit on the appropriate use of faecal calprotectin testing within the Taranaki DHB: a case for a more discerning approach

Authors: Lance S, White C

Summary: As these researchers explain, the correct use of faecal calprotectin testing can be extremely useful in excluding inflammatory bowel disease (IBD). However, due to poor specificity, inappropriate use can lead to a number of unnecessary investigations. This audit aimed to determine the current rate of request of faecal calprotectin testing within the Taranaki DHB during the 6-month period from 1 July 2013 to 31 December 2013, to determine the clinical indications for requesting this test, and the outcomes for the patients involved. Of 206 patients who were identified, 75 were excluded due to inadequate clinical information. Of the remaining 131 patients, 49 (37%) did not benefit. Twenty-nine (22%) of the patients avoided further investigation with a negative result. Of the 11 patients with a known history of IBD, only 1 subsequently had a colonoscopy (91% avoided invasive investigation with a negative result). A strong correlation was observed between very high invasive investigation with a negative result (HR 0.89; 95% CI, 0.76 to 1.04).

Comment: Faecal calprotectin is not an inexpensive test, and it is useful to either confirm or exclude IBD and differentiate between this and irritable bowel syndrome (IBS). A single faecal calprotectin of <60 μg/g is a good negative predictor for inflammatory change but it does not help determine the cause of inflammation. The message — useful, but consider the cost and be selective.


Abstract

Goodfellow Gems

“Pentoxifylline effective for venous leg ulcers and simvastatin may also work”

A Cochrane review of pentoxifylline (Trental) 400mg TDS, with and without compression, found it to be effective for healing or significantly improving venous leg ulcers.1 This is based on 11 randomised trials and the numbers needed to treat were 5. This is an option for those who do not tolerate compression and is of good quality evidence. The second study randomised 66 patients to 40 mg of simvastatin or placebo. The authors report that over 50% of leg ulcers completely healed at 10 weeks.2

This study has been criticised as being too good to be true with a large effect size in a small study.3 There are larger trials being conducted but results are not available. Simvastatin may be an option when all else had failed for this sometimes difficult to treat condition as it is a relatively safe medication.

References:

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.goodfellowlearning.org.nz/gems
Benzodiazepine use and risk of Alzheimer’s disease: case-control study

Authors: de Gage SB et al.

Summary: Data from the Quebec health insurance programme database (RAMQ) was used to identify a random sample of 1796 community-dwelling people aged ≥66 years with a first diagnosis of Alzheimer’s disease or were first prescribed benzodiazepines between 2000 and 2009, at least 5 years before the study started. Using the same database, these patients were matched with 7184 controls on sex, age group, and duration of follow-up. Exposure to benzodiazepines was categorised according to the cumulative dose expressed as prescribed daily doses (1–90, 91–180, >180) and the drug elimination half-life (short [<20 h] vs long ≥20 h). Benzodiazepine ever-use was associated with an increased risk of Alzheimer’s disease (adjusted OR 1.51; 95% CI, 1.36 to 1.69); this finding was not markedly altered after further adjustment for anxiety, depression, and insomnia (1.43; 1.28 to 1.60). No association was found for a cumulative dose <91 prescribed daily doses. The strength of association increased with exposure density (OR 1.32 [95% CI, 1.01 to 1.74] for 91–180 prescribed daily doses and 1.84 [1.62 to 2.08] for >180 prescribed daily doses) and with the drug half-life (1.43 [1.27 to 1.61] for short-acting drugs and 1.70 [1.46 to 1.98] for long-acting ones).

Comment: This study shows that if a person older than 66 years has ever taken benzodiazepines then they seem have an increased risk of 1.5 times for Alzheimer type dementia. However, this risk increases with exposure density – the longer it is prescribed the greater the risk, which is also higher with long-acting agents (diazepam and nitrazepam) as compared with those with short half-lives (triazolam and midazolam). The message – use only as compared with those with long half-lives (diazepam and nitrazepam) prescribed the greater the risk, which is also higher.

Reference: BMJ. 2014;349:g5205

Supplementation with a blend of krill and salmon oil is associated with increased metabolic risk in overweight men

Authors: Albert BB et al.

Summary: In this study, 47 men (mean age 46.5 years) who were overweight (body mass index 25–30 kg/m²) but otherwise healthy received krill-salmon oil supplementation in the form of five 1-g capsules daily or a control (canola oil) for 8 weeks; after an 8-week washout period, they crossed over to the other treatment. The primary outcome was insulin sensitivity, assessed by the Matsuda method from an oral-glucose-tolerance test. According to the Matsuda index, insulin sensitivity was 14% lower with the KS oil than with the control oil (p=0.049). In a mediation analysis, after controlling for the likely positive effects of blood eicosapentaenoic acid and docosahexaenoic acid (i.e. the omega-3 index), the reduction in insulin sensitivity after KS-oil supplementation was more marked (27% lower than with the control oil; p=0.009).

Comment: Increasingly, krill oil is seen as the next step up from cod liver oil in terms of quality and health benefits. However, according to this NZ/Australian study, a krill/salmon oil combination led to reduced insulin sensitivity in overweight men. Probably not a good choice for our type 2 diabetic patients then. Still, I would like to see further research before giving up on krill oil.


Crude garlic extract inhibits cell proliferation and induces cell cycle arrest and apoptosis of cancer cells in vitro

Authors: Bagul M et al.

Summary: This paper reports outcomes from a series of experiments that examined the effects of crude garlic extract (CGE) on the proliferation of human breast, prostate, hepatic, and colon cancer cell lines and mouse macrophageal cells. The human cancer cell lines included hepatic (Hep-G2), colon (Caco-2), prostate (PC-3), and breast (MCF-7) cells, which were propagated at 37°C in a 5% CO₂ in air atmosphere, using the ATCC-formulated RPMI-1640 medium and 10% fetal bovine serum (FBS). The mouse macrophage cell line (TIB-71) was propagated at 37°C in a 5% CO₂ in air atmosphere using the ATCC-formulated DMEM and 10% FBS. All cells were plated at a density of ~5000 cells/well. After overnight incubation, the cells were treated with 0.125, 0.25, 0.5, or 1 µg/mL of CGE for a further 72 h. Inhibition of cell proliferation of 80–90% was observed for Hep-G2, MCF-7, TIB-71 and PC-3 cells, but only 40–55% for the Caco-2 cells when treated with 0.25, 0.5, or 1 µg/mL. In a co-culture study of Caco-2 and TIB-71 cells, inhibition of cell proliferation of 90% was observed for Caco-2 cells compared with 40–55% when cultured separately. When PC-3 cells were treated with GCE at a dose of 0.5 or 1 µg/mL, the cell cycle was arrested and caspase activity (apoptosis) was increased by 4-fold.

Comment: Garlic is already famed for its effects on cardiovascular health, and now it seems cancer may well be added to the list. This research studied effects of garlic on cells of three of the top four cancers- colon, prostate and breast- and found significant inhibition of cell proliferation, cell cycle arrest and apoptosis. Pretty impressive for a scraggly little plant that grows in the wild.


Dr Christopher Tofield

Dr Tofield completed his medical training at St Bartholomew’s and the Royal London Hospital in London and is now a fulltime General Practitioner in Tauranga. Chris has extensive experience in medical writing and editing and while at medical school published a medical textbook on pharmacology.

For full bio CLICK HERE.

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