GP Research Review™

Making Education Easy

Issue 122 – 2017

In this issue:

Abbreviations used in this issue
AED = anti-epilieptic drug
COPD = chronic obstructive pulmonary disease
HR = hazard ratio
MI = myocardial infarction
OA = osteoarthritis
OR = odds ratio

Welcome to issue 122 of GP Research Review.

One of the papers in this issue reports a 17-fold higher risk of an acute myocardial infarction (MI) in the 7 days following a respiratory tract infection. Moreover, the study evidence showed that the increased risk of MI peaks in the first week and reduces thereafter, but remains elevated for up to a month. The study researchers call for further studies to identify preventative strategies that could lower this risk, particularly in those who may be more susceptible.

Magnesium supplements are commonly used for nocturnal leg cramps, although the evidence in support of magnesium is very limited. However, those studies did not use oral magnesium oxide and some evidence suggests that, unlike magnesium citrate, magnesium oxide may increase intracellular magnesium levels. Unfortunately, according to the results of a paper in our Natural Health section, oral magnesium oxide was not superior to placebo in the treatment of nocturnal leg cramps.

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

Kind regards,

Jim

Assoc Professor Jim Reid
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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 Deputy Dean of the Dunedin School of Medicine. He 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.

He has a special interest in Respiratory Medicine and has published widely in Asthma and COPD. He is active in research in respiratory medicine and has had wide international lecturing experience.

Risk of acute myocardial infarction with NSAIDs in real world use: Bayesian meta-analysis of individual patient data

Authors: Bally M et al.

Summary: These researchers performed a Bayesian meta-analysis of individual patient data from studies held in Canadian and European healthcare databases. All studies were conducted in the general or an elderly population, documented acute myocardial infarction (MI) as a specific outcome, studied selective cyclo-oxygenase-2 inhibitors (including rofecoxib) and traditional NSAIDs, compared the risk of acute MI in NSAID users with non-users, allowed for time-dependent analyses, and minimised effects of confounding and misclassification bias. The study cohort included 446,763 individuals, 61,460 of whom had acute MI. Taking any NSAID dose for 1 week, 1 month, or >1 month increased the risk of acute MI. With use for 1–7 days, the probability of increased MI risk (posterior probability of OR >1.0) was 92% for celecoxib, 97% for ibuprofen, and 99% for diclofenac, naproxen, and rofecoxib. Corresponding odds ratios (95% credible intervals [CrIs]) were 1.24 (0.91 to 1.82) for celecoxib, 1.48 (1.00 to 2.26) for ibuprofen, 1.50 (1.06 to 2.04) for diclofenac, 1.53 (1.07 to 2.33) for naproxen, and 1.58 (1.07 to 2.17) for rofecoxib. Short-term use for 8–30 days at a high dose (celecoxib>200 mg, diclofenac >100 mg, and naproxen >750 mg) was associated with the greatest harms; beyond the first 30 days, there were no apparent further increases in risk.

Comment: I found the statistics for this study challenging. I needed to look up Bayesian meta-analysis and found that the methodology includes "a method of statistical inference which is used to update the probability for a hypothesis as more evidence or information becomes available". So now you know. Thus, I am completely reliant on the conclusion for comment. It seems all NSAIs (including COX2s) increase the risk of myocardial infarction (I was surprised to see naproxen included, which previously has been considered cardioprotective). This risk is greatest in the first month of treatment and does not increase with duration, but does with increasing dose. But please do not ask me about the statistics.

Reference: BMJ. 2017;357:j1909
Abstract

Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes

Authors: Veroniki AA et al.

Summary: This search of the MEDLINE, EMBASE, and Cochrane CENTRAL databases from inception up to 15 December 2015 screened all experimental and observational studies comparing the safety of mono- or poly-therapy anti-epileptic drugs (AEDs) during pregnancy versus no AED exposure (control) or other AEDs. Ultimately, 96 studies were deemed appropriate for inclusion (n=58,461 patients) in a Bayesian random-effects network meta-analysis. The primary outcome was incidence of major congenital malformations, overall and by specific type (cardiac malformations, hypospadias, cleft lip and/or palate, club foot, inguinal hernia, and undescended testes). Across all major congenital malformations, many AEDs were associated with higher risk compared to control. For major congenital malformations, ethosuximide (OR 3.04; 95% CrI, 1.23–7.07), valproate (OR 2.93; 95% CrI, 2.36–3.69), topiramate (OR 1.90; 95% CrI, 1.17–2.97), phenobarbital (OR 1.83; 95% CrI, 1.35–2.47), phenytoin (OR 1.67; 95% CrI, 1.30–2.17), carbamazepine (OR 1.37; 95% CrI, 1.10–1.71), and 11 polytherapies were significantly more harmful than control, whereas in contrast, lamotrigine (OR 0.96; 95% CrI, 0.72–1.25) and levetiracetam (OR 0.72; 95% CrI, 0.43–1.16) were not.

Comment: This is a valuable paper that has direct relevance to general practice. It is a large meta-analysis of the teratogenic effects of anti-epileptic drugs. The paper states that any decision to prescribe medications during pregnancy requires a risk/benefit analysis and in none is this more so than in treatment of essential pre-existing conditions such as epilepsy. The decision to prescribe must be balanced against the need for seizure control. The newer generation anti-epileptic drugs were not associated with foetal defect and the medication of choice seemed to be lamotrigine or levetiracetam. Where at all possible, polypharmacy should be avoided.

Reference: BMC Med. 2017;15(1):95
Abstract

Goodfellow Gems

Topical corticosteroids may be a safe alternative to treat phimosis

Phimosis, where the foreskin cannot be fully drawn back over the penis is normal at birth and often self-corrects without needing treatment during the first four years of life; only 10% of three-year-old boys have phimosis (congenital phimosis).

Treatment for phimosis has become controversial. Circumcision operations and prepuce plasty have been widely used.

Topical corticosteroid treatment aims to reduce skin tightening around the tip of the penis. Cochrane reviewers assessed the effects of topical corticosteroids to treat phimosis in boys aged between 18 days and 17 years compared with non-active treatment (placebo) or no treatment at all.1 The review included 1395 boys, and while they found that potent topical corticosteroids (e.g. mometasone, hydrocortisone butyrate 0.1%, betamethasone 0.05 to 0.2%) may increase the likelihood of full or partial resolution of phimosis without significant adverse effects, many studies did not report adverse events.

References:
Moreno G, et al., Topical corticosteroids for treating phimosis in boys. Cochrane Database of Systematic Reviews 2014. 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.

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Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial

Authors: Vestbo J et al.

Summary: This multinational study recruited 2691 patients aged ≥40 years with symptomatic chronic obstructive pulmonary disease (COPD), post-bronchodilator FEV_1 of <50%, ≥1 moderate-to-severe COPD exacerbation in the previous 12 months, and a COPD Assessment Test total score of ≥10. The study aimed to determine the efficacy of a single inhaler triple therapy consisting of extrafine beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB; fixed triple; n=1078) versus long-acting muscarinic antagonist monotherapy (tiotropium; n=1075), and a free combination of BDP/FF in one inhaler and tiotropium in a second inhaler (open triple; n=538) as a control. Patients initially entered a 2-week run-in period, during which they received tiotropium 18 µg, 1 inhalation per day via single-dose dry-powder inhaler. After completing the run-in, patients were randomised to 52 weeks treatment with tiotropium, fixed triple, or open triple. The rates of moderate-to-severe COPD exacerbations were 0.46 per patient per year for fixed triple, 0.57 for tiotropium and 0.45 for open triple; fixed triple was superior to tiotropium (rate ratio 0.80; 95% CI, 0.69 to 0.92; p=0.0025). In analyses of the change from baseline in pre-dose FEV_1 at week 52, fixed triple was superior to tiotropium (mean difference 0.061 L; p<0.0001) and non-inferior to open triple (–0.003L; p=0.85). Adverse events were reported by 594 (55%) patients with fixed triple, 622 (58%) with tiotropium, and 309 (58%) with open triple.

Comment: I found this abstract confusing. The authors compared a combination of beclometasone dipropionate, formoterol fumarate, and glycopyrronium in an extrafine formulation in a single inhaler (fixed triple) with tiotropium alone, vs administration of a combination of beclometasone dipropionate/formoterol fumarate in one inhaler and tiotropium in another (open triple). Patients had significant COPD (FEV_1 <50% predicted), and had had at least one exacerbation in the preceding 12 months. Triple therapy for COPD is upon us, though not currently available in a single inhaler in New Zealand. While the authors state that the extrafine fixed triple therapy (fixed triple) had benefits over tiotropium alone, these were modest, and there was no real practical difference between fixed triple and open triple.

Reference: Lancet. 2017;389(10082):1919-29

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.

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Effect of reminder devices on medication adherence: the REMIND randomized clinical trial

Authors: Choudhry NK et al.

Summary: This trial compared the effect of three low-cost reminder devices on medication adherence in a cohort of 53,480 enrollees of CVS Caremark, a US nationwide pharmacy benefit manager. Study participants were 18–64 years old (56% were female) and were taking up to 3 oral medications for common chronic conditions. All were suboptimally adherent to all of their prescribed therapies (with a medication possession ratio of 30% to 80%) in the 12 months before randomisation. Participants were stratified at study entry according to what medications they were using: medications for cardiovascular or other nondepression chronic conditions (the chronic disease stratum) and antidepressants (the antidepressant stratum). Patients were randomised to receive in the mail a pill bottle strip with toggles, digital timer cap, or standard pillbox. The control group received neither notification nor a device. During 12 months of follow-up, optimal adherence (medication possession ratio ≥80%, determined using pharmacy claims data) to prescribed medications was achieved by 15.5% of patients in the chronic disease stratum assigned to the standard pillbox, 15.1% assigned to the digital timer cap, 16.3% assigned to the pill bottle strip with toggles, and 15.1% of controls. None of the reminder devices significantly improved medication adherence as compared to the no-intervention arm. In direct comparisons, those using a standard pillbox had higher adherence than those using the pill bottle strip (OR 1.10; 95% CI, 1.00 to 1.21). Results were similar in analyses that investigated levels of optimal adherence to cardiovascular medications in the chronic disease cohort as well as optimal adherence to antidepressants.

Comment: Interesting that these devices did nothing to improve adherence. I have seen a smartphone application, and I await the outcome of a study that is currently running. It requires a reply when medication time (previously set) comes around. Maybe the digital age will help things.

Reference: JAMA Intern Med. 2017;177(5):624-31

Abstract

Triggering of acute myocardial infarction by respiratory infection

Authors: Ruane L et al.

Summary: This Australian investigation interviewed 578 patients with angiographically-confirmed MI, to assess for recent exposure to respiratory infection symptoms and the usual annual frequency of these symptoms. 100 (17%) patients reported symptoms of respiratory infection within 7 days prior to MI; 123 (21%) reported respiratory symptoms within 35 days of the MI. The relative risk (RR) for MI occurring within 1–7 days after respiratory infection symptoms was 17.0 (95% CI, 13.2 to 21.8), and declined thereafter. In a subgroup analysis, the RR tended to be lower in patients on regular cardiac medications. For those who reported milder, upper respiratory tract infection symptoms, the increased risk of MI during the first 7 days was 13.5 (95% CI, 10.2 to 17.7).

Comment: This is an interesting study about a relationship of which I was completely unaware. 17% of those suffering a myocardial infarct reported a respiratory tract infection within 1 to 7 days preceding the event, and a further 21% between 7 and 35 days. Basically, this means that 38% of those afflicted had a respiratory tract infection during the preceding month or so. Not at all sure of the mechanism of this and it would be interesting to see if this statistic applied to other infections.

Reference: Intern Med J. 2017;47(5):522-9
Abstract

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Effect of intra-articular triamcinolone vs saline on knee cartilage volume and pain in patients with knee osteoarthritis

Authors: McAlindon TE et al.

Summary: This study recruited 140 patients (mean age 58 years) fulfilling the American College of Rheumatology criteria for symptomatic knee osteoarthritis (OA), Kellgren-Lawrence grades 2 or 3, and randomised them to receive intra-articular injections of triamcinolone 40 mg (n=70) or saline (n=70) every 12 weeks for 2 years. The study participants underwent annual knee magnetic resonance imaging for quantitative evaluation of cartilage volume (minimal clinically important difference not yet defined), and Western Ontario and McMaster Universities Osteoarthritis index scores were collected every 3 months (Likert pain subscale range, 0 [no pain] to 20 [extreme pain]; minimal clinically important improvement, 3.94). At 2 years, intra-articular triamcinolone was associated with significantly greater cartilage volume loss compared with saline (mean change in index compartment cartilage thickness of –0.21 mm vs –0.10 mm) and no significant difference in knee OA pain (–1.2 vs –1.9). Moreover, triamcinolone was associated with a higher number of treatment-related adverse events compared with the saline group (5 vs 3), as well as a small increase in haemoglobin A1c levels.

Comment: It seems to me that the underlying pathology in osteoarthritis of the knee is of a degenerative nature and not inflammatory. It is not surprising that this study demonstrated lack of effect of triamcinolone. In actual fact, it had an adverse effect – demonstrating cartilage loss. Add to this the possibility of joint infection and, as such, steroid injections for osteoarthritis are a no brainer.

Reference: JAMA. 2017;317(19):1967-75
Abstract

Use of antibiotics during pregnancy and risk of spontaneous abortion

Authors: Muanda FT et al.

Summary: This investigation analysed data from the Quebec Pregnancy Cohort (1998–2009) to evaluate the association between antibiotic exposure during pregnancy and risk of spontaneous abortion (defined as having a diagnosis or procedure related to spontaneous abortion before gestation week 20). Each case was matched by gestational age and year of pregnancy with 10 randomly selected controls. In analyses adjusted for potential confounders, use of azithromycin (adjusted OR 1.65; 95% CI, 1.34 to 2.02; 110 exposed cases), clarithromycin (adjusted OR 2.35; 95% CI, 1.90 to 2.91; 111 exposed cases), metronidazole (adjusted OR 1.70; 95% CI, 1.27 to 2.26; 53 exposed cases), sulphonamides (adjusted OR 2.01; 95% CI, 1.36 to 2.97; 30 exposed cases), tetracyclines (adjusted OR 2.59; 95% CI, 1.97 to 3.41; 67 exposed cases) and quinolones (adjusted OR 2.72; 95% CI, 2.27 to 3.27; 160 exposed cases) was associated with an increased risk of spontaneous abortion. Similar results were found when use of antibiotics was compared with exposure to penicillins or cephalosporins.

Comment: Attention general and nurse practitioners. If an antibiotic is really necessary in early pregnancy it is better not to use macrolides (excluding erythromycin), quinolones, tetracyclines (which should not be prescribed in pregnancy anyway), sulphonamides and metronidazole. If the need for such a prescription is necessary, it is best to use penicillins or cephalosporins.

Reference: CMAJ. 2017;189(17):E625-E633
Abstract

Silk garments plus standard care compared with standard care for treating eczema in children: A randomised, controlled, observer-blind, pragmatic trial (CLOTHES Trial)

Authors: Thomas KS et al.

Summary: This UK study enrolled 300 children aged 1–15 years with moderate to severe eczema and randomised them to receive standard eczema care plus silk clothing (100% sericin-free silk garments; DermaSilk or DreamSkin) or standard care alone. Silk garments were worn for 6 months. After 6 months, an intention-to-treat analysis revealed no between-group difference in eczema severity, according to the Eczema Area and Severity Index (EASI) score assessed by research nurses. A small observed treatment effect was observed for the EASI score in favour of silk garments, but the confidence interval ranged from 1.5 points favouring silk clothing to 0.5 points favouring standard care, which is not a clinically important difference. Skin infections occurred in 25% and 28% of children in the silk clothing and standard care groups, respectively. Even if the small observed treatment effect was genuine, the researchers report an incremental cost per quality-adjusted life year of £56,811 in a base case analysis from a National Health Service perspective, suggesting that silk garments are unlikely to be cost-effective using currently accepted thresholds.

Comment: I am often asked if children with eczema should avoid being dressed in either wool, cotton, or polyester clothing. Except in very rare instances I have observed no difference with any. Silk has never arisen and it is good to read from this paper that it also makes no difference.

Reference: PLoS Med. 2017;14(4):e1002280
Abstract

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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.

EVIDENCE-BASED NATURAL HEALTH BY DR CHRIS TOFIELD

Effect of magnesium oxide supplementation on nocturnal leg cramps: a randomized clinical trial

Authors: Roguin MN et al.

Summary: This Israeli trial recruited 94 community-dwelling individuals (39% male; mean age, 64.9 years) with ≥4 documented episodes of nocturnal leg cramps (NLCs) during the previous 2 weeks and randomised them to once-nightly oral magnesium oxide (865 mg; equivalent to 520 mg of elemental magnesium; n=48) or placebo (n=46) for 4 weeks. During the treatment period, both groups experienced reductions in NLC episodes, from about 8 weekly to 5 weekly. At 4 weeks, there were no significant between-group differences in severity or duration of NLCs, quality of life, or quality of sleep.

Comment: Leg cramps are extremely common in general practice and other than quinine (which we are now discouraged from using) there is little else in terms of medication that we can offer. I usually suggest a trial of magnesium to patients, but in light of this research showing no benefit, I may have to amend my recommendations.

Reference: JAMA Intern Med. 2017;177(5):617-23
Abstract

Prenatal listening to songs composed for pregnancy and symptoms of anxiety and depression: a pilot study

Authors: Nwebube C et al.

Summary: This pilot study recruited 222 pregnant women online via a specially designed website, The Relaxation in Pregnancy Study. Pregnant women aged >18 years from English-speaking countries were eligible. The study aimed to determine whether listening to specially composed songs would be an effective intervention for reducing symptoms of prenatal anxiety and depression. Participants were randomly assigned to either a music group (daily listening to specially composed songs for 20 min; n=111) or to daily relaxation (control group; n=111) for 12 weeks each. Self-report questionnaires assessed symptoms of State and Trait anxiety (the Spielberger) and depression (Edinburgh Postnatal Depression Scale [EPDS]). 20 participants in the intervention group and 16 participants in the active control group completed the study. At week 12, symptoms of anxiety and depression had decreased significantly from baseline in the music group, whereas there were no such changes in the control group.

Comment: The influence of maternal health is now well-documented as being of crucial importance for the baby's future, in terms of both physical and mental health. Research has gone as far as showing that certain maternal behaviours and eating habits can change gene expression in the foetus. Precisely what effects music (or noise, for that matter) have on unborn babies is not known, but helping the mother's anxiety/depression symptoms with calming music as shown in this study is a great start.

Reference: BMC Complement Altern Med. 2017;17:256
Abstract