Welcome to the July issue of General Practice Research Review.

If you want a useful conference to give you a view of what Australian general practice is up to I suggest you go to the AAAPC conference. I went last week and recommend you look out for the paper from Daniella Mazza’s group on long-acting reversible contraceptives when it is published. We still have a North American bias this month although one article is a British group publishing in JAMA. Practice nurse Valerie Edge continues her valuable contribution, this time looking at simple yet effective ways of mitigating vaccination pain in infants, and the potential acceptability of self-testing for cervical screening in never/under-screened women.

Please let us know what research area you are interested in so we can look out for it.

Kind Regards,
Professor Gerard Gill
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Association of serum cholesterol levels with peripheral nerve damage in patients with type 2 diabetes

Authors: Jende J et al.

Summary: This German cohort study investigated the association between serum cholesterol levels and peripheral nerve damage in patients with type 2 diabetes. 100 patients with type 2 diabetes (with or without diabetic neuropathy) underwent magnetic resonance neurography of the right leg at Heidelberg University Hospital, as well as clinical, serological and electrophysiological assessments. The lipid equivalent lesion (LEL) load was found to be positively correlated with the mean cross-sectional area of the sciatic nerve and the maximum length of a nerve lesion, and was negatively correlated with serum levels of total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol. LEL load was also negatively correlated with nerve conduction velocities and amplitudes of the tibial and peroneal nerves.

Comment (GG): Diabetes is the quintessential general practice disease. While our prime emphasis should be on managing the increased cardiovascular risk, the small vessel complications remain a major source of concern to GPs. This small observational study from Germany has identified that there may be an increased risk of peripheral neuropathy with aggressive lipid-lowering therapy using statins. What is missing from our evidence base are studies a little like those that we see with antihypertensive agents suggesting that smaller doses may have the best therapeutic effect. As I say to medical students, what we aim to do in hypertension is poison people with small doses of several agents as this best lowers BP without causing side effects. What we need is someone with some time to go through all the studies and identify the optimal dose of statins. It would be nice to know if other small vessel conditions are also affected by aggressive cholesterol lowering.

Full text

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PBS Information: This product is not listed on the PBS.

Servier Laboratories (Aust.) Pty. Ltd. 8 Calo Street, Hawthorn, VIC 3122. October 2018.
Association of nonfasting vs fasting lipid levels with risk of major coronary events in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm

Authors: Mora S et al.

Summary: This post hoc analysis of ASCOT-LLA data compared the association of baseline non-fasting and fasting lipid levels with coronary and vascular outcomes. 8270 patients with no prior vascular disease had their non-fasting and fasting lipid levels measured 4 weeks apart and were then followed up for a median 3.3 years for major coronary events (non-fatal myocardial infarction and fatal coronary heart disease). Non-fasting samples had slightly higher triglyceride levels but similar cholesterol levels to fasting samples. Multivariable Cox models (adjusted for cardiovascular risk factors) showed that the association between non-fasting lipid levels and major coronary events was similar to that for fasting lipid levels. Concordance of fasting and non-fasting lipid levels for classifying participants into appropriate atherosclerotic cardiovascular disease risk categories was high.

Comment (GG): This is a very useful study which shows that there is minimal difference between the lipid values when the samples are collected either fasting or non-fasting. For general practice, critically with unreliable patients, this means that we can confidently and safely calculate the risk using non-fasting lipids. There remains some confusion however around what to do with patients with hypertriglyceridaemia and perhaps this is an area where the Heart Foundation could offer us some guidance in the next lipid guidelines.

Full text

Long-term drug therapy and drug discontinuations and holidays for osteoporosis fracture prevention

Authors: Fink H et al.

Summary: This systematic review evaluated the effects of long-term drug therapy and drug discontinuation/holidays for osteoporosis fracture prevention. A search of various electronic databases identified 48 studies in men and postmenopausal women that were suitable for inclusion. Analysis of the data showed that 4 years of alendronate reduced clinical fractures and radiographic vertebral fractures in women with osteoporosis, whereas 4 years of raloxifene reduced vertebral but not nonvertebral fractures. In women with osteopenia or osteoporosis, 6 years of zoledronic acid reduced nonvertebral and vertebral fractures. Long-term bisphosphonates were associated with an increased risk of atypical femoral fractures and osteonecrosis of the jaw. In women with unspecified osteoporosis status, 5–7 years of hormone therapy reduced clinical fractures (including hip fractures) but increased serious harms. After 3–5 years’ treatment, bisphosphonate continuation vs discontinuation reduced radiographic vertebral fractures (zoledronic acid) and clinical vertebral fractures (alendronate) but not nonvertebral fractures.

Comment (GG): This is a most helpful review to guide us in what agents we should use as osteoporosis therapy, and for how long. It points out that men remain an unexplored gender in osteoporosis therapy. We know that men who develop hip fractures are more likely to die than women. Perhaps our osteoporosis gurus need to give us some clear advice on which men without fractures we should target for bone density studies. It does seem however that the bisphosphonates have effects which persist long after they cease to be taken.

Full text

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Abbreviations: PsA, psoriatic arthritis.
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Association of disease definition, comorbidity burden, and prognosis with hip fracture probability among late-life women

Authors: Ensrud K et al.

Summary: This prospective cohort study in the US determined 5-year hip fracture and mortality probabilities in women aged ≥80 years. 1528 community-dwelling women were contacted every 4 months to ascertain vital status and hip fracture. The women were classified into 2 groups: osteoporosis (n=761) and no osteoporosis but high fracture risk (n=767). 125 (8.0%) women had a hip fracture during follow-up and 287 (18.8%) died before experiencing a hip fracture. Five-year mortality probability was calculated to be 24.9% in women with osteoporosis and 19.4% in women without osteoporosis but at high fracture risk. In both groups, mortality probability increased with more comorbidities and poorer prognosis. 5-year hip fracture probability was 13.0% in women with osteoporosis and 4.0% in women without osteoporosis but at high fracture risk.

Comment (GG): This article complements the preceding article on the osteoporotic treatment agents. This is a useful cohort study from the US giving us clear evidence of who is at risk of fracture and death. It is helpful combined with the previous article in giving you the evidence you need to make the decision as to who needs osteoporosis therapy and for how long.

Reference: JAMA Intern Med 2019; published online Jun 17

Anticholinergic drug exposure and the risk of dementia

Authors: Coupland C et al.

Summary: This nested case-control study in general practices in England investigated the association between anticholinergic drugs and risk of dementia. 58,769 patients aged ≥55 years with dementia were compared with 225,574 matched controls without dementia. Prescription data for 56 drugs with strong anticholinergic properties (anticholinergic antidepressants, antiparkinson drugs, antipsychotics, bladder antimuscarinic drugs, and antiepileptic drugs) were used to calculate cumulative anticholinergic drug exposure. The primary exposure was the total standardised daily dose (TSDD) of anticholinergic drugs prescribed in the 11 years prior to the date of diagnosis of dementia (index date) or equivalent date in controls. The adjusted odds ratio for dementia increased from 1.06 in the lowest overall anticholinergic exposure category (1–90 TSDDs) to 1.49 in the highest category (>1095 TSDDs).

Comment (GG): Medical students are often surprised at the high rate of iatrogenesis. One in six patients admitted to an acute hospital suffers harm during their stay. While the figures for general practice consultations are reported as being around six per thousand consultations, this article suggests we may be missing some of this. Just as the benefits of general practice care take a long time to evolve it may be that the negative side of general practice also does. This large cohort study from UK general practice indicates a significant association between the use of highly cholinergic drugs and the development of dementia. It is important to realise that this does not confirm causation. It is difficult to see how many of these drugs would have a wide use in current general practice but given one of them was a selective serotonin reuptake inhibitor, and the incredibly high use of this medication among older women in particular, we need to consider the utility of long-term medication usage.

Reference: JAMA Intern Med 2019; published online Jun 24

A practical approach to low-dose aspirin for primary prevention

Authors: Chiang K et al.

Summary: This viewpoint article discussed the place of aspirin for primary prevention, in the light of recent clinical trials that found a reduced benefit of aspirin in primary prevention accompanied by a sizable bleeding risk. Decisions about the use of aspirin for primary prevention should focus on individual patient risks and preferences, and identifying patients for whom discontinuation is appropriate is a new task dictated by the recent evidence. Clinicians should not abandon aspirin for primary prevention, nor should they use it without full consideration of harms. The use of aspirin, another antplatelet agent, or both remains mandatory for secondary prevention.

Comment (GG): Many of our readers took part in the ASPREE trial. It was somewhat sobering to discover that bleeding from aspirin was more lethal than cardiovascular disease in this older population. However, as this review article points out aspirin has a place in secondary prevention. What to do about those individuals who are currently taking it for primary prevention requires an individualised approach. This short article offers much useful help to GPs in assisting their patients through this decision.

Reference: JAMA 2019; published online Jun 28

Comparing automated office blood pressure readings with other methods of blood pressure measurement for identifying patients with possible hypertension

Authors: Roerecke M et al.

Summary: This systematic review and meta-analysis investigated whether automated office BP (AOBP) measurements are better than readings recorded by nurses and physicians in routine clinical practice. A search of MEDLINE, Embase, and Cochrane Library for the period 2003–2018 identified 31 articles that compared AOBP with awake ambulatory BP, routine office BP, or research BP measurements in a total of 9279 patients. In samples with systolic AOBP ≥130mm Hg, routine office and research systolic BP readings were substantially higher than AOBP readings, with a pooled mean difference of +14.5mm Hg (p<0.001) for routine office systolic BP and +7.0mm Hg (p<0.001) for research systolic BP. AOBP measurements were similar to awake ambulatory BP measurements.

Comment (GG): We know we are currently over-diagnosing some people as having essential hypertension. This large meta-analysis of a number of studies suggests that it is eminently sensible to rely on automated BP recordings taken on patients resting in a quiet location using an automatic BP monitoring device. The results are as good as the more invasive and ambulatory BP monitoring. The problem for us in general practice is to find such a location in rather cramped surgeries. Unfortunately we have not been given advice on what to do for the 10% of people for whom the automated machines are not able to give us a reliable reading.


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A four-group urine risk classifier for predicting outcome in prostate cancer patients

Authors: Connell S et al.

Summary: This study reported the development of a urine risk classifier (based on urine-derived extracellular vesicle RNA) for providing diagnostic information in prostate cancer patients. A LASSO-based Continuation-Ratio model was built to generate four Prostate-Urine-Risk (PUR) signatures for predicting the probability of normal tissue (PUR-1), D’Amico low-risk (PUR-2), intermediate-risk (PUR-3), and high-risk (PUR-4) prostate cancer. The model was applied to a test cohort for diagnostic evaluation, and to an active surveillance sub-cohort for prognostic evaluation. In the diagnostic evaluation, each PUR signature was significantly associated with its corresponding clinical category, and PUR-4 status predicted the presence of clinically significant intermediate or high-risk disease. In the AS sub-cohort, groups defined by PUR status and proportion of PUR-4 had a significant association with time to progression.

Comment (GG): One could not say in this review that I neglect prostate cancer. This is one of those ‘watch this space’ articles. It seems that this technology has considerable promise in helping identify those who may have prostate cancer in a far less invasive manner. There also seems to be some potential to give a prognostic indication to guide future therapeutic endeavours.

Reference: BJU Int 2019; published online May 20
Full text

Investigating causal relations between sleep traits and risk of breast cancer in women

Authors: Richmond R et al.

Summary: This study examined whether sleep traits have a causal effect on breast cancer risk. Data were analysed from the UK Biobank (n=156,848) and Breast Cancer Association Consortium (BCAC) case-control genome-wide association study (n=228,951). Multivariable regression analysis of UK Biobank data showed that morning chronotype was inversely associated with breast cancer, but there was little evidence for an association of sleep duration and insomnia symptoms with breast cancer risk. Mendelian randomisation analysis of UK Biobank and BCAC data supported the protective effect of morning preference on breast cancer risk.

Comment (GG): It seems that early to bed and early to rise may have other benefits apart from the three traditional ones in the nursery rhyme. Might other lifestyle factors need to be considered in assessing the risk of many diseases such as cancers? Or is this a reflection that the well-recognised risks of alcohol and obesity in breast cancer causation are associated with those who are night owls? Is lack of sleep carcinogenic?

Reference: BMJ 2019;365:l2327
Full text

How many older adults receive drugs of questionable clinical benefit near the end of life?

Authors: Morin L et al.

Summary: This Swedish cohort study evaluated the use of drugs of questionable clinical benefit during the last 3 months of life in older adults. A total of 58,415 individuals who died in 2015 were included (mean age, 87 years). During their last 3 months of life, patients received an average of 8.9 different drugs. 32.0% of them continued and 14.0% initiated at least one drug of questionable clinical benefit (e.g., statins, calcium supplements, vitamin D, bisphosphonates, or antidementia drugs).

Comment (GG): At the recent AAAPC conference in Adelaide I was listening to a presentation on how difficult registars found it to de-prescribe. How do we do this in circumstances where the medications are not likely to make a significant impact on the quality of life but withdrawal of therapy may be seen by the patient as therapeutic abandonment? This article will not give you the answers to this question but it will get you thinking about whether the polypharmacy prevalent in nursing homes is worthwhile.

Reference: Palliat Med 2019;269216319854013
Full text

The effect of aromatherapy by lavender oil on infant vaccination pain

Authors: Vaziri F et al.

Summary: This double-blind study evaluated the effects of lavender oil inhalation on infant pain associated with pentavalent vaccination. Infants were randomised to start using the lavender oil or placebo aromatherapy 1 minute before the injection; pain was assessed before and after vaccination using the Neonatal Infant Pain Scale (NIPS). NIPS pain scores were significantly lower in the lavender oil aromatherapy group than in controls 5 min after vaccination, and crying duration was significantly shorter in the lavender oil group (75.47s vs 105.22s).

Comment (VE): This article was extracted from a thesis in midwifery and presents findings from a double-blind randomised controlled trial. While babies in both groups grimaced and cried at injection time and there was no difference between the babies 15 seconds later, pain scores at 5 minutes post vaccination were lower in the group receiving the lavender oil aromatherapy. As part of health professional responsibility to mitigate vaccination pain as much as possible, it is important to be aware of any new evidence-based pain relieving strategies and this could be a simple one to implement.

Abstract

Using feeding to reduce pain during vaccination of formula-fed infants

Authors: Bos-Veneman N et al.

Summary: This study evaluated the use of formula feeding to reduce pain during infant vaccination. A community-based sample of 48 infants aged 4–10 weeks who were already being formula fed were randomised to have a formula feed before, during and after vaccination, or to not have a formula feed (controls). Pain at the time of injection did not differ between groups, but crying duration was 33.5s shorter in infants who received a formula feed compared with those who did not. In the first minute after injection, formula-fed infants had a faster pain reduction according to the Neonatal Infant Pain Scale.

Comment (VE): It is known that breast feeding infants before, during and after vaccinations can help infants experience less pain. This is thought to be due to close contact with the parent, sucking, sweet taste and distraction. For those not being breastfed, this study provides some evidence that formula feeding in infants up to 10 weeks of age can also be effective in providing a level of pain relief. The formula feeding did not reduce the acute injection pain but led to a faster forgetting of the pain. There may be concern about choking while formula feeding and receiving a vaccination but this study had only one mild choking episode in the 24 drinking infants. Although there was not a huge number of infants in the study, it was adequately powered to be able to detect a result. Along with breast feeding, distraction, and caregiver holding, formula feeding is another option to assist in reducing pain directly after vaccinations.

Reference: Arch Dis Child 2018;103(12):1132-37
Abstract
Acceptability of self-taken vaginal HPV sample for cervical screening among an under-screened Indigenous population

Authors: Adcock A et al.

Summary: This NZ study explored the acceptability of human papillomavirus (HPV) self-testing in never/under-screened Māori women. Survey data were collected from 397 women in four regions of NZ. Most survey participants were enrolled with a Primary Health Organisation (87.15%), but did not attend for regular cervical screening. The most frequently reported barriers to cervical screening included a desire for bodily autonomy, and embarrassment/shyness/reticence. 75% of respondents said they would be likely/very likely to do an HPV self-test, and 90% of them said they would attend follow-up if they received a positive HPV result.

Comment (VE): The findings of this study support other research and meta-analyses that show strong acceptance and often preference for self-collection over clinician sampling, particularly in women from low socioeconomic groups and minority populations. A literature review in the Frontiers in Public Health journal last year outlined evidence that vaginal self-collected samples provided equal sensitivity and specificity to detect high-risk HPV types and intraepithelial neoplasia to clinician-collected samples. In Australia, the National Cervical Screening Program has provided guidelines for self-collection and advises that this needs to be done in a clinic environment with health professional support and education. It is not recommended for all women but may be considered if women are overdue for their screening or have not had one before. While there are many barriers to women not getting screening tests, research has identified common concerns as embarrassment or shyness, cultural or religious beliefs, or worries about an uncomfortable/painful test. Self-collection may help with some of these concerns.


Full text