RGH E-Bulletin Digest Number 74

The next in our 2014 series of continuing professional development activities is the RGH E-Bulletin Digest No. 74 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 55-2, 3, 5 & 6 (June/July 2014).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Explain the concept of prescribing cascades
- Discuss the role of aspirin for stroke prevention in atrial fibrillation
- Outline the use of iloprost for Raynaud's phenomenon
- Describe options for the treatment of depression during pregnancy.

Successful completion of this activity is demonstrated by answering seven of the eight multiple choice questions correctly.

Information in this E-Bulletin Digest is derived from critical analysis of available evidence – individual clinical circumstances should be considered when making treatment decisions.

Competencies addressed by this activity include: 4.1, 4.2, 4.3, 6.1, 6.2, 7.1, 7.2

This activity has been accredited for 0.5 hrs of Group 1 CPD (or 0.5 CPD credits) suitable for inclusion in an individual pharmacist's CPD plan which can be converted to 1 hr of Group 2 CPD (or 1 CPD credit) upon successful completion of relevant assessment activities.
Accreditation number: A1410AP0.

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He is a past president of the Society of Hospital Pharmacists of Australia and achieved admission as a Fellow of SHPA in 1993. He is the author of over 80 peer-reviewed publications and several book chapters, and his research interests focus upon strategies to achieve safe and effective use of psychotropic drugs. He has a special interest in veteran psychiatry, in particular in the management of post-traumatic stress disorder.

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RGH Pharmacy E-Bulletin

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A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.
Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH
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Prescribing cascades

Polypharmacy is a relatively common issue, particularly amongst the elderly and people with multiple morbidities. Sometimes defined as a situation whereby there are five or more regular medicines prescribed, or 12 or more occasions of medication administration per day, polypharmacy is associated with an increased incidence of adverse drug reactions and drug interactions, as well as poorer adherence to prescribed treatment regimens, and potentially compromised clinical outcomes. If it is known that polypharmacy is associated with outcomes that are not positive, what drives this phenomenon?

A range of reasons have been cited as the factors underpinning polypharmacy, but one of particular concern is the development of prescribing cascades. Put simply, a prescribing cascade evolves when one drug is added to the therapeutic regimen with the objective of treating symptoms that are actually attributable to the adverse effects of medications that have been added to a regimen. Especially in the case of the older person, it is important to have a high index of suspicion that new symptoms emerging around the time of changes to a treatment regimen may in fact be related to a recently added drug.

Ironically, it is sometimes the case that polypharmacy and prescribing cascades may actually be driven by the effects of evidence based guidelines. Consider, for example, the case of a patient who develops metabolic syndrome and type II diabetes mellitus after the prescription of an antipsychotic agent such as olanzapine: if evidence-based guidance is applied, this same person may well eventually be prescribed aspirin, a statin, metformin and an ACE inhibitor.

There are numerous examples of prescribing cascades in clinical practice. Some examples include:

- PPIs or other modulators of gastric acidity to supress symptoms that arise after the addition of a NSAID, aspirin or other medications that contribute to GI distress
- Alterations to treatment for Parkinson's disease after the addition of metoclopramide for nausea
- Addition of loperamide or other anti-diarrhoeal agents after commencement of SSRIs
- Use of inhaled bronchodilators for wheeze/bronchoconstriction after initiation of beta blockers
- Prescription of diuretics for ankle oedema associated with calcium channel blockers such as felodipine and amlodipine – this may actually be followed by a need to prescribe potassium supplements for diuretic-induced hypokalaemia
- Additional of anticholinergic drugs for urinary symptoms after initiation of cholinesterase inhibitors, or to treat Parkinsonism after the commencement of antipsychotic agents.

The emergence of new symptoms or clinical syndromes after changes to the medication profile, especially for older people, may well provide a trigger for a comprehensive clinical review, perhaps in the form of a Home Medicines Review (HMR) or Residential Medication Management Review (RMMRS). These services may provide the opportunity for rationalising treatment, simplification of regimens, and the adoption of changes that can decrease the numbers of medications that are needed.

Acknowledgment – This E-Bulletin is based on work by Chris Alderman, Senior Clinical Pharmacist, SA Pharmacy

FOR FURTHER INFORMATION – CONTACT PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@health.sa.gov.au.
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Aspirin and atrial fibrillation

Atrial fibrillation (AF) is the most common sustained arrhythmia and its prevalence increases with age, affecting 10% of people over 80 years. Patients with AF have an increased risk of stroke and usually have associated cardiovascular disease.

Prevention of thrombotic complications in the elderly is a challenging issue, and is characterised by the need to balance the risks and benefits of different therapies with multiple comorbidities and an increased risk of bleeding. The elderly also have an increased risk of stroke, which approaches 30% for those aged between 80-89 years.

Warfarin remains the gold standard for stroke prevention however many patients will not be prescribed warfarin based on the perceived risks associated with warfarin use in the elderly – issues such as mismanagement of dosing, falls risk and increased bleeding risk are influential.

The most recent 2014 ACC/AHA/HRS guidelines for the management of AF emphasize the fact that there is weak evidence to support the use of aspirin in patients with AF.

A meta-analysis of 7 trials compared aspirin to placebo for prevention of AF in doses ranging from 25mg twice daily to 1300mg daily. The results showed a 19%, non-significant reduction in stroke. This result was mainly driven by the SPAF-1 trial, which was the only trial to show a benefit for aspirin alone in preventing stroke in patients with AF. In this study patients were prescribed 325mg aspirin daily for stroke prevention. This trial was stopped early, and there were inconsistencies between two arms in the trial. The European 2012 guidelines suggest that the benefits observed may have been driven by reductions in vascular disease, rather than stroke risk itself. In the SPAF-1 trial aspirin was ineffective in preventing strokes in those aged >75 years.

The BAFTA trial included 973 patients over 75 years and randomly assigned them to receive either warfarin or aspirin. Warfarin was significantly more effective than aspirin (1.8 vs 3.8% per year risk of stroke) and there was no significant difference between the groups in terms of bleeding risk.

An analysis of 8932 patients from 12 trials found that compared with placebo, the relative benefit for aspirin for preventing ischemic stroke decreased significantly as patients aged, but this decline was not observed with warfarin. In addition to these results, aspirin has not been studied in a low risk population – this is unfortunate as lower risk patients are often treated with aspirin with the presumption that it will be more suitable for them.

The role of aspirin in the prevention of stroke in AF remains unclear, but currently insufficient to recommend as an alternative to antithrombotic therapy. It is essential that all patients with AF and at high risk for stroke are considered for antithrombotic therapy, with the risks and benefits of each therapy explained to them and/or their families.

Acknowledgment – This E-Bulletin is based on work by Heather Forbes, Senior Clinical Pharmacist, RGH

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Iloprost for symptoms of Reynaud's phenomenon

Systemic Sclerosis (SSc) is an autoimmune disease associated with an excessive deposit of collagen at visceral and cutaneous levels. SSc is associated with a variety of clinical features ranging from Raynaud's disease to cutaneous fibrosis. Most patients with systemic sclerosis display symptoms of Reynaud's phenomenon, which could be defined as vasospasm of arteries or arterioles due to microvascular endothelial damage, and collagen accumulation which can lead to narrowing and obliteration of vascular lumen. This contributes to digital ulcers and ischaemic complications.

Treatment of Reynaud's phenomenon aims to reduce vasospastic phenomena, improving vascular permeability and thereby supporting ulcer healing and preventing tissue damage and visceral involvement. Pharmacotherapeutic options that can be used include calcium channel blockers, prostanoids, bosentan, sildenafil, antithrombotic agents, antibiotics and analgesics.

Iloprost is an analogue of the vasodilator prostacyclin. In addition to vasodilating properties at the systemic and lung levels, it also inhibits platelet aggregation. In small clinical studies iloprost has been shown to improve symptoms, increase digital blood circulation and improve ulcer healing post-infusion. Iloprost is given as an intravenous infusion over six hours for a minimum of five successive days. Patients with ischaemic tissue loss or ulceration may require prolonged treatment (up to 4 weeks). There is evidence to suggest that a prolonged course of therapy is beneficial in treatment of digital ulcers. The initial infusion rate and dose titration are weight-adjusted and outlined in a local treatment protocol at RGH.

Headache and flushing are the most common adverse reactions caused by iloprost, but can be alleviated by tapering the infusion rate down to the highest tolerable level for each patient. Other common adverse effects include local reactions such as redness and pain at the infusion site, as well as nausea and vomiting. Paradoxical Renaud's phenomenon has also been reported.

Iloprost is not currently registered with the Australian Therapeutic Goods Administration and can only be accessed via category A Special Access Scheme.

Acknowledgment – This E-Bulletin is based on work by Wassana Sorich, Clinical Pharmacy Coordinator, RGH

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Antidepressants in pregnancy

Depression is very common in pregnant women and in the postnatal period, with an estimated 13% affected. Treatment of depression in pregnant women remains a challenge as exposure of a foetus to severe maternal depression may well be as risky as exposure to antidepressants. Factors such as a deficiency in randomized controlled trials, the limited power of studies, failure to control for confounding variables and the lack of information about disease state of the women contribute to the challenge of deriving a solid evidence base for the treatment of depression in this context. As a result clinicians have to work in a clinical situation that is characterised by less information and more risk.

Untreated depression in pregnancy
Women who cease antidepressant medications early in pregnancy have an estimated five-fold increased risk of relapse of depression by the time the baby is delivered. Untreated depression is not without its own risks for the child, with some studies suggesting it is linked with increased risk of premature babies, still birth and irritability in newborns. Severe depression can put the foetus at indirect risk as it may lead to risk of poor self-care, inadequate nutrition, excessive alcohol and tobacco use and even suicide.

Use of antidepressants in pregnancy
Selective serotonin reuptake inhibitors are the most widely used and studied in pregnancy but there are cases when they are not indicated: these include lack of response, when they are not tolerated, or an established history of effective treatment with a non-SSRI for an individual patient. Patient preference must also be considered.

The use of SSRIs has been associated with low birth weight and has conflictingly been associated with miscarriage, foetal growth defects and pre-term birth. Paroxetine is linked with cardiovascular abnormalities in early pregnancy, with studies suggesting doses more than 25mg are implicated.

Tricyclic antidepressants are generally not recommended as first line treatment in depression. They have been associated with transient neonatal toxicity and withdrawal symptoms in late pregnancy.

Monoamine oxidase inhibitors are rarely used in clinical practice due to their severe adverse effect profile. They have been linked to increased rate of congenital abnormalities in animal studies and are generally not recommended in pregnant women.

Other antidepressants are less well studied than SSRIs. The general lack of negative findings in animal studies should be interpreted with caution as it probably relates to lack of data rather than reflecting definitively less risks - therefore these should be used with great caution in pregnancy.

Ultimately, the decision whether to initiate or cease antidepressants in pregnant women needs to be weighed on risk versus benefits to the mother and foetus in the context of the individual psychopathological condition.

Acknowledgment – This E-Bulletin is based on work by Perfect Ncube, Pharmacy Intern, RGH

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AusPharm CPD MCQs

Questions based on the above articles:

Select ONE alternative that best represents the correct answer to each of the following multiple choice questions

Polypharmacy is known to be associated with which of the following?

a) increased incidence of adverse drug reactions
b) poorer therapeutic outcomes
c) decreased adherence
d) all of the above

Which of the following is a situation that probably represents a prescribing cascade?

a) addition of a beta blocker with an ACE inhibitor for heart failure
b) addition of lithium augmentation after sub-optimal antidepressant response
c) addition of loperamide for diarrhoea associated with an SSRI
d) none of the above

The prevalence of atrial fibrillation (AF) amongst people older than 80 years of age is:

a) about 1%
b) nearly 5%
c) approximately 10%
d) over 15%

A pooled analysis from 12 trials found that in relation to prevention of ischemic stroke:

a) the benefit of aspirin for stroke prevention in AF decreased with age
b) the benefit of aspirin for stroke prevention in AF increased with age
c) the benefit of warfarin for stroke prevention in AF decreased with age
d) the benefit of warfarin for stroke prevention in AF increased with age

Which of the flowing classes of agents has been used for adjuvant management of Raynaud's phenomenon?

a) ACE inhibitors
b) calcium channel blockers
c) SSRIs
d) none of the above

In addition to vasodilating properties at the systemic and lung levels, iloprost also

a) increases flexibility of erythocytes
b) decreases small vessel compliance
c) inhibits platelet aggregation.
d) decreases cardiac output

The incidence of depression amongst pregnant women and in the post-natal period has been estimated to be:

a) 1.3%
b) 13%
c) 2.3%
d) 23%

Which of the following could be considered as a first line treatment for a depressed woman in the first trimester of pregnancy?

a) duloxetine
b) desvenlafaxine
c) sertraline
d) phenelzine