RGH E-Bulletin Digest Number 76

The next in our 2014 series of continuing professional development activities is the RGH E-Bulletin Digest No. 76 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 55-11→56-2 (September 2014).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Describe key principles from the 2014 update of the Australian Asthma Handbook
- Discuss the important issues to consider in reporting of adverse drug reactions
- Outline findings in relation to the effects of aspirin in reducing cancer risk
- Discuss the clinical pharmacology of dipeptidyl peptidase inhibitors.

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.

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

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: A1412AP0.

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He has over 25 years' experience as a specialist clinical pharmacist in psychiatry, and holds specialist qualifications in psychiatry and geriatric pharmacy with the US Board of Pharmaceutical Specialties.

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

Australian Asthma Handbook: key changes from 2006 edition

In March 2014, the National Asthma Council Australia published the much anticipated update of the Asthma Management Handbook, last published in 2006. The handbook is now called the Australian Asthma Handbook and at this stage the full version is only available online at http://www.asthmahandbook.org.au The Australian Asthma Handbook – Quick Reference Guide, a companion to the full online version, is available as a hard copy or to download (http://www.asthmahandbook.org.au/download-order/guide). Key changes since 2006 are discussed here.

Diagnosis and classification in adults
Assessment of asthma severity at the time of diagnosis is no longer recommended. Severity of asthma can now only be assessed after treatment has been initiated, and is now defined by the type/intensity of treatment required to achieve good control. For example, a patient who has good asthma control using a regular low dose of inhaled corticosteroid (ICS) would have mild asthma, whereas a patient needing a regular high dose of an ICS and a long acting beta2 agonist (LABA) to maintain good asthma control would be classified as having severe asthma. Assessment of the pattern of asthma (e.g. infrequent or frequent intermittent asthma or mild, moderate or severe persistent asthma) is no longer recommended (and initial preventer treatment is no longer based on this classification of asthma). Instead, recent asthma control, risk factors for flare-ups & possible medication-related adverse effects, need to be assessed.

Classes of asthma medicines
There are now only two main classes of asthma medications: relievers and preventers (there is no longer the category of symptom controllers for the LABAs). One reason for this change was that LABAs should not be used without an ICS; therefore, the combination of both medicines is now considered to be a preventer. For safety reasons, if a LABA is required, a combination preparation should be prescribed if possible to avoid the LABA being used without ICS. This would not be possible for patients using beclomethasone or ciclesonide inhalers. If a LABA needed, the patient would need to be educated about the importance of using both the ICS and LABA inhalers and not to stop using one of them (especially the ICS inhaler) when they feel better.

Indications for preventer treatment in adults
One scenario where regular treatment with a low dose ICS is recommended is if a patient has asthma symptoms at least twice per month (replacing the previous recommendation to start preventers if there are symptoms > three times/week). Several clinical trials have found that for patients with mild and infrequent asthma symptoms, improvement not only in symptoms but also a reduction in the risk of serious asthma flare ups and accelerated decline in lung function.

Updated stepwise treatment of asthma in adults
There is an updated approach for stepping up and stepping down of asthma treatment in the new handbook. For further information, please refer to: http://www.asthmahandbook.org.au/management/adults

Focus on inhaler technique and adherence
Poor adherence & inhaler technique are common causes of poor asthma control. It is important to check adherence and technique at each visit before adjusting treatment. For videos and checklists on how to use asthma inhalers, please refer to the National Asthma Council Australia website: http://www.nationalasthma.org.au/how-to-videos/using-your-inhaler or the NPS MedicineWise website: http://www.nps.org.au/topics/how-to-be-medicinewise/managing-your-medicines/inhaler-devices-for-respiratory-medicines For a full list of the key changes in the updated Australian Asthma Handbook, please refer to: http://www.asthmahandbook.org.au/about/highlights

Acknowledgment – This E-Bulletin is based on work by Tania Colarco, Senior Clinical Pharmacist, DATIS, RGH

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Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

Reporting Adverse Drug Reactions (ADRs)

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as 'any response to a drug which is noxious, unintended and occurs at doses normally used for prophylaxis, diagnosis or therapy of disease'. ADR categorization incorporates a wide spectrum of definitions and may include:

Allergy/Hypersensitivity: Immunological, often unpredictable, typically either acute IgE-mediated (type 1) or cell-mediated (type 4s).
Adverse effects: Unintended effects, typically common & predictable, related to basic pharmacological properties
Intolerance: Lower threshold to normal pharmacological action (often unpredictable) associated with genetic variants in metabolism.
Drug Interaction: Interaction between medications leading to altered metabolism or pharmacologic effects.
Other: Toxicity/excess dosage, idiosyncrasy, genetic susceptibility to ADR
Pseudo-allergy: Mimics allergic reaction, not mediated by immunological mechanisms.

All types of ADRs vary in relation to severity and susceptibility factors. Physiological variables such as age, gender and genetics also influence predisposition to ADRs. Typically the very old and the very young, those with multiple comorbidities, intercurrent illnesses and/or polypharmacy have factors predisposing to an ADR.

Reporting of ADRs is important for ongoing monitoring of safety, effectiveness and quality of medications and therapeutic goods. In Australia reports of adverse events are compiled in a database by the Therapeutic Goods Administration (TGA), and are continually reviewed to assist in identifying and investigating medication safety concerns. Safety updates, dissemination of educational tools, further post marketing trials or even regulatory actions may be undertaken or recommended. Reporting suspected adverse event is important regardless of medication scheduling (prescription, over-the-counter, complementary, vaccination) and/or level of certainty of the medication causing the event. All serious adverse events should be reported, especially if considered to have contributed to healthcare stay or costs, morbidity and/or mortality. Newer medications are particularly of interest, enabling monitoring to facilitate better understanding of use post marketing within general populations that may be dissimilar with clinical trial cohorts. Reports of suspected drug interactions are also valuable.

Reporting of ADRS in Australia is coordinated through the TGA. ADR reports should include:

- Details of reporter
- Details of generic & brand name
- Description of Adverse event
- Severity & management required
- De-identified patient index information
- Dose, frequency and administration route
- Timing of onset and offset
- Medication indication & other relevant cofactors

Multiple methods are available for reporting including online, email, fax, telephone and post.

Further details on reporting for all therapeutic goods are available at: http://www.tga.gov.au/hp/problem.htm.
The database is publically accessible at: http://www.tga.gov.au/daen/daen-entry.aspx

Development and use of genomic predictive tests may be a possibility in the future, allowing a potential reduction in the incidence of ADRs, but proper reporting proves an important method for education, as well as managing and avoiding ADRs.

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

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Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

Role of aspirin in cancer prevention

A review of the literature surrounding aspirin's use in cancer prevention was recently published, utilising follow-up data from a number of systematic reviews and individual studies.

It is well established that aspirin at any dose can reduce the incidence of colorectal cancer (CRC). A 20-year follow-up of two high-dose aspirin randomised controlled trials (RCTs) showed an overall reduction in CRC incidence of 73% in participants scheduled on treatment for > 5 years, but the effect was seen only 10 years after randomisation. Similarly, long-term follow-up of three trials of aspirin at doses 75-300 mg/day showed a 25% reduction in CRC incidence but the effects were not apparent immediately and showed larger benefit with increasing duration of aspirin use. Two trials of alternate day aspirin use have not shown any reduction within 10 years of follow-up although a 43% reduction after 10 years was observed in the Women's Health Study.

Evidence for mortality reduction in CRC is based on a greater number of studies, and the effect size appears to be larger, than for incidence: a 40% overall reduction in mortality which rises to 52% with at least five years of scheduled treatment on aspirin.

Effects from observational studies in CRC are largely consistent with those from RCTs, and tend to show larger reductions for standard or high dose aspirin compared with low dose aspirin. In individuals at high risk of CRC (carriers of Lynch syndrome) a RCT showed a 63% reduction in CRC incidence among those completing two years of treatment with aspirin 600 mg daily.

Although data are less extensive, consistent reductions in mortality have also been seen for oesophageal cancer: a 58% reduction after five years of follow up in RCTs has been observed. A 43% reduction in incidence of oesophageal cancer was seen in case-control studies; cohort studies reported a 27% reduction. Similar, although smaller, reductions of incidence and mortality are seen with stomach cancer, although the data are less extensive and more variable. Small effects are seen for breast cancer and prostate cancer, with non-significant reductions in mortality. Evidence for mortality reduction in lung cancer is variable but generally favourable.

There is consistent evidence that long term use of aspirin is necessary to achieve a cancer prevention benefit, although the optimum dose and duration are not fully defined and the benefits are primarily seen in malignancies of the gastrointestinal tract. While aspirin's effects on cardiovascular mortality are only apparent during its time of administration, there is increasing evidence to suggest that aspirin's effect on overall long-term mortality may relate to its effect in reducing cancer deaths.

However, aspirin use is associated with an age-dependent risk of bleeding (especially gastrointestinal bleeding in people older than 70 years of age) as well as peptic ulcer. The incidence of haemorrhagic stroke is increased by approximately 30% from a baseline of 0.03% per year.

In the recently published literature review, the authors' 'best estimates' for individuals taking aspirin for 10 years give a relative reduction of 9% in the number of men and 7% in the number of women with a cancer, myocardial infarction or stroke over a 15-year period. Reductions in cancer incidence would account for 61-80% of the overall benefit and reductions in CRC alone would account for 30-36% of it. Major bleeding events would increase – depending on age and gender – by between 0.16% and 0.81% over their baseline rates of 0.57% to 2.37% over a 15 year period.

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

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Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

Dipeptidyl peptidase inhibitors for Type 2 diabetes

Diabetes is one of the world's fastest growing chronic diseases with 382 million people thought to be affected globally in 2013. It is currently estimated that this number will escalate to approximately 592 million by 2035. The prevalence of Type 2 Diabetes Mellitus (T2DM) is increasing in every country and the global financial cost associated with T2DM is estimated to be in the order of $10.3 billion. The use of dipeptidyl peptidase-4 (DPP-4) inhibitors as monotherapy agents can be expected to decrease glycated haemoglobin (HbA1c) by approximately 5 to 10%. However under the auspices of the Australian Pharmaceutical Benefits Scheme (PBS), DPP-4 inhibitors are not subsidised for use as monotherapy agents – instead, the clinical criteria for use in T2DM (obtained from the PBS website) are as follows:

- Treatment must be in combination with metformin OR a sulfonylurea
- Must have/have had HbA1c measurement > 7% despite treatment with either metformin/sulfonylurea, OR where HbA1c measurement is clinically inappropriate, blood glucose levels are greater than 10 mmol/L in more than 20% of tests over a two week period despite treatment with either metformin or a sulfonylurea
- Date and level of the qualifying HbA1c measurement must be/must have been, documented at the time treatment is initiated (HbA1c must be no more than 4 months old at the time treatment was initiated)
- Blood glucose monitoring may be used as an alternative assessment to HbA1c levels in the following circumstances (results must be no more than 4 months old at the time treatment was initiated): clinical condition with reduced red blood cell survival, including haemolytic anaemias and haemoglobinopathies and/or had red cell transfusion within the previous three months
- Those previously demonstrated to be unable to achieve adequate BGL control with metformin/sulfonylurea does not need to re-qualify on this criterion before being eligible for PBS-subsidised treatment

Below is a table summary of the DPP-4 inhibitors with the available dosages, trade name and combination products with metformin that are available as subsidised benefits through the Australian PBS:

DPP-4 Inhibitor	*Dosage*	*Trade Name*	*Combination Products with Metformin*
Alogliptin	25 mg daily	Nesina®	Nesina Met®
	12.5 mg daily if CrCl 30 to 50 mL/min		
	6.25 mg daily if CrCl less than 30 mL/min		
Linagliptin	5 mg daily	Trajenta®	Trajentamet®
Saxagliptin	5 mg daily	Onglyza®	Kombiglyze XR®
	2.5 mg daily if CrCl less than 50 mL/min		
Sitagliptin	100 mg daily	Januvia®	Janumet® Janumet XR®
	50 mg daily if CrCl 30 to 50 mL/min		
	25 mg daily if CrCl less than 50 mL/min		
Vildagliptin	50 mg daily OR twice daily	Galvus®	Galvumet®
	50 mg daily if CrCl less than 60 mL/min		

XR = extended release; CrCl = creatinine clearance; please note various different strengths are available with DPP-4 inhibitor combination products with metformin – visit Australian Medicines Handbook, MIMS Online or the PBS website for more information about combinations.

It is important to note that long-term safety and efficacy of the DPP-4 inhibitors are still limited and are still undergoing further studies.

Acknowledgment – This E-Bulletin is based on work by Allen Lau, Utility Pharmacist, RGH

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

References used in the preparation of the relevant E-Bulletins:

Australian Asthma Handbook website – www.asthmahandbook.org.au. Accessed 11 August 2014.

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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

In the 2014 update of the Australian Asthma Handbook, a key management principle is that:

a. long-acting beta agonist medications should always be used for symptom management only
b. long-acting beta agonist medications should always be used in combination with inhaled corticosteroids
c. long-acting beta agonist medications should never be used in combination with inhaled corticosteroids
d. none of the above

In the parameters of the 2014 update of the Australian Asthma Handbook a patient needing a regular high dose of an ICS and a long acting beta2 agonist (LABA) to maintain good asthma control would be classified as having:

a) mild persistent asthma
b) chronic moderate asthma
c) severe asthma
d) intermittent asthma

Which of the following types of allergic adverse drug reaction is typically mediated by IgE?

a) type I
b) type II
c) type III
d) type IV

Which of the following reactions would best be described as a drug intolerance?

a) rash following administration of penicillin
b) nausea after administration of an opioid
c) elevated INR in an anticoagulated patient treated with itraconazole
d) anaphylaxis after administration of docetaxol

The long-term administration of aspirin has been shown to reduce the incidence of:

a) mesothelioma
b) melanoma
c) astrocytoma
d) colorectal cancer

Which of the following statements is most accurate about the effects of aspirin in reduction of cancer risk?

a) the effects become apparent after as little as several months of aspirin use
b) alternate day dosage regimens are just as good as those involving daily use
c) the effect size increases with longer duration of therapy
d) the effects are not accompanied by a change in the risk for bleeding

The usual dosage of sitagliptan in the absence of significant renal impairment is:

a) 12.5 mg daily
b) 25 mg daily
c) 50 mg daily
d) 100 mg daily

Which of the following issues potentially invalidates the use of HbA1c measurement for assessment of diabetic control?

a) treatment with iron supplements
b) haemolytic anaemia
c) recent bruising
d) kidney failure