RGH E-Bulletin Digest Number 88

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 88 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 59-12→ 60-3 (August and September 2015).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Describe risk factors for cardiovascular syndromes associated with NSAID use
- Understand potential relationships between CCF exacerbation and some treatments for diabetes
- Discuss the potential relationship between varenicline treatment and neuropsychiatric adverse effects
- List contraceptive options for women affected by migraine.

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.

Accreditation number: A1512AP1.
This activity has been accredited for 0.5 hours of Group 1 CPD (or 0.5 CPD credits) suitable for inclusion in an individual pharmacist's CPD plan which can be converted to 0.5 hours of Group 2 CPD (or 1 CPD credit) upon successful completion of relevant assessment activities.

apc ACCREDITED CPD

Chris Alderman B Pharm, FSHP, BCPP (USA), CGP

Chris Alderman is the Director of Pharmacy at the Repatriation General Hospital in Daw Park, South Australia, and also holds a dual appointment as Associate Professor, Pharmacy Practice at the Quality Use of Medicines and Pharmacy Research Centre, University of South Australia.

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.

AusPharm gratefully acknowledges the financial support provided by the sponsors of our CPD program, **MIMS**

MIMS 100% pure knowledge

RGH Pharmacy E-Bulletin

Volume 59 (12): August 31 2015

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

Concerns over NSAIDS & adverse cardiovascular effects

Anti-inflammatory drugs are among the most commonly used medications in the world, being available over-the-counter and by prescription. Adverse effects on renal function, blood pressure and gastrointestinal mucosa have been well-defined in the literature and in practice. Their potential to cause cardiovascular adverse events such as MI, stroke, HF and even death is known but less well-defined. The Australian Therapeutic Goods Administration has conducted a review on the cardiovascular safety of non-steroidal anti-inflammatory drugs, releasing the findings in October 2014.

Selective COX-2 inhibitors were developed as promising new agents thought to be associated with less gastrointestinal side effects compared to non-selective NSAIDs, however they were not without their drawbacks. Rofecoxib was one of the first marketed selective COX-2 Inhibitors but this was pulled from the market in 2004 as it was associated with increased incidence of heart attack and stroke, thought to have caused as many at 140,000 heart attacks in the US. This raised awareness of the cardiovascular adverse effects of NSAIDs and led to their black box warning in 2005.

It is thought that concomitant use of non-selective NSAIDs (particularly ibuprofen) with low dose aspirin negates its antiplatelet effect by competing with aspirin at the COX-1 binding site in platelets, thereby preventing the irreversible acetylation of platelets. Diclofenac has not been shown to interact with aspirin in this way and neither has celecoxib (a selective COX-2 inhibitor which has also exerts some COX-1 inhibition). A nationwide study in Denmark followed patients from 2002 to 2011 whilst they were taking antithrombotic agents after their first MI. Patients taking NSAIDs (90% were non-selective) had a significantly greater risk of experiencing a cardiovascular event (HR 1.40). Taking the NSAID separately (2 hours apart from aspirin) may prevent this issue, but it is better to avoid the NSAID altogether.

More recent studies have revealed that both selective and non-selective NSAIDs carry a risk of cardiovascular adverse events even in relatively healthy patients. It was previously thought that short term use for acute inflammation was considered safe, however emerging data suggests that even short term use is associated with adverse events in patients with no known cardiovascular disease. With most non-steroidal anti-inflammatories higher doses and longer durations of treatment carry the greatest risk. Naproxen is an exception which appears to have anti-platelet activity at higher doses, whereas lower doses are associated with increased risk of MI and stroke (however the higher doses still confer greatest risk of renal and gastrointestinal adverse effects). No studies have been designed to determine which NSAID is superior over another for safety, however naproxen appears to be the preferred agent in terms of cardiovascular adverse effects.

NSAIDs (both selective and non-selective) cause fluid retention, renal insufficiency and can exacerbate heart failure. NSAIDs have been shown to double the risk of heart failure, with selective COX- Inhibitors being the worst offenders. They are unlikely to cause heart failure in the absence of cardiovascular disease but they have been shown to increase the risk of hospitalisation for heart failure two-fold and they display a dose dependent increased overall mortality risk. The risk of AF and VTE have been described in the literature however further studies are required to draw firm conclusions. The mechanism for which NSAIDs may cause AF is unknown.

The available evidence regarding the safety of NSAIDS when used in patients with cardiovascular risk factors is highly complex. The individual risk factors for each individual patient and the risk profile of individual NSAIDs needs to be considered when recommending NSAIDs to people with cardiovascular conditions, even when the planned use is short term. The relative risk of a cardiovascular event is estimated to range from 10 to greater than 50% depending on the patient's baseline risk, the NSAID used and dose. Using the lowest dose (naproxen being an exception) for the shortest duration may minimise the risk of cardiovascular events. In patients with known cardiovascular disease who require anti-inflammatory treatment for short or long term, naproxen appears to be the preferred agent. Alternative therapies should also be considered however emerging data suggests that opioids may also be associated with cardiovascular risk.

Acknowledgment – This E-Bulletin based on work by Juliet Kurtze, Clinical Pharmacist, RGH

FOR FURTHER INFORMATION – CONTACT PHARMACY DEPARTMENT ON 08 7425 0040 or email: chris.alderman@sa.gov.au

RGH Pharmacy E-Bulletin

Volume 60 (1): September 7 2015

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

Gliptins and heart failure

Dipeptidyl-peptidase 4 (DPP-4) inhibitors, or gliptins, have become a popular choice for treatment of type 2 diabetes. There are currently five different DPP4 inhibitors registered in Australia, four of which have FDA approval (sitagliptin, saxagliptin, linagliptin and aloglitpin). The side effect profile of these medications is of particular interest, being a relatively new class of medication, and the first class of oral diabetic medications to enter the market since the post-marketing cardiac safety concerns with rosiglitazone and pioglitazone. In 2008, the FDA mandated that new diabetic medications undergo rigorous evaluation to determine potential cardiac risks. As a result, multiple safety trials have been developed to elucidate the safety of the gliptins.

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) trial was developed to determine cardiovascular safety of saxaglitpin. 16,942 patients at risk for cardiovascular events, were randomly assigned to saxaglitin or placebo, and followed over 2 years. No increase in acute myocardial infarction, strokes or cardiovascular death were found, however there was a 27% increase in hospitalisation for cardiac failure. The FDA has since requested further trial data from the drug company and will undertake further safety analyses.

The cardiovascular safety of alogliptin was tested in the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) trial, which included patients with type 2 diabetes and acute myocardial infarction, or unstable angina, within 15–90 days before randomization. The primary endpoint was a composite of death from cardiovascular causes, non-fatal myocardial infarction, and non-fatal stroke. No difference in the primary outcome was found between alogliptin and placebo. Similarly, the EXAMINE trial did not find a significant increase in hospitalizations for heart failure, however, there was a trend towards an increase in hospitalizations.

The Trial Evaluating Cardiovascular Outcomes of Sitaglitpin (TECOS) has recently been published in the New England Journal of Medicine. 14,761 Patients were assigned to sitagliptin or placebo, and followed up for 3 years. There was no significant difference in in the risk of cardiovascular death, non-fatal MI or non-fatal stroke. Importantly, rates of hospitalization did not differ between groups.

Currently, The Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients with Type 2 Diabetes (CAROLINA), is underway and will provide further insight into the safety risks associated with linagliptin.

It appears that there may be a difference in risk of heart failure between the gliptins, however there is no current mechanistic explanation for this. The latest TECOS trial has provided some reassurance to prescribers that the most popular gliptin may still be a reasonable option for use in heart failure patients. Earlier this year, the FDA sub-committee voted to update label changes for saxagliptin and aloglitpin, however no prescribing restrictions have been put in place at this stage.

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

FOR FURTHER INFORMATION – CONTACT PHARMACY DEPARTMENT ON 08 7425 0040 or email: chris.alderman@sa.gov.au

RGH Pharmacy E-Bulletin

Volume 60 (2): September 14 2015

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

Varenicline and neuropsychiatric adverse effects: an update

Varenicline is a selective α4β2 nicotine acetylcholine receptor partial agonist indicated as an aid to stopping cigarette smoking. It reduces withdrawal symptoms from nicotine dependence and the pleasurable effects of smoking.

In terms of comparative efficacy compared against other agents for nicotine dependence, a *Cochrane* systematic review from 2013 found that varenicline more than doubled the chances of quitting compared with placebo, so that for every 10 who quit with placebo about 28 could be expected to quit with varenicline (compared to 18 expected to quit with nicotine replacement therapy (NRT) or with bupropion). For every 10 people who quit with NRT patch or lozenge, about 15 could be expected to quit with varenicline, and for every 10 who quit with NRT gum about 17 could be expected to quit with varenicline. Combining two types of NRT was estimated to be as effective as using varenicline.

However, in terms of safety, there has been much discussion of the possible association between varenicline and neuropsychiatric adverse effects (AEs). In post-marketing surveillance there were a number of reports of new onset or worsening depression, suicidal ideation and suicide associated with varenicline. The US FDA and European Medicines Agency issued warnings that serious neuropsychiatric symptoms had occurred in smokers trying to quit with varenicline, and the FDA applied a black box warning about neuropsychiatric events. A confounding factor is that smoking cessation and nicotine withdrawal are closely linked with sleep disturbance and depression.

Despite the developments discussed above, there has been evolving evidence that challenges the basis for a direct causal relationship between varenicline and neuropsychiatric AEs. The 2013 Cochrane review concluded there is no compelling evidence that varenicline is linked to an increased risk of neuropsychiatric AEs. This is supported by another metaanalysis published March 2015, which found no evidence of an increased risk of suicide or attempted suicide, suicidal ideation, depression, or death associated with varenicline. Furthermore, subgroup analysis of those with psychiatric illness at baseline found the risk of depression or suicidal ideation amongst those who used varenicline did not differ from the group without psychiatric illness at baseline. There was evidence that varenicline was associated with already recognised AE of insomnia, abnormal dreams and fatigue. Similarly, the results of two recent cohort studies from Sweden and England found no increase in depression or self-harm with varenicline.

While it remains important to closely monitor patients taking varenicline, especially those with pre-existing psychiatric conditions, there is evidence that this sub-group do not appear to be an increased risk of neuropsychiatric AE when attempting smoking cessation aided by the use of varenicline, when compared to other modalities.

Acknowledgment – This E-Bulletin based on work by Joy Gailer, Senior Clinical Pharmacist, DATIS, RGH

FOR FURTHER INFORMATION – CONTACT PHARMACY DEPARTMENT ON 08 7425 0040 or email: chris.alderman@sa.gov.au

RGH Pharmacy E-Bulletin

Volume 60 (3): September 21 2015

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

Contraception in women with a history of migraine

A recent E-Bulletin discussed the World Health Organization (WHO) "Medical eligibility criteria for contraceptive use" (see http://www.auspharmlist.net.au/ebulletin/vol58/eb58-2.pdf). The 5th edition of the WHO document was recently published. To view the updates for the full document, the executive summary and the medical eligibility criteria wheel for contraceptive use, see the following link: http://www.who.int/reproductivehealth/publications/family_planning/en/ A quick reference chart can be found at the following link: http://www.fhi360.org/sites/default/files/media/documents/chart-medical-eligibility-contraceptives-english.pdf When considering the choice of a contraceptive method, one of the important considerations is whether the woman has a history of migraine with or without aura. This will influence the decision as to which contraceptive method may be used.

Migraine with aura

Migraine with aura is common in females of reproductive age & increases relative risk of ischaemic stroke two-fold, and this risk may be increased further if the woman smokes cigarettes or uses a combined oral contraceptive (COC). Use of a COC for a person with a history of migraine with aura is considered to be an unacceptable health risk and has a Medical Eligibity Category (MEC) category of 4 (refer table below). The Australian Medicines Handbook (AMH) states that COCs are contraindicated in women with migraine with aura. For those with a history of migraine with aura who have not had an episode for more than five years, the risk of using a COC usually outweighs the benefit and has a MEC category of 3. It is also important to note that those who use COCs and have a history of migraine with aura have 6–14 times increased odds of ischaemic stroke compared with non-users of COCs who do not have a history of migraine with aura.

Migraine without aura

Previous evidence suggested that females with migraine without aura were at increased risk of ischaemic stroke; however, this was not confirmed in a subsequent meta-analysis. The AMH states that COCs are generally not recommended at an age of ≥ 35 years for those with migraine without aura. While it is generally safe to use hormonal contraceptives other than COCs in most females with a history of migraine without aura, it is important that additional risk factors for ischaemic stroke, such as cigarette smoking, high blood pressure and obesity, be should be considered.

The following table provides a summary of the recommendations from the WHO's "Medical eligibility criteria for contraceptive use" for the various contraceptives available in Australia.

Condition		**Medical eligibility criteria (MEC) category for contraceptive use**			
		COC, CVR	**POP**	**ENG implant, DMPA, LNG-IUD**	**Cu-IUD**
Migraine with aura (at any age)	Initiation	4	2	2	1
	Continuation	4	3	3	1
Migraine without aura and age < 35 years	Initiation	2	1	2	1
	Continuation	3	2	2	1
Migraine without aura and age ≥ 35 years	Initiation	3	1	2	1
	Continuation	4	2	2	1

COC = combined oral contraceptive; CVR = combined contraceptive vaginal ring; POP = progestogen only pill, ENG = etonogestrel; DMPA = depot medroxyprogesterone acetate; LNG-IUD = levonorgestrel intrauterine device; Cu-IUD = copper intrauterine device
MEC 1 = a condition for which there is no restriction for the use of the contraceptive method.
MEC 2 = a condition where the advantages of using the method generally outweigh the theoretical or proven risks.
MEC 3 = a condition where the theoretical or proven risks usually outweigh the advantages of using the method.
MEC 4 = a condition which represents an unacceptable health risk if the contraceptive method is used.

Acknowledgment – This E-Bulletin based on work by Tania Colarco and Tricia Warrick, Senior Clinical Pharmacists, DATIS, RGH

FOR FURTHER INFORMATION – CONTACT PHARMACY DEPARTMENT ON 08 7425 0040 or email: chris.alderman@sa.gov.au

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

Australian Government Department of Health, 2014, Review of Cardiovascular safety of non-steroidal anti-inflammatory drugs - Version 2.1, TGA, Released Oct 2014

Shao-Yuan Chuang, Yunxian Yu, Wayne Huey-Herng SHeu, Yu-Ting Tsai, Xin Liu, Chao A. Hsiung and Hui-Ju Tsai, 2015, 'Associatin of short-term use of Nonsteroidal Anti-inflammaotry drugs with stroke in patients with Hypertension', Stroke, 46:996-1003

Soloman, D, UpToDate – Nonselective NSAIDs: Adverse cardiovascular effects, Last updated Mar 23 2015, accessed 13/8/15

Solomon, D, UpToDate – COX-2 Selective Inhibitors: Adverse cardiovascular effects, Last updated Jul 08 2015, accessed 13/8/15

US Department of Health and Human Services, FDA Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks and strokes, released 7/9/15, accessed 13/8/15 www.fda.gov/Drugs/DrugSafety/ucm451800.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery

Brown, Parker (2015, April 04). FDA Panel Wants HF Warning on Gliptin Drugs. Medpagetoday. Retrieved 20/08/2015 from http://www.medpagetoday.com/Cardiology/Diabetes/51003

Green JB, Bethel MA, Armstrong PW, Buse JB, et al.; TECOS Study Group. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2015 Jul 16;373(3):232-42.

O'Riordan, MIchael (2015, June 08). TECOS: No CVD Risks or Heart Failure With Sitagliptin In High-Risk Diabetic Patients. Medscape. Retrieved 20/08/2015 from http://www.medscape.com/viewarticle/846075

Scirica BM, Bhatt DL, Braunwald E, et al; for the SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317-1326

White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327-1335

World Health Organization. Medical eligibility criteria for contraceptive use. 5th edition, 2015. Accessed on 14 September 2015. http://apps.who.int/iris/bitstream/10665/181468/1/9789241549158_eng.pdf?ua=1

World Health Organization. Medical eligibility criteria for contraceptive use. 5th edition, 2015. Executive summary. Accessed on 14 September 2015. http://apps.who.int/iris/bitstream/10665/172915/1/WHO_RHR_15.07_eng.pdf?ua=1

World Health Organization. Medical eligibility criteria wheel for contraceptive use. 2015. Accessed on 14 September 2015. http://apps.who.int/iris/bitstream/10665/173585/1/9789241549257_eng.pdf?ua=1
Australian Medicines Handbook 2015 [online]. Adelaide: Australian Medicines Handbook Pty Ltd; 2015 January. http://www.amh.net.au. Accessed on 14 September 2015.

Family Planning New South Wales, Queensland and Victoria. Contraception: an Australian clinical practice handbook. 3rd ed. Family Planning New South Wales, Queensland and Victoria, 2012.

Quick reference chart for the WHO Medical eligibility criteria for contraceptive use. http://www.fhi360.org/sites/default/files/media/documents/chart-medical-eligibility-contraceptives-english.pdf Accessed on 14 September 2015.

AusPharm CPD MCQs

Questions based on the above articles:

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

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

Concomitant use of non-selective NSAIDs with low dose aspirin influences the antiplatelet effect of the latter by:

a) competing with aspirin at the COX-1 binding site preventing the irreversible acetylation of platelets
b) adding to the effects of aspirin at the COX-1 binding site
c) competing with aspirin at the COX-2 binding site preventing the irreversible acetylation of platelets
d) adding to the effects of aspirin at the COX-2 binding site

An adverse effect NOT usually associated with NSAIDS is:

a) GIT toxicity
b) cognitive decline
c) elevation of blood pressure
d) fluid retention

Which of the following is a Dipeptidyl-peptidase 4 (DPP-4) inhibitor?

a) exanatide
b) sildenafil
c) paracoxib
d) sitagliptin

The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) trial:

a) found association between treatment and increased risk of myocardial infarction
b) showed that treatment was associated with haemorrhagic strike
c) revealed an association between treatment and increased risk of hospital admission secondary to CCF
d) none of the above

A Cochrane systematic review found that varenicline increased the chances of quitting compared with placebo, so that for every 10 who quit with placebo:

a) about 10 could be expected to quit with varenicline
b) about 12 could be expected to quit with varenicline
c) about 16 could be expected to quit with varenicline
d) about 28 could be expected to quit with varenicline

A 2013 Cochrane review found:

a) no evidence that varenicline is linked to increased neuropsychiatric side effects
b) weak evidence that varenicline is linked to increased neuropsychiatric side effects
c) moderate evidence that varenicline is linked to increased neuropsychiatric side effects
d) strong evidence that varenicline is linked to increased neuropsychiatric side effects

The Australian Medicines Handbook (AMH) states that Combined Oral Contraceptives (COCs) are:

a) useful for women affected by with migraine with aura.
b) should be used with care by women affected by with migraine with aura
c) contraindicated for women affected by migraine with aura
d) may be lethal for women affected by with migraine with aura

While it is generally safe to use hormonal contraceptives other than COCs in most women with a history of migraine without aura, important additional risk factors for ischaemic stroke include:

a) cigarette smoking
b) hypotension
c) alcohol use
d) none of the above