RGH E-Bulletin Digest Number 69

The next in our 2014 series of continuing professional development activities is the RGH E-Bulletin Digest No. 69 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 53-4 → 53-7 (January/February 2014).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Describe the various geriatric syndromes caused by medicines
- Discuss aspects of the relationship between hypomagnesaemia and treatment with PPIs
- List safety concerns related to the use of Electronic Cigarettes
- Outline principles that should be considered during antidepressant changeover.

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 hr of Group One CPD (0.5 CPD Credits) that may be converted to 1 Group Two CPD Credit upon successful completion of the corresponding assessment for inclusion on an individual pharmacist's CPD Record. **Accreditation number: A1405AP2**.

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RGH Pharmacy E-Bulletin

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

Medication-related geriatric syndromes

Many (if not most) older people will eventually develop medical complications that are referred to as *geriatric syndromes*. It is common for the underlying cause to be multifactorial and to have manifestations that involve multiple organ systems. There may be a cascade effect, where one geriatric syndrome may contribute to/exacerbate several others. It is quite common for a number of geriatric syndromes to be present in the same patient simultaneously, rendering treatment complex and difficult. Drug treatment can both contribute to, and be a part of the management of geriatric syndromes: polypharmacy is common amongst the elderly, and there is a complicated balance required in the adjustment of pharmacotherapy to achieve optimal treatment outcomes and reduce the likelihood of iatrogenic complications for older people. Doctors, pharmacists and nurses and other health professionals will need to work cooperatively to identify, document, manage and prevent geriatric syndromes that are potentially medication-related. Although not exhaustive, a range of examples of geriatric syndromes that may be related to medications is provided here:

Weight-loss, nutritional defects
Drugs may contribute to inadequate calorie intake through adverse effects such as dysphagia, anorexia, nausea, dysguesia (distortion of the sense of taste) and a lack of saliva production. Drugs associated with weight loss include antidepressants (particularly serotonin reuptake inhibitors and venlafaxine), some anticonvulsants (especially topiramate, which is also used for other therapeutic applications, such as migraine prophylaxis), theophylline and some antibiotics. Some medications are associated with specific nutritional defects: vitamin D deficiency can result from treatment with anticonvulsants such as carbamazepine, phenytoin and valproate), vitamin B12 deficiency is sometimes related to treatment with metformin; phenytoin and possibly also proton pump inhibitors (PPIs). Hypomagnesaemia has been associated with PPI treatment, and may cause symptoms such as leg cramps and cardiac rhythm abnormalities.

Falls
Many drugs may contribute to falls and injuries experienced by older people, mediated through a range of mechanisms. Medications that can alter orthostasis may contribute to falls through postural hypotension – examples include antidepressants (especially tricyclic antidepressants and MAOIs), antipsychotics, diuretics, calcium channel blockers, clonidine, nitrates and others. Other mechanisms for drug-related falls include CNS suppression (antidepressants, analgesics, antipsychotics, benzodiazepines and many others), and disturbances in eyesight (refer below).

Delirium
Although the precise cause for delirium in an older person may not be isolated, medications can certainly contribute: common examples include corticosteroids, psychotropic drugs, and drugs with significant anticholinergic effects.

Visual impairment
Medications can contribute to visual disturbances through many mechanisms – examples are as diverse as scotoma (an area of partial alteration in the field of vision) related to digoxin toxicity, anticholinergic-induced blurred vision, steroid-associated cataracts, and many others.

Many other geriatric syndromes may be related to medications, including clinically important syndromes such as pressure sores, incontinence, muscle weakness, constipation, osteoporosis, sleep disturbance and pain syndromes.

Acknowledgment – This E-Bulletin is based on work by Chris Alderman, RGH.

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Hypomagnesaemia and Proton Pump Inhibitors

Magnesium is an essential electrolyte involved in a large number of enzymatic processes including muscle contraction, hormonal reactions and energy metabolism. It is also used in the Na+/K+-ATPase cellular pump. Low serum magnesium results in an increase in intracellular sodium with reduction in intracellular potassium. Hypomagnesaemia can also be associated with lower calcium and phosphate concentrations. Clinical consequences of hypomagnesaemia include nausea, fatigue, delirium, muscle cramps, cardiac arrhythmias and seizures; however some patients do not report any symptoms.

Hypomagnesaemia associated with medicines
Low magnesium has been associated with a number of medicines including aminoglycosides, amphotericin, cyclosporin, tacrolimus, alcohol, thiazide and loop diuretics. The toxicity of digoxin is increased in patients with low magnesium (as well as those with low potassium). Proton pump inhibitors (PPIs) have also been implicated in hypomagnesaemia.

Evidence linking PPIs and hypomagnesaemia
In 2006 two Australian case reports identified a link between long-term use of PPIs and hypomagnesaemia. In 2011 the Therapeutic Goods Administration (TGA) in Australia reported six cases and the same year the US FDA advised prescribers of this potential adverse effect based on more than 38 cases in the USA. While there are case reports, there have been few clinical trials examining hypomagnesaemia with PPIs. Most cases occurred after long-term PPI therapy (greater than one year) and were independent of dose. Hypomagnesaemia appears to be an effect seen across all drugs in the class.

Suggested Pathophysiology
Magnesium regulation is controlled by intestinal absorption and renal excretion. Case reports have demonstrated that PPIs do not affect renal excretion but interfere with transport mechanisms in the small intestine. The simple diffusion/passive transport mechanism results in the absorption of approximately about 7% of orally ingested magnesium. As magnesium concentrations in the intestine increase, more magnesium is absorbed. The active transport mechanism involving the transient receptor potential melastin (TRPM-6 and -7) channels increase in activity when GI magnesium levels are low, increasing magnesium absorption. It is postulated that the change in gastrointestinal pH caused by PPIs affects the active transport channels or their protein kinase activity, resulting in hypomagnesaemia once body stores are eventually reduced.

Management
Stopping PPI treatment usually results in the return of magnesium concentrations to the normal range, usually within one to two weeks. In the hospital setting patients can be supplemented intravenously with 10mmol (one 5ml ampoule) in 100ml of 0.9% sodium chloride infused over an hour, repeated if necessary. Calcium concentrations should also be monitored as sulphate anions may bind calcium. Intravenous magnesium may also initially reduce potassium levels. Sustained oral correction may be necessary with magnesium aspartate (1.66 mmol per Mg tablet), using two to four tablets daily (there is a slow adjustment between the serum concentration and that in intracellular spaces and tissues). Patients who require ongoing treatment with a PPI will need to continue with oral magnesium supplementation.

Summary
Serum magnesium concentrations should be monitored for patients treated with long-term PPI therapy. Long-term oral magnesium replacement may be required or the proton pump inhibitor may need to be ceased if supplementation is not sufficient. Magnesium supplements can cause diarrhoea for some patients. Absorption of tetracyclines and quinolones is compromised by co-administration or oral magnesium, so these antibiotics should be spaced at least two hours apart from magnesium.

Acknowledgment – This E-Bulletin is based on work by Lenore Janssen, Senior Clinical Pharmacist, RGH.

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Electronic cigarettes for smoking cessation

Electronic cigarettes (E-cigarettes) are battery operated devices for making mists for inhalation that usually simulate cigarette smoking. They may or may not contain nicotine plus other chemicals or flavouring. E-cigarettes may appeal to some smokers as a smoking cessation aid. They can be accessed in many countries without the restrictions around medicines that apply to licensed nicotine replacement therapy (NRT), or without costly involvement of health professionals. They may be considered safer than cigarettes.

A randomised controlled trial comparing E-cigarettes to nicotine patches or placebo e-cigarettes for smoking cessation was published in 2013. The abstinence from cigarettes was substantially lower than expected so there was insufficient statistical power to draw conclusions about the possibility that e-cigarettes might prove to be superior to nicotine patches or placebo cigarettes. In this study the authors did conclude that e-cigarettes were at least as effective as nicotine patches. The 6 month tobacco smoking abstinence rates achieved with E-cigarettes, nicotine patches and placebo E-cigarettes were 7.3%, 5.8% and 4.1% respectively). Prior to this trial, NRT trials have included careful supervision and monitoring of treatment adherence, but this trial incorporated minimal patient support. The quit rates were low, perhaps demonstrating the need for more support or counselling (i.e. more healthcare involvement).

Concerns about E-cigarettes include a belief that they may attract new recruits – that is, people who have never smoked. It is also thought that it is possible that this approach may actually reduce quit attempts, therefore increasing smoking rates - ”renormalising smoking”. In public places where smoking tobacco cigarettes is banned, access to nicotine with e-cigarettes is possible, providing a mechanism for maintaining addiction.

Tobacco smoking has become socially unacceptable but e-cigarettes are gradually being promoted, with advertising that includes endorsement by celebrities who are role models to young people. E-cigarettes have not been tested for quality and safety (unlike NRT which has been approved by the TGA and is regulated under various frameworks in different jurisdictions). Some studies suggest that e-cigarettes may deliver unreliable doses of nicotine, may contain toxic chemicals or carcinogens, and that the devices may leak nicotine, posing a hazard to users and others around. Lethal doses of nicotine can be absorbed topically.

The European Union and UK are proposing to regulate E-cigarettes as medicinal devices. Denmark, Lithuania and Slovenia already regulate them as medicines. E-cigarettes in Australia are not approved quit smoking devices or NRT devices. In South Australia the Tobacco Products Regulation Act 1997 states “A person must not sell by retail any product (other than a tobacco product) that is designed to resemble a tobacco product.” Other Australian states have similar legislation.

The increasing use of e-cigarettes as an aid to quit smoking cannot be ignored. Whether they are made available to consumers as a health care product or not may impact a future generation of nicotine dependence.

Acknowledgment – This E-Bulletin is based on work by Nicky Gordon, Senior Clinical Pharmacist, RGH.

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

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Antidepressant changeover

Selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs) and mirtazapine are usually the first line pharmacological treatment choices for depression, but antidepressant choice also depends on individual patient factors. Different antidepressants may need to be trialed to find the most effective and best tolerated therapy in an individual patient. Switching antidepressants may be necessary if there has been an inadequate response, or the patient has experienced an adverse drug reaction. The general principles of antidepressant changeover are to taper and cease the current antidepressant, ensure a drug- free period or 'washout' before commencing the new antidepressant, and introduce the new antidepressant at a low dose. When ceasing antidepressants, higher doses should be gradually tapered to reduce the risk of withdrawal effects, unless there is a medical reason that necessitates abrupt cessation (e.g. adverse drug reaction). Discontinuation symptoms may include dizziness, flu-like symptoms, nausea and anxiety. Discontinuation symptoms are more likely with drugs that have a short half-life such as paroxetine and venlafaxine. Fluoxetine is the least likely antidepressant to cause discontinuation symptoms due to its long half-life.

Antidepressant free intervals are recommended when changing antidepressants, to reduce the risk of serotonin toxicity and other drug interactions. The drug free intervals are based on the pharmacokinetics of the antidepressant being ceased as well as its metabolites. No antidepressant free interval is necessary when changing between two short acting SSRIs or between two tricyclic antidepressants. When changing from fluoxetine to another antidepressant, antidepressant free periods of at least a week are recommended as fluoxetine or its metabolites can be present for 5 weeks after cessation, which may result in drug interactions. Patients should be carefully monitored during antidepressant changeover and assessed individually to determine how quickly the changeover should occur. In cases of severe depression, hospitalisation may be necessary during this time.

Category A changeover: drug (or metabolites) with long half-life or persistent effects	
Fluoxetine, phenelzine, tranylcypromine	• gradual withdrawal generally unnecessary; withdrawal symptoms very unlikely • wait for at least 14 days before starting next antidepressant • consider hospitalisation during washout/changeover if severely depressed
Category B changeover: drug (or metabolites) with intermediate half-life of 24–48 hours	
TCAs, SSRIs (except fluoxetine), mianserin, mirtazapine	• withdraw gradually to prevent withdrawal symptoms (particularly if higher dose or long-term use); usually reduce dose by 25% per day • wait for 2–4 days before starting next antidepressant • consider hospitalisation during washout/changeover if severely depressed • *mianserin*: withdrawal symptoms rare
Category C changeover: drug (or metabolites) with short half-life of <18 hours	
Agomelatine, moclobemide, reboxetine, SNRIs	• *SNRIs*: withdraw gradually to prevent withdrawal symptoms • *agomelatine, moclobemide, reboxetine*: withdrawal symptoms not reported or rare • wait for 1–2 days before starting next antidepressant

Source: Australian Medicines Handbook, 2013 edition

Acknowledgment – This E-Bulletin is based on work by Dasha Loutchkina, Senior Clinical 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:

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Epstein M, McGrath S, Law F. Proton-pump inhibitors and hyomagnesemic hypoparathyroidism. The New England Journal of Medicine. 2006:335(17): 1834-6.

Shabajee N, Lamb Ej, Sturgess I, Sumathipala RW. Omeprazole and refractory hyomagesaemia. BMJ. 2008; 337:173-5.

U.S. Food and Drug Administration. FDA Drug Safety Communication: Low magnesium levels can be associated with long-term use of Proton Pump Inhibitor Drugs (PPIs): www.fda.gov/Drugs/DrugSafety/ucm245011.htm

Australian Government Department of Health TGA: www.tga.gov.au/consumers/ecigarettes.htm

Bullen C et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet 2013; 382: 1629 – 37

UpToDate Topic 1716 v 12.0 Antidepressant medication in adults: switching and discontinuing medication. www.uptodate.com

MCQs

Questions based on the above articles:

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

Treatment with which of the following is NOT regarded as an iatrogenic risk factor for falls amongst the elderly?

a) antibiotics
b) antihypertensives
c) antidepressants
d) anticonvulsants

Scotoma is an ocular effect associated with which of the following drugs?

a) amiodarone
b) sotalol
c) quinidine
d) digoxin

Hypomagnesaemia is associated with which of the following drugs?

a) cyclosporin
b) frusemide
c) gentamicin
d) all of the above

Which of the following statements is correct in relation to hypomagnesaemia related to treatment with Proton Pump Inhibitors?

a) hypomagnesaemia is most common with pantoprazole
b) the severity of hypomagnesaemia is greatest with esomeprazole
c) hypomagnesaemia has been observed with all of the PPI agents
d) none of the statements could be regarded as correct

Electronic cigarettes are used to deliver mist that simulates smoking. The devices are:

a) electrically powered using a battery
b) powered by the user's own respiratory force
c) only set up to deliver vaporised nicotine and contain no other substances
d) much less costly to use than actual cigarettes

Concerns expressed about Electronic Cigarettes include:

a) this form of nicotine use may contribute to greater social acceptability of the practice
b) new "smokers" could be recruited to the practice by aggressive advertising or celebrity endorsement
c) unlike other forms of nicotine replacement therapy, the dose of nicotine delivered may be unreliable
d) all of the above

Caution is required when changing from one antidepressant to the next, to avoid:

a) serotonin toxicity
b) excessive sedation
c) cholinergic toxicity
d) intractable insomnia

Under normal circumstances, which of the following agents would require the longest drug-free washout period before commencing the next antidepressant drug during changeover:

a) paroxetine
b) moclobemide
c) fluoxetine
d) doxepin