RGH E-Bulletin Digest Number 75

The next in our 2014 series of continuing professional development activities is the RGH E-Bulletin Digest No. 75 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 57-2→10 (August 2014).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Discuss the principles of treatment of psoriatic arthritis with apremilast
- Outline key aspects of the "Choosing Wisely®" geriatrics guidance
- Describe the clinical pharmacology of midodrine.

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: A1411AP0.

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.

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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.

Psoriatic arthritis and apremilast

Apremilast has been approved in 2014 by the United States Food and Drug Administration – it is an orally administered agent that is used for the treatment of psoriatic arthritis. At the time of writing, this agent does not currently have approval from the Therapeutic Goods Administration for use in Australia.

Psoriatic arthritis treatment is based upon interventions for the cutaneous manifestations of psoriasis and for the management of associated inflammatory arthritis. With current therapy, some, but not most, of those treated may achieve a remission but the majority of treated patients will relapse. The choice of drug is best co-ordinated between rheumatologist and dermatologist (as some drugs to treat arthritis may have a deleterious effect on the skin). Also, the various agents used for psoriatic arthritis may produce quite different responses for manifestations affecting the skin and joints.

It is known that apremilast inhibits phosphodiesterase 4 (PDE 4)), an action specific for cyclic adenosine monophosphate (cAMP) and resulting in increased intracellular cAMP levels. cAMP signals various physiological cell changes, mediates the action of many hormones and controls a range of pro-inflammatory and anti-inflammatory mediators. Other drugs for psoriatic arthritis tend to be specific for particular inflammatory mechanisms – these include NSAIDs, orally administered DMARDs, TNF inhibitors, interleukin inhibitors etc.). In contrast, apremilast works higher up the inflammatory cascade. Its actions are known to include reduced expression of inducible nitric oxide synthetase, reduced tumour necrosis factor alpha (TNF-alpha), reduced interleukin-23 and increased interleukin-10. Overall, treatment with apremilast is thought to restore the balance of pro-inflammatory and anti-inflammatory mediators.

The FDA approval of apremilast was based on results from three placebo controlled randomized trials. Benefit was observed for patients not receiving background treatment with DMARDs, and also for patients receiving background therapy with methotrexate, leflunomide and/or sulfasalazine. The primary endpoint was the percentage of patients achieving the American College of Rheumatology (ACR) 20 response at week 16.

Apremilast is a major substrate of CYP3A4 therefore strong inducers of this enzyme will result in decreased serum apremilast serum concentrations, and concomitant use of these agents should be avoided (e.g. carbamazepine, phenytoin). Other minor metabolic pathways for clearance of apremilast include CYP 1A2 and CYP 2A6. Caution is suggested for those with renal impairment, and a dose reduction is required where the estimated creatinine clearance is less than 30ml/min.

Side effects of concern include depression and suicide ideation, and use in patients with a history of depression requires caution. A weight loss of 5-10% of body weight has been reported in 10% of patients: weight should be monitored. The usual approach uses an initial dose titration over six days to reduce gastro-intestinal symptoms and the target dose is administered twice a day without regard to meals

In summary, apremilast may become another option for the treatment of psoriatic arthritis but with its own toxicities to consider. The high price of the drug is likely to limit use. Head to head comparisons with other existing treatment have not yet been conducted, and the overall place in therapy for this drug is not presently clear.

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

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

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

Choosing wisely – Geriatrics (part one)

A previous RGH E-Bulletin – edition 55-4 – introduced the Choosing Wisely® initiative and provided some basic background addressing the structure and function of the information provided. In this E-Bulletin we explore the Choosing Wisely® geriatrics guidance. For the five issues covered here, the American Geriatrics Society (AGS) established an expert work group that provided expertise in various key areas. AGS members were invited to provide feedback and recommendations via an electronic survey. The workgroup selected a top 10 potential tests or procedures, and then reviewed the evidence and sought expert advice to further refine the list to five recommendations, which were approved by the AGS Executive Committee. The first five issues/recommendations are reproduced here:

Don't recommend percutaneous feeding tubes in patients with advanced dementia; instead offer oral assisted feeding.
Careful hand-feeding for patients with severe dementia is at least as good as tube-feeding for the outcomes of death, aspiration pneumonia, functional status and patient comfort. Food is the preferred nutrient. Tube-feeding is associated with agitation, increased use of physical and chemical restraints and worsening pressure ulcers.

Don't use antipsychotics as first choice to treat behavioural and psychological symptoms of dementia.
People with dementia often exhibit aggression, resistance to care and other challenging or disruptive behaviours. In such instances, antipsychotic medicines are often prescribed, but they provide limited benefit and can cause serious harm, including stroke and premature death. Use of these drugs should be limited to cases where non-pharmacologic measures have failed and patients pose an imminent threat to themselves or others. Identifying and addressing causes of behaviour change can make drug treatment unnecessary.

Avoid using medications to achieve haemoglobin A1c <7.5% in most adults ≥ 65; moderate control is generally better.
There is no evidence that using medications to achieve tight glycaemic control in older adults with type 2 diabetes is beneficial. Among non-older adults, except for long-term reductions in myocardial infarction and mortality with metformin, using medications to achieve glycosylated haemoglobin levels less than 7% is associated with harms, including higher mortality rates. Tight control has been consistently shown to produce higher rates of hypoglycaemia in older adults. Given the long timeframe to achieve theorized microvascular benefits of tight control, glycaemic targets should reflect patient goals, health status, and life expectancy. Reasonable glycaemic targets would be 7.0 – 7.5% in healthy older adults with long life expectancy, 7.5 – 8.0% in those with moderate comorbidity and a life expectancy < 1 0 years, and 8.0 – 9.0% in those with multiple morbidities and shorter life expectancy.

Don't use benzodiazepines or other sedative-hypnotics in older adults as first choice for insomnia, agitation or delirium.
Large scale studies consistently show that the risk of motor vehicle accidents, falls and hip fractures leading to hospitalization and death can more than double in older adults taking benzodiazepines and other sedative-hypnotics. Older patients, their caregivers and their providers should recognize these potential harms when considering treatment strategies for insomnia, agitation or delirium. Use of benzodiazepines should be reserved for alcohol withdrawal symptoms/delirium tremens or severe generalized anxiety disorder unresponsive to other therapies.

Don't use antimicrobials to treat bacteruria in older adults unless specific urinary tract symptoms are present.
Cohort studies have found no adverse outcomes for older men or women associated with asymptomatic bacteruria. Antimicrobial treatment studies for asymptomatic bacteruria in older adults demonstrate no benefits and show increased adverse antimicrobial effects. Consensus criteria has been developed to characterize the specific clinical symptoms that, when associated with bacteruria, define urinary tract infection. Screening for and treatment of asymptomatic bacteruria is recommended before urologic procedures for which mucosal bleeding is anticipated.

Acknowledgment – This E-Bulletin is based on work by Chris Alderman, Senior Clinical Pharmacist, SA Pharmacy and the Choosing Wisely® initiative

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

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

Choosing wisely – Geriatrics (part two)

In this week's RGH E-Bulletin we continue coverage of the Choosing Wisely® geriatrics guidance. For the five issues covered in this edition, the American Geriatrics Society (AGS) used a similar methodology to that employed for previous items. The final five issues/recommendations are summarised here:

Don't prescribe cholinesterase inhibitors for dementia without periodic assessment for perceived cognitive benefits and adverse gastrointestinal effects.
In randomized controlled trials, some patients with mild-to-moderate and moderate-to-severe Alzheimer's disease (AD) achieve modest benefits, but impact on institutionalization, quality of life and caregiver burden are less well established. Clinicians, caregivers & patients should discuss cognitive, functional and behavioural goals of treatment prior to beginning a trial of cholinesterase inhibitors. If goals of treatment are not attained after a reasonable trial (e.g., 12 weeks), then consider discontinuing the medication. Benefits beyond a year have not been investigated and the risks and benefits of long-term therapy have not been well-established.

Don't recommend screening for breast or colorectal cancer, nor prostate cancer (with the PSA test) without considering life expectancy and the risks of testing, over-diagnosis and overtreatment.
Cancer screening is associated with short-term risks, including complications from testing, over-diagnosis and treatment of tumours that would not have led to symptoms. For prostate cancer, 1,055 men would need to be screened and 37 would need to be treated to avoid one death in 11 years. For breast and colorectal cancer, 1,000 patients would need to be screened to prevent one death in 10 years. For patients with a life expectancy under 10 years, screening for these three cancers exposes them to immediate harms with little chance of benefit.

Avoid using prescription appetite stimulants or high-calorie supplements for treatment of anorexia or cachexia in older adults; instead, optimize social supports, provide feeding assistance and clarify patient goals and expectations.
Although high-calorie supplements increase weight in older people, there is no evidence that they affect other important clinical outcomes (e.g. quality of life). Use of megestrol acetate results in minimal improvements in appetite and weight gain, no improvement in quality of life or survival, and increased risk of thrombotic events, fluid retention and death. In patients treated with megestrol, 1 in 12 will gain weight and 1 in 23 will die. The 2012 AGS Beers criteria lists megestrol and cyproheptadine as medications to avoid in older adults. Systematic reviews of other agents have not identified adequate evidence for the efficacy and safety. Mirtazapine is likely to cause weight gain or increased appetite when used for depression, but there is little evidence to support use to promote appetite and weight gain in the absence of depression.

Don't prescribe a medication without conducting a drug regimen review.
Older patients disproportionately use more prescription and non-prescription drugs than others, increasing the risk for side effects/inappropriate prescribing. Polypharmacy may lead to diminished adherence, ADRs and increased risk of cognitive impairment, falls and functional decline. Medication review identifies high-risk medications, drug interactions and those continued beyond their indication. Additionally, medication review elucidates unnecessary medications and underuse of medications, and may reduce medication burden.

Avoid physical restraints to manage behavioural symptoms of hospitalized older adults with delirium.
Persons with delirium may display behaviours that risk injury or interference with treatment. There is little evidence to support the effectiveness of physical restraints in these situations. Physical restraints can lead to serious injury or death and may worsen agitation and delirium. Pharmacological interventions are occasionally utilized after medical evaluation. Physical restraints should only be used as a very last resort and should be discontinued at the earliest possible time.

Acknowledgment – This E-Bulletin is based on work by Chris Alderman, Senior Clinical Pharmacist, SA Pharmacy and the Choosing Wisely® initiative

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

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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

Midodrine for orthostatic hypotension

Orthostatic (or postural) hypotension is described as a blood pressure drop of greater than 20 mm Hg systolic, or greater than 10 mm Hg diastolic, within three minutes of standing up. This can lead to symptoms such as dizziness, blurred vision and confusion which can result in syncope or falls. There are many potential causes of orthostatic hypotension, including autonomic dysfunction (e.g. Parkinson's disease, pure autonomic failure); cardiovascular disorders (e.g. hypovolemia) and medications (e.g. alpha-blockers, diuretics).

The incidence of orthostatic hypotension is highest in the elderly, partly due to decreases in the baroreceptor reflex and parasympathetic tone, as well as a higher frequency of comorbid medical conditions. Orthostatic hypotension is particularly concerning in this population, as it can increase the risk of falls and associated morbidity and mortality.

The first step in managing orthostatic hypotension is to identify and address any underlying causes such as medications or medical conditions. Non-pharmacological treatment measures should then be implemented, as these forms the foundation of therapy. Potentially effective non-pharmacological strategies include adequate hydration, increasing dietary salt intake, compression stockings and exercises.

If non-pharmacological techniques are inadequate at controlling symptoms, pharmacological options can be considered. Fludrocortisone, which increases blood volume, is generally the first treatment choice. Another treatment option is midodrine, a direct sympathomimetic agent. Midodrine is a prodrug which is converted to its active metabolite desglymidodrine. A selective alpha1-receptor agonist, desglymidodrine increases blood pressure through peripheral vasoconstriction without stimulating an increase in heart rate. Peak plasma levels of this metabolite are achieved around one hour after an oral midodrine dose. Its elimination half-life is around three hours and most is excreted via the urine.

Several individual trials have assessed the efficacy of midodrine in treating orthostatic hypotension. In particular, a number of trials report increased standing blood pressure in patients treated with midodrine compared placebo, as well as improvements in patients' symptoms and quality of life (as reported using various assessment scores). However, good quality evidence is limited by the lack of large, well-designed clinical trials evaluating midodrine's efficacy. Two reviews from 2013, one evaluating pharmacological management of orthostatic hypotension and one evaluating midodrine specifically, concluded that there is insufficient evidence to make clear recommendations about therapy.

Nevertheless, midodrine may represent a good alternative to other treatment options such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and stimulants such as phenylephrine, particularly for the elderly where these medications can have significant risks and adverse effects. Midodrine is said to be generally well-tolerated. The most commonly reported adverse events are piloerection (and associated skin or scalp tingling/paraesthesia), pruritis and urinary retention in males. The general starting dose of midodrine is 2.5 mg two to three times daily, titrating up to 10 mg three times daily. The last dose of the day should be taken at least four hours before bed to minimise supine hypertension.

Midodrine may be an effective and well-tolerated treatment option for orthostatic hypotension; however quality evidence for its use is limited. It is not currently licensed for use in Australia but may be obtained through the Special Access Scheme.

Acknowledgment – This E-Bulletin is based on work by Eleanor Kelly, 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:

Study to evaluate safety and effectiveness of oral Apremilast (CC-10004) in patients with moderate to sever plaque psoriasis (ESTEEM 1): http://clinicaltrials.gov/show/NCT01194219

Kavanaugh A et al. Treatment of psoriatic arthritis in a phase 3 randomised, placebo controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor (PALACE 1). Ann Rheum Dis doi:10.1136/annrheumdis-2013-205056

www.choosingwisely.org/doctor-patient-lists/american-geriatrics-society/

McClellan KJ, Wiseman LR, Wilde MI 1998 Midodrine: A Review of its Therapeutic Use in the Management of Orthostatic Hypotension, Drugs and Aging 12(1) 75-86

Ong AC, Myint PK, Shepstone L, Potter JF 2013 A systematic review of the pharmacological management of orthostatic hypotension, International Journal of Clinical Practice 67: 633-646

Parsaik AK et al 2013 Midodrine for Orthostatic Hypotension: A systematic Review and Meta-Analysis of Clinical Trials, Journal of General Internal Medicine 28(11) 1496-1503

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

Apremilast was recently approved for the treatment of psoriatic arthritis. The usual route of administration is:

a) orally
b) subcutaneously
c) intramuscularly
d) rectally

Apremilast is a major substrate of which cytochrome P450 isoenzyme?

a) CYP2D6
b) CYP1A2
c) CYP2C19
d) CYP3A4

According to the "Choosing Wisely®" geriatrics guidance for diabetes produced by the American Geriatrics Society:

a) a reasonable target HbA1c would be 7.0 – 7.5% for healthy older people with long life expectancy
b) older people with long life expectancy should be treated to attain HbA1c of < 7%
c) tight glycaemic control is associated with lower rates of hypoglycaemia for older people
d) there is no need to target HbA1c of < 10% in the presence of comorbidities

The "Choosing Wisely®" resources suggest that antimicrobial treatment for asymptomatic bacteruria in older adults:

a) produces no benefits and shows increased adverse antimicrobial effects.
b) produces benefits and shows increased adverse antimicrobial effects.
c) produces benefits and shows no adverse antimicrobial effects.
d) produces no benefits and shows a very low level of adverse antimicrobial effects.

The "Choosing Wisely®" resources suggest that:

a) megestrol may be routinely used as an appetite stimulant for older people
b) cyroheptadine may be routinely used as an appetite stimulant for older people
c) both megestrol and cyprohepatadine may be routinely used as an appetite stimulant for older people
d) neither megestrol nor cyprohepatadine should be routinely used as appetite stimulants for older people

The "Choosing Wisely®" resources re-enforce that if prescribed cholinesterase inhibitors, elderly people should be periodically assessed for:

a) renal advesre effects
b) gastrointestinal adverse effects
c) cardiac adverse effects
d) none of the above

Which of the following has been extensively prescribed as a management strategy to address postural hypotension?

a) hydrocortisone
b) testosterone
c) fludrocortisone
d) nandrolone

Which of the following best describes the mechanism of action for the active metabolite of midodrine?

a) selective alpha1 adrenoreceptor agonist
b) selective alpha1 adrenoreceptor antagonist
c) selective beta1 adrenoreceptor agonist
d) selective beta1 adrenoreceptor antagonist