RGH E-Bulletin Digest Number 90

The first in our 2016 series of continuing professional development activities is the RGH E-Bulletin Digest No. 90 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 60-8 → 60-11 (October 26 → November 16, 2015).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Outline the clinical pharmacology of medicinal cannabinoid agents
- Discuss the treatment of relapsed/refractory multiple myeloma
- Describe issues to consider when selecting an antidepressant agent for a person with significant cardiovascular disease
- Discuss the clinical pharmacology of ponatinib.

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: A1601AP2.
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.

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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

Cannabinoids and its medicinal uses

The cannabis plant was first cultivated and used in Europe and Asia around 5000 years ago, and has been used for medicinal purposes from as early as 2737 B.C. The glandular hairs of the *Cannabis Sativa* plant contain over 60 types of phytocannabinoids, most of which are believed to act to some extent on human cannabinoid receptors. The cannabinoid receptor type 1 (CB1) is expressed in abundance in the central nervous system and plays a role in modulating motor activity, sensory processing, thought, memory, sleep and appetite, while receptor type 2 receptors (CB2) are generally present on immune cells and tissues and may be related to modulating inflammatory and immune responses.

Perhaps the most well-known cannabinoid is tetrahydrocannabinol (THC), in particular its main isomer Δ9-THC, to which the plant's characteristic psychoactive effects are attributed to. Δ9-THC exerts its actions primarily through partial activation of the CB1 cannabinoid receptors, producing effects such as mild to moderate analgesia, relaxation, altered visual, auditory and olfactory senses, fatigue, and appetite stimulation. THC has also been shown to be an effective antiemetic, and this has led to the approval of two synthetic cannabinoids, dronabinol (Marinol®) and nabilone (Cesamet®), in the US for the relief of nausea and vomiting in chemotherapy patients who have failed other forms of treatment. In 1992, dronabinol was also approved for appetite stimulation and the prevention of anorexia in patients with AIDS. However, CB1 activation has also been linked to impaired memory, motor deficits and increased risk of psychotic and cardiovascular disease. Also, despite frequent claims of the contrary, the risk for psychological dependence appears to be equal to that of alcohol.

The activity of the plant's non-psychoactive component, cannabidiol (CBD), is still yet to be fully elucidated. It is postulated that CBD acts as an antagonist or inverse agonist to the CB1 and CB2 receptors and acts to modulate the effects of THC and endocannabinoids. Early studies on CBD's mechanism of action have suggested that its action may involve a variety of non-cannabinoid receptors, such as Vanilloid receptor type 1 and 5HT1A receptors, to produce its anticonvulsive, anxiolytic, anti-oxidative, anti-inflammatory and neuro-protective effects. CBD has shown to be an effective antiepileptic in both animal models and human trials, reducing the frequency and severity of major seizure episodes. In 2014, Epidiolex®, an oral liquid containing CBD , was designated orphan drug status by the FDA in 2014 for Dravet and Lennox-Gastaut syndromes. Further research will need to be conducted regarding potential interactions with other drugs, especially conventional antiepileptics such as phenytoin, as CBD has been shown to be a potent inhibitor of several Cytochrome P450 isozymes.

There is currently one cannabinoid-based formulation that is approved for use in Australia. Nabiximols (Sativex®), an extract containing approximately 90% 1:1 tetrahydrocannabinol and cannabidiol, was approved by the TGA in 2013 for the treatment of moderate to severe neuropathic pain and spasticity in patients with multiple sclerosis.

Although THC and CBD have shown promise in in-vitro and observational studies, especially in refractory epileptic conditions, there is still very little scientific evidence to support the use of cannabinoids for medicinal purposes. In addition, legal issues and concerns of dependence and long-term safety have greatly hampered research. However, with the recent changes in the law, patients with serious refractory conditions are optimistic that ongoing research in this area will provide results that will allow them to live a normal life.

Acknowledgment – This E-Bulletin based on work by Jessica Mao, Senior Pharmacist, RGH

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

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Editor: Assoc. Prof. Chris Alderman, University of South Australia

Treatment options for relapsed/refractory multiple myeloma

Multiple myeloma (MM) is the second most common haematological malignancy, and of those patients who survive initial treatment relapse the need for further therapy is inevitable.

Treatment options for patients who have relapsed or have refractory disease include haematopoietic stem cell transplantation (HCT), a rechallenge with the previous chemotherapy regimen or a trial of a new regimen. Factors that determine choice of therapy include risk stratification for myeloma (i.e. high, or standard risk disease), prior treatments used and the duration of response to these treatments. Other factors to consider include side effect profiles of medicines and patient co-morbidities. Haematopoietic cell transplant will not be discussed further here.

For those patients that are not candidates for HCT the choice of therapy is determined by duration of response to prior therapy. If time to relapse is greater than one year after chemotherapy it is highly likely they will respond to a repeat course of previous therapy. Therapy is continued to a maximum response for up to one year or until disease progression. Beyond this stage other regimens need to be considered.

Combination therapy with thalidomide, lenalidomide, pomalidomide, bortezomib, or carfilzomid is usually next the recommended treatment. All of these agents have activity as single agents but produce higher response rates when given in combination with dexamethasone. Thalidomide, lenalidomide and pomalidomide are immunomodulatory drugs (IMiDs) which have anti-angiogenic, anti-inflammatory, anti-proliferative and immune-modulatory effects. Lenalidomide and pomalidomide are analogues of thalidomide which are more potent and are less likely to cause peripheral neuropathy but more likely to cause myelosuppression than thalidomide. Like thalidomide these analogues are teratogenic so precautions must be taken to avoid pregnancy four weeks prior to therapy, during therapy and four weeks after finishing therapy with any of these agents.

Access to these drugs in Australia is restricted and they are only available via the Celgene controlled distribution system called the i−access®. These drugs are available on a subsidised basis under the Pharmaceutical Benefits Scheme under the section 100 *highly specialised drugs program* via authority prescription through Australian public and private hospitals.

Differences in pharmacokinetics and dose limiting toxicities may dictate the choice of one agent over another. For example, due to the renal excretion of lenalidomide and pomalidomide, thalidomide would be the preferred drug of choice where renal impairment is a concern and also for those patients who develop severe thrombocytopenia (lenolidamide and pomalidomide are more likely to cause myelosupression). Thalidomide on the other hand is more likely to cause severe neuropathy and thromboembolism.

Proteasome inhibitors bortezomib and carfilzomib are other drugs available for relapsed or refractory MM. Either agent can be administered alone or in combination with dexamethasone, anthracyclines, alkylating agents or IMiDs.

Ultimately, at this stage MM remains an incurable disease. Future research into the use of these agents in MM will aim to optimize treatment and disease free survival by exploring synergies between IMiDs, other novel therapeutic agents and conventional chemotherapies. Many trials investigating these advances are underway.

Acknowledgment – This E-Bulletin based on work by Annabel Calder, Senior Clinical Pharmacist, RGH

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

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Antidepressants and cardiovascular disease

Patients who are depressed are at higher risk of cardiovascular disease and patients who have had a myocardial infarction are at increased risk of depression. The choice of antidepressant needs to take into account side-effects, previous treatments tried, safety in overdose, cost, patient preference and important drug interactions. Drug-drug interactions can alter the metabolism of drugs secondary to the inhibition of certain isoenzymes of the cytochrome P450 enzyme system. Interactions may be unpredictable due to patient genetic variability and the fact that some drugs are metabolised by multiple pathways. P-glycoprotein, a drug transporter protein found in the gut wall can also be inhibited or induced by drugs.

Selective serotonin reuptake inhibitors (SSRIs) (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline) are generally preferred in the management of depression in patients with cardiac disease. Fluoxetine and paroxetine should be avoided in patients treated with metoprolol or perhexiline as they are significant inhibitors of cytochrome P450 CYP2D6 (the pathway by which both drugs are metabolised) and this combination can result in in dizziness, bradycardia and hypotension (with metoprolol) or severe perhexiline toxicity. Sertraline at high doses (> 100 mg per day) may interact with metoprolol, however citalopram and escitalopram are not potent inhibitors of most cytochrome enzymes. Fluvoxamine can increase the plasma level of propranolol due to the inhibition of CYP2D6 and CYP1A2. Metoprolol and propranolol are lipophilic beta blockers which are hepatically cleared, however atenolol and sotalol are not subject to these interactions as they are predominately renally cleared. Citalopram can, in a dose-dependent manner, prolong QT interval, so doses above 40 mg should be avoided, and limited to a maximum of 20 mg daily in patients over 65 years of age.

SSRIs can also inhibit platelet aggregation. One review of more than 9,000 patients with atrial fibrillation found that those patients concurrently treated with SSRIs and warfarin had an increased relative risk for haemorrhage of 1.41 (95% CI 1.04 to 1.92, p = 0.03) compared to those patients not treated with SSRIs. Similar risks are likely with the newer oral anticoagulants (apixaban, dabigatran and rivaroxaban).

Tricyclic antidepressants (TCAs) (amitriptyline, clomipramide, dothiepin, doxepin, imipramine, nortriptyline, trimipramine) are not considered first line in cardiovascular disease and should be used cautiously in patients with cardiac disease. They can increase heart rate, prolong QT interval, cause arrhythmias, postural hypotension and can be fatal in overdose. Tricyclics are contraindicated in patients with a recent myocardial infarction (MI). Amitriptyline is an inhibitor of CYP2D6.

Other antidepressants have been much less studied than SSRs and TCAs. Serotonin/noradrenaline reuptake inhibitors (SNRIs) include desvenlafaxine, duloxetine, and venlafaxine. Duloxetine, but not venlafaxine, may reduce the metabolism of metoprolol. SNRIs can increase blood pressure, thus counter-acting the effects of treatments for hypertension. Bupropion can increase blood pressure but it can also inhibit the cytochrome CYP2D6 and thus can increase the effects of metoprolol. It may also increase flecainide and digoxin serum concentrations. Mirtazapine should be used cautiously in patients post MI or with angina but is an alternative for patients with cardiac disease. It can cause weight gain which does not improve cardiac outcomes. Reboxetine can increase blood pressure and heart rate. Moclobemide (a reversible MAO-A inhibitor) can cause orthostatic hypotension.

Depression and cardiovascular comorbidity is a significant health concern. Medications can cause adverse effects and interact with one another: more studies are needed comparing drugs and psychotherapy for the treatment of depression.

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

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

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Editor: Assoc. Prof. Chris Alderman, University of South Australia

Ponatinib

Ponatinib (Iclusig®) is a tyrosine kinase inhibitor which has recently been approved for subsidised supply via the Pharmaceutical Benefits Scheme (PBS) as of 1 November 2015 with the following indications (see PBS website for full criteria for eligibility of patients):

- Treatment in chronic-phase, accelerated-phase or blast-phase chronic myeloid leukaemia (CML) patients who are resisting or not tolerating at least two other tyrosine kinase inhibitors (e.g. imatinib, dasatinib, nilotinib) OR in patients with a T315I mutation
- Treatment in Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) patients who are resisting or not tolerating dasatinib and where imatinib would not be a clinically appropriate option OR in patients with a T315I mutation

The approval of indications for ponatinib was based on a phase II, single-arm trial with 449 patients enrolled in the study (417 patients with CML and 32 patients with Ph + ALL). 96% of the patients enrolled had experienced treatment failure with imatinib. Patients with CML were grouped into 3 cohorts according to the phase (chronic-, accelerated- or blast-CML). The primary end-points and results for the different cohorts are as follows:

- Chronic-phase CML (n = 267), with primary end-point as a major cytogenetic response (proportion of Ph+ white blood cells has fallen < 35%) within the first 12 months = 56%
- Accelerated-phase CML (n = 83), blast-phase CML (n = 62) and Ph+ ALL (n = 32), with primary end-point as a major haematological response (normalised white blood cell counts or no evidence of leukaemia) within the first 6 months; accelerated-phase CML = 55%, blast-phase CML = 31% and Ph+ ALL = 41%

Fewer previous treatments, younger age and shorter duration between diagnosis and treatment tended to provide patients with a better response to ponatinib, as revealed in pre-specific subgroup analyses. The patients in the trial were started on 45 mg once daily ponatinib dosing.

Peak serum concentrations of ponatinib were obtained approximately four hours after oral administration irrespective of meal content or fasting conditions. The recommended starting dose of ponatinib is 45 mg once daily; however the reduction of the starting dose at 30 mg should be considered in patients with concurrent use of ponatinib and strong CYP3A4 inhibitors (e.g. ketoconazole, ritonavir) OR in patients with hepatic impairment (as the drug has not been studied in patients with hepatic impairment at doses above 30 mg). Furthermore, consideration should be taken in the reduction of dose to 30 mg or 15 mg in patients with chronic-phase CML who have achieved a major cytogenetic response and especially those who are at risk of vascular adverse events.

Ponatinib is extensively metabolised to oxidative metabolites by CYP3A4 and to a lesser extent by CYP2C8 and CYP2D6, with faecal elimination as the main route of excretion (approximately 87%). The product information does contain a black box warning regarding vascular occlusion, heart failure and hypertension. Adverse reactions were common in the trial; these include thrombocytopenia (most common reason for dose interruption), rash, dry skin, vascular occlusion, abdominal pain, neutropenia and anaemia. It is important to note that infections occurred in more than half the patients been treated with ponatinib (serious infections in 20% of the cases).

Acknowledgment – This E-Bulletin based on work by Allen Lau, Senior Clinical Pharmacist, RGH

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

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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

1. Which of the following is an example of a cannabinoid product approved for human therapeutic use?
    a) nandrolone
    b) naloxone
    c) nabilone
    d) none of the above

2. Cannabidiol has been used for the management of which of the following conditions?
    a) Creutzfeldt-Jakob disease
    b) Lennox-Gastaut syndrome
    c) Dunn-Wiss disease
    d) Hallervorden-Spatz disease

3. Which of the following drugs have been used for the treatment of relapsed/refractory multiple myeloma?
    a) thalidomide
    b) lenolidamide
    c) bortezomib
    d) all of the above

4. Compared to thalidomide, lenalidomide and pomalidomide are:
    a) more potent and are less likely to cause peripheral neuropathy
    b) less potent and are more likely to cause peripheral neuropathy
    c) more potent and are more likely to cause peripheral neuropathy
    d) less potent and are less likely to cause peripheral neuropathy

5. Which of the following drugs should be avoided for a person concurrently treated with perhexiline?
    a) desvenlafaxine
    b) agomelatine
    c) paroxetine
    d) moclobemide

6. Research suggests that anticoagulated patients who are concurrently treated with SSRIs have:
    a) increased risk of embolic stroke
    b) reduced risk of embolic stroke
    c) increased risk of haemorrhage
    d) decreased risk of haemorrhage

7. Ponatinib is used for the treatment of:
    a) chronic myeloid leukaemia
    b) chronic lymphocytic leukaemia
    c) acute lymphoma
    d) none of the above

8. A reduced dose of ponatinib should be considered for people concurrently treated with potent inhibitors of:
    a) CYP1A2
    b) CYP2D6
    c) CYP2C19
    d) CYP3A4