# RGH E-Bulletin Digest Number 89

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 89 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 60-4 → 60-7 (September and October 2015).

**Learning Objectives:**

After completing this activity, pharmacists should be able to:

- Identify potential candidates for discontinuation from the medication regiment of palliative care patients
- Understand the nature of concerns regarding the use of antipsychotics for the management of insomnia
- Describe the basis for the approval of biosimilar pharmaceutical products for therapeutic use
- Discuss the risk factors associated with liver injury associated with exposure to flucloxacillin.

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.

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**Accreditation number: A1601AP1**.
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

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**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

**Volume 60 (4): September 28 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


# Medication rationalisation towards end of life

A limited amount of literature is available regarding algorithms for best practice when it comes to discontinuation of medications towards the end of a life-limiting illness. Although medications for comorbid conditions are eventually ceased, this often happens quite late in disease progression, towards the terminal phase of the illness, at which time a number of medications for management of symptoms have already been added, leading to a significant medication burden. According to some research, the total number of medications may in fact be increased at the end of life.

In the USA, where hospice care is formally defined as the treatment received during the time window anticipated to be the last six months of life, a patient who has been transferred to hospice care is no longer eligible for treatment by physicians from other specialities. One group have identified that in patients who were expected to live between 1 month and 1 year, discontinuation of statin therapy improved patient-reported quality of life and did not lead to an excess of cardiovascular events or deaths within 60 days of cessation. Median survival time was 7 months, and cancer diagnoses made up approx. 50% of the study participants, who could be taking statins for primary or secondary prevention.

Potentially inappropriate medications (PIMs) are common in palliative cancer patients; however, there is a lack of criteria to easily identify PIMs in this group. An oncological palliative care deprescribing guideline has recently been developed and validated by an Australian group, with the intention of identifying medications with a limited benefit that are suitable targets for discontinuation in palliative cancer patients. If the foreseeable benefits of any medications do not outweigh the adverse effects and/or associated risks, it is recommended to consider appropriate de-escalation. Drug classes identified in the guideline include:

- aspirin for primary prevention
- dyslipidaemia medications for all indications
- antihypertensives when used for mild to moderate hypertension, secondary prevention of cardiovascular events, management of stable coronary artery disease (noting that these may still be necessary for symptomatic management of heart failure or arrhythmia)
- osteoporosis medications except when used for treatment of hypercalcaemia or prevention of skeletal-related events in malignancy
- peptic ulcer prophylaxis in patients who don't have any relevant medical history (gastrointestinal bleeding, peptic ulcer, gastritis, GORD) or are not on NSAIDS/steroids
- oral hypoglycaemics where used as secondary prevention for diabetic-associated events
- vitamins & minerals (if not indicated to treat clinically significant deficiency), complementary & alternative medicines

From 61 identified hospital inpatients whose life expectancy was 6 months or less, 617 medicines were assessed in order to identify PIMS: both by an expert panel (consisting of a radiation oncologist, medical consultant and palliative care specialist); and by a clinical pharmacist using the OncPal Deprescribing Guideline. In all, 43 patients were taking at least one PIM and 21.4% of the total medicines were identified as PIMs. Systematic use of the guideline matched 94% of the medicines to the expert panel's assessment, with a Kappa value of 0.83 demonstrating an 'outstanding concordance'.

This research confirms that the medication regimens of those patients receiving palliative care should be reviewed to seek to ensure that potentially inappropriate medications can be ceased and that pharmacological interventions can be focused upon strategies designed to provide symptom relief and enhanced quality of life;

Acknowledgment – This E-Bulletin based on work by Jenny Casanova, 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

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


# Antipsychotic use in insomnia

Insomnia, the most commonly encountered sleep disorder in the general population, is the subjective perception of difficulties with sleep initiation, duration and quality despite sufficient opportunities. A diagnosis of insomnia requires evidence of daytime dysfunction, which may include fatigue, difficulties concentrating, demotivation, irritability, tension or even cognitive changes. Insomnia potentially contributes to decreased quality of life, risk of accidents (e.g. motor vehicle, work-related), decreased work productivity and increased burden on healthcare resources.

Symptoms accompanying insomnia are often chronic in nature and investigation of underlying causes is important. Insomnia is frequently associated with psychiatric conditions including depression, anxiety and psychotic disorders. Insomnia occurring without an underlying psychiatric or medical condition is referred to as primary insomnia.

Use of antipsychotics for insomnia management is not uncommon within psychiatric practice; however concerns have recently been raised in the medical literature over the increased off-label use for insomnia treatment without an associated psychiatric disorder. Drug utilization analysis within Australia has identified increased prescribing, particularly of quetiapine and olanzapine.

The primary mechanism of sedation with antipsychotics is through the strong affinity for antagonism at histamine H1 receptors and 5HT2A receptors. Potential for numerous adverse effects (including orthostatic hypotension, morning sedation, dry mouth, metabolic and cardiovascular complications) influence current insomnia guidelines which recommend use only with specific psychiatric comorbidities. Further potential risks (e.g. contributing towards risk for neuroleptic malignant syndrome and arrhythmias) should not be overlooked when prescribing antipsychotics for insomnia. Furthermore, cost implications for patients prescribed antipsychotics as non-PBS indications, such as insomnia, need to be considered.

Currently limited data exists for the beneficial use of quetiapine in treatment of insomnia; with one study indicating non-psychotic insomniac patients have no sustained sedation benefit if used for periods of longer than one week. Likewise, robust studies evaluating the safety and efficacy of olanzapine for the treatment of insomnia are lacking. Antipsychotics for insomnia should ideally be reserved for those individuals with associated psychiatric comorbidities where good evidence exists to support use. Off label use for insomnia carries both short and long term risks unlikely to outweigh any benefits.

Insomnia management guidelines focus on identifying and treating underlying causes, and ensuring psychological and social interventions are provided along with consideration of drug treatment. Environmental factors and sleep hygiene interventions are vital issues to address in all patients with insomnia, and remain first line measures. The persisting nature of insomnia, coupled with withdrawal reactions, rebound insomnia and varied half-lives of drug treatments complicate the balance between medication safety and quality of life outcomes. If medication is required in insomnia, it should be used at lowest possible dose and short time periods are the preferred approach.

Acknowledgment – This E-Bulletin based on work by Lauren Wierenga, 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



# An introduction to biosimilars

Most generic drug products available on the market are based on small molecules. However, there has been a recent increase in the use of large molecules that are sometimes referred to as biologics, a term that includes monoclonal antibodies and vaccines. These therapeutic proteins often have large, complex and heterogeneous molecular structures consisting of primary, secondary, tertiary and quaternary entities. There is a marked contrast with small molecules: for example, acetylsalicylic acid has a molecular weight of 180 Daltons, compared to the average molecular weight of monoclonal antibodies at 150k Daltons.

Whereas small molecules can be synthesised by chemical manipulation to create exact copies, biologics require post-translation modification and can only be achieved from a living organism (bacteria, yeast, mammalian or yeast cell lines). It is impossible to create an exact replica of a protein when using living organism and these agents are produced using different manufacturing processes due to patent considerations, usually by different sponsors. Therefore, biosimilars are not exactly the same as the biologics they may be intended to replace. It has been asserted that the small differences in structure that occur in biosimilars may give rise to differences in clinical response. Determination of the precise structure requires the use of highly complex techniques from HLPC to x-ray crystallography; however these techniques are insufficient to confirm that they are exact copies of another biologic due their large size and complex tertiary structure.

The slow entry of biosimilars into the market has been attributed in part to concern regarding immunogenic responses that can potentially compromise the safety (autoimmunity, allergic reaction) and efficacy (non-neutralising and neutralising antidrug antibodies) of the biosimilar due to the slight differences between the originator and the biosimilar. An early attempt at generating a biosimilar showed that minor changes in the formulation of epoetin alfa product resulted in the development of anti-epoetin antibodies that neutralised both endogenous erythropoietin and injected epoetin in a number of patients.

The Australian Therapeutic Goods Administration compares the physiocochemical characteristics, efficacy and safety outcomes for the listed indications before approval. This is not the case with ‘normal’ generics. The sponsor is required to provide a pharmacokinetic/pharmacodynamics comparison, phase III trials to show safety and efficacy and to demonstrate no increase in the risk of antibody formation. To date, Aczicrit (epoetin lambda), Basaglar (insulin glargine), Grandicrit (epoetin lambda), SciTropin A (somatropin) are biosimilars that have been approved by the TGA. Nivestim (filgrastim), Novicrit (epoetin lambda), Omnitrope (somatropin), Tevagrastim (filgrastim), Zarzio (filgrastim) are listed on the PBS. Currently, a swap to a biosimilar can only be performed by clinicians and not at the pharmacy level. However, recent recommendations of the Pharmaceutical Benefits Advisory Committee (PBAC) support substitution at pharmacy level provided sufficient data is available to show no changes in clinical outcome when brands are switched.

Infliximab (Inflectra) was registered by the TGA as a biosimilar in August 2015 for rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn’s disease, ulcerative colitis and plaque psoriasis. In July 2015, the PBAC made recommendations to “a” flag Remicade (originator) and Inflectra, therefore allowing substitution to occur at the pharmacy level.

Acknowledgment – This E-Bulletin based on work by Michelle Tie, Pharmacist, RGH

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

# RGH Pharmacy E-Bulletin

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



# How common is flucloxacillin-induced cholestatic hepatitis?

It is well known that flucloxacillin can induce liver injury. First reported in 1982, cases have been reported in Australia, Sweden and the UK. In Australia, the increasing incidence of reports of liver damage has been proportional to the usage of the drug. By 1995, 350 reports to the relevant Australian regulatory agency had been made, with 17 fatalities.

Flucloxacillin induces liver injury, mostly in the form of cholestatic hepatitis, with elevation of ALP and bilirubin and, at most, modest elevation of transaminases. The LFTs usually return to normal after 3-4 weeks after treatment ceases, although a significant minority of patients will develop a very prolonged cholestatic syndrome.

A previous estimate has put the incidence of cholestatic hepatitis secondary to flucloxacillin to be in the order of approximately 1/13,000 to 1/100,000 prescriptions. Studies from Sweden, estimated that incidence varies between 1/10,000 to 1/30,000 (depending on whether 'possible' cases are included or not). A retrospective cohort study, using the UK population-based General Practice Research Database (GPRD), reports the estimated incidence of cholestatic liver disease at 6.1 per 100 000 users.

Based on reports to Australian regulatory agencies, pre-disposing factors of flucloxacillin hepatitis include age > 55 yrs and duration of therapy > 14 days. These findings accord with those of an Australian case-control study done in 1992, where patients over 55 years of age had an 18 times higher risk of developing jaundice relative to those aged under 30 years. Patients treated for more than 14 days had a risk of jaundice estimated at 7 times that of patients treated for less than 2 weeks. In contrast, using data from the UK GPRD over a period of 10 years, another study found that here was only a 6-fold higher risk of cholestatic liver disease after flucloxacillin treatment in patients ≥ 60 years when compared with younger patients.

Flucloxacillin remains the drug of choice for moderate to severe Staphylococcus aureus infection. Its advantages are its potency, narrow spectrum, and limited effects on normal flora. There are no alternatives that have as narrow an antimicrobial spectrum as flucloxacillin (apart from fusidic acid, which also has established hepatotoxicity).

Dicloxacillin was introduced in Australia in 1997, with the aim of providing an alternative to flucloxacillin with a lower incidence of hepatic ADRs. However, after the first two years of marketing (1997-98) there were 24/493,000 incidences of hepatic reactions due to dicloxacillin (approximately 4.9 per 100,000 prescriptions) compared to 62/1,182,000 (approximately 5.2 per 100 000 prescriptions) for flucloxacillin; suggesting the associated hepatitis may be a class-specific toxic reaction. The reported incidence of cholestasis however, was considerably lower for dicloxacillin compared to flucloxacillin (3/493,000 and 17/1,182,000, respectively).

Flucloxacillin-associated hepatitis is still considered to be an uncommon event and most cases are reversible with courses of less than two weeks duration. Age and duration of treatment have been shown to be strong risk factors. Due to the potentially irreversible and lethal nature of the reaction, flucloxacillin should only be used in severe infections or where S. aureus has been identified as the pathogen.

Acknowledgment – This E-Bulletin based on work by Cuc Hua, 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 would be regarded as candidates for rationalisation in the context of end of life care?
    a) aspirin for primary prevention
    b) dyslipidaemia medications for all indications
    c) antihypertensives when used for mild to moderate hypertension
    d) all of the above

2. Which of the following would be regarded as a candidate for rationalisation in end of life care?
    a) anti-resorptive agents when used for treatment of hypercalcaemia
    b) peptic ulcer prophylaxis for patients with a history of GI bleeding
    c) oral hypoglycaemics where used as secondary prevention for diabetic-associated events
    d) frusemide administered for management of congestive heart failure

3. Substantial concern has recently been noted in relation to the rate of off-label prescribing of which of the following drugs?
    a) agomelatine
    b) quetiapine
    c) temazepam
    d) zopiclone

4. Much of the sedative effect associated with antipsychotics is thought to be mediated by:
    a) agonist effects at the histamine H1 receptor
    b) antagonist effects at the histamine H1 receptor
    c) agonist effects at the histamine H2 receptor
    d) antagonist effects at the histamine H2 receptor

5. When proposing an application for listing of a biosimilar on the Australian market, sponsor companies must provide:
    a) pharmacokinetic comparisons to the originator compound
    b) efficacy comparisons the originator compound
    c) evidence to confirm that the biosimilar is not associated with enhanced antibody production
    d) all of the above

6. Compounds that have biosimilar entities approved for use in Australia include
    a) somatropin
    b) filgrastim
    c) infliximab
    d) all of the above

7. The most common form of acute liver injury associated with flucloxacillin is:
    a) autoimmune hepatitis
    b) interstitial hepatocellular lysis
    c) cholestatic hepatitis
    d) hepatorenal syndrome

8. Risk factors for the development of flucloxacillin-induced liver injury include:
    a) age < 30 years
    b) cigarette smoking
    c) concurrent treatment with a macrolide antibiotic
    d) course of treatment > 14 days