RGH E-Bulletin Digest Number 87

The next in our 2015 series of continuing professional development activities is the RGH E-Bulletin Digest No. 87 – edited by Associate Professor Chris Alderman.

This CPD activity assesses your understanding of four recent RGH Pharmacy E-Bulletins, Volumes 59-8→59-11 (August 2015).

Learning Objectives:

After completing this activity, pharmacists should be able to:

- Describe clinical features of dysguesia
- Discuss factors relevant to the use of antidepressants for people with epilepsy
- Discuss the aetiology and treatment of Complex Regional Pain Syndrome
- Describe the clinical application of the SAMe-TT2R2 score.

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: A1511AP0.
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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RGH Pharmacy E-Bulletin

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

Taste Disturbance (Dysgeusia)

Taste disturbance, or dysgeusia, can occur as an adverse effect of medications, or can be secondary to certain disease states. Medications can affect taste acuity by either interfering with the chemical composition or the flow of saliva, or by affecting taste receptor function or signal transduction. Many medications (particularly antimicrobials) taste bitter, metallic or sour at concentrations that occur in salivary secretions.

There may be large differences among individuals in terms of their susceptibility to medication-induced, taste-related adverse effects, likely to involve factors such as age, gender and genetic variations in taste sensitivity. While in some cases the issue resolves despite continuation of the offending medication (e.g. with ACE inhibitors), most patients require discontinuation of the medication. It may take weeks to months for the taste disturbance to resolve. Where the effect is long-lasting, this may reflect damage to the taste receptors/nerves or possibly accumulation of a metabolite which can cause taste disturbance. Thus, some case reports of taste disturbances attributed to medications required either a significant period of time to recovery, or appeared to be permanent.

Dysgeusia has been associated with many medications such as acetazolamide, aspirin, baclofen, dexamphetamine, lincomycin, fluoxetine, nifedipine, omeprazole, perindopril, simvastatin, spironolactone, zolpidem and others. However, dysgeusia has also been associated with many disease processes; these include viral and bacterial illness, allergic rhinitis, head injury, gingivitis, surgical procedures (including tonsillectomy), psychiatric disorders (including depression, dementia and psychosis) and pernicious anaemia. Zinc deficiency has been associated with taste disorders. Some medications have been proposed to cause dysgeusia by chelating zinc, however zinc supplementation may not result in resolution of symptoms. Hyponatraemia can also affect taste perception, and may be a result of SIADH secondary to medications.

It is well established that taste can become impaired in the elderly, and it has been noted that this can be more pronounced in acutely hospitalised elderly patients. Psychiatric patients may have an increased incidence of taste disturbance related to disease states: in a survey of 89 elderly hospitalised psychiatric patients, dysgeusia was commonly reported (28% of patients). Higher rates were noted in those with mood disorders (depression, bipolar disorder) compared to that observed with psychotic disorders or dementia. Gustatory hallucinations are relatively uncommon, but can be a result in an unpleasant taste in the mouth and may be experienced by psychotic patients, or those with epilepsy or migraine.

Suggested management of pharmacologically induced taste disturbances involves good oral hygiene. Strategies include limiting the use of topical agents such as mouthwashes or peroxide and avoiding repetitive oral trauma (e.g. aggressive tooth brushing, misaligned dentures or braces). Artificial saliva may be helpful in cases of xerostomia

Other measures which may assist include the use of lozenges, breath mints or sugarless gum. However, the effects are not long lasting and require repeated dosing. If a patient's medication is a likely cause of taste disturbance, the drug can be continued if the taste disturbance is mild, but if the symptoms become severe or intolerable, drug cessation may be necessary. Other causes may be investigated (as listed above) if the taste disturbance is ongoing, and speech pathology or ENT may be consulted if the symptoms are significant and affecting the patient's quality of life.

Acknowledgment – This E-Bulletin based on work by Daniella Tocchetti, Adult Medicines Information Service, SA Pharmacy.

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

Complex regional pain syndrome

Complex Regional Pain Syndrome (CRPS) is a debilitating condition which can occur either spontaneously or is triggered by injury (strain or sprain), distal fracture or surgery. Symptoms include oedema and sweating, erythema and changes in skin temperature, motor dysfunction, allodynia (increased pain sensed with non-painful stimulus), hyperalgesia and trophic changes in skin hair and nails.

Severity of pain is often greater than the expected from the inciting injury and pain can spread regionally beyond a single dermatome (e.g. from hand to forearm). Pain is often described as shooting, burning or sharp. Symptoms can resolve spontaneously in a matter of weeks or months while other patients can have persistent pain, stiffness and allodynia. Some can develop a wasted, shiny, contractured limb. Relapses can occur with spread to other limbs. Prognosis in children is better as more patients achieve full recovery.

There are two types of CRPS:

- Type I (also known as reflex sympathetic dystrophy) where there is no definable nerve lesion, representing around 90% of CRPS presentations
- Type II: where a definable nerve lesion is present.

Prognosis for this condition is fair if treated early, but poor when it becomes chronic. Treatment can be difficult owing to the range of symptoms, the small number of patients and differing diagnostic criteria, the broad range of multidisciplinary treatments. This is also complicated because it is sometimes difficult to know if an improvement represents recovery due to treatment, or is actually spontaneous remission.

Treatment includes physiotherapy, psychological therapy and drug therapy. Unfortunately, drug therapy can become expensive for the patient as there is a lack of subsidy offered by the Pharmaceutical Benefits Scheme for this condition. Drug therapy may include simple analgesia (even though there is no specific evidence in CRPS for the use of paracetamol), NSAIDs and COX-2 inhibitors (with or without paracetamol), tramadol and opioids for acute pain management, corticosteroids in the early inflammatory stages, and sometimes antidepressants or gabapentinoids.

Interestingly, there has been some limited evidence to suggest that ascorbic acid in a dose of 500 mg daily for 50 days can reduce complex regional pain after wrist fracture or limb surgery, although the mechanism by which it does so is unclear, It has been postulated that the antioxidant properties of ascorbic acid may be responsible for stabilizing the free radicals that normally damage lipid membranes or microcirculation. As ascorbic acid is a relatively safe, easily accessible and inexpensive supplement, it can be used in the early management of CRPS.

Acknowledgment – This E-Bulletin based on work by Joanna Hogan, Senior Pharmacist, RGH

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

Effects of antidepressants upon seizure threshold

Depressive disorders in patients with epilepsy have been reported with a higher prevalence than the general population, stated at 9-22%. The association between the conditions may be due to the depletion of serotonin, although an exact mechanism is unclear. Depression and psychosis are also risk factors for epilepsy, and the increased risk of seizures with concurrent SSRI/SNRI treatments should be interpreted in the context of this background risk (approximately 15-fold increase). Another important consideration is that all antidepressants have been associated with hyponatremia, which may predispose a patient to seizures - these affects appear to be dose dependent.

A concern regarding treating patients with epilepsy who also have comorbid depression is largely related to the pro-convulsive potential and pharmacokinetic interactions related to antidepressant therapy. Depression may be left untreated in patients with epilepsy, partially due to apprehension and concerns regarding starting an antidepressant that can in itself lower the patient's seizure threshold. However, at least one study that investigated the impact of antidepressants upon seizure threshold suggested that a very large sample size would be required to detect even the smallest difference in seizure risk when compared to placebo. The exact mechanism underlying the effects of antidepressants in lowering the seizure threshold is currently poorly understood and not clearly defined, although some evidence suggests in therapeutic doses, antidepressants may have anticonvulsive properties, and in higher doses more pro-convulsive effects.

Selective serotonin re-uptake inhibitors (SSRI) are regarded as first line antidepressant options for patients with epilepsy, with evidence suggesting they are least likely to affect seizure threshold. The incidence of inducing a seizure using paroxetine was found to be increases by only 0.1% compared with patients not receiving an SSRI in one study. There is evidence to suggest that SSRIs may be anticonvulsive at therapeutic doses, and protect against hypoxic damage – no clear difference between the various SSRIs has been reported in this regard. A trial analysing seizure frequency amongst patients using citalopram 20 mg/day and with comorbid epilepsy found $\geq$ 50% of patients has a therapeutic response (according to the Hamilton Rating Scale for Depression (HAM-D21)), but there were no significant changes were reported in seizure frequency.

There is less evidence and clinical experience with the use of Selective Noradrenalin Re-Uptake Inhibitors (SNRIs). The risk of seizures in a premarketing clinical trial involving 3082 patients on venlafaxine found rate of 0.3%, with most seizures occurring at a dose of 150 mg/day or less. Similarly, duloxetine was associated with a seizure rate of 0.2% in a clinical trial involving 2418 patients.

Tricyclic antidepressants (TCAs) have been shown to reduce seizure threshold and may increase seizure frequency due to pro-convulsive properties. Estimates of the incidence of seizures with TCAs at therapeutic doses range from 0.4 -2%. Tricyclic antidepressants should be used cautiously and reserved for patients who have responded poorly or not tolerated a first line agent such as an SSRI's.

In summary, there is limited information available for the use of antidepressants in epilepsy. The consensus based on the limited literature available suggests that concurrent SSRI treatment in patients with epilepsy does not increase the seizure frequency to an extent greater than that in observed patients not receiving therapy. The risks of untreated depression should also be closely considered when balancing the risk of lowering seizure threshold and potentially worsening the patient's epilepsy. Irrespective of treatment choice, a conservative approach should be taken with all antidepressants during treatment initiation for patients with existing epilepsy, 'start low, go slow'.

Acknowledgment – This E-Bulletin based on work by Fares Al-Sarawi, Pharmacy Intern, RGH

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

The SAMEe-TT2R2 Score

The extent of effective anticoagulation with Vitamin K antagonists (i.e. warfarin) is reflected by the time that the International Normalised Ratio (INR) is within the therapeutic range. Deviations from desired INR may be associated with under-anticoagulation leading to thromboembolism, or over-anticoagulation that may result in bleeding. The SAMeTT2R2 score was developed to predict the likelihood of achieving a high proportion of time in the therapeutic range (TTR) for patients with atrial fibrillation. Clinical & demographic factors that influence the quality of oral anticoagulation were identified using data from the AFFIRM trial population. The acronym SAMe-TT2R2 is derived from the following:

Acronym	Definitions	Points
S	Sex (female)	1
A	Age (< 60years)	1
Me	Medical history More than 2 of: Hypertension Diabetes Coronary artery disease/Myocardial infarction Peripheral arterial disease Congestive heart failure Previous stroke Pulmonary disease Hepatic or renal disease	1
T	Treatment - interacting drugs e.g. amiodarone for rhythm control	1
T	Tobacco use (within 2 yrs)	2
R	Race (non-white)	2
Maximum points		8

A score of 0 to 1 may identify those who would be likely to do well on warfarin (achieve a high proportion of time in the therapeutic range) whereas a score of 2 or more identifies those who may require further intervention to achieve good quality anticoagulation on warfarin. Interestingly young patients were less likely than older patients to achieve a good TTR. The authors of this scoring system speculated that the more active lifestyle of the young affected compliance. Female patients have poorer anticoagulant control with warfarin, as do smokers and those of non-white race. There were other predictors of TTR but the above score was based on six simple clinical variables with good discriminatory performance for TTR.

The SAMe-TT2R2 has been validated in various populations and has recently been suggested as a tool to determine whether patients should be selected for prescription of a new oral anticoagulant (NOAC) in preference to warfarin. A common approach for using the NOACs is to reserve them for when TTR on warfarin is low. The SAMe-TT2R2 score, however, does not predict how well a patient will achieve anticoagulation on a NOAC, so caution is advisable when using the score in this way. If poor compliance is the reason why younger patients fair worse on warfarin, then they are just as likely to non-comply with a NOAC with the added disadvantage of lack of monitoring to demonstrate this. Where the SAMe-TT2R2 score may be useful is to identify those patients on warfarin who will need additional monitoring.

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

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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

Dysgeusia is a medical term used to describe disturbance or derangement of:

a) positional sense
b) sense of smell
c) sense of taste
d) vibration sense

Which of the following drugs is known to be an iatrogenic cause of dysgeusia?

a) perindopril
b) acetazolamide
c) lincomycin
d) all of the above

Which of the following statements is correct in regards to Complex Regional Pain Syndrome (CRPS)?

a) 90% of cases of CPRS are classified as type I (no identifiable neurological deficit)
b) 90% of cases of CPRS are classified as type II (with an identifiable neurological deficit)
c) CPRS is usually relatively minor and short-lived
d) overall prognosis is usually good, even in cases with a protracted course

There is evidence to suggest that the development of CPRS after wrist fracture or limb surgery is reduced by use of:

a) oral vitamin B12
b) parenteral vitamin B12
c) oral thiamine
d) oral ascorbic acid

Depression and psychosis are risk factors for epilepsy, with the increased risk of seizures cited as approximately:

a) 2-fold
b) 5-fold
c) 15-fold
d) 25-fold

The class of antidepressants regarded as agents of first choice for people with epilepsy is:

a) TCAs
b) SNRIs
c) SSRIs
d) MAOIs

The SAMe-TT2R2 score predicts the likelihood of achieving a high proportion of time in the therapeutic range (TTR) for patients with AF treated with warfarin. Which of the following variables is not used when generating a patient's score?

a) gender
b) age
c) ethnicity
d) concurrent treatment with aspirin or clopidogrel

Which of the following contributes to the generation of a higher SAMe-TT2R2 score (less likely to do well on warfarin)?

a) male gender
b) alcohol consumption
c) current or recent smoking
d) caucasian race