Neuroleptic Malignant Syndrome or Serotonin Syndrome? _______________ 31
Hypomagnesaemia — a Risk Associated with All Proton Pump Inhibitors ______ 32
The Burning Issue with Pain Relief Creams ______________________________ 32
Bupropion (Zyban): Association with Congenital Malformations? ____________ 33
Do All Antidepressants Cause QT Prolongation? __________________________ 33
Complementary Corner: Aristolochic Acid and Urothelial Cancer ____________ 35
What Happens to your Adverse Reaction Reports? ________________________ 35
Haloperidol — Dose Recommendations _________________________________ 36
Corticosteroids and Musculoskeletal Adverse Events _______________________ 37
MARC’s Remarks: September 2012 Meeting ______________________________ 38
Patent Blue V — Anaphylaxis is a Risk ________________________________ 38
MEDICINES MONITORING: Ondansetron Added __________________________ 39
Prescriber Update Quiz 2012 _________________________________________ 40
Neuroleptic Malignant Syndrome or Serotonin Syndrome?

Neuroleptic malignant syndrome (NMS) and serotonin syndrome are rare, life-threatening, medicine-induced disorders. Both syndromes share clinical features, such as pyrexia, hypertonia and changes in mental state, making differentiation difficult. Differentiation is important as pharmacologic treatment is dependent on the causative agent.

The presence of neuromuscular excitation such as clonus (involuntary, rhythmic muscular contractions and relaxations) and hyperreflexia are strongly predictive of serotonin syndrome (Table 1). In contrast, NMS is characterised by muscular ‘lead-pipe’ rigidity, haemodynamic dysregulation and hyporeflexia.

Knowledge of medication use may also aid diagnosis. Dopamine antagonists including atypical antipsychotics have been implicated in NMS. Serotonergic agents, either alone in high doses or in combination, are associated with serotonin syndrome. However, selective serotonin reuptake inhibitors may contribute to NMS as they are also indirect dopamine antagonists.

Symptoms of NMS and serotonin syndrome have been misinterpreted as symptoms of mental illness. If a patient develops signs and symptoms indicative of NMS or serotonin syndrome, or presents with unexplained high fever without additional clinical manifestations, treatment with dopamine antagonists or serotonergic medicines should be discontinued immediately and supportive therapy administered.

Administration of serotonin antagonists may be considered for serotonin toxicity, whilst dopaminergic agents and dantrolene may be considered for NMS. If treatment for the underlying condition is restarted, knowledge of the causative medicines and resulting syndrome must be considered to prevent recurrence. Specialist advice should be sought and alternative treatments may be required.

Healthcare professionals are encouraged to report these reactions to the Centre for Adverse Reactions Monitoring (CARM) and to include as much information as possible to help identify other risk factors for these syndromes.

Reports can be made via the CARM website or by filling in a yellow reporting card found in MIMS.

Table 1: Characteristics of NMS and serotonin syndrome

<table>
<thead>
<tr>
<th></th>
<th>Neuroleptic malignant syndrome</th>
<th>Serotonin syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Precipitated By</strong></td>
<td>Dopamine Antagonists</td>
<td>Serotonergic Agents</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Variable, 1–3 days</td>
<td>Variable, &lt; 12 hours</td>
</tr>
<tr>
<td><strong>Identical Features</strong></td>
<td>Vital Signs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>Hypertension</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>Tachycardia</td>
</tr>
<tr>
<td></td>
<td>Tachypnoea</td>
<td>Tachypnoea</td>
</tr>
<tr>
<td></td>
<td>Hyperthermia (&gt; 40ºC)</td>
<td>Hyperthermia (&gt; 40ºC)</td>
</tr>
<tr>
<td><strong>Mucosa</strong></td>
<td>Hypersalivation</td>
<td>Hypersalivation</td>
</tr>
<tr>
<td><strong>Overlapping Features</strong></td>
<td>Skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diaphoresis</td>
<td>Diaphoresis</td>
</tr>
<tr>
<td></td>
<td>Pallor</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Variable, stupor, coma, alert</td>
<td>Variable, agitation, coma</td>
</tr>
<tr>
<td><strong>Muscles</strong></td>
<td>‘Lead-pipe’ rigidity in all muscle groups</td>
<td>Increased tone, especially in lower extremities</td>
</tr>
<tr>
<td><strong>Distinct Features</strong></td>
<td>Reflexes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hyporeflexia</td>
<td>Hyperreflexia</td>
</tr>
<tr>
<td></td>
<td>Clonus (unless masked by increased muscle tone)</td>
<td></td>
</tr>
<tr>
<td><strong>Pupils</strong></td>
<td>Normal</td>
<td>Dilated</td>
</tr>
<tr>
<td><strong>Bowel Sounds</strong></td>
<td>Normal or decreased</td>
<td>Hyperactive</td>
</tr>
</tbody>
</table>
Key Messages

• NMS and serotonin syndrome are rare, but potentially life-threatening, medicine-induced disorders.

• Features of these syndromes may overlap making diagnosis difficult. However, NMS is characterised by ‘lead-pipe’ rigidity, whilst serotonin syndrome is characterised by hyperreflexia and clonus.

• Precipitating medicines also allow differentiation. Dopamine antagonists precipitate NMS, whilst serotonergic medicines are indicative of serotonin syndrome.

• Differentiation is important when considering treatment options and future use of causative medicines.

References


Hypomagnesaemia — a Risk Associated with All Proton Pump Inhibitors

Hypomagnesaemia has now been linked to the long-term use of all proton pump inhibitors (PPIs).

The risk of hypomagnesaemia associated with long-term omeprazole use has been highlighted previously. Medsafe’s monitoring scheme sought further information regarding the risk of hypomagnesaemia for the other PPIs following a CARM report of hypomagnesaemia in a patient taking pantoprazole. The results obtained from and a review of additional data were considered by the Medicines Adverse Reactions Committee (MARC) at the September 2012 meeting.

In most cases, hypomagnesaemia was identified in patients who had taken a PPI for longer than a year. However, in some cases the onset time was only three months.

Low serum magnesium levels can result in serious events such as fatigue, tetany, delirium, convulsions and arrhythmias. The symptoms may be insidious and easily overlooked. In some patients, magnesium supplementation may be sufficient to improve serum magnesium levels but others may need to cease PPI treatment.

CARM have also received a case report which highlights that restarting a PPI (even a different PPI) may result in a recurrence of hypomagnesaemia, within a much shorter time period than previously experienced.

The outcome of the review can be found on the Medsafe website www.medsafe.govt.nz/profs/M2MedicinesMonitoringOutcomes.asp

Key Messages

• Hypomagnesaemia is associated with long-term use of all PPIs.

• Monitoring of serum magnesium levels prior to and during treatment should be considered for:
  – patients expected to require long-term PPI treatment
  – patients who take other medicines such as digoxin or medicines that may cause hypomagnesaemia (such as diuretics).

• Restoration of magnesium levels may require magnesium supplementation and cessation of PPI treatment.

• In patients who have experienced PPI associated hypomagnesaemia, retreatment with any PPI may result in hypomagnesaemia within a short time frame.

References


The Burning Issue with Pain Relief Creams

The Food and Drug Administration (FDA) has recently advised of serious application site injuries being reported following the use of over-the-counter (OTC) topical muscle and joint
pain relievers. Injuries included first- to third-degree chemical burns, with some requiring hospitalisation. In many cases, burns occurred after only one application, with severe burning or blistering occurring within 24 hours.

OTC topical muscle and joint pain relievers are available as single or combination-ingredient products. In the majority of the FDA reports, severe burns occurred with the use of menthol or menthol/methyl salicylate combination products with the concentration of menthol greater than 3% and methyl salicylate greater than 10%. However, a few of the cases involved capsaicin-containing products.

In New Zealand, the Centre for Adverse Reactions Monitoring (CARM) has received four reports of burns following the use of OTC topical muscle and joint pain relievers. Of the four reports, one patient required hospitalisation following the use of a methyl salicylate-containing product. The remaining reports involved the use of capsaicin-containing products.

OTC topical muscle and joint pain relievers following application should cause a local sensation of warmth or coolness. However, if any pain, swelling or blistering of the skin develops, patients should be advised to stop using the product and to wash the affected area to remove any remaining product. If symptoms persist, patients should be advised to see a healthcare professional.

In order to reduce the risk of adverse effects, patients should be advised to:

- use a small amount of product for each application and to gently rub in to the affected area
- wash residue from hands after use (or 30 minutes after application if treating hands)
- avoid applying these products to broken or irritated skin
- avoid contact with eyes and mucous membranes
- avoid applying bandages or heat (heating pads, hot water bottles, heat lamps) to the area where the product has been used
- avoid hot showers or baths immediately before or after application.

OTC topical muscle and joint pain relievers available in New Zealand include Zostrix (capsaicin), Deep Heat (menthol/methyl salicylate), Metsal (menthol/methyl salicylate), Ice Gel (menthol), and Tiger Balm (multiple actives).

Healthcare professionals are reminded of the importance of counselling patients about how to use the products appropriately when recommending topical muscle and joint pain relievers to patients. Any serious suspected adverse effects should be reported to CARM.

References


Bupropion (Zyban): Association with Congenital Malformations?

Data from a recent epidemiological study shows a possible increased risk of congenital cardiovascular malformations after exposure to bupropion (Zyban) in the first trimester of pregnancy. All women who are pregnant or planning to become pregnant should be informed of this potential risk associated with bupropion treatment. The bupropion data sheet is being updated to provide more information on this potential risk. The Zyban data sheet is available at www.medsafe.govt.nz/profs/Datasheet/z/zybantab.pdf

Do All Antidepressants Cause QT Prolongation?

Medsafe and the Medicines Adverse Reactions Committee (MARC) have recently completed a review of the risk of QT prolongation and/or Torsades de pointes (TdP) associated with antidepressants used in New Zealand. The MARC concluded that QT prolongation/TdP is a risk of treatment with most of the antidepressants approved for use in New Zealand.

QT prolongation is a measure of delayed ventricular repolarisation and is a surrogate marker for the risk of developing the potentially fatal arrhythmia TdP. The definition of QT prolongation depends on the age and gender of the patient. However, a QTc greater than 500ms or
an increase of greater than 60ms during treatment is considered to confer a high risk of TdP. QTc is the QT interval corrected for heart rate.

Risk factors for QT prolongation include female gender, increasing age, family history, hypokalaemia and interactions with other medicines (Table 1). Further information on QT prolongation can be found in the *Prescriber Update* article ‘Drug-induced QT prolongation and Torsades de Pointes — the facts’.

The MARC concluded that the available data supports an association between the use of tricyclic antidepressants, selective serotonin reuptake inhibitors, maprotiline, mianserin, moclobemide, mirtazapine and venlafaxine and the development of QT prolongation. The MARC considered, due to a lack of comparative data, the relative risk of QT prolongation/TdP between antidepressants or different classes of antidepressants is generally unknown.

Further information on the MARC’s opinion regarding the individual antidepressants can be found in the MARC meeting minutes published on the Medsafe website website [www.medsafe.govt.nz/profs/adverse/Minutes151.htm#3.2.1](http://www.medsafe.govt.nz/profs/adverse/Minutes151.htm#3.2.1)

Prescribers are advised to consider the risk of QT prolongation as part of their assessment of the risk-benefit balance of antidepressants therapy. Particular care should be taken in patients taking other medicines associated with QT prolongation (eg, antipsychotics) and those with risk factors in addition to age and gender. Specialist advice should also be considered.

### Table 1: Risk factors for drug-induced QT prolongation/TdP

<table>
<thead>
<tr>
<th>Unmodifiable risk factors</th>
<th>Potentially modifiable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender (present in 70% of cases)</td>
<td>Hypokalaemia or severe hypomagnesaemia</td>
</tr>
<tr>
<td>Increasing age (particularly age &gt;60)</td>
<td>Absolute or relative bradycardia (including recent conversion from atrial fibrillation)</td>
</tr>
<tr>
<td>Genetic predisposition</td>
<td>Medicine interactions (refer to Medsafe data sheets for further information)</td>
</tr>
<tr>
<td>• Congenital long QT syndrome</td>
<td>• Use of &gt;1 QT prolonging medicine</td>
</tr>
<tr>
<td>• Family history of sudden death</td>
<td>• Medicines that inhibit the metabolism of another QT prolonging medicine</td>
</tr>
<tr>
<td>• Previous history of drug-induced QT prolongation</td>
<td>• Medicines that cause electrolyte abnormalities or may cause renal or hepatic dysfunction</td>
</tr>
<tr>
<td>Structural heart disease/left ventricular dysfunction</td>
<td>Starvation, obesity or metabolic disorders (eg, hyperthyroidism, hypothyroidism, diabetes)</td>
</tr>
<tr>
<td>Impaired elimination due to renal or hepatic disease</td>
<td>High drug concentrations (eg, rapid intravenous administration, high doses or overdose)</td>
</tr>
</tbody>
</table>

**Key messages**

- All classes of antidepressants approved for use in New Zealand appear to carry some degree of risk of QT prolongation.
- Specialist advice should be sought if QT prolongation is suspected.
- Patients should be evaluated for risk factors for QT prolongation prior to starting antidepressant treatment.
- Antidepressants should be used with caution in patients with risk factors in addition to age and gender for QT prolongation. An ECG should be considered at baseline, steady state, at the time of dose increases and if another QT prolonging medicine is added to their treatment regimen.
- The possibility of drug-induced QT prolongation or TdP should be considered in patients presenting with new onset dizziness, syncope, palpitations or seizures.
- If QT prolongation or symptomatic arrhythmia occurs, the antidepressant should be stopped unless there are compelling reasons to continue and specialist advice sought.
Complementary Corner: Aristolochic Acid and Urothelial Cancer

Healthcare professionals are encouraged to ask patients about past use of traditional Chinese medicines, specifically medicines derived from Aristolochia species following reported cases of nephrotoxicity and carcinogenicity in Europe, China and Japan. Products containing Aristolochia have been classified as human carcinogens by the International Agency for Research on Cancer as all Aristolochia plant species contain aristolochic acid.

Recently, a study has linked the high rate of urothelial cancer of the upper urinary tract in Taiwan with the widespread use of herbal medicines containing aristolochic acid. In Taiwan, the incidence of urothelial cancer of the upper urinary tract is the highest reported anywhere in the world. Due to the lifelong persistence of mutations caused by aristolochic acid, patients treated with Aristolochia are at risk of developing urothelial cancer of the upper urinary tract at any time in their life.

This study in Taiwan is supported by research carried out in Belgium on patients who were inadvertently exposed to Aristolochia in weight loss pills. Aristolochic acid was found to be associated with progressive interstitial nephritis in these patients leading to terminal renal failure. Subsequently, a number of the patients being treated for terminal renal failure were found to have developed urothelial cancer.

Despite being banned in many countries, it appears that many aristolochic acid-containing products are still available over the internet. A report in the Medical Journal of Australia described a fatal case of a 75-year-old man with a three year history of using Chinese herbal medicines containing aristolochic acid. The patient was diagnosed with renal failure and died four years after initial presentation. Although Australia banned products suspected of containing aristolochic acid in 2002, the medicines had been obtained from outside Australia via mail order.

In 2003, Medsafe released an urgent product alert advising of the withdrawal from distribution in New Zealand of some traditional Chinese medicines after they were found to contain aristolochic acid. This alert included a list of herbs which are commonly substituted with Aristolochia species, along with a list of products which have been tested and found to contain aristolochic acids.

References


this year, CARM and Medsafe wrote to stakeholders in New Zealand to inform them of this minor change. This change does not impact on the confidentiality and privacy of information included in adverse reaction reports.

Sharing of all report details between CARM and Medsafe has previously been on an ad hoc basis. However, as of 1 November 2012 this sharing of reports is now routine. Access to full report details is consistent with international practices as pharmacovigilance centres are usually situated within the medicines regulator.

CARM and Medsafe have concluded that routine sharing of all report details will further facilitate the monitoring of medicines and patient safety. This change will help CARM and Medsafe to identify medicine related safety issues in New Zealand and provide information to healthcare professionals in a more timely fashion.

CARM will continue to anonymise reports where possible. However, CARM and Medsafe emphasise that all details contained within reports remain confidential. There will be no change to the ‘no blame’ reporting of adverse reactions in New Zealand.

There are no changes to how to report adverse reactions in New Zealand. Healthcare professionals are encouraged to continue to report all suspected adverse reactions to CARM in the usual way. Further information about how to report adverse reactions is available on the CARM and Medsafe websites [https://nzphvc-01.otago.ac.nz](https://nzphvc-01.otago.ac.nz) and [www.medsafe.govt.nz](http://www.medsafe.govt.nz).

CARM and Medsafe would like to thank healthcare professionals for their diligence in reporting adverse reactions and thereby contributing to pharmacovigilance in New Zealand.

References

## Haloperidol — Dose Recommendations

Healthcare professionals are advised that, due to the risk of life-threatening arrhythmia, the dosing recommendations for immediate release haloperidol have changed. The initial starting dose for oral and intravenous (IV) administration is now 0.5mg and the maximum recommended daily dose is now 30mg. This maximum dose should only be used in exceptional circumstances.

Medsafe and the Medicines Adverse Reactions Committee (MARC) have reviewed the available evidence regarding effective and safe dosing levels. The evidence suggests that doses greater than 10mg per day are unlikely to provide further efficacy, yet may lead to increased adverse events. It is possible that some individuals may benefit from higher doses of haloperidol (greater than 10mg per day). However, the research review was unable to characterise patients who may benefit from higher doses.

Information on adverse events associated with the route of administration was also considered. The evidence reviewed suggests that IV administration of haloperidol is associated with an increased risk of QT prolongation and Torsades de Pointes (TdP).

Prescribers should carefully consider the risk of QT prolongation and TdP when deciding on administration route for patients. Patients with multiple risk factors for QT prolongation should be monitored carefully (including ECGs and potassium levels), particularly during the initial phase of treatment. Further information on risk factors can be found in Table 1 of the article ‘Do all antidepressants cause QT prolongation?’ in this edition of *Prescriber Update*.

When prescribing haloperidol, prescribers should consider that:

- the initial recommended starting dose for oral and IV administration is 0.5mg
- doses greater than 10mg per day are unlikely to provide further efficacy, yet may lead to increased adverse events
- IV administration carries a higher risk of QT prolongation or TdP and patients with risk factors for QT prolongation should be monitored accordingly.

References
Corticosteroids and Musculoskeletal Adverse Events

Healthcare professionals are reminded that corticosteroids are associated with multiple musculoskeletal adverse reactions including avascular necrosis of the bone, osteoporosis and tendinopathies.

Avascular Necrosis of the bone

Avascular necrosis of the bone is an uncommon adverse reaction associated with corticosteroids. Higher doses of corticosteroids are associated with a greater risk of avascular necrosis even when used for short periods. Importantly, avascular necrosis has also been reported with topical application of corticosteroids.

Osteoporosis

Osteoporosis is a common adverse reaction associated with long-term corticosteroid treatment, where up to 50% of patients are affected. Bone loss is more rapid during the early stages of therapy, is dose-dependent and primarily occurs in trabecular bone. Daily doses of greater than 7.5mg prednisolone (or equivalent) have been associated with a higher risk of fracture than daily doses of less than 2.5mg prednisolone (or equivalent).

Tendinopathies

Tendinopathies associated with corticosteroid use are predominantly reported in the Achilles and patellar tendons. Tendon ruptures have also been reported. Tendinopathies have been associated mainly with oral and intra-articular corticosteroid use.

New Zealand Reports

In New Zealand, 40 reports of musculoskeletal adverse events associated with corticosteroids were reported to the Centre for Adverse Reaction Monitoring (CARM) between January 2000 and June 2012. The majority of the reports were associated with prednisone (30 reports). The remaining reports were associated with dexamethasone (nine reports), triamcinolone (two reports) and methylprednisolone (one report). In two cases, the patient was on more than one corticosteroid. It is worth noting that in all but one case of tendon rupture the patient was also taking a quinolone antibiotic.

The types of musculoskeletal adverse reactions reported in these 40 reports are shown in Figure 1. Avascular necrosis (55.6%) and osteonecrosis (13.3%) were the most commonly reported musculoskeletal adverse reactions. Of the reported cases of avascular necrosis, two thirds reported avascular necrosis of the femoral head.

Figure 1: CARM reports of musculoskeletal adverse reactions associated with corticosteroids for the period January 2000 to June 2012

Healthcare professionals are encouraged to educate patients about possible adverse reactions associated with corticosteroid use and to ensure treatment and dose is regularly reviewed. Use of more than one medicine with the potential to cause adverse musculoskeletal effects is likely to increase the risk of an adverse reaction, such as avascular necrosis, osteoporosis and tendon disorders.

References


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**MARC’s Remarks: September 2012 Meeting**

The latest meeting of the Medicines Adverse Reactions Committee (MARC) took place on 13 September 2012.

The MARC undertook a comprehensive review of antidepressants and the risk of QT prolongation. The MARC considered that the available data supported an association between many of the antidepressants reviewed and the development of QT prolongation. The MARC recommended a number of updates to the relevant data sheets. Further information on antidepressants and QT prolongation can be found in this edition of *Prescriber Update*.

The MARC undertook a review of a possible association between serotonin syndrome and fentanyl, ondansetron or donepezil when taken in combination with a serotonergic agent. The MARC agreed that the published literature supports an association between fentanyl and serotonin syndrome and recommended that this information be added to the data sheet.

The MARC agreed that there is insufficient evidence at present to support an association between ondansetron and serotonin syndrome. As the use of ondansetron is increasing, the MARC recommended that further information be sought by placing ondansetron and the risk of serotonin syndrome on Medsafe’s monitoring scheme.

The MARC agreed that there is insufficient evidence at present to support an association between donepezil and serotonin syndrome. However, the MARC considered that there was sufficient evidence for an increased risk of neuroleptic malignant syndrome in patients treated with donepezil and recommended data sheet updates. An article on the differential diagnosis of serotonin syndrome and neuroleptic malignant syndrome has been included in this edition of *Prescriber Update*.

The MARC considered the outcome of the recent review of pantoprazole/lansoprazole and the risk of hypomagnesaemia. The MARC considered that there was enough evidence for an association between pantoprazole, lansoprazole and hypomagnesaemia and that the data sheets be updated. Additional information regarding this issue can be found in this edition of *Prescriber Update*.

The MARC also reviewed a report from the Intensive Medicines Monitoring Programme (IMMP) regarding varenicline (Champix). This report included a final analysis of the data collected since varenicline monitoring was started in 2007. The MARC identified a number of issues that needed to be addressed before a robust assessment of the safety profile of varenicline in New Zealand could be made. The MARC recommended that the updated report be provided to Medsafe.

Further information regarding these issues is available from the MARC meeting minutes published on the Medsafe website [www.medsafe.govt.nz/profs/adverse/Minutes151.htm](http://www.medsafe.govt.nz/profs/adverse/Minutes151.htm).

**References**


**Patent Blue V — Anaphylaxis is a Risk**

Patent Blue V dye has been associated with the occurrence of serious allergic reactions including anaphylaxis.

A recent investigation by the Breast Surgeons of Australia and New Zealand Incorporated indicated that the incidence of anaphylactic reactions of...
any severity associated with Patent Blue V is around 0.15%. In this survey, the median onset time was reported as 20 minutes with a range of 0–90 minutes.

The Centre for Adverse Reactions Monitoring (CARM) has received a total of 36 reports of allergic reactions to Patent Blue V. Of the 36 reports, there were 11 reports of anaphylaxis or anaphylactic shock. In 31 cases, a positive skin test was also reported.

Reporting of these reactions is important to allow CARM to record a warning on the National Alert System for that patient.

Key Messages

• Patients should be informed about the risk of allergic reactions to Patent Blue V during the consent process.
• Emergency facilities should be available for up to 90 minutes after administration.
• Reporting these reactions to CARM allows for a warning to be recorded on the National Alert System.

References

TEST YOUR KNOWLEDGE

Have you read your copy of *Prescriber Update* in 2012?
Have you kept up to date with emerging safety signals?
Test your knowledge with the end of year *Prescriber Update* quiz.

Answers to the quiz are available at:

1. Name three medicines that are currently on Medsafe’s \( \square \) scheme?
   a) ……………………………………………….
   b) ……………………………………………….
   c) ……………………………………………….

2. PML is caused by which virus?
   a) CJ virus  b) JC virus  c) Richie Cunningham virus  d) Creutzfeldt-Jakob virus

3. What does RCVS stand for?
   a) Reversible cerebral vascular swelling
   b) Reversible cardiac vasoconstriction swelling
   c) Reversible cerebral vasoconstriction syndrome
   d) Recurrent cardiac vasoconstriction syndrome

4. True or false: Donepezil is associated with an increased risk of serotonin syndrome.

5. In Zealand, which class of non-tuberculosis antibiotics is most often implicated in liver injury?
   a) Macrolides  b) Tetracyclines  c) Quinolones  d) β-lactam penicillins

6. What are some risk factors for statin-induced myopathy?
   a) female gender, high body-mass index, hyperthyroidism
   b) male gender, low body-mass index, hyperthyroidism
   c) male gender, high body-mass index, hypothyroidism
   d) female gender, low body-mass index, hypothyroidism

7. Which healthcare professionals reported the most adverse reactions in 2011?
   a) General Practitioners  b) Hospital Doctors  c) Nurses  d) Pharmacists

8. Butterbur has been associated with adverse effects of the:
   a) skin  b) cardiovascular system  c) liver  d) kidneys

9. Which of these statements about interferon use is false?
   a) Patients should be screened for psychiatric symptoms before treatment.
   b) Mood and suicidal ideation should be monitored closely during therapy.
   c) Medical advice should be sought if symptoms of depression occur during interferon treatment.
   d) None of the above.

10. The maximum recommended intravenous dose of ondansetron is:
    a) 8mg  b) 16mg  c) 32mg  d) 64mg
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