FORMAL ASSESSMENT – MODULE p02

PART 1: FORMATIVE COMPETENCY ASSESSMENT

MEMORANDUM

MODULE p02: REPORT ON DRUG INTERACTIONS
Patient Case: George Mitchell
(Chapter 5: Volume 1 Course Manual)

The Formative Competency Assessment instrument is designed to test deeper understanding of the module and contains open questions which are structured to establish:

- The degree of the Learner’s overall familiarity with the content of the module by setting ‘Content’ questions that require simply that the Learner can quickly find the relevant section and extract the points required to answer the question. These types of questions test Foundational Competence – does the Learner know where to find the information?

- The degree to which the Learner is able integrate and apply knowledge of the module by setting ‘Problem-based’ questions that test the ability to solve problems requiring the application of the knowledge gained to real-life examples. These types of questions test Practical and Reflexive Competence – is the learner able to demonstrate an Applied Competence that will enable them to solve problems they will encounter in a Practical Setting.
IMPORTANT - PLEASE NOTE CAREFULLY

1) The Formative Competency Assessments contain questions that are similar to those that may be set in the FINAL WRITTEN ASSESSMENT.

2) The FORMAT of these FCA’s can be regarded therefore as an example, or template, of the type of questions you may encounter in the final written assessment.

3) You must compare YOUR answers for this FCA against this model answer as a self-evaluation exercise.

4) Allocate yourself an assessed percentage mark for this FCA.

5) Where required, MAKE A NOTE THE APPROPRIATE CORRECTIONS on your answer sheet (use a RED PEN for this purpose).

6) Once you have reviewed, marked and revised your FCA for this module, you are deemed to have COMPLETED THIS FORMAL ASSESSMENT, return to the Learning Portal, click on the “assessments” button and select the “Click for Declaration of Authenticity for the Formal Competency Assessment” option.

7) NOTE THAT THERE IS NO ADDITIONAL PRACTICAL ASSIGNMENT FOR THIS MODULE.

YOUR completed Formative Competency Assessment must be included in your PORTFOLIO of PRACTICAL ASSIGNMENTS.
The patient is a male – George Mitchell

Past Medical History

George M is a 68-year-old clinically obese white male (92 Kg; 1.73m; Waist 133cm; Hip 95cm) who has suffered from poorly controlled hypertension since age 48. His antihypertensive medication has remained unchanged for the last 12 years.

George M was diagnosed with coronary heart disease in the first week of November of the preceding year and underwent a triple Coronary Artery Bypass Graft (CABG).

In the 2nd week of January of the current year, after complaints of feeling light-headed and experiencing nausea and palpitations, an ECG revealed the presence of Persistent Atrial Fibrillation for which Amiodarone was prescribed by George M’s specialist.

Therapy was initiated with Cordarone® (Amiodarone). He was started on 200 mg Cordarone 3 times a day, for one week, followed by 200mg twice a day for the second week. He continued on 100 mg Cordarone twice a day thereafter. The drug was effective at this dosage in controlling his arrhythmia. He was told that he would be closely monitored for the next 6 months.

He was also prescribed Warfarin 5mg per day for anticoagulation with the instruction to keep regular appointments for INR monitoring and adjustment of the Warfarin dose.

Acute Medical Problem

On the 20th of May George M returned to his general practitioner with complaints of fatigue, laboured breathing, non-cardiac chest pains, respiratory crackle, cough with phlegm (clear), nasal congestion. He also complained of “feeling depressed” and asked his GP if he could prescribe something for this.

His GP diagnosed George M to be suffering from an upper and lower respiratory tract infection for which he prescribed Kestine® (Ebastine) 10mg in the morning (30) and Erythrocin® (Erythromycin) 500mg four times a day for 14 days. He also prescribed Prozac® (Fluoxetine) 20mg in the morning (30).

Three days later on 23rd May, George M’s wife, phoned the general practitioner asking what to do? Her husband had complained of shortness of breath and palpitations and had fainted after an afternoon cup of tea. At this point George M’s medications were:

- **Chronic Meds**
  - Cordarone® (Amiodarone) 100 mg twice a day
  - Warfarin 5 mg daily – Monday to Friday
  - Inderal LA® (Propranolol) 80 mg twice a day
  - Ridaq® (Hydrochlorothiazide) 25 mg in the morning
  - Prozac® (Fluoxetine) 20mg in the morning

- **Acute Meds**
  - Erythrocin® (Erythromycin) 500mg four times a day
  - Kestine® (Ebastine) 10 mg in the morning
This case history suggests that the patient’s problems may be due to:

1) Misdiagnosis of the presenting symptoms of a possible Adverse Drug Reaction to Amiodarone by George M’s General Practitioner on the 20th of May, followed by

2) Inappropriate prescribing resulting in Drug Interactions that precipitated his acute problem of Syncope.

ASSESSMENT TASK: INVESTIGATE THE POSSIBLE DRUG INTERACTIONS THAT MAY HAVE PRECIPITATED TORSADE DE POINTES IN PATIENT GEORGE M

PROCEDURE TO FOLLOW TO COMPLETE THIS ASSIGNMENT TASK

1) Refer to your Medicines Formulary to identify the possible Drug Interactions that may have precipitated the episode of Torsade De Pointes in George M.

2) List ALL the patients’ current conditions the patient was receiving at the time of the episode.

3) Identify any Predisposing Factors and the Potential Risk of a Drug Interaction in the patient concerned (Chapter 5: Section 2 (i) and (ii) page 85).

4) Establish the Number of Possible Interactions for the number of medications the patient is taking (Chapter 5: Section 2 (iii) page 86).

5) For each potentially significant interaction you identify:
   (i) List the Interacting Drugs (there 3 or more) by their International Nonproprietary Name (INN).
   (ii) Indicate the possible Clinical Consequences of each Interaction may be (use you SAMF for this – Refer Chapter 1: Section 5 (v) page 25).
   (iii) Indicate what you would estimate to be a possible Time Course for Onset of the Interaction – would it occur within hours, days, weeks or longer? (Chapter 5: Section 2 (iv) pages 87-88).
   (iv) Indicate what Category any Interaction or Potential Interaction you identify falls into i.e. whether it can be classified as a:
       (a) Type 1 Interaction: Absolutely Contraindicated
       (b) Type 2 Interaction: Preventable Interaction
       (c) Type 3 Interaction: Alternative Drug Available or
       (d) Type 4 Interaction: Continue using the drug but Monitor Patient Response
       (e) A combination of Types 1 – 4 Interaction
   (v) Suggest how an Interaction you identify should be clinically managed (Chap 5: Section 4: p89-90).
   (vi) Suggest possible Underlying Mechanism(s) of the interactions – e.g. Pharmacokinetic etc. (Pay particular attention to Vol 1 - Chapter 5: Section 5 (3) (iii) pages 99-109).
AS A GUIDE TO ESTABLISH THE POSSIBLE INTERACTIONS IN THIS EXAMPLE CASE – REFER TO THE SUMMARY CHART OF CYP 450 SUBSTRATES AND INHIBITORS BELOW AND CONSIDER USING THE PIVOT TABLE

Refer to Source Table: Volume 1 Manual: Chapter 5 – Drug Interactions (Pages 106 and 107)

### CYTOCHROME P450 SUBSTRATES

<table>
<thead>
<tr>
<th>CYP 1A2</th>
<th>CYP 2C9</th>
<th>CYP 2C19</th>
<th>CYP 2D6</th>
<th>CYP3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol Warfarin (R)</td>
<td>Fluoxetine Warfarin (L)</td>
<td>Fluoxetine Warfarin (R)</td>
<td>Fluoxetine Propranolol</td>
<td>Amiodarone Ebastine Erythromycin Fluoxetine Warfarin (R)</td>
</tr>
</tbody>
</table>

### CYTOCHROME P450 INHIBITORS

<table>
<thead>
<tr>
<th>Amiodarone (M)</th>
<th>Erythromycin</th>
<th>Amiodarone (M)</th>
<th>Fluoxetine (M)</th>
<th>Amiodarone (M)</th>
<th>Erythromycin (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone (M)</td>
<td>Erythromycin</td>
<td>Fluoxetine (M)</td>
<td>Amiodarone (M)</td>
<td>Amiodarone (M)</td>
<td>Erythromycin (M)</td>
</tr>
</tbody>
</table>

(S) = Strong Inhibitor (5 fold ↑ AUC or > 80% ↓ in renal clearance)
(M) = Moderate Inhibitor (> 2fold ↑ AUC or 50 – 80% ↓ in renal clearance)

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As a guide to establish the possible interactions in this example case, refer to the summary chart of CYP 450 substrates and inhibitors below and consider using the pivot table.
When browsing your SAMF for potential interactions between the 7 medications that George M is receiving the two most striking aspects that attract your attention are the potential for the combinations in the table below to increase the patients’ susceptibility to arrhythmia and to affect Warfarin metabolism as well as Propranolol metabolism.

<table>
<thead>
<tr>
<th>PRIMARY DRUG</th>
<th>INTERACTING DRUG COMBINATIONS ON PIVOT TABLE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interaction No.</td>
<td>1*</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Ebastine</td>
</tr>
<tr>
<td>Interaction No.</td>
<td>(1*)</td>
</tr>
<tr>
<td>Ebastine</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Interaction No.</td>
<td>(2*)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Interaction No.</td>
<td>(3*)</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Interaction No.</td>
<td>(4*)</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Amiodarone</td>
</tr>
</tbody>
</table>

Key:
N* = Sequential Interaction Number: There are 10 Clinically significant interactions from the PIVOT TABLE
(N*) = Interaction Cross-reference Number: This interaction has been already been listed in one of the rows above

He is also on a high dose of Hydrochlorthiazide (25mg) and the possibility of low potassium will exaggerate the proarhythmic drug interactions that he may experience.

DISPENSING FOR HEALTH PRACTITIONERS
FORMATIVE COMPETENCY ASSESSMENT

DATE: 23 / 04 / 2015

NAME (PRINT): FLORENCE NIGHTINGALE

SIGNATURE: Florence Nightingale : SANC/HPCSA Reg. No: SANC 177 0722

MODULE: IDENTIFY AND DESCRIBE THE DRUG INTERACTIONS IN GEORGE M.

<table>
<thead>
<tr>
<th>Patient Demoraphic data</th>
<th>Patient General Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family Name: Mitchell</td>
<td>Sex M ✓ F Date of Birth 1946</td>
</tr>
<tr>
<td></td>
<td>Mass (Kg) 92 Height (m) 1.73 BMI (m/h²) 30.7</td>
</tr>
<tr>
<td>First Name: George</td>
<td>Waist (cm) 133 Hip (cm) 95 Waist:Hip 1.4</td>
</tr>
</tbody>
</table>

# | Condition | Date Dx | # | Condition | Date Dx
---|-----------|---------|---|-----------|---------
1 | Hypertension | 20 years ago | 2 | Coronary Artery Disease | 7 months ago
3 | CABG | 7 months ago | 4 | Persistent Atrial Fib | 4 months ago

CURRENT MEDICATIONS

<table>
<thead>
<tr>
<th>INN name of Active(s)</th>
<th>Dose</th>
<th>Prescribed for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone (Cordarone®)</td>
<td>100 mg 2 x d</td>
<td>Persistent AF</td>
</tr>
<tr>
<td>Warfarin</td>
<td>5 mg 1 x d</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Propranolol (Inderal LA®)</td>
<td>80 mg 2 x d</td>
<td>Hypertension</td>
</tr>
<tr>
<td>HCTZ (Ridaq®)</td>
<td>25 mg am</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Erythromycin (Erythrocin®)</td>
<td>500mg 4 x d</td>
<td>Lower respiratory tract infection</td>
</tr>
<tr>
<td>Ebastine (Kestine®)</td>
<td>10 mg am</td>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>Fluoxetine (Prozac®)</td>
<td>20 mg am</td>
<td>Depression</td>
</tr>
</tbody>
</table>

1). PREDISPOSING FACTORS FOR DRUG INTERACTIONS IN THIS PATIENT

This is a HIGH RISK patient for a D–I in terms of his CVD history (HPT; CABG and Persistent Atrial Fibrillation)

2). POTENTIAL RISK OF CLINICALLY SIGNIFICANT INTERACTIONS IN THIS PATIENT

Risk of Clinically Significant Interactions is HIGH. He is on 3 CYP 450 Inhibitors (Amiodarone, Fluoxetine and Erythromycin) with high risk drugs for an Interaction which include Amiodarone, Warfarin and Antihypertensives

3). MAXIMUM NUMBER OF POSSIBLE INTERACTIONS IN THIS PATIENT

He is on 7 medications – there are 21 possible interactions on this number of meds
There are 10 Clinically Significant Interactions out of these 21 possible interactions
1) DRUG INTERACTION (1) DETAILS

<table>
<thead>
<tr>
<th>Interacting drugs (List INN Names)</th>
<th>Date of Interaction</th>
<th>23 May</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Drug</td>
<td>Drug 2</td>
<td>Drug 3</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Erythromycin</td>
<td>Ebastine</td>
</tr>
</tbody>
</table>

2) Clinical Consequences of Interaction: Combination of 4 agents which increase QT interval with Life-threatening Arrhythmia. Symptoms of Palpitations, shortness of breath and Syncope (20th May). Acute syncope was precipitated by an episode of ventricular arrhythmia – Torsades de Pointes.

3) Estimated time for ONSET of Interaction

3 Days – Ebastine and Erythromycin administered 20 May – Onset 23 May

4) Category of Interaction

<table>
<thead>
<tr>
<th>Category I</th>
<th>Category 2</th>
<th>Category 3</th>
<th>Category 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolutely Contraindicated</td>
<td>Preventable interaction</td>
<td>Alternative drug available</td>
<td>Monitor response</td>
</tr>
<tr>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5) Clinical Management Strategy

Stop Erythromycin, Ebastine and Fluoxetine. Avoid these Meds in this patient

6) INTERACTION NOTES

Mechanism of Interactions

(i) Pharmacokinetic (Inhibition of Substrate Metabolism with increase in serum levels) and Pharmacodynamic (pro-arrhythmic combination due to prolongation of QT interval)

(ii) Erythromycin and Amiodarone both prolong the QT interval and inhibit their own metabolism (= Auto-inhibition) via CYP 3A4. This increases the pharmacological action of both agents and reinforces the effect of QT interval prolongation.

(iii) Erythromycin and Amiodarone inhibit the metabolism of Ebastine via CYP 3A4; this increases the blood levels and pharmacological action of Ebastine. By implication this will increase the QT interval prolongation by Ebastine with increased susceptibility to arrhythmia.

(iv) Fluoxetine has also been documented as effecting QT interval – in presence of the other 3 agents it further increases risk of Torsades De Pointes.

Predicted Onset time of Interaction

(i) Relatively rapid. Erythromycin (T½ ± 2 hours) and Ebastine (T½ ± 16 hours) therefore serum levels of both will peak in ± 3 days (i.e. within 3–4 half lives). They were given 3 days before George M’s episode of Torsade de Pointes.
1) DRUG INTERACTION (2) DETAILS

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</thead>
<tbody>
<tr>
<td><strong>Primary Drug</strong></td>
<td><strong>Drug 2</strong></td>
</tr>
<tr>
<td>Warfarin</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Fluoxetine</td>
</tr>
</tbody>
</table>

2) Clinical Consequences of Interaction: No INR data is provided with this patient’s case history. Therefore no conclusions can be drawn about how swings in his INR status were affected by changes to his regimen over the period of January to May. However increases in INR with clinical consequences are very likely.

3) Onset time of Interaction (if known)
   - Variable – between 2 to 7 weeks

4) Category of Interaction
   - Category I: Absolutely Contraindicated
   - Category 2: Preventable interaction
   - Category 3: Alternative drug available
   - Category 4: Monitor response

<table>
<thead>
<tr>
<th>Category 1</th>
<th>Category 2</th>
<th>Category 3</th>
<th>Category 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

5) Clinical Management Strategy: Monitor INR within 3 – 4 days of introduction of any agent to therapy. No need for Erythromycin and Fluoxetine in this patient

6) INTERACTION NOTES

   Mechanism of Interactions
   (i) Pharmacokinetic (Inhibition of Warfarin metabolism with ↑ serum levels)
   (ii) Amiodarone inhibits the metabolism of Warfarin by 3 pathways: the R form of Warfarin by the CYP 1A2 and 3A4 pathways and the L form of Warfarin by the CYP 2C9 pathway.
   (iii) Erythromycin inhibits the metabolism of Warfarin by 2 pathways: the R form of Warfarin by the CYP 1A2 and 3A4 pathways.
   (iv) Fluoxetine inhibits the metabolism of warfarin by 2 pathways: the L form of Warfarin by CYP 2C9 and the R form of Warfarin by the 2C19 pathway.

   Predicted Onset time of Interaction
   (i) Variable – between 2 to 7 weeks with Amiodarone and Warfarin due to the long half life of Amiodarone (T½ varies between 25–110 days).
   (ii) ONSET of the interaction between Warfarin and Erythromycin (T½ ± 2 hours) as well as between Warfarin and Fluoxetine (T½ ± 16 hours) can be anticipated within 3 to 5 half-lives of these two agents.
   (iii) The time course for the full effect to manifest is likely to range between 1 to 3 weeks because of the existence of individual patient metabolic phenotypes which result in warfarin's variable half-life; from 36 – 48 hours in ‘Normal’ metabolizers (EM’s) and up to 12 days in ‘Poor’ Metabolizers (PM’s).
1) DRUG INTERACTION (3) DETAILS

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<thead>
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<th>Interacting drugs (List INN Names)</th>
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<th>23 May</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>Drug 2</td>
<td>Drug 3</td>
</tr>
<tr>
<td>Amiodarone</td>
<td></td>
<td>Fluoxetine</td>
</tr>
</tbody>
</table>

2) Clinical Consequences of Interaction

*Enhanced Beta Blocking side effects with hypotension, cold extremeties, decreased exercise tolerance and bradycardia; possibility of heart block.*

3) Onset time of Interaction (if known)

*No noted evidence of this interaction occurring in this patient*

4) Category of Interaction

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<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5) Clinical Management Strategy

*Stop or avoid Fluoxetine in this patient and monitor the combination of Amiodarone and Propranolol carefully for symptoms of pronounced bradycardia or heart block*

6) INTERACTION NOTES

**Mechanism of Interactions**

(i) Pharmacokinetic (Inhibition of Substrate Metabolism with increase in serum levels of propranolol).

(ii) Amiodarone inhibits the metabolism of Propranolol by two pathways – by CYP 2D6 and 1A2.

(iii) Fluoxetine inhibits the metabolism of Propranolol by CYP 2D6.

**Predicted Onset time of Interaction**

(i) Unpredictable with this combination due to the long half life of Amiodarone.

(ii) In the case of Fluoxetine, with a T½ of approximately 16 hours – it may be anticipated that the increase in Fluoxetine serum levels would peak within 3 to 5 days with a corresponding increase in Propranolol serum levels in this time frame.
SUMMARY PRACTITIONERS’ COMMENTS AND RECOMMENDATIONS

1) Precipitation of a dangerous Ventricular Torsades De Pointes in George M

Three of George M's medications, Amiodarone, Erythromycin, Ebastine and Fluoxetine are all pro-arrhythmic agents because they prolong the QT interval. There is also evidence that Fluoxetine may contribute to QT interval prolongation.

Therefore any factors that enhance the activity of these three compounds by inhibiting their metabolism will potentiate their pro-arrhythmic activity substantially. To verify this aspect, examine the table in the front of the 11th edition of SAMF "Prescribing drugs that may prolong the QT interval and induce Torsades de Pointes

2) Inhibition of Warfarin Metabolism with consequences of substantial increase in INR.

There are 3 agents – Amiodarone, Erythromycin and Fluoxetine – all of which inhibit the metabolism of Warfarin by various Cytochrome P450 Pathways.

Amiodarone – the first agent administered with the start of Warfarin therapy – reduces Warfarin clearance which can lead to sudden and pronounced increases in INR. Because of Amiodarone’s long T½ (± 50 days), the peak effects of this interaction generally occurs approximately seven weeks after initiation of therapy.

3) Inhibition of Propranolol Metabolism by Amiodarone and Fluoxetine

Amiodarone inhibits the metabolism of Propranolol by two pathways – on CYP 2D6 and 1A2 while Fluoxetine inhibits the metabolism of Propranolol by CYP 2D6.

Clinical implication is enhancement of Beta Blocking side effects, with hypotension, cold extremeties and decreased exercise tolerance.

While there are studies that have shown improved outcome, in terms of heart rate and heart rhythm control, when Amiodarone and Propranolol are used in combination in the treatment of Atrial Fibrillation, the main cause for concern is bradycardia and possibility of heart block. Therefore use of this combination in Atrial Fibrillation requires close supervision and monitoring.