Case Study PH1:

For Pharmacists

June 2000

Scenario

Mrs Harriet Miller is a 67 year old retired teacher who has diabetes mellitus type II and hypertension.

She is currently taking the following medication:

irbesartan	150mg once daily
Mixtard 30/70® insulin	twice daily
metformin	850mg three times daily

Mrs Miller tells you that she had been previously taking enalapril 10mg daily but suffered a persistent cough and her doctor switched her to irbesartan. Mrs Miller tells you that after three months of therapy with the new tablet the cough is back. A description of the cough indicates that it is a tickling sensation at the back of the throat, unproductive and is often worse at night when she is lying down.

Mrs Miller is a regular smoker and overweight. Her diabetes and hypertension are well controlled on the current medication combination.

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Case Study Results

52 pharmacists and 8 GPs responded to the case study. The responses are detailed below. Some people made multiple responses.

Question 1
What questions would you ask about the patient's cough?

Response	Responses - Specific	Number of respondents	Percentage of respondents
Describe symptoms/cough	How long has it been present? Productive? Dry? Painful?	23	38
When does it occur?	Daytime? Nighttime? Does it keep her awake?	9	15
What precipitates the cough?	Worsened by exercise? Smoking induced?	8	13
What relieves the cough?	Not specified	4	7
	Improved when sitting up?	2	3
Are there other symptoms/signs?	Hoarseness? Shortness of breath? Tightness of chest? Difficulty breathing? Sore throat? Tingling of lips and mouth? Blood in sputum? (Haemoptysis) Postnasal drip?	31	52
How long does an episode last?		2	3
Is it being medicated?	Not specified	4	7
	Cough suppressants	3	5
	Inhalers	1	2
Has the doctor investigated this cough?		1	2
Medication induced?	Not specified	6	10
	ACE inhibitor	4	7
	Angiotensin II receptor antagonist	4	7
Change in cough since medication changed?	Not specified	10	17
	Does cough cease if irbesartan ceased?	1	2
Do you have any other medical conditions?	Recent URTI Sore throat/fever/runny nose	15	25
	Not specified	9	15
	Asthma related	8	13
	GORD (post prandial)	7	12
	Allergic rhinitis	6	10
	Heart failure (swollen feet)	5	8
	Cancer (loss of weight)	3	5
	Whooping cough	1	2

A range of questions were asked of the patient regarding the cough. There were 23 responses (38%) with questions regarding other symptoms, 25 responses (48%) were questions regarding how the cough was related to medication use, 8 responses (14%) were questions relating to drug treatment and 54 responses asked the patient further questions regarding possible coexisting diseases.

Question 2
What are the possible medication related problems?

Response	Responses - Specific	Number of respondents	Percentage of respondents
Angiotensin II receptor antagonist induced cough (irbesartan)		43	72
ACE inhibitor induced cough		7	12
Hypotension		1	2
Overdose of metformin:	Lactic acidosis	9	15
	Not specified	3	5
	Hypoglycaemia	3	5
	GIT symptoms	1	2
Bruising/Infection from injection		1	2
Cough (Source unspecified)		6	10
Diabetic mismanagement		6	10
Nicotine causing increased blood pressure		2	3

Medication related problems were considered to be very likely, with 43 responses regarding the angiotensin II receptor antagonist (irbesartan) as a possible cause of cough, whilst 7 responses regarded the ACE inhibitor previously taken still a possible cause of the cough. Metformin overdose was a possibility with 27% of responses indicating such adverse effects as hypoglycaemia (5%) and/or lactic acidosis (15%), a potentially fatal condition. A further 6 responses (10%) attributed possible problems to the medication overall.

Question 3
What pharmaceutical care would you offer Mrs Miller?

Referral to GP	Number of respondents	Percentage of respondents
For further investigation (not specified)	22	37
Medication review	27	45
Investigate cause of cough	12	20
Investigate heart/lung disease	8	13
Check kidney/liver function	4	7
Check for angioedema	4	7
Measure blood pressure	1	2
Measure blood sugar level	1	2

Counselling for medication related issues	Number of respondents	Percentage of respondents
Not specified	13	22
Explain possible irbesartan induced cough	9	15
Possible side effects	3	5
Insulin management	1	2
Metformin with food	1	2
Avoid alcohol	1	2

Counseling for non-pharmacological issues	Number of respondents	Percentage of respondents
Not specified	7	12
Stop smoking	30	50
Exercise/diet/weight loss	22	37
Sleep in elevated position	4	7

Provide information	Number of respondents	Percentage of respondents
Not specified	9	15
Quitting smoking	25	42
Diet/exercise/weight control	11	18
Possible side effects	9	15
Diabetes	6	10
BP/Hypertension	4	7
Cough management	3	5
Injection technique	1	2

Recommend over the counter products	Number of respondents	Percentage of respondents
Anti-tussive	12	20
Nicotine replacement therapy	8	13
Antacid/H_2 receptor antagonist	1	2
Expectorant	1	2
Vitamin C	1	2
Non-sedating anti-histamine	1	2
Lozenges	1	2

A diverse range of pharmaceutical care options were suggested in response to this case study. 27 responses (45%) regarded that a medication review was in order and 22 responses (37%) called for further investigation. 8 responses (13%) specifically requested heart/lung investigation and 13 responses (22%) felt Mrs Miller needed counselling. Half of the respondents called for the patient to stop smoking and 22 respondents (37%) indicated a benefit from weight loss. Overall there was a strong response to counsel Mrs Miller and provide her with information regarding her medication (how to take it, possible side effects) and her lifestyle (quitting smoking and weight reduction).

Question 4
What options might Mrs Miller's doctor pursue to deal with this problem?

Option	Response	Response - Specific	Number of respondents	Percentage of respondents
Investigations	Not specified		7	12
	Chest X-ray		5	8
	Endoscopy		1	2
	FBE		3	5
	Lung Function Tests		3	5
	Lipid levels		2	3
	Echocardiograph		1	2
	CT scan of sinuses		1	2
Underlying condition/s	Not specified		6	10
	GORD/hiatus hernia		7	12
	COPD/emphysema		3	5
	Lung cancer		4	7
	Asthma		6	10
	Pulmonary oedema		1	2
	Heart failure		5	8
	Lactic acidosis		1	2
	Cancer		3	5
Referral to	ENT specialist		3	5
	Dietitian		1	2

	Endocrinologist		1	2
Lifestyle Changes	Not specified		2	3
	Diet	Not specified	4	7
		Caffeine reduction	1	2
	Stop smoking		14	23
	Weight reduction		13	22
	Exercise		4	7
Regular follow up			2	3
Medication Changes	Not specified		2	3
	Alternative antihypertensive therapy	Not specified	7	12
		Alternative angiotensin II receptor antagonist	6	10
		Another ACE inhibitor	5	8
		Beta blocker	4	7
		Alpha blocker	1	2
		Calcium channel blocker	22	37
		diuretic	6	10
			10	17
	Decrease dosage of current angiotensin II receptor antagonist		3	5
		Not specified	3	5
		thiazide	3	5
	Additional drug therapy	Nedocromil / Cromoglycate	1	2
		Anti-asthmatic drugs	1	2
		Inhaled corticosteroid	4	7
		NRT	3	5
		Anti-tussives		
	Review diabetic medication	Not specified		
		Increase insulin	1	2
	Add complementary medicine	Tahitian noni juice	1	2

Many respondents reacted positively to the doctor investigating and elucidating the patient's condition. A variety of tests as well as altering medication were amongst suggestions proffered. 7 responses (12%) suggested a further investigation important and 5 responses (8%) called for chest X-ray. Possible underlying conditions were considered by 6 responses (10%) and another 10% indicated asthma. Almost 10% of responses indicated a referral to some type of specialist whilst there were major indications for lifestyle changes - 23% said stop smoking and 22% proposed weight reduction. Medication change was considered an important factor with 16 respondents (27%) recommending irbesartan be replaced with a diuretic. 17% of these suggested a thiazide. 22 respondents (37%) recommended a change to a calcium channel blocker and 7 respondents (12%) just called for a change in the antihypertensive therapy.

Expert Commentary

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What questions would you ask about the patient's cough?

Cough is a symptom. Attempts should always be made to identify the cause of a persistent cough. A full assessment of the severity, incidence and nature of the cough needs to be obtained. An appropriate history is vital to establish a possible cause of the cough, in guiding further investigation and selecting management options. Persistent cough in a smoker always requires further investigation because of the risk of malignancy or other serious pathology.

We basically agree with the range of questions asked by the pharmacists and if Mrs Miller was our patient questions we would ask include:-

- Could you describe the cough?
- Do you have any other symptoms? (e.g. sore throat or fever as associated symptoms often provide valuable information regarding the cause of a cough)
- How long have you had the cough?
- Is the cough getting better or worse or staying the same?
- Does anything specifically precipitate the cough e.g. eating, exercise or lying down?
- Have you taken any medication for the cough and was it helpful?
- How would you compare the cough to that caused previously by enalapril?

What are the possible medication related problems?

The majority of pharmacists (72%) suggested that Mrs Miller has a Angiotensin II Receptor Antagonist (AIIRA) induced cough caused by irbesartan. This is probably because of the description of the cough as "*a tickling sensation at the back of the throat, unproductive and is often worse at night when she is lying down*" which has all the characteristics of the cough which may produced by Angiotensin Converting Enzyme (ACE) inhibitors.

While initial data from clinical trials indicated that AIIRAs have an incidence of cough similar to that of placebo and considerably less than that produced by ACE inhibitors, recent reports from the Adverse Drug Reaction Advisory Committee (ADRAC) show that cough has occurred in patients taking AIIRAs. The true incidence of cough associated with AIIRA therapy is probably yet to be established.

Some pharmacists rightly identified that Mrs Miller's dose of metformin was high. Gastrointestinal side effects occur in about 30% of patients taking metformin and include bloating, nausea, cramping and diarrhoea. Thankfully for most patients these are self limiting and can be minimised by starting at a low initial dose and taking the drug with food. Lactic acidosis is a less common (0.03 cases per 1000 patients) but very serious side effect of metformin. The risk of this side effect increases in patients receiving a metformin dose greater than 2 g/day and also in people with renal or hepatic dysfunction, alcohol abuse, heart failure and the elderly.

What pharmaceutical care would you offer Mrs Miller?

Again, we agree with the suggestions offered by the majority of pharmacists.

Appropriate pharmaceutical care for Mrs Miller should involve optimising the management of her diabetes and hypertension, and resolution of drug related problems. Reduction of Mrs Miller's other cardiovascular risk factors including weight reduction, smoking cessation and assessment of her lipid profile are essential in the overall management strategy for Mrs Miller. Given her medical history and weight, it is highly likely that Mrs Miller will have elevated triglycerides and possibly cholesterol. This may warrant pharmacological intervention given her risk factors.

A medication review is an appropriate course of action for Mrs Miller. She has two serious medical conditions (and numerous cardiovascular risk factors) and Mrs Miller has experienced what might have been a drug related problem.

Metformin is an appropriate drug choice for Mrs Miller because she is overweight, but her dose of metformin is possibility high. As described above, the risk of lactic acidosis with this drug increases with increasing dose. A reduction of her dose to 850 mg twice daily with meals would be appropriate. This could require some reconsideration of her insulin dose based on blood glucose control and measurement of her glycosylated hemoglobin

The cause of her cough needs to be established. Prematurely implicating irbesartan as causing Mrs Miller's cough might lead to poor adherence with her prescribed medicines. Depending on her response to the questions listed above, a reasonable course of action might be to give Mrs Miller a 2 to 3 day trial of a cough suppressant (e.g. dextromethorphan or pholcodine) and review her cough after this time. Alternatively, if the cough is identical to that caused previously by enalapril, a review of Mrs Miller's antihypertensive therapy would be appropriate.

Smoking cessation should also be an important goal for Mrs Miller. Discussing her cough will provide a valuable opportunity to raise this issue with her and allow you to indicate how you could help her achieve this goal.

Weight reduction is also appropriate, not only for her general well being but also for the improved control of her diabetes and blood pressure. This needs to be carefully explained to Mrs Miller and you should provide her with possible options to achieve this outcome.

What options might Mrs Miller's doctor pursue to deal with this problem?

The central problem experienced by Mrs Miller is cough. Although, the possibility exists that Mrs Miller's cough may be caused by irbesartan, other causes of the cough need to be excluded.

The options for Mrs Miller's doctor would include:

- Chest examination including x-ray to exclude underlying pathology
- Respiratory function tests to exclude conditions such as asthma
- Examination of the throat to exclude infection and inflammation
- Assessment for oesophageal reflux as a possible cause of her cough
- A trial of an ibersartan free period to see if her cough abates (if no other cause for the cough can be found)

Other actions for her doctor to consider would be:

- To strongly encourage Mrs Miller to consider smoking cessation
- To encourage Mrs Miller to achieve her optimum weight
- To measure Mrs Miller's lipid profile (cholesterol and triglycerides) and glycosylated haemoglobin level