Drug and Therapeutics Committee Training Course

Session 4.
Assessing and Managing Medicine Safety

Trainer’s Guide
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Developed in Collaboration with the
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Geneva, Switzerland
# ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbr.</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADR</td>
<td>adverse drug reaction</td>
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<tr>
<td>DOB</td>
<td>date of birth</td>
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<tr>
<td>DPT</td>
<td>diphtheria, pertussis, tetanus</td>
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<tr>
<td>DTC</td>
<td>Drug and Therapeutics Committee</td>
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<tr>
<td>HMO</td>
<td>health maintenance organization</td>
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<tr>
<td>IM</td>
<td>intramuscular</td>
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<td>IV</td>
<td>intravenous</td>
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<tr>
<td>NDA</td>
<td>national drug authority</td>
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<tr>
<td>RCT</td>
<td>randomized control trials</td>
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<tr>
<td>VA</td>
<td>visual aid</td>
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<td>WHO</td>
<td>World Health Organization</td>
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SESSION 4. ASSESSING AND MANAGING MEDICINE SAFETY

Purpose and Content

Session 4 provides participants with basic information about assessing and managing medicine safety issues.

Objectives

After attending this session, participants will be able to—

- Describe the significance of adverse drug reactions (ADRs)
- Describe the significance of medication and prescribing errors
- Understand the principles of medicine safety evaluation
- Understand the evaluation of spontaneous case reports of ADRs and medication and prescribing errors
- Understand the process of monitoring, evaluating, and preventing ADRs and adverse drug events.

Outline

- Key Definitions
- Introduction
- ADRs—Pre- and Postmarketing Surveillance
- Causality
- Implications for the Drug and Therapeutics Committee (DTC)
- Adverse Drug Events and Medication Errors
- Activities
- Summary

Preparation and Materials

- Read the Trainer’s Guide and Participant’s Guide, and review the visual aids (VAs).
- Instruct participants to read the Participant’s Guide the evening before the session presentation.

Further Reading


**Visual Aid Listing**

1. Title slide
2. Objectives
3. Outline
4. Key Definitions (1)
5. Key Definitions (2)
6. Key Definitions (3)
7. Introduction
8. Adverse Drug Reactions (1)
9. Adverse Drug Reactions (2)
10. Determining Medicine Safety
11. Postmarketing Surveillance of ADRs: Spontaneous Reporting of ADRs
12. Postmarketing Surveillance of ADRs: Postmarketing Clinical Studies
13. Postmarketing Surveillance of ADRs: Other Methods
14. Action for Newly Discovered ADRs
15. Determining Causality of an ADR
16. Classifying Causality of an ADR
17. Classifying Causality of an ADR: Naranjo Algorithm
18. Implications for the DTC: Surveillance of ADRs
19. Potential Role of the DTC in ADR Reporting
20. Managing ADRs: Step 1. Evaluate the nature of the event.
21. Managing ADRs: Step 2. Establish the cause.
23. Prevention of ADRs
24. DTC’s Role in Preventing ADRs
25. Adverse Drug Events (1)
26. Adverse Drug Events (2)
27. Causes of Adverse Drug Events
28. Cost of Adverse Drug Events
29. Medication Errors (1)
30. Medication Errors (2)
31. Causes of Medication Errors
32. Where Medication Errors Occur (1)
33. Where Medication Errors Occur (2)
34. Preventing Medication Errors (1)
35. Preventing Medication Errors (2)
36. Preventing Medication Errors (3)
37. Using Pharmacists to Prevent Errors
38. Activities
39. Summary (1)
40. Summary (2)

Organization of the Session

Total time: 3 hours

Session 4 is intended to provide the participants with basic information about assessing and managing medicine safety issues.

First Component: 15 minutes
VAs 1–9: Definitions and Introduction

Introduce the session by asking participants what their specific concerns are about medicine safety. What are the main concerns concerning safety of medicines? How common are ADRs? What are the consequences of ADRs: morbidity, mortality, costs, hospitalization? Next, summarize the definitions on the VAs. Please remember that the literature has many definitions for these terms. The ones listed here are consistent with World Health Organization (WHO) definitions.

Second Component: 15 minutes
VAs 10–14: Premarketing Clinical Studies and Postmarketing Surveillance

This section is designed to give the participants an appreciation of the activities and efforts that go into proving safety and the limitations of these efforts. Explain that medicines do not have sufficient evaluation in premarketing studies, so DTCs must have a system of postmarketing surveillance to determine true safety. Ask the participants how they handle ADR reporting in their countries. Point out that spontaneous reporting is the most common form of reporting and the most effective at identifying new ADRs. Despite this, many health professionals do not bother to report, so the spontaneous reporting often results in the false identification of new ADRs.
Third Component: 30 minutes
VAs 15–24: Managing and Preventing ADRs

This component is designed to give the participants practical knowledge of how to manage and prevent ADRs. Brainstorm with the participants about how they handle an ADR that is reported in their home institutions. After a short discussion, summarize the main steps on how to manage ADRs. Ask the participants what the DTC can do to prevent and reduce the rate of ADRs.

When explaining the Naranjo algorithm, explain that this chart (which is old) is one of many that may help in determining causality. Stress that it does not replace clinical judgment.

After a short discussion, summarize the main points on prevention from VAs 20 and 21. Point out that closer monitoring is needed of high-risk patients (e.g., pregnant or breast-feeding patients, children, the elderly, or those with liver or renal impairment) and of patients taking high-risk drugs (e.g., digoxin, warfarin, antineoplastics, aminoglycosides).

Fourth component: 30 minutes
VAs 25–37: Adverse Drug Events and Medication Errors

Define clearly how adverse drug events differ from ADRs. Participants may be confused, so do not proceed until this distinction is clear to all. Adverse drug events involve a medicine, but no causal relationship between the event and the medicine is evident. Therefore, the reaction could be related to medication errors, genetic factors, environment, other diseases, diet, or some other cause.

Use the VAs on studies from the United States to clarify the different types of adverse drug events, their frequency, and cost. Approach the section on medication errors by brainstorming with participants, first—on the different types of error; second—on their causes; and third—on how to prevent them. After brainstorming each aspect of medication errors, use the VAs to summarize the main points. Point out that a surveillance system for medication errors is needed just as it is for ADRs. All errors should be compiled and reported in a non-confrontational way without mentioning the names of the responsible persons. This approach is necessary to gain the cooperation and trust of the staff who would not otherwise report. Stress that without any reports, the DTC cannot improve the situation.

Fifth component: 60–90 minutes
VA 38: Activities

The participants should work on the three activities as a group at their tables (ideally five or six persons per group) for 30–45 minutes. At the end of the group work, one group can be randomly chosen to present the answers for activity 1, another group for activity 2, and a third group for activity 3. After each presentation, allow time for discussion, and ensure that the correct answers are finally revealed. (Possible answers are in italics following each discussion question below.) Discussion may take an additional 30–45 minutes (10–15 minutes per activity). If time allows, groups may like to use a flipchart or overhead projector.
Activity 1. Penicillin Anaphylaxis Reported

A DTC in Panama serves 11 clinics and a hospital. Recently, a different brand of procaine penicillin had been purchased and distributed. Shortly after introduction of the new penicillin product, one clinic reported to the DTC that they had experienced an unusually high number of adverse events associated with intramuscular penicillin injections within a short period. The nursing staff became alarmed, refused to use the product that had been distributed, and asked the clinic director to replace the suspect product with an equivalent product from another supplier. They described the adverse event as an adult patient suddenly (within seconds of the injection) experiencing feelings of doom, anxiety, and faintness, which necessitated lying down. Patients were reported to be pale but with normal or slightly high blood pressure. The nurses immediately gave the patients diphenhydramine IV or IM for a suspected anaphylactic reaction to penicillin. Patients would recover 10 to 15 minutes later and would leave the clinic without further assistance. Following this intervention, the DTC again measured recorded event rates and found that the ADR rate had decreased and was similar in all clinics.

- How would you analyze this situation? What investigations would you carry out?
  
  o The DTC should evaluate the situation carefully, including a detailed description of the reaction, methods of injection, sources of the medicine, and location of the clinics where the reaction occurred.

  o The DTC needs to determine causality, that is, the strength of association, consistency of reaction, temporality of the reaction, dose-response, and confounding factor. Determining causality would also involve reviewing the literature to determine what medicine the reaction might be attributed to (i.e., penicillin or procaine). The Naranjo algorithm can be used to help guide in investigating the reaction.

You might explain to the participants that the DTC in Panama investigated the ADR outbreak and resolved the issue as follows—

1. Upon reviewing the standard medicine information literature, the clinical syndrome was found to be consistent with Hoigné’s syndrome or pseudo-allergy to penicillin, caused by the procaine component of accidental intravascular (rather than intramuscular) injection of penicillin. Diphenhydramine was thought to be inappropriate treatment of this reaction.

2. Using the number of penicillin-related ADR events recorded in clinic injection rooms and the number of procaine penicillin doses used, DTC staff calculated an event rate for each facility for a fixed-time period. This analysis revealed that the rate of related adverse events in two clinics was double the rate found in the other clinics and that those two clinics also had a relatively high work load.

3. DTC staff visited the two clinics with the higher event rates, interviewed the nursing staff, and observed injection practice. They observed that the nursing
assistants were using less water to reconstitute the injections. The DTC concluded that accidental intravascular injection of more concentrated procaine penicillin was accounting for the ADRs.

4. DTC staff discussed the findings and conclusions of the investigation with the corresponding nursing staff, which reviewed how to prepare and give penicillin injections and agreed to continue using the product. DTC staff also discouraged the use of diphenhydramine for treatment of this clinical syndrome, because it was not an allergic reaction.

- What would you recommend to management regarding the procurement of an alternative or equivalent product?

_Continue same procurement. There is no evidence that quality of the product is in question._

- What would you communicate to the nursing staff and physicians?

_Educate in proper administration and dosing. Educate concerning generic equivalents. Continue ADR reporting. This particular report was instrumental in identifying the actual cause of the reaction and preventing the unnecessary labeling of the patients as having allergic reactions to penicillin._

**Activity 2. Acute Respiratory Infection in a Two-Year-Old**

A two-year-old patient and mother present at the clinic on May 19, 1999. The child has a 48-hour history of fever, irritability, cough, and altered consciousness. Questioning of the mother reveals the following—

- 5/14/99—child was administered DPT and oral polio vaccine
- 5/15/99—child was seen with mild upper respiratory tract infection symptoms and treated with amoxicillin and cough syrup
- 5/17/99—child experienced the onset of fever, irritability, altered consciousness
- 5/18/99—child had been seen at the health center and diagnosed with acute respiratory infection and treated with co-trimoxazole and paracetamol

Consider the following—

- What is the possibility of the patient having an ADR in addition to the acute respiratory infection?

_This picture is confusing. This patient may have an acute respiratory infection, a central nervous system infection, an ADR to one of the medicines, or a combination of these_
events. (Pertussis vaccine that is a component of DPT vaccine in particular may cause these symptoms and may be delayed for up to seven days.)

- If you think it is an ADR, which medicine or medicines might be responsible? How did you arrive at this conclusion?
  
  - It could be one of several medicines, but this a classic example of a pertussis reaction. It is a delayed reaction (3 days), but this happens with pertussis.
  
  - The DTC needs to determine causality (strength of association, consistency of reaction, temporality to the medicine, dose-response, and confounding factors). In this case, the correlation with pertussis vaccine is high. Confounding factors include acute respiratory infection and other medicines.
  
  - Many participants in past courses thought that the reaction could have been due to anticholinergic reaction to a possible antihistamine in the cough syrup. Good insight.

- What kind of action by the DTC is warranted in this case?
  
  - Review the literature concerning the ADR and the medicines in question.
  - Educate the medical staff about ADRs concerning pertussis.
  - Collect and monitor reports of pertussis ADR (and other medicines).

Activity 3. Serious ADRs with Phen-Fen Combination Medicine

The combination medicine phenteramine and fenfluramine (commonly called phen-fen) was a popular diet medicine throughout Europe and North America. Like all anti-obesity medicines, this combination leads to tolerance after several months of use, and weight gain invariably occurs when the medicine is discontinued. Short-term effectiveness was dramatic, however, with countless success stories and many patients demanding prescriptions. Safety of this combination was confirmed through the usual premarketing clinical trials. Because phen-fen was another weight control product, testing and evaluation were extensive, and the approval process was not fast-tracked. Soon after the marketing of the medicine, spontaneous reports began to appear describing serious cardiovascular problems including valvular heart disease and pulmonary hypertension—including among younger women. Spontaneous reports continued until it became obvious that the combination was highly suspect for causing the adverse effect.

- What are some other possible causes for the cardiac conditions listed in the activity?
  
  - This activity is definitely American, but provides an excellent example of a serious ADR that can be detected via spontaneous reports.
  
  - These cardiovascular disorders are extremely rare in women this age as are other cardiovascular disorders at this age.
- The association with this particular combination medicine is significant because no other reasons for the outcome could be found.

- What would have prevented this serious side effect from being detected in premarketing trials?
  Small number of patients in clinical trials

- Why would spontaneous reports be so effective in detecting this ADR after phen-fen’s distribution to the general market?
  - Spontaneous reports will be observed over a larger number of patients and will eventually indicate that a medicine may have an ADR associated with it. The large number of women using phen-fen made spontaneous reports an ideal method to detect a serious reaction like this.
  - Without spontaneous reports it would have been difficult to determine that phen-fen was the causative agent in these cardiovascular problems.

**Sixth component: 5-10 minutes**
**VAs 39–40: Summary**

Summarize the key points of the session. Emphasize the practical things DTCs can do to prevent ADRs, adverse drug events, and medication errors.