Clinical Analysis of Adverse Drug Reactions

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Objectives

* Define adverse drug reactions
* Discuss epidemiology and classification of ADRs
* Describe basic methods to detect, evaluate, and document ADRs

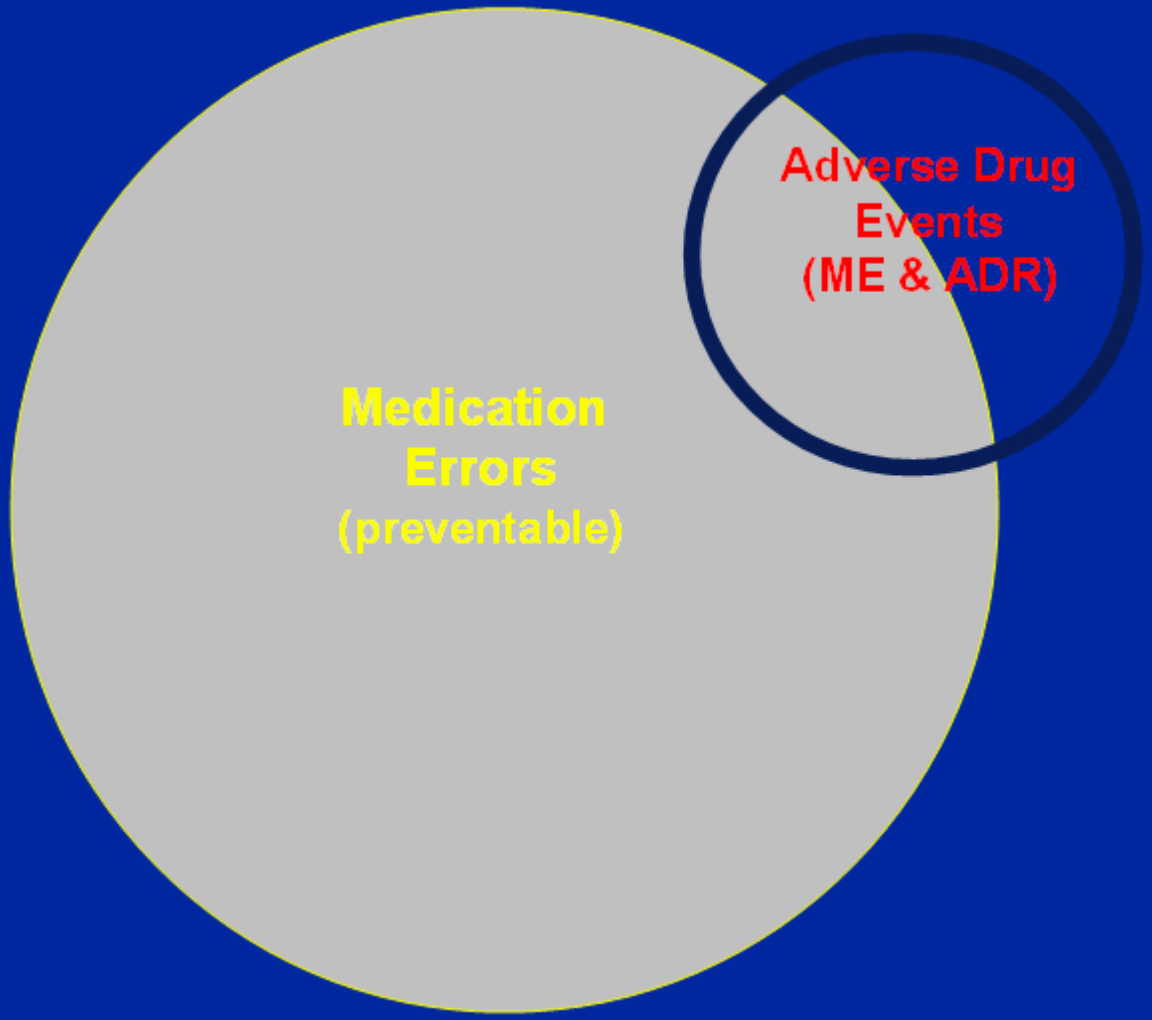
Definition

* **WHO**
  - **response to a drug that is *noxious and unintended* and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiologic function**

  - **excludes therapeutic failures, overdose, drug abuse, noncompliance, and medication errors**

Adverse Drug Events

Adapted from Bates et al.



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Epidemiology of ADRs

- substantial morbidity and mortality
- estimates of incidence vary with study methods, population, and ADR definition
- 4th to 6th leading cause of death among hospitalized patients*
- 6.7% incidence of serious ADRs*
- 0.3% to 7% of all hospital admissions
- annual dollar costs in the billions
- 30% to 60% are preventable

*JAMA. 1998;279:1200-1205.

Classification

* Onset
* Severity
* Type

Classification

Onset of event:

* **Acute**
  - **within 60 minutes**
* **Sub-acute**
  - **1 to 24 hours**
* **Latent**
  - **> 2 days**

Classification - Severity

Severity of reaction:

* **Mild**
  - **bothersome but requires no change in therapy**
* **Moderate**
  - **requires change in therapy, additional treatment, hospitalization**
* **Severe**
  - **disabling or life-threatening**

Classification - Severity

FDA Serious ADR:

- **Result in death**
- **Life-threatening**
- **Require hospitalization**
- **Prolong hospitalization**
- **Cause disability**
- **Cause congenital anomalies**
- **Require intervention to prevent permanent injury**

Classification

* Type A
  - extension of pharmacologic effect
  - often predictable and dose dependent
  - responsible for at least two-thirds of ADRs
  - e.g., propranolol and heart block, anticholinergics and dry mouth

Classification

* Type B
  - idiosyncratic or immunologic reactions
  - rare and unpredictable
  - e.g., chloramphenicol and aplastic anemia

Classification

* Type C
  - associated with long-term use
  - involves dose accumulation
  - e.g., phenacetin and interstitial nephritis or antimalarials and ocular toxicity

Classification

* **Type D**
  - **delayed effects (dose independent)**
  - **Carcinogenicity (e.g., immunosuppressants)**
  - **Teratogenicity (e.g., fetal hydantoin syndrome)**

Classification

* Types of allergic reactions
  - Type I - immediate, anaphylactic (IgE)
    * e.g., anaphylaxis with penicillins
  - Type II - cytotoxic antibody (IgG, IgM)
    * e.g., methyldopa and hemolytic anemia
  - Type III - serum sickness (IgG, IgM)
    * antigen-antibody complex
    * e.g., procainamide-induced lupus
  - Type IV - delayed hypersensitivity (T cell)
    * e.g., contact dermatitis

Classification - Type

Reportable

* All significant or unusual adverse drug reactions as well as unanticipated or novel events that are suspected to be drug related

Classification - Type

Reportable

* Hypersensitivity
  - Life-threatening
  - Cause disability
  - Idiosyncratic
  - Secondary to Drug interactions

- Unexpected detrimental effect
- Drug intolerance
- Any ADR with investigational drug

Common Causes of ADRs

- Antibiotics
- Antineoplastics*
- Anticoagulants
- Cardiovascular drugs*
- Hypoglycemics
- Antihypertensives
- NSAID/Analgesics
- Diagnostic agents
- CNS drugs*

* account for 69% of fatal ADRs

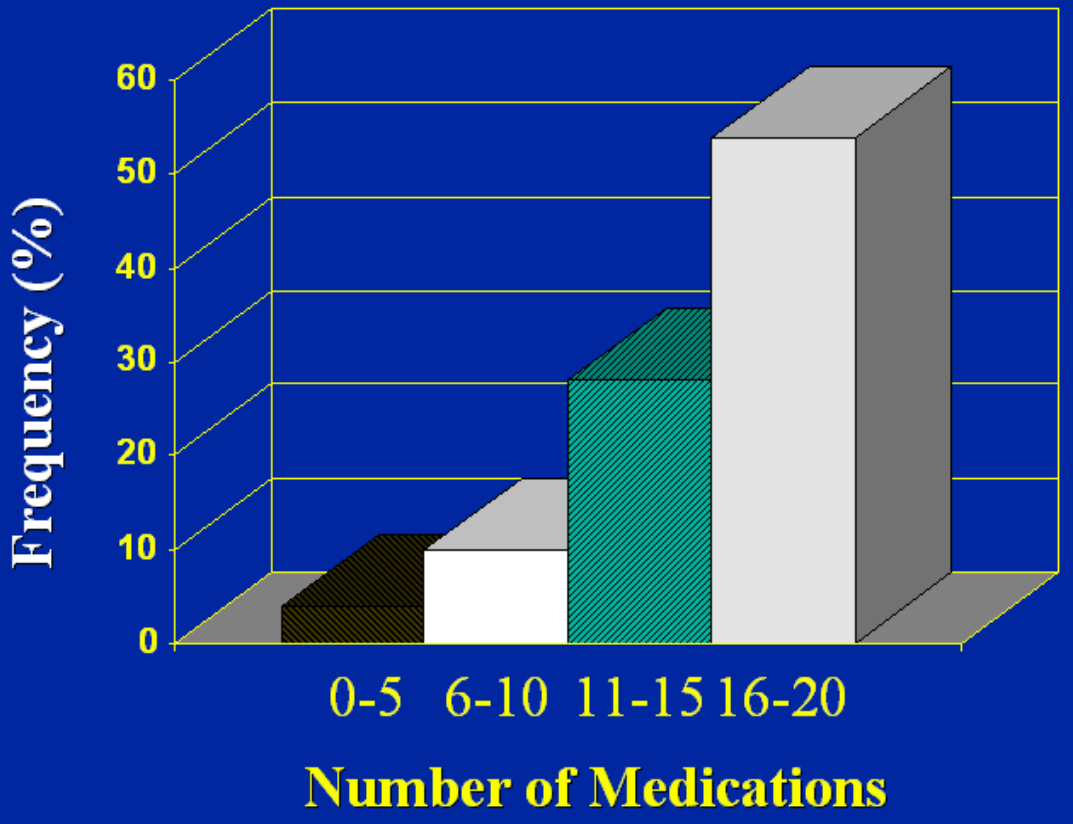
Body Systems Commonly Involved

- Hematologic
- CNS
- Dermatologic/Allergic
- Metabolic
- Cardiovascular
- Gastrointestinal
- Renal/Genitourinary
- Respiratory
- Sensory

ADR Risk Factors

* Age (children and elderly)
* Multiple medications
* Multiple co-morbid conditions
* Inappropriate medication prescribing, use, or monitoring
* End-organ dysfunction
* Altered physiology
* Prior history of ADRs
* Extent (dose) and duration of exposure
* Genetic predisposition

ADR Frequency by Drug Use



May FE. Clin Pharmacol Ther 1977;22:322-8

ADR Detection

* Subjective report
  - patient complaint
* Objective report:
  - direct observation of event
  - abnormal findings
    * physical exam
    * laboratory test
    * diagnostic procedure

ADR Detection

* Medication order screening
  - abrupt medication discontinuation
  - abrupt dosage reduction
  - orders for “tracer” or “trigger” substances
  - orders for special tests or serum drug concentrations
* Spontaneous reporting
* Medication utilization review
  - Computerized screening
  - Chart review and concurrent audits

ADR Detection in Clinical Trials

* Methods
  - Standard laboratory tests
  - Diagnostic tests
  - Complete history and physical
  - Adverse drug event questionnaire
    * Extensive checklist of symptoms categorized by body system
    * Review-of-systems approach
    * Qualitative and quantitative

ADR Detection in Clinical Trials

Limitations:

* exposure limited to few individuals
  - rare and unusual ADRs not detected
  - 3000 patients at risk are needed to detect ADR with incidence of 1/1000 with 95% certainty
* exposure is often short-term
  - latent ADRs missed
* external validity
  - may exclude children, elderly, women of child-bearing age; and patients with severe form of disease, multiple co-morbidities, and those taking multiple medications

Preliminary Assessment

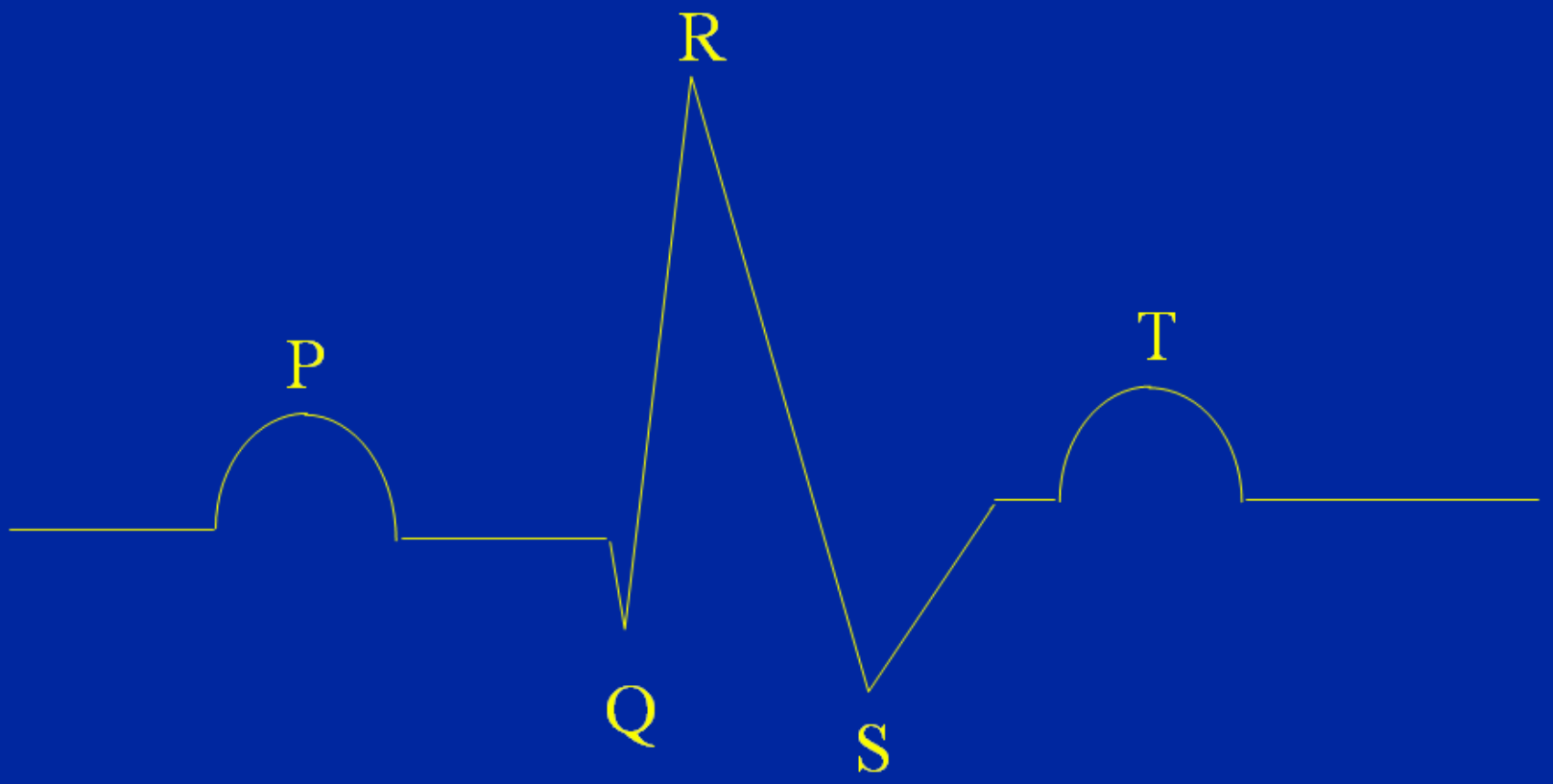
* **Preliminary description of event:**
  - **Who, what, when, where, how?**
  - ***Who*** **is involved?**
  - ***What*** **is the most likely causative agent?**
    * **Is this an exacerbation of a pre-existing condition?**
    * **Alternative explanations / differential diagnosis**
  - ***When*** **did the event take place?**
  - ***Where*** **did the event occur?**
  - ***How*** **has the event been managed thus far?**

Preliminary Assessment

* **Determination of urgency:**
  - **What is the patient's current clinical status?**
  - **How severe is the reaction?**

* **Appropriate triage:**
  - **Acute (ER, ICU, Poison Control)**

Detailed Description of Event PQRSTA Acronym



Detailed Description of Event

* History of present illness
* Signs / Symptoms: PQRSTA
  - Provoking or palliative factors
  - Quality (character or intensity)
  - Response to treatment, Radiation, Reports in literature
  - Severity / extent, Site (location)
  - Temporal relationship (onset, duration, frequency)
  - Associated signs and symptoms

Pertinent Patient/Disease Factors

* **Demographics**
  - age, race, ethnicity, gender, height, weight
* **Medical history and physical exam**
  - Concurrent conditions or special circumstances
    * e.g., dehydration, autoimmune condition, HIV infection, pregnancy, dialysis, breast feeding
  - Recent procedures or surgeries and any resultant complications
    * e.g., contrast material, radiation treatment, hypotension, shock, renal insufficiency

Pertinent Patient/Disease Factors

* End-organ function
* Review of systems
* Laboratory tests and diagnostics
* Social history
  - tobacco, alcohol, substance abuse, physical activity, environmental or occupational hazards or exposures
* Pertinent family history
* Nutritional status
  - special diets, malnutrition, weight loss

Pertinent Medication Factors

* **Medication history**
  - **Prescription medications**
  - **Non-prescription medications**
  - **Alternative and investigational therapies**
  - **Medication use within previous 6 months**
  - **Allergies or intolerances**
  - **History of medication reactions**
  - **Adherence to prescribed regimens**
  - **Cumulative mediation dosages**

Pertinent Medication Factors

* Medication
  - Indication, dose, diluent, volume
* Administration
  - Route, method, site, schedule, rate, duration
* Formulation
  - Pharmaceutical excipients
    * e.g., colorings, flavorings, preservatives
  - Other components
    * e.g., DEHP, latex

Pertinent Medication Factors

* Pharmacology
* Pharmacokinetics (LADME)
* Pharmacodynamics
* Adverse effect profiles
* Interactions
  - drug-drug
  - drug-nutrient
  - drug-lab test interference
* Cross-allergenicity or cross-reactivity

ADR Information

* Incidence and prevalence
* Mechanism and pathogenesis
* Clinical presentation and diagnosis
* Time course
* Dose relationship
* Reversibility
* Cross-reactivity/Cross-allergenicity
* Treatment and prognosis

ADR Information Resources

* Tertiary
  - Reference books
    * Medical and pharmacotherapy textbooks
    * Package inserts, PDR, AHFS, USPDI
    * Specialized ADR resources
      - Meyler's Side Effects of Drugs
      - Textbook of Adverse Drug Reactions
    * Drug interactions resources
    * Micromedex databases (e.g., TOMES, POISINDEX, DRUGDEX)
  - Review articles

ADR Information Resources

* **Secondary**
  - **MEDLARS databases (e.g., Medline, Toxline, Cancerline, Toxnet)**
  - **Excerpta Medica's Embase**
  - **International Pharmaceutical Abstracts**
  - **Current Contents**
  - **Biological Abstracts (Biosis)**
  - **Science Citation Index**
  - **Clin-Alert and Reactions**

ADR Information Resources

* Primary
  - Spontaneous reports or unpublished data
    * FDA
    * Manufacturer
  - Anecdotal and descriptive reports
    * Case reports, case series
  - Observational studies
    * Case-control, cross-sectional, cohort
  - Experimental and other studies
    * Clinical trials
    * Meta-analyses

Causality Assessment

* Prior reports of reaction
* Temporal relationship
* De-challenge
* Re-challenge
* Dose-response relationship
* Alternative etiologies
* Objective confirmation
* Past history of reaction to same or similar medication

Causality Assessment

* Examples of causality algorithms
  - Kramer
  - Naranjo and Jones
* Causality outcomes
  - Highly probable
  - Probable
  - Possible
  - Doubtful

Naranjo ADR Probability Scale

To assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score.

		Yes	No	Do Not Know	Score
1.	Are there previous *conclusive* reports on this reaction?	+1	0	0	____
2.	Did the adverse event appear after the suspected drug was administered?	+2	-1	0	____
3.	Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	____
4.	Did the adverse reactions appear when the drug was readministered?	+2	-1	0	____
5.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	____
6.	Did the reaction reappear when a placebo was given?	-1	+1	0	____
7.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	____
8.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	____
9.	Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	____
10.	Was the adverse event confirmed by any objective evidence?	+1	0	0	____
				Total Score	____

Total Score	*ADR Probability Classification*
9	Highly Probable
5-8	Probable
1-4	Possible
0	Doubtful

Naranjo CA. Clin Pharmacol Ther 1981;30:239-45

Management Options

* Discontinue the offending agent if:
  - it can be safely stopped
  - the event is life-threatening or intolerable
  - there is a reasonable alternative
  - continuing the medication will further exacerbate the patient's condition
* Continue the medication (modified as needed) if:
  - it is medically necessary
  - there is no reasonable alternative
  - the problem is mild and will resolve with time

Management Options

* Discontinue non-essential medications
* Administer appropriate treatment
  - e.g., atropine, benztropine, dextrose, antihistamines, epinephrine, naloxone, phenytoin, phytonadione, protamine, sodium polystyrene sulfonate, digibind, flumazenil, corticosteroids, glucagon
* Provide supportive or palliative care
  - e.g., hydration, glucocorticoids, warm / cold compresses, analgesics or antipruritics
* Consider rechallenge or desensitization

Follow-up and Re-evaluation

* Patient’s progress
* Course of event
* Delayed reactions
* Response to treatment
* Specific monitoring parameters

Documentation and Reporting

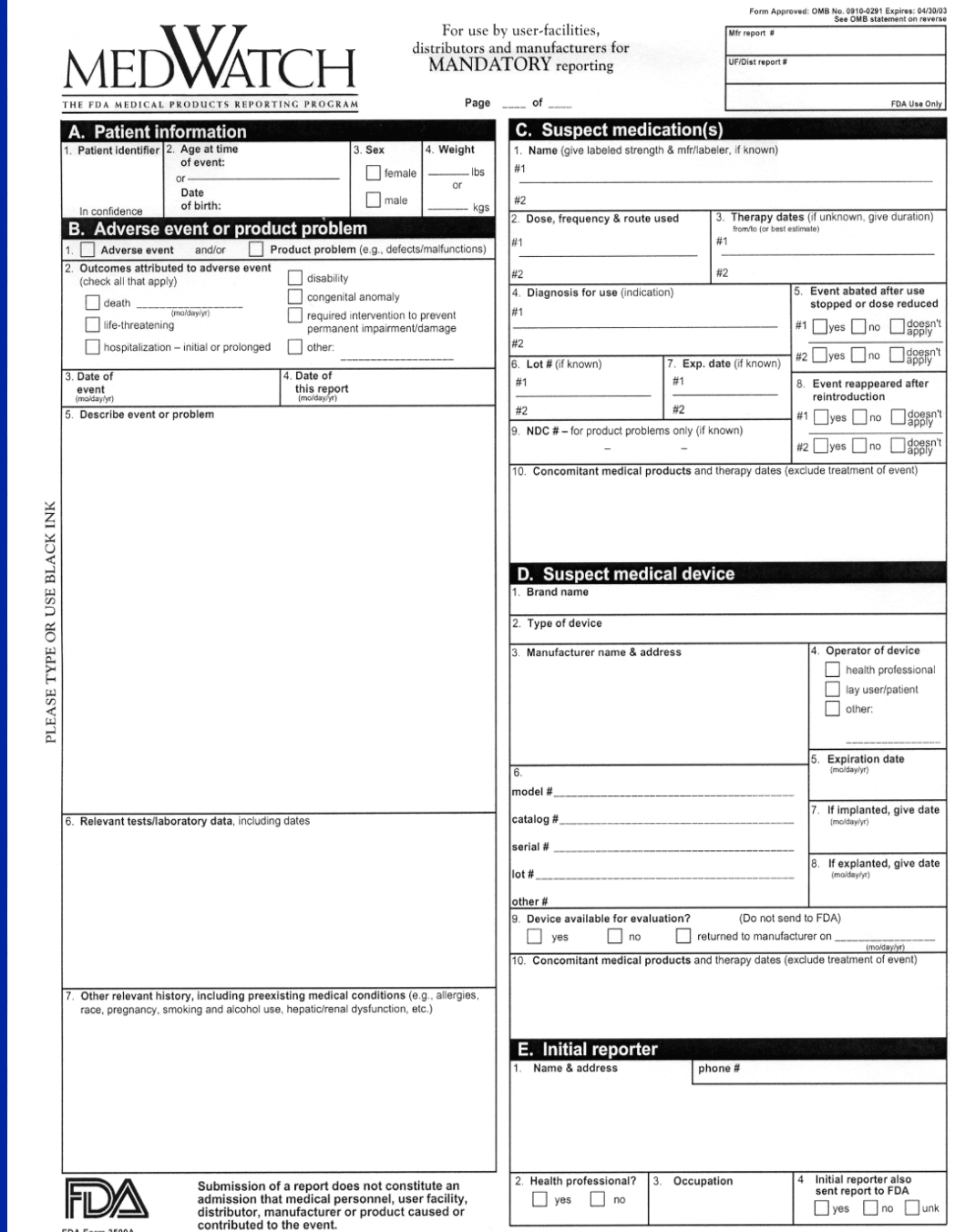
* Medical record
  - Description
  - Management
  - Outcome
* Reporting responsibility
  - JCAHO-mandated reporting programs
  - Food and Drug Administration
    * post-marketing surveillance
    * particular interest in serious reactions involving new chemical entities
  - Pharmaceutical manufacturers
  - Publishing in the medical literature

Components of an ADR Report

* Product name and manufacturer
* Patient demographics
* Description of adverse event and outcome
* Date of onset
* Drug start and stop dates/times
* Dose, frequency, and method
* Relevant lab test results or other objective evidence
* De-challenge and re-challenge information
* Confounding variables

MEDWATCH 3500A Reporting Form

https://www.accessdata.fda.gov/scripts/medwatch



Form Approved: OMB No. 0910-0291 Expires: 04/30/03
See OMB statement on reverse

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Page ____ of ____

Mfr report #
UF/Dist report #
FDA Use Only

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: / or Date of birth:
3. Sex — female / male
4. Weight — ____ lbs or ____ kgs

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - death ____ (mo/day/yr)
   - life-threatening
   - hospitalization – initial or prolonged
   - disability
   - congenital anomaly
   - required intervention to prevent permanent impairment/damage
   - other: ____
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #1 / #2
2. Dose, frequency & route used #1 / #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 / #2
4. Diagnosis for use (indication) #1 / #2
5. Event abated after use stopped or dose reduced #1 yes no doesn't apply / #2 yes no doesn't apply
6. Lot # (if known) #1 / #2
7. Exp. date (if known) #1 / #2
8. Event reappeared after reintroduction #1 yes no doesn't apply / #2 yes no doesn't apply
9. NDC # – for product problems only (if known) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name & address
4. Operator of device
   - health professional
   - lay user/patient
   - other: ____
5. Expiration date (mo/day/yr)
6. model # ____ catalog # ____ serial # ____ lot # ____ other #
7. If implanted, give date (mo/day/yr)
8. If explanted, give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA) yes no returned to manufacturer on ____ (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name & address
   phone #
2. Health professional? yes no
3. Occupation
4. Initial reporter also sent report to FDA yes no unk

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.