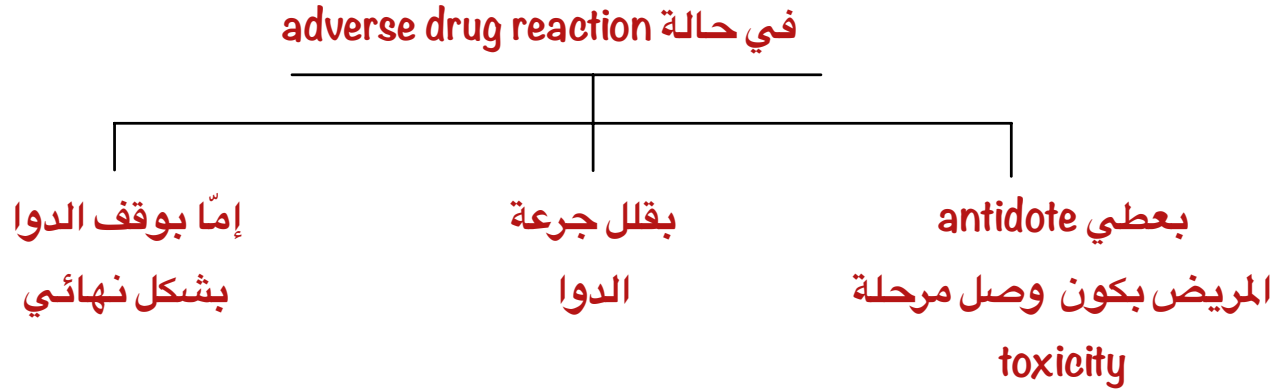

Adverse Drug Reactions

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Adverse Drug Reactions

Definitions:

- **The WHO defines an adverse drug reaction (ADR) as " a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function".**

- Therapeutic dose ⇒ ADR
- over dose ⇒ toxic effect.

Adverse Drug Reactions

- **The use of the phrase 'at doses normally used in man' distinguishes the noxious effect during normal medical use from the toxic effect caused by poisoning (over dose).**
- **There is no need to prove a pharmacological mechanism for any noxious response to be termed as ADR.**

very important

Adverse Drug Reactions

- **The term "side effect" is distinct from ADR.**
- **A side effect is an unintended effect of a drug related to its pharmacological properties and can include unexpected benefits of treatment.**

Adverse Drug Reactions

- **The WHO definition has been criticized for excluding the potential for contamination of the product (dosage form) and ADRs associated with pharmacologically inactive excipients in the product.**
- **The use of the term 'drug' also excluded the use of complementary and alternative treatments such as herbal products.**

Adverse Drug Reactions

- **In an attempt to overcome these issues, the following definition of ADR was proposed:**

  "A harmful or unpleasant reaction, resulting from the intervention related to the use of a medicinal product, which:

1. **predicts hazard for future administration.**
2. **warrants prevention or specific treatment.**
3. **requires alteration of dosage regimen.**
4. **requires withdrawal of the product.**

Adverse Drug Reactions

- **It is also important to avoid confusion with the term "adverse drug event (ADE)".**
- **ADE is an adverse outcome that occurs after the use of the drug, but which may or may not be linked to this use.**
- **Therefore, all ADRs are ADEs, but not all ADEs will be ADRs.**

Adverse Drug Reactions

- **ADE can be used when it is NOT possible to suggest a causal link between a drug treatment and an adverse outcome.**
- **The suspicion of a causal relationship between the drug and the adverse effect is central to the definition of an ADR.**

Adverse Drug Reactions

Epidemiology of ADRs:

1. **ADRs are responsible for 2.6% - 6.5% of admissions to hospitals.**
2. **3.5-14.7% of inpatients develop ADRs.**
3. **2.3% of patients die as a result of ADRs.**
4. **In primary care, estimates of the incidence of ADRs range from 25-30%.**
5. **ADRs are the 4^{th} - 6^{th} leading cause of death in USA.**

Adverse Drug Reactions

- **Stay in hospital for patients having ADR was ~ 20 days compared to ~ 8 days without ADRs, leading to escalation of cost.**

Adverse Drug Reactions

Rawlins-Thompson Classification of ADRs:

1. **Type A: normal but exaggerated (augmented) pharmacological effects of the drug. Predictable, dose-dependent, common (80% of all ADRs), preventable, low morbidity and mortality.**

   The major / the most common adverse drug reaction are due to exaggerated pharmacological effects of the drug

   ⇒ Diuretics

   Dehydration ⇒ exaggerated pharmacological effect of the drug

   anti-histamines are sedatives ⇒ Sedation sleep

- **Example: bradycardia associated with β-adrenergic blockers.**

Type A

Side effect
- Unavoidable
- بتصير مع كل المرضى الي بياخذوا الدواء

Like atropine
antispasmodic بعطيه ك
Side effects :dry mouth
muscarinic receptors بروح يشتغل على كل receptors on the salivary glands بالتالي بسكّر
.... secretions ما في
Dry mouth

Secondary effect
- Drug-related consequences
- ما بتصير عند كل المرضى

Like board spectrum antibiotics بعملوا normal suppression on the normal flora in the GIT
- vitamins k ↓B
- antibiotics
  - Vitamin deficiency (In short)
  - Normal flora supression
  - Pseudo membranous colitis

Over dose
Large dose., like insulin.... جرعة كبيرة لمريض سكري hypoglycemia بتعمل

Accumulation Like digoxin بتراكم بعضلة القلب ، Elimination rate

Super sensitivity
"Drug intolerance"

Clearance

Hypokalemia

By receptors increase ⇒ sensitivity

Cytotoxicity
Cardiac toxicity
Halothane

Hepato toxicity
Halothane
Paracetamole

toxic dose

anti-thyroid drugs

bone marrow depression

Nephrotoxic
Aspirin NSAID

like RA

Nephro & neuro toxicity

* Aminoglycosides (Gentamycin / Streptomycin)

Damage kidney function.

Neurotoxicity
aminoglycosids

(Vestibulocochlear nerve)

2 divisions
- Hearing → Toxicity ⇒ Deafness
- equilibrium → Toxicity ⇒ Vertigo

Drug interactions

Type B (Bizzar)

Hypersensitivity (allergy)
abnormal unpredictable drug reaction due to antigen-antibody reaction

* Type 1 Hypersensitivity (anaphylactic reaction / IgE mediated)
  - anaphylactic shock
  - * Angioneurotic edema ⇒ adrenalin
    - Penicillin
    - Lifesaving drug in anaphylactic shock

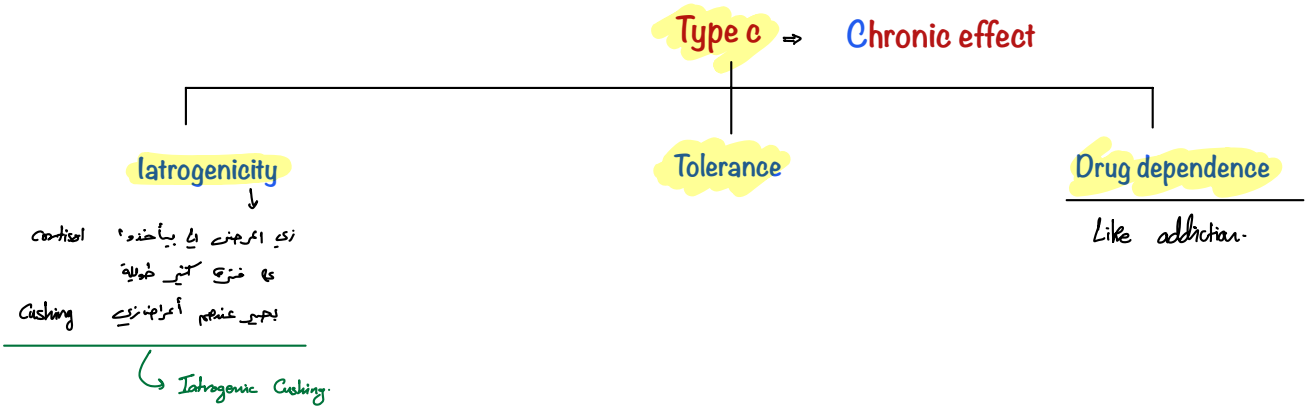
Idiosyncrasy
abnormal unpredictable drug response due to genetic defect

Like succinyl choline apnea.

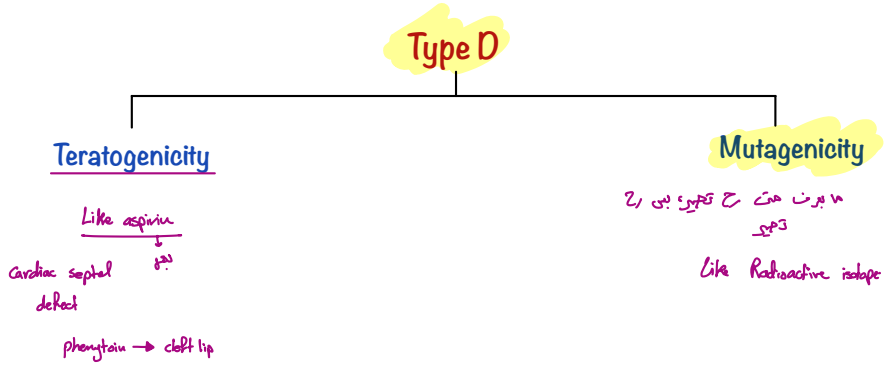
Table 5.3 Classification of immunological (hypersensitivity) reactions

Classification	Mechanism	Symptoms/signs and examples
Type I (immediate)	Drug/IgE complex binds to mast cells which release histamine and leukotrienes	Pruritus, urticaria, bronchoconstriction, angioedema, hypotension, shock, e.g. penicillin anaphylaxis
Type II (cytotoxic)	IgG and complement binding to (usually) red blood cell Cytotoxic T cells lyse the cell	Haemolytic anaemia and thrombocytopaenia, e.g. associated with cephalosporins, penicillins and rifampicin
Type III (immune complex)	Drug antigen and IgG or IgM form immune complex, attracting macrophages and complement activation	Cutaneous vasculitis, serum sickness, e.g. associated with chlorpromazine and sulfonamides
Type IV (delayed type)	Antigen presentation with major histocompatibility complex protein to T cells and cytokine and inflammatory mediator release	Usually occur after 7–20 days; macular rashes and organ failure, including Stevens–Johnson syndrome and toxic epidermal necrolysis, e.g. associated with neomycin, sulfonamides

Ig, Immunoglobulin.



NSAIDs ⇒ Iatrogenic peptic ulcer



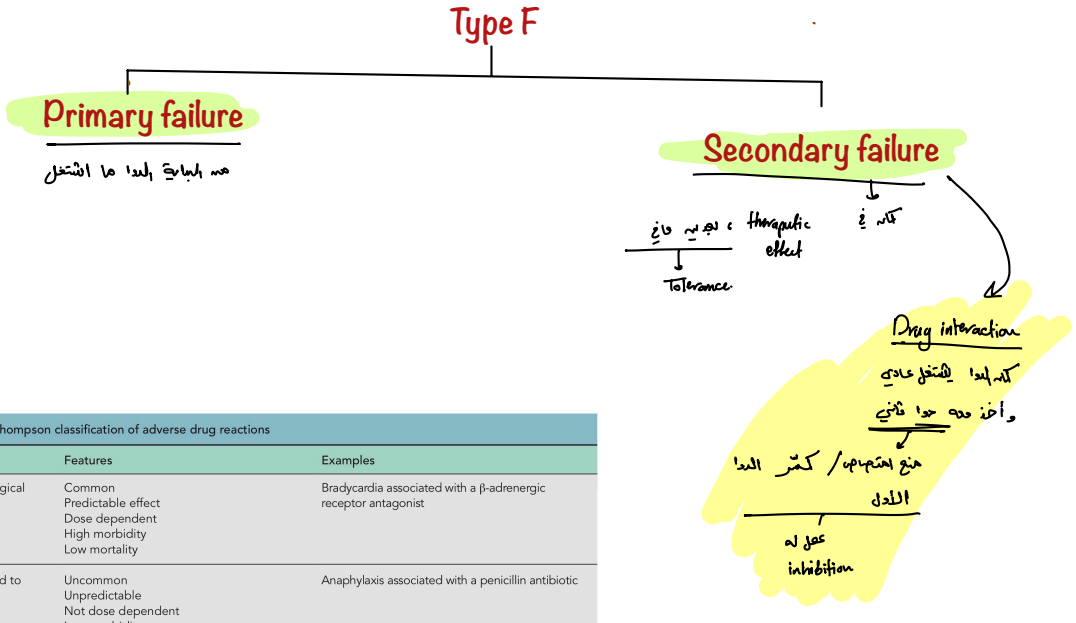


Table 5.1 Extended Rawlins–Thompson classification of adverse drug reactions

Type of reaction	Features	Examples
Type A: augmented pharmacological effect	Common Predictable effect Dose dependent High morbidity Low mortality	Bradycardia associated with a β-adrenergic receptor antagonist
Type B: bizarre effects not related to pharmacological effect	Uncommon Unpredictable Not dose dependent Low morbidity High mortality	Anaphylaxis associated with a penicillin antibiotic
Type C: dose-related and time-related	Uncommon Related to the cumulative dose	Hypothalamic-pituitary-adrenal axis suppression by corticosteroids
Type D: time-related	Uncommon Usually dose-related Occurs or becomes apparent sometime after use of the drug	Carcinogenesis
Type E: withdrawal	Uncommon Occurs soon after withdrawal of the drug	Opiate withdrawal syndrome
Type F: unexpected failure of therapy	Common Dose-related Often caused by drug interactions	Failure of oral contraceptive in presence of enzyme inducer

Adverse Drug Reactions

2. Type B: abnormal (bizzare) effects not related to the pharmacological effects of the drug, more serious, could be fatal, often discovered after marketing of the drug, uncommon, unpredictable, not dose-dependent, high morbidity and mortality

- Examples: hepatotoxicity of isoniazid, and allergic reactions.

Adverse Drug Reactions

3. **Type C: dose-related and time related: uncommon, related to the cumulative dose.**

- **Example: Hypothalamic-pituitary adrenal axis suppression by corticosteroids.**

4. **Type D: uncommon, time-related, usually dose related, occurs or becomes apparent some time after the use of the drug.**

- **Example: carcinogenesis**

Adverse Drug Reactions

5. Type E (end of use): occurs soon after withdrawal of the drug, uncommon.
   - Example: opiate withdrawal syndrome.
6. Type F (unexpected failure of therapy): common, dose-related, often caused by drug interactions.
   - Example: failure of contraceptives in the presence of metabolizing enzyme inducers.

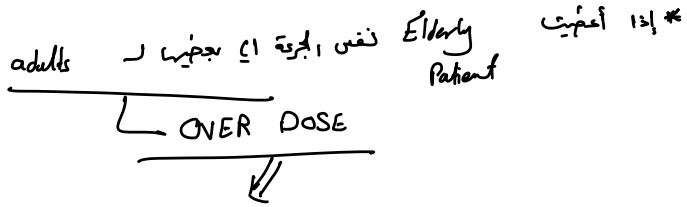
Adverse Drug Reactions

Factors affecting susceptibility to ADRs:

1. **Age:**

Elderly patients:

- **are more prone to ADRs because of age-related decline in both metabolism and elimination of drugs from the body. They also have multiple co-morbidities and thus more prescribed drugs.**



Adverse Drug Reactions

Children:

1. **Differ from adults in drug response.**
2. **Neonatal differences in body composition, metabolism, and other physiological parameters increase the risk of specific ADRs.**
3. **Higher body water content can increase the volume of distribution of water soluble drugs.**
4. **Reduced albumin may be associated of high free concentrations of highly protein-bound drugs.** in neonate & elderly

→ means more action ⇒ OVER DOSE.

Adverse Drug Reactions

5. **Immature blood-brain barrier can increase sensitivity to morphine and other drugs.**

- **Differences in drug metabolism and elimination and end-organ responses can increase risk.**
  - In neonates, metabolizing enzymes not very well developed (glucose siltransferase) especially the premature neonates.
  - adverse effect ⇒ Gray baby syndrome
- **Chloramphenicol, digoxin, and ototoxic antibiotics have higher risks of toxicity in the first weeks of life.**

Adverse Drug Reactions

Older children and young adults:

- are more susceptible to some ADRs:

1. Increased risk of extrapyramidal effects associated with metoclopramide.
2. Use of aspirin is restricted under age of 12 years because of association with Reye's syndrome.
3. Heightened probability of dosing errors and the relative lack of evidence for both safety and efficacy put children at high risk.

Adverse Drug Reactions

2. Gender:

- **Women may be more susceptible to ADRs.**
- **Some ADRs are more common in women than men:**

1) **Impairment of concentration and psychiatric adverse events associated with anti-malarial agent mefloquine.**
2) **Drug-induced *torsade de pointes*, may be because of their longer QTc interval compared to men.**

Adverse Drug Reactions

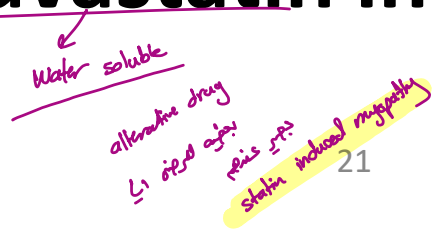
3. <u>Co-morbidities and concomitant drug use:</u>

- **Reduction in hepatic and renal functions increase the risk of ADRs.**
- **Co-morbidities such as congestive heart failure, diabetes, and peripheral vascular, chronic pulmonary, rheumatological, hepatic, renal, and malignant diseases were strong predictors of readmissions for ADRs.**
- **This might be due to pharmacokinetic or pharmacodynamic changes in these diseases, or drug interactions due to multiple therapy.**

Adverse Drug Reactions

4. **Ethnicity:**

- **This is related to ADRs due to inherited traits of metabolism, and environmental factors.**
- **There is increased risk of angioedema with the use of ACE-inhibitors in Africans.**
- **Increased susceptibility of whites and blacks to CNS adverse effects of mefloquine compared to Chinese and Japanese.**
- **Increased risk of myopathy after rosuvastatin in Asians.**



Adverse Drug Reactions

5. **Pharmacogenetics:**

- **Pharmacogenetics is the science of understanding how variability in a single gene can influences drug treatment outcomes.**
- **Pharmacogenomics refer to the collective influence of variability across the genome to modulate an individual's drug response profile.**
- **Genomic Variations led to the concept of "Personalised Medicine".** ⟹ Give the treatment for a particular Patient that is suitable according to his/her genome.

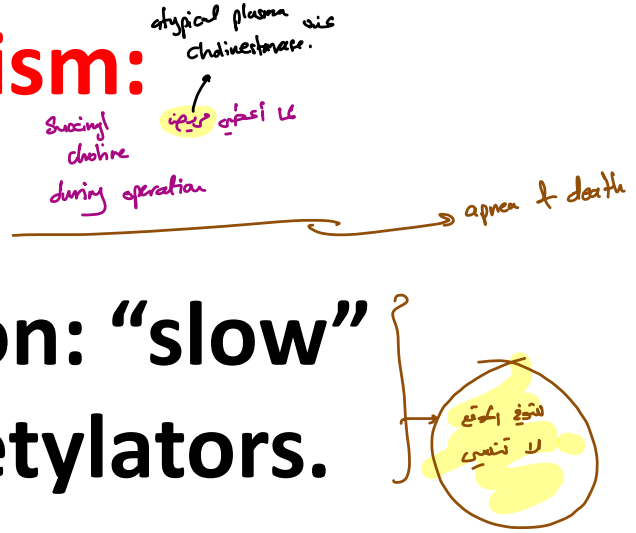
Adverse Drug Reactions

- **Variation can be caused by different concentrations at sites of drug action – pharmacokinetic variation.**
- **Or by different responses to the same drug concentration – pharmacodynamics variation.**

Adverse Drug Reactions

Genetic variation in drug metabolism:

1. Atypical plasma cholinesterase
2. Genetic deficiency in acetylation: “slow” “intermediate” and “rapid” acetylators.
3. Polymorphic oxidation: ultrarapid, extensive, intermediate or poor metabolizers.



Adverse Drug Reactions

Inherited Variation in Pharmacodynamics:

1. Hereditary Warfarin Resistance
2. Heparin Resistance
3. Vitamin D resistance
4. Favism (drug-induced hemolytic anemia)
5. Malignant Hyperthermia with Muscle Rigidity
6. Glaucoma due to abnormal response to intraocular steroids

Adverse Drug Reactions

Immunological Reactions:

- **The immune system is able to recognize drugs as foreign leading to allergic reactions.**
- **Small molecules can bind to proteins to trigger an immune response, and larger molecules can trigger an immune response directly.**
- **The immune response is NOT related to the pharmacological action of the drug.**
- **Prior exposure to the drug is required.**

Adverse Drug Reactions

- **Allergic reactions range from rashes, serum sickness and angioedema to life-threatening bronchospasm and anaphylaxis.**
- **Patients with a history of atopic or allergic disorders are at higher risk.**
- **All types of immunological reaction may occur with drug use: type I (immediate), type II (cytotoxic), type III (immune complex) and type IV (delayed).**

Adverse Drug Reactions

Causality Assessment:

- **Causality is very difficult to prove and a high degree of suspicion is all that is needed for "Regulatory Authority" action.**

Adverse Drug Reactions

- **An objective method to assess causality that reduce assessor bias is the "Naranjo algorithm".**
- **It uses a questionnaire, and points are added or subtracted based on responses to each question.**
- **The total score is then used to place assessment as: highly probable, probable, possible, or doubtful.**

4 classifications :-

not definite

Table 1-2. Naranjo ADR Probability Scale

Question	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 event appear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that, on their own, could 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	ADR Probability Classification
9	Highly Probable
5–8	Probable
1-4	Possible
0	Doubtful

Adapted with permission from: Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.

Adverse Drug Reactions

Preventing ADRs:

- **The majority of ADRs are preventable, thus reducing cost and even death. (How?)**

1. **Checking previous ADR history.**
2. **Minimizing the use of drugs with high risk to develop ADRs.**
3. **Tailoring drug selection to individuals based on factors that predispose to ADRs.**

Adverse Drug Reactions

4. **Rational prescribing.** (evidence – based medicine prescribing)
5. **Improved sharing of information about patients between health-care providers.**
6. **Monitoring Therapy:**

- **Monitoring the effect of drugs by measurement of serum concentration or by measurement of physiological markers is another method of reducing the risk of ADRs.**

Adverse Drug Reactions

- **It has been estimated that 25% of preventable drug-related hospital admissions are caused by failure to monitor renal function and electrolytes.**
- **Clozapine used for management of treatment – resistant schizophrenia is associated of significant risk of agranulocytosis, that can be eliminated by mandatory monitoring of white blood cells.**

Adverse Drug Reactions

- **Advice on monitoring should be clear, provide an evidence-based frequency of monitoring, and acceptable outcomes or values.**

7. **Explaining risks to patients:**

- **Patients have the right to receive understandable information about the potential for ADR, to enable them to make an informed decision**

Adverse Drug Reactions

Definition of serious adverse event:

1. **Results in death.**
2. **Is life-threatening (places the subject at immediate risk of death from the event as it occurred).**
3. **Results in inpatient hospitalization or prolongation of existing hospitalization.**
4. **Results in a persistent or significant disability/incapacity.**
5. **Results in a congenital anomaly/birth defect.**

Adverse Events Severity Classification

Rank	Definition
Mild	Causing no limitation of usual activities, the participant may experience slight discomfort
Moderate	Causing some limitation of usual activities, the participant may experience annoying discomfort
Severe	Causing inability to carry out usual activities, the participant may experience intolerable discomfort or pain

Adverse Effect Prevalence

Very common	More than 1/10 of subjects. >10%
Common	More than 1/100 to less than 1/10. >1% - <10%
Uncommon	More than 1/1000 to less than 1/100. >0.1% - <1%
Rare	Less than 1/1000. < 0.1%