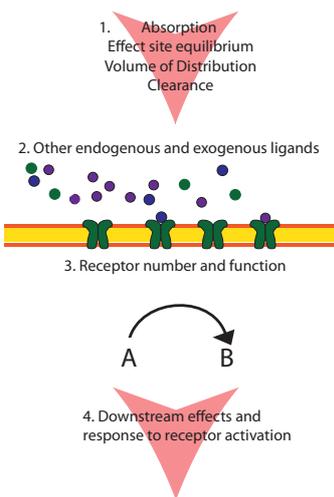


VARIABILITY IN DRUG RESPONSE

Four general mechanisms contribute to **variability in responsiveness to drugs**.



1. Alteration in the amount of drug that reached the receptor. This is usually due to changes in the total absorption of the drug and the rate that this occurs, the volume of distribution and the clearance of the drug (PHARMACOKINETIC FACTORS). This may sometimes be predicted in terms of age, race, weight, physiological or pathological state (especially lung function, renal and hepatic function) and specific genetic factors which may be predicted with a careful history and genetic testing if indicated (find example).

2. Differences in the presence of endogenous and exogenous ligands This mechanism contributes significantly to antagonist response. In patients with pheochromocytoma (high endogenous ligand) propranolol will have a large effect, in marathon runners the response will be negligible (low catecholamines)

3. Variation in the number or function of receptors This may be due to both genetic and environmental factors, hormone responses (eg thyroid hormone up regulates beta adrenoreceptors in the heart and response to catecholamines), or as a specific response to drug therapy. In particular agonists may reduce the number of receptors (down regulation) or coupling efficiency (desensitisation). Antagonists may prevent endogenous down regulation of receptors leading to a relative increase in receptors (PHARMACODYNAMIC FACTORS). These mechanisms contribute to the concept of tolerance, tachyphylaxis, dependence and importantly withdrawal (discussed below).

4. Changes in components of the response distal to the receptor Although a drug initiates a response by binding to receptors, the response is dependent on the functional integrity of the biological system and associated cellular and physiological responses. Physiological and pathological states may lead to variability of response.

Tolerance to the effect of opioids or other drugs simply means that the drug loses its effectiveness over time and an increased dose is required to produce the same physiological response. When a drug rapidly loses its responsiveness it is termed **tachyphylaxis** ("fast guarding").

Dependence refers to a complex and poorly understood set of changes in the homeostasis of an organism that causes a disturbance of the homeostatic set point of the organism if the drug is stopped. This disturbance often is revealed when administration of an opioid is stopped abruptly, resulting in withdrawal.

Withdrawal is the pathological response to the removal of a drug. An example is the agonist clonidine used to lower blood pressure by potentiating alpha-2 adrenoreceptors. Administration of this medication leads to down regulation of these receptors and acute withdrawal may lead to a hypertensive crisis.

Addiction is a behavioral pattern characterized by compulsive use of a drug and overwhelming involvement with its procurement and use. **Tolerance and dependence are physiological responses seen in all patients and are not predictors of addiction.**

Pharmacogenetics is the study of the molecular mechanisms that underlie the individual differences in drug metabolism, efficacy and side effects. Important genes with respect to anaesthetics are RYR1 mutations which are associated with malignant hyperthermia syndrome and the gene that codes for butyrylcholinesterase, a precursor to pseudocholinesterase which hydrolyses suxmethonium.

Neonates: An important generality is that **pharmacokinetic variability is likely to be greatest at times of physiological change** (e.g., the newborn or premature baby or at puberty) such that dosing adjustment, often aided by drug monitoring for drugs with narrow therapeutic indices, becomes critical for safe, effective therapeutics. **Most drug-metabolizing enzymes are expressed at low levels at birth**, followed by an isozymespecific postnatal induction. CYP2E1 and CYP2D6 appear in the first day, followed within 1 week by CYP3A4 and the CYP2C subfamily. CYP2A1 is not expressed until 1–3 months after birth. Some glucuronidation pathways are decreased in the newborn, and an inability of newborns to glucuronidate chloramphenicol was responsible for the "gray baby syndrome". Renal elimination of drugs also is reduced in the neonatal period. **Neonates at term have markedly reduced GFR** (2–4 mL/min/1.73 m²), and prematurity reduces renal function even further. As a result, neonatal dosing regimens for a number of drugs (e.g., aminoglycosides) must be reduced to avoid toxic drug accumulation. GFR (corrected for body surface area) increases progressively to adult levels by 8–12 months of age.

Elderly: As adults age, gradual **changes in pharmacokinetics and pharmacodynamics increase the interindividual variability** of doses required for a given effect. Pharmacokinetic changes result from changes in body composition and the function of drug-eliminating organs. The reduction in lean body mass, serum albumin, and total-body water, coupled with the increase in percentage of body fat, alters drug distribution in a manner dependent on lipid solubility and protein binding. The clearance of many drugs is reduced in the elderly. **Renal function variably declines to ~50%** of that in young adults. Hepatic blood flow and drug metabolism also are reduced in the elderly but vary considerably. **In general, the activities of hepatic CYPs are reduced, but conjugation mechanisms are relatively preserved.** Frequently, the elimination half-lives of drugs are increased as a consequence of larger apparent volumes of distribution of lipid-soluble drugs and/or reductions in the renal or metabolic clearance.

Alterations in **renal function** may lead to impairment of renally excreted drugs. Drug dosage should be adjusted according to the estimation of GFR. Patients with cirrhosis, hepatitis and other **hepatic disease** also have impairment of drug metabolising enzymes particularly microsomal oxidases, but unlike the kidneys there is no quantitative basis for dose adjustment beyond plasma levels and clinical response. **Cardiac disease** may result in a reduction of blood flow to the liver, modifying clearance of flow dependent drugs. In patients with circulatory shock neuroendocrine response may drastically reduce renal and hepatic blood flow reducing the clearance of many drugs. **Pulmonary disease** may also affect drug metabolism as indicated by impaired hydrolysis of procainamide and procaine in patients with COPD. Finally disease states may lead to reductions in circulating proteins and in drugs with high protein binding this may lead to an increase in free drug and therefore potency. In this case measurement of free drug is more accurate than total drug.