COMBINED EFFECT OF DRUGS

When two or more drugs are given simultaneously or in quick succession, they may be either indifferent to each other or exhibit *synergism* or *antagonism*. The interaction may take place at pharmacokinetic level or at pharmacodynamic level.

SYNERGISM

(Greek: *Syn*—together; *ergon*—work)

When the action of one drug is facilitated or increased by the other, they are said to be synergistic.
In a synergistic pair, both the drugs can have action in the same direction or given alone one may be inactive but still enhance the action of the other when given together.

Synergism can be:
(a) Additive The effect of the two drugs is in the same direction and simply adds up:
effect of drugs A + B = effect of drug A + effect of drug B

Additive drug combinations
Aspirin + paracetamol as analgesic/ antipyretic
Amlodipine + atenolol as antihypertensive
Glibenclamide + metformin as hypoglycaemic

Side effects of the components of an additive pair may be different—do not add up. Thus, the combination is better tolerated than higher dose of one component.

(b) Supraadditive (potentiation) The effect of combination is greater than the individual effects of the components:

effect of drug A + B > effect of drug A + effect of drug B
This is always the case when one component

Sulfamethoxazole + Trimethoprim --- equential blockade

ANTAGONISM

When one drug decreases or abolishes the action of another, they are said to be antagonistic:
effect of drugs A + B < effect of drug A +effect of drug B

Usually in an antagonistic pair one drug is inactive as such but decreases the effect of the other. Depending on the mechanism involved, antagonism may be:

(a) Physical antagonism Based on the physical property of the drugs, e.g. charcoal adsorbs alkaloids and can prevent their absorption—used in alkaloidal poisonings.

(b) Chemical antagonism The two drugs react chemically and form an inactive product, e.g.
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• Chelating agents (BAL, Cal. disod. edetate) complex toxic metals (As, Pb).

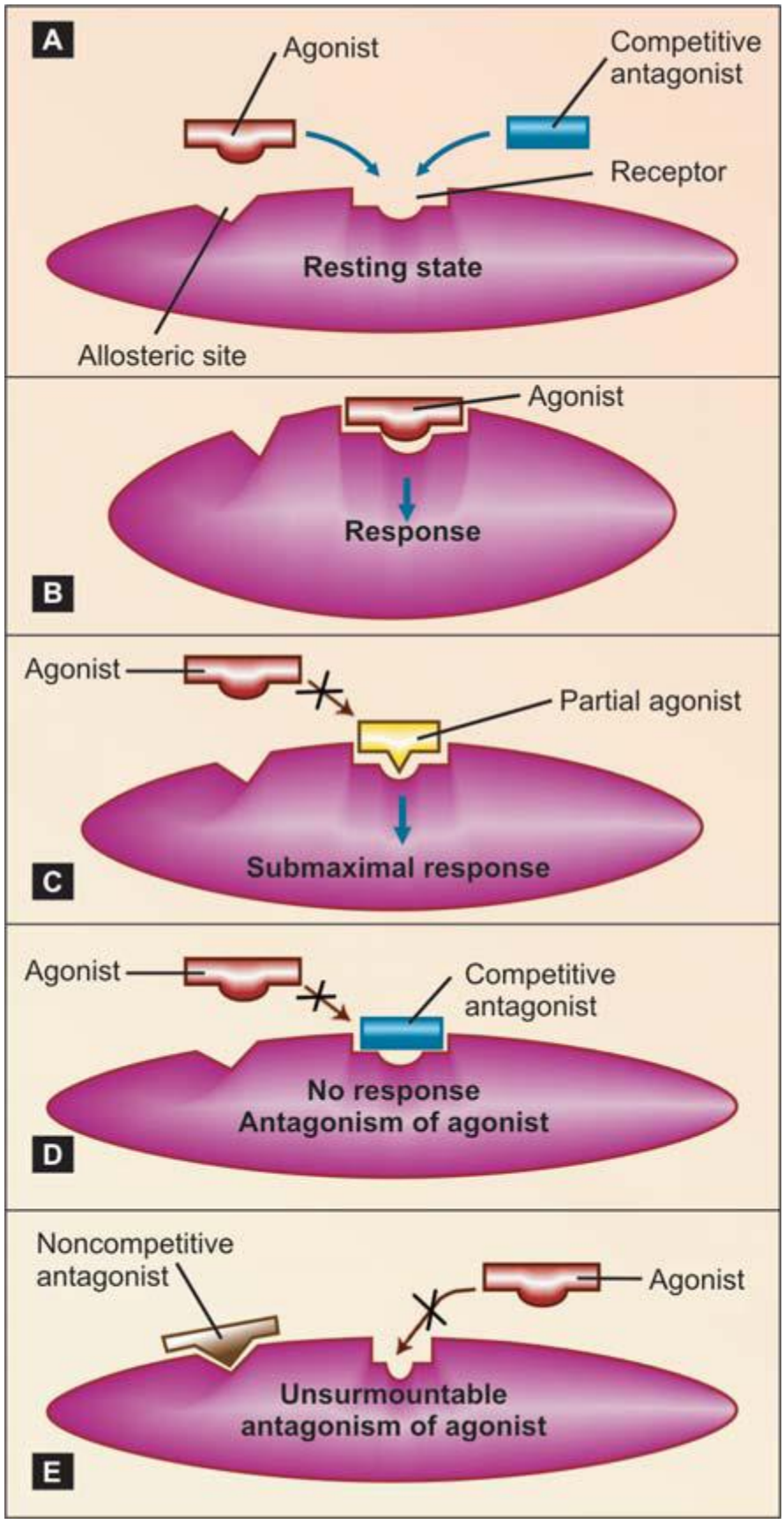
(c) Physiological/functional antagonism The two drugs act on different receptors or by different mechanisms, but have opposite overt effects on the same physiological function, i.e. have pharmacological effects in opposite direction, e.g.

• Glucagon and insulin on blood sugar level.

(d) Receptor antagonism One drug (antagonist) blocks the receptor action of the other (agonist).
This is a very important mechanism of drug action, because physiological signal molecules act through their receptors, blockade of which can produce specific and often profound pharmacological effects.

Competitive antagonism (equilibrium type) The antagonist is chemically similar to the agonist, competes with it and binds to the same site to the exclusion of the agonist molecules. Because the antagonist has affinity but no intrinsic activity

Noncompetitive antagonism The antagonist is chemically unrelated to the agonist, binds to a different *allosteric site* altering the receptor in such a way that it is unable to combine with the agonist , or unable to transduce the response, so that the downstream chain of events are uncoupled.


A
Agonist
Competitive antagonist
Receptor
Resting state
Allosteric site
Agonist
Response
B
Agonist
Partial agonist
Submaximal response
C
Agonist
Competitive antagonist
No response
Antagonism of agonist
D
Noncompetitive antagonist
Agonist
Unsurmountable antagonism of agonist
E