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# Paradoxical and Bidirectional Drug Effects

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## Abstract

A *paradoxical drug reaction* constitutes an outcome that is opposite from the outcome that would be expected from the drug's known actions. There are three types:

1. A paradoxical response in a condition for which the drug is being explicitly prescribed.
2. Paradoxical precipitation of a condition for which the drug is indicated, when the drug is being used for an alternative indication.
3. Effects that are paradoxical in relation to an aspect of the pharmacology of the drug but unrelated to the usual indication.

In *bidirectional drug reactions*, a drug may produce opposite effects, either in the same or different individuals, the effects usually being different from the expected beneficial effect. Paradoxical and bidirectional drug effects can sometimes be harnessed for benefit; some may be adverse.

Such reactions arise in a wide variety of drug classes. Some are common; others are reported in single case reports. Paradoxical effects are often adverse, since they are opposite the direction of the expected effect. They may complicate the assessment of adverse drug reactions, pharmacovigilance, and clinical management. Bidirectional effects may be clinically useful or adverse. From a clinical toxicological perspective, altered pharmacokinetics or

pharmacodynamics in overdose may exacerbate paradoxical and bidirectional effects. Certain antidotes have paradoxical attributes, complicating management.

Apparent clinical paradoxical or bidirectional effects and reactions ensue when conflicts arise at different levels in self-regulating biological systems, as complexity increases from subcellular components, such as receptors, to cells, tissues, organs, and the whole individual. These may be incompletely understood. Mechanisms of such effects include different actions at the same receptor, owing to changes with time and downstream effects; stereochemical effects; multiple receptor targets with or without associated temporal effects; antibody-mediated reactions; three-dimensional architectural constraints; pharmacokinetic competing compartment effects; disruption and non-linear effects in oscillating systems, systemic overcompensation, and other higher-level feedback mechanisms and feedback response loops at multiple levels. Here we review and provide a compendium of multiple class effects and individual reactions, relevant mechanisms, and specific clinical toxicological considerations of antibiotics, immune modulators, antineoplastic drugs, and cardiovascular, CNS, dermal, endocrine, musculoskeletal, gastrointestinal, haematological, respiratory, and psychotropic agents.

*Next to knowing the truth itself, is to know the direction in which it lies. And this is the peculiar praise of a sound conjecture.*
Peter Mere Latham (1789–1875)

## 1. Introduction

Paradoxical reactions, such as 'paradoxical undressing' that sometimes accompanies disorientation associated with hypothermia, may puzzle clinicians.[1] Paradoxical effects may be difficult to distinguish from a disease or pathophysiological state and may be misinterpreted as disease exacerbation or progression.

### 1.1 Definitions

A *paradoxical drug reaction* constitutes a result opposite to the expected outcome (figure 1). There are three types:
1. A paradoxical response in a condition for which the drug is being explicitly prescribed.
2. Paradoxical precipitation of a condition for which the drug is indicated, when the drug is being used for an alternative indication.
3. An effect that is paradoxical in relation to an aspect of the pharmacology of the drug but unrelated to the usual indication.

*Unanticipated* effects are insufficient for paradoxical categorization. Erythropoietin-associated tumour progression in cancer patients was unanticipated, but not paradoxical.[2] However, erythropoietin-associated erythrocytopenia and erythrocyte aplasia in chronic kidney disease was paradoxical, since it was opposite to the intended effect (erythropoiesis).[3] A separate, unanticipated effect of emerging global concern arises when pharmaceuticals of inferior manufacturing quality fail to produce the 'correct' therapeutic outcome in patients owing to an insufficiency or absence of the active ingredient.[4] The apparent clinical effect is not secondary to the presence of drug or chemical moiety (which is absent). Therefore, worsening infection following administration of a substandard antibiotic would constitute therapeutic inefficacy, but not a paradoxical response. This may confound clinicians and complicate therapy, and would best be defined as *pseudo-paradoxical*. Similarly, adverse reactions that were opposite to the anticipated physiological response, but are due to the presence of an unintended contaminant, excipient, or impurity are also *pseudo-paradoxical*. Gentamicin prescribed for a range of serious bacterial infections caused fever, tachycardia, and hypotension,

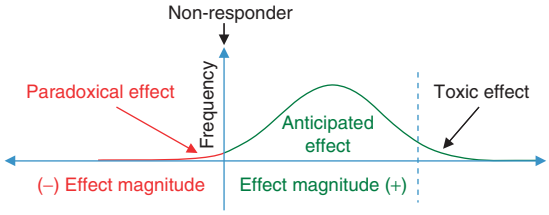


**Fig. 1.** At a particular dose (fixed or weight-based) in a population, a xenobiotic may produce anticipated effects with a range of effect magnitudes, including excessive or toxic effects. Non-responders lie along the ordinate axis. A paradoxical effect occurs, opposite to that which is expected. While a hypothetical, unimodal, dose-normalized response curve is depicted, the proportion producing a paradoxical or negligible effect (left- or right-shift) and the shape of the distribution differ for each xenobiotic and population.

opposite the anticipated physiological response and consistent with worsening infection. Product contamination with endotoxin (as well as once-daily gentamicin dosing) accounted for the observed *pseudo-paradoxical* clinical deterioration.[5] The observed adverse physiological response would have been anticipated if the presence of the contaminant (endotoxin) and pharmacokinetics had been appreciated.

*Bidirectional drug reactions* occur when a drug produces opposing effects either in the same or different individuals, but the effects are usually in systems different from or unrelated to that in which the drug is expected to produce an effect (figure 2).

### 1.2 General Considerations

Unrecognized paradoxical and bidirectional reactions complicate assessment of new chemical entities. In pharmacovigilance, they may obscure signal detection and adverse drug reaction assessments within proposed frameworks.[6] Paradoxical reactions might be misattributed to a worsening disease state (e.g. confounding by indication). Through the process of averaging data or concentration on central tendency, important bidirectional effects might be lost. However, elucidating paradoxical mechanisms may uncover new targets for drug development and improve drug safety monitoring and surveillance.[7] From a toxicological perspective, altered pharmacokinetics or pharmacodynamics in overdose may exacerbate paradoxical and bidirectional effects, complicating management.

Some paradoxical and bidirectional adverse effects are common and well known, e.g. agitation during paediatric sedation with midazolam, dysrhythmias from antidysrhythmic drugs that slow atrioventricular nodal conduction in patients with accessory pathways, adverse effects of diuretics, nitrates, opioids, and β-blockers in right-sided myocardial infarction, and paradoxical bradycardia with low-dose atropine.[8] They may be associated with a class of medications (increased early suicidality with antidepressants) or specific entities (pulmonary oedema with hydrochlorothiazide).[9-11] Certain toxicological antidotes may produce known paradoxical harmful effects: parenteral dextrose may exacerbate hypoglycaemic episodes in sulfonylurea poisoning, and methylthioninium chloride (methylene blue) may induce haemolysis.[12]

Paradoxical and bidirectional responses may be harnessed for benefit. While estrogens stimulate pituitary luteinizing hormone (LH) release (triggering ovulation and increased progesterone concentrations, favouring implantation), this is time dependent. Continued estrogen exposure in

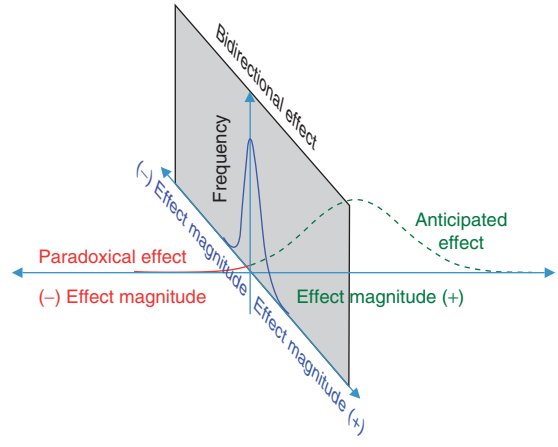


**Fig. 2.** When a xenobiotic produces its anticipated effects, it may also produce bidirectional drug effects in systems unrelated to the primary mechanism of the drug (e.g. fluoroquinolone-induced hypo/hyperglycaemia). A hypothetical unimodal curve is depicted, although for each xenobiotic, the shape of the bidirectional distribution, the extent of the central tendency (i.e. absence of any bidirectional drug effect), and the proportion producing a positive or negative effect differ.

oral contraceptives or post-coital provision suppresses follicle-stimulating hormone (FSH) and LH surges and ovulation/implantation. β-adrenoceptor antagonists, once anticipated to compromise the failing heart further, may improve functioning, reduce mortality, and avoid the need for hospitalization.[13] Thiazides have long provided paradoxical antidiuretic benefit in the treatment of diabetes insipidus.[14]

Reviews of paradoxical and bidirectional xenobiotic reactions are infrequent,[7,15] despite an increasing appreciation of 'paradoxical pharmacology'.[13,16] Here, we review mechanisms of paradoxical and bidirectional reactions, provide a visualization framework for understanding their effects, and provide an extensive Compendium of Paradoxical Drug Reactions (see Supplemental Digital Content [SDC], http://links.adisonline.com/DSZ/A61) of published human reactions that we have discovered to date, including cases in which causality may or may not have been established. We have included reports that might be ineligible in other systematic review methods,[17] including, for the sake of completeness, reports for which the evidence is less than good.

## 2. Mechanisms

### 2.1 Hormesis

Hormesis, "a biphasic dose-response curve, with beneficial or stimulatory effects at low doses and adverse or inhibitory effects at high doses",[18] provides a useful starting point to explore paradoxical effects. A more inclusive definition is "a reversal of single response between low and high doses".[19] Hormesis was originally applied in toxicology to resolve the inability of linear no-threshold dose-response models to align with certain empirical datasets. In many cases, the observed effects of ionizing radiation, chemicals, drugs, pesticides, and other xenobiotics at low doses was not harmful, but actually protective, not only against the adverse effect of the agent, but also against the stress induced by normal oxidative metabolism.[20] Enhanced detoxification, cellular efflux, and excretion; altered gene expression and cell cycling; augmented DNA repair, damaged protein clearance, immune functions, and antioxidant defenses; and apoptosis are offered as explanations.[20,21] The hormesis framework was extended to include the influence of pre- or post-exposure conditioning (and time dependence) on response, and conceptually to the concept of the therapeutic window.[20,22] While it has been proposed to withhold judgement on whether or not a given response is beneficial,[23] such equipoise is nearly impossible to maintain with clinical diagnostic or therapeutic intent – opposite effects are generally perceived to be (and generally are) adverse.

However, hormesis explains only a subset of clinical paradoxical and bidirectional effects. Much of the evidence on hormesis arises from animal, tissue, or cell studies,[24] and there are relatively few definitive examples from the human clinical literature. Furthermore, hormesis is characterized by the observation of opposite effects at different drug concentrations, permitting the construction of a dose-response curve, even if this dose-responsiveness includes paradoxical or unanticipated responses at different doses. Indeed, this has been linked explicitly – "the hormetic dose response".[19,23] Clinical bidirectional and paradoxical effects are not necessarily of explicit dose responsiveness. Many examples are not dose-range finding assessments in a given patient or populations of patients – more usually, a specific dose of a specific drug is given to a specific patient for a specific condition, anticipating a specific response. Bidirectional and paradoxical reactions do not necessarily occur at doses different from those producing anticipated effects. They may occur at entirely appropriate doses or regardless of dose, in intended or unintended target systems. They may arise in the same patient at the same doses in different circumstances (known or unknown physiological or pathological states in time). Alternatively, opposite effects can occur in different patients. Hormesis is insufficient to explain all-or-none phenomena, immune-mediated effects, and effects in oscillating/periodic systems.[19]

### 2.2 Complex Systems

Xenobiotics are introduced into complex, self-regulating, nested, multi-level, biological systems

(humans in the case of clinical medicine). 'Hormetic' curves, while described above as applied to biological systems, also emerge from competing reactions in many non-biological complex systems. J-shaped, U-shaped, or biphasic curves are described in economics, physics, chemistry, and engineering. For example, in aviation, as airspeed increases, the differential observed responses in lift, induced drag, and parasitic drag yield a J-shaped response curve (the *power curve*). Formal evaluation of biological dose-response curves from a complex systems theory perspective demonstrates that the shape of a dose-response curve depends on the specific values of local response coefficients (gains) distributed within the system.[25,26] A feed-forward response can produce a J-shaped curve in the low-dose region, and these can be isolated to certain measured responses. Biphasic dose-response curves can also be produced by inhibition and can vary by altering the sensitivity of particular components.[27] Even more complex curves are possible with the existence of alternative stable steady states and alterations in exposure duration.[28] Hormesis aptly describes a subset of behaviours within complex systems.

In complex systems, *emergent behaviours* occur that are not necessarily obvious or evident from individual components. Viewed from a complex systems perspective, clinical paradoxical or bidirectional effects surface from the conflicts, integrations, and emergent behaviours that arise at different levels, as complexity increases from subcellular components (channels, enzymes, receptors, transporters, organelles, etc.) to cells, tissues, organs, and the whole individual. A complex systems approach subsumes and anticipates two originally competing premises in hormesis – ''direct stimulation or via compensatory response''.[19,23] Accordingly, unique determinants may play a role at each level. Szabadi's models[29] demonstrated how a single xenobiotic (agonist or antagonist) could produce opposing dose-response effects, given the existence of different receptor subpopulations. The ''total effect observed''[29] is derived from xenobiotic concentrations, the effect magnitude of a given xenobiotic-receptor interaction (in one direction or the other), and dissociation constants of receptor subpopulations. The models also demonstrated how a xenobiotic could unmask or uncover competing receptor interactions to produce paradoxical results. However, 'spare receptors', receptor internalization, and recycling were not considered. Complexity at the receptor level is expanded in organisms by stereochemical binding preferences, receptor desensitization or multiple receptor states, heterodimerization, xenobiotic autoinhibition or metabolite inhibition, and partial agonists/inverse agonists, which may stabilize conformations that alter basal signalling, among others.

Conceptually, the ''total effect observed'' may be extended to higher biological systems levels arising from the cellular, tissue, and organ subpopulations on which a xenobiotic may act. For example, the ''total effect observed'' of a given xenobiotic at the cellular level might include the results of induction of competing downstream pathways of a given receptor, processes external to actions at a given receptor (uptake, storage, release, degradation, gene expression) or induction of alternative stable steady states.[28] The ''total effect observed'' at the organ level represents the effects in various tissue types (e.g. myocardial conduction tissue compared with muscle tissue) or sub-organ macrostructures (particularly in the CNS). Intricacy and emergent effects at the organ level are evident in examining cardiac output (CO). CO depends on multiple, complex macrosystems interactions, each mediated by various subsystems: sympathetic and parasympathetic tone on contractility and rate (which itself affects filling time, may affect intraventricular conduction, and has bidirectional effects on CO); preload effects (captured by the *Frank-Starling curve*, where CO increases with increased left ventricular end-diastolic volume up to a certain point and then decreases[30]); transmitted pleural pressures; atrial kick (which may be rate or rhythm dependent); ventricular compliance; afterload (with its own determinants); and vascular coupling phenomena.

Bidirectional effects may occur in 'bystander' systems unrelated to primary drug mechanisms in a complex system into which a drug is introduced (figure 2). As there are few exclusively one-to-one

relationships in complex systems, the relative specificity of the drug for a receptor or system (normally selected *for* during drug development) may influence how frequently bidirectional effects are evident.

Complex systems are also dynamic systems. Hysteresis may be observed (in pulmonary, neuronal, cardiovascular, and other systems).[31-35] Oscillations, periodicity, and compensation (or feedback) are also inherent in biological complex systems.[36] Thus, a xenobiotic's effects may depend upon the system's state immediately before its introduction. Patients have unique histories and heterogeneous sets of initial conditions (genetic polymorphisms, distinctive phenotypic expressions, preconditioning, cross-tolerance, disease manifestations, other therapies, etc.). Paradoxical results may thus be influenced by current and prior circumstances (whether inherited, expressed, or experienced).

The particular system and systems level affected by the xenobiotic will dictate the influences on the observed outcome, and each level has an inherent time-scale of responsiveness. At the response level of the cell, the complex properties of oxygen and its diverse physiological roles yield both its unequivocal necessity for cellular existence and its propensity for pathological and potentially lethal oxidation.[37,38] At the response level of tissues, antiepileptic drugs, acting through a variety of inhibitory ion channel, uptake, or catabolic mechanisms at the individual cellular level, may ultimately trigger populations of neurons to become proconvulsant (e.g. by excess inhibition of inhibitory neurons).[39] Tumours that contain multiple tissue lines may demonstrate paradoxical responses to chemotherapy (e.g. an embryonal component may respond, while a mature component may progress in immature teratoma).[40] Paradoxical response at the level of the organ is seen in narcotic bowel dysfunction in chronic opioid use, which may lead to spurious diarrhoea due to 'narcotic bowel syndrome' or overflow diarrhoea due to mechanical faecal impaction.[41,42] Given that $\beta_1$ and $\beta_2$ adrenoceptors are present in both the heart and the vasculature, and the existence of various neurally mediated systemic baroreflex functions, it is not surprising that the integrated response at the level of the individual to non-selective β agonists such as isoprenaline (isoproterenol) may be hypertension or hypotension and tachycardia or bradycardia.[43-45] Certain drugs may affect multiple systemic levels. Amiodarone may cause either hypo- or hyperthyroidism because of multiple competing effects, which include blockade of thyroid hormone entry into cells (subcellular level), inhibition of type 1 and type 2 5′-deiodinase (subcellular level), reduced T3 binding to its receptors (subcellular level), the *Jod–Basedow effect* (cellular level), failure to escape from *Wolff-Chaikoff effect* (cellular level), thyroid cytotoxicity (cellular and tissue levels), and potentiation of thyroid autoimmunity (tissue and organ levels).[46] Paradoxical reactions may also result from integrated responses at significantly separated systemic levels or distributions, e.g. salicylate antipyresis in the hypothalamus versus prothermic uncoupling of respiration in mitochondria. The additional temporal factors may be related to intrinsic factors within the system (inactivation, internalization, or feedback response times, etc.) or related to extrinsic xenobiotic administration or exposure parameters. As shown in figures 3a and 3b, a given dose may produce divergent effects during its administration or based on the time course of its administration.

While paradoxical and bidirectional effects may occur at any level, they are generally recognized when the summation/integration of xenobiotic effects generates clinical detection of atypical signs or symptoms. Some paradoxical reactions at lower systems levels may even be clinically irrelevant. For example, *N*-acetylcysteine treats paracetamol (acetaminophen) overdose complicated by hepatic failure and coagulopathy (increased international normalized ratio [INR]); however, *N*-acetylcysteine itself reduces clotting factor II, VII, and X activity, mildly increasing INR.[47]

It is to be expected that paradoxical reactions will demonstrate a diversity of etiologies that "cannot be characterized adequately by a single general mechanism".[19] The myriad of different interactions at diverse levels in a host complex system that can potentially be disrupted by xenobiotics anticipates this. Rational drug

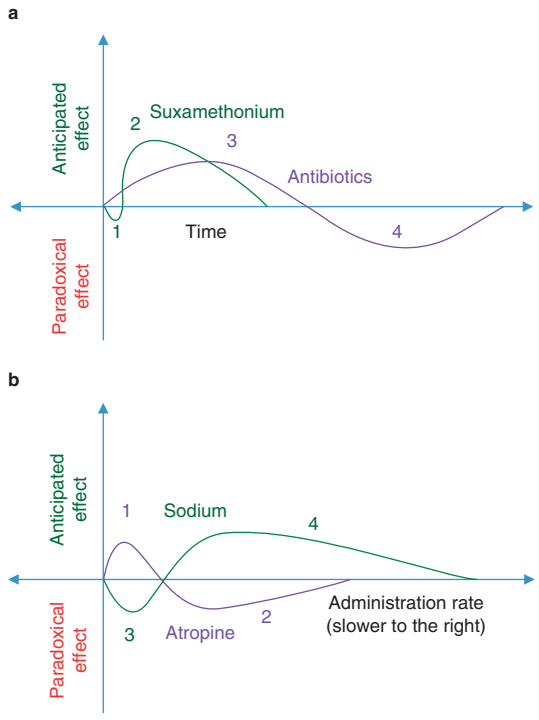


**Fig. 3.** Temporal aspects of some paradoxical effects. (**a**) After suxamethonium, fasciculations and muscle hyperactivity (1) are followed by muscle paralysis (2) lasting minutes. Over the time course of hours to days, antibiotics may produce defervescence (3), followed by fever recurrence (4) due, for example, to a drug reaction (drug fever) or in certain infections, the *Jarisch-Herxheimer reaction*. Depending on the cause, fever might abate only on antibiotic withdrawal. Effect and time (log scale) are in arbitrary units. (**b**) Rapid administration of atropine produces the desired tachycardia (1); slow administration may produce paradoxical bradycardia (2). Conversely, too rapid provision of sodium to treat hyponatraemia-associated encephalopathy may cause central pontine and extrapontine myelinolysis, reproducing encephalopathy (3); slower administration is advocated (4). Effects and administration rate (log scale) are in arbitrary units.

development, therapeutics, and predicting toxicological events will proceed based on understanding the relevant regulatory networks involved, as well as determining if the paradoxical reaction is more evident in general or in more unique systems (e.g. hosts with specific genetic determinants or disease states). Examples include outcomes mediated by differential drug distributions/pharmacokinetics (e.g. xenobiotics with peripheral and CNS targets), disruption and non-linear effects in oscillating systems (e.g. hypnosedatives), systemic overcompensation (e.g. immune reconstitution inflammatory syndrome [IRIS]), or specific anatomical characteristics (e.g. hypertrophic cardiomyopathy and accessory pathways).

While not exhaustive, several schemes of paradoxical and bidirectional drug effects are presented in table I. A compound may have partial agonist or inverse agonist action (flumazenil, β-blockers with intrinsic sympathomimetic activity, and partial β-adrenoceptor agonists).[50-52] Given the potential for chiral compounds to experience distinct pharmacokinetics, enzyme and receptor interactions, and DNA binding,[74] racemic mixtures may have paradoxical effect profiles. In addition to differences seen with salbutamol, opposite effects with atropine, pyranenamine, and some cannabinoid enantiomers are reported.[53,75] A metabolite may act on an unanticipated, confounding receptor (acecainide, *N*-acetylprocainamide).[54] Time-dependent effects may occur within the same system due to receptor inactivation (suxamethonium), a system's oscillatory nature (β-blockers), or because of competing downstream effects (vitamin K antagonists).[57] Alternatively, pharmacokinetic effects may contribute to paradoxical results, such as when a compound is metabolized to a different form, allowing access to an alternative compartment (bicarbonate), or where the same receptor is present in an additional compartment (α-adrenoceptor receptor agonists and antagonists).[59,76] Despite a similar receptor, competing contemporaneous effects/interactions may occur in different systems, either through activation (acetylcholine via acetylcholinesterase inhibitors) or interference with constitutively active oscillatory or phasic systems (dopaminergic agents).[60,62] Competing targets within a systems level may up-end anticipated effects (antidysrhythmics).[64] Alternatively, targets may exist at and within multiple systems levels (antihypertensives). Antibody-mediated reactions also comprise a number of paradoxical reactions (heparin-induced thromboembolism, platelet adenosine diphosphate receptor antagonist-associated TTP, methylprednisolone succinate anaphylaxis).[57,67,68,77] Overcompensation may occur, even at higher hierarchical levels within the organism (IRIS).[69] Lastly, despite anticipated effects at one systems level, a paradoxical reaction may emerge at a higher systems level

**Table I.** Some mechanisms of paradoxical and bidirectional drug effects

| Mechanism | Example(s) |
|---|---|
| 1. Single target, partial agonist, or inverse agonist action (effects depend on the initial state and competing xenobiotics) | Flumazenil: inverse agonist or partial agonist capacity at $GABA_A$ receptors;[48,49] *reduced* aggression and hostility when given to patients with benzodiazepine dependence[50]<br>β-blockers with intrinsic sympathomimetic activity: despite sympathetic antagonism, mitigation of negative chronotropic and inotropic activity, peripheral vasoconstriction, and bronchoconstriction in low sympathetic activity[51]<br>Partial β-adrenoceptor agonists (e.g. xamoterol): functional agonists when sympathetic nervous system activity is low; antagonists when activity is high[52] |
| 2. Single target, stereochemical effects | Salbutamol: *R*(–) isomer causes hypokalaemia by stimulating the $Na^+/K^+$ pump; *S*(+) isomer may cause hyperkalaemia[53] |
| 3. Single target, parent and metabolite effects at different receptors | Procainamide: pro-dysrhythmic, independent class III (potassium channel) effects of the metabolite, acecainide (*N*-acetylprocainamide) may conflict with class Ia (sodium channel) antidysrhythmic effects of the parent compound, particularly in renal insufficiency[54] |
| 4 Single target, same system, balanced competing effects | β-blockers: improved cardiac function via a lusitropic effect in diastole; impaired cardiac function by a negative inotropic effect in systole (both via β-blockade)<br>Acetylcholine: dilates normal blood vessels by nitric oxide release, but vasoconstricts vessels denuded of endothelium and atherosclerotic, angiographically abnormal coronary arteries[55] |
| 5. Single target, same system, time-dependent receptor or downstream effects | Suxamethonium: muscle paralysis via sustained agonism by inactivation of voltage-gated sodium channels via desensitization block. Excess acetylcholine from organophosphorus or carbamate exposure may produce similar fasciculations followed by paralysis[56]<br>Vitamin K antagonists: transient early hypercoagulability via a more rapid fall in concentrations of activated protein S and protein C relative to coagulation factors II, IX, and X[57] |
| 6. Single target, same system, contemporaneous effects/interactions, reflecting distributional effects | Bicarbonate: when used to promote alkalinization in severe acidaemia, bicarbonate reaction with acid forms water and large amounts of $CO_2$; $CO_2$ diffuses intracellularly to generate protons on reaction with intracellular water, producing paradoxical intracellular acidosis[58] |
| 7. Single target, different systems, contemporaneous effects/interactions, reflecting distributional effects | Clonidine (particularly in overdose): immediate hypertension by peripheral α-adrenoceptor activation; subsequent agonism at central presynaptic neurons with sympatholysis and hypotension[59]<br>Yohimbine: effects opposite to those of clonidine |
| 8. Single target, different systems, competing contemporaneous effects/interactions, reflecting systems effects | Acetylcholinesterase inhibitors: competing parasympathetic and sympathetic effects in various systems, depending on relative contributions (organophosphorus pesticide-induced miosis or mydriasis, bradycardia or tachycardia, and hypertension or hypotension)[60] |
| 9. Single target, interference with constitutively active oscillatory or phasic systems | DBS or brain lesioning: improves opposite pathologies of dystonia, levodopa-induced tardive dyskinesia, and parkinsonism[61] In dystonias, *decreased* tonic inhibition of the thalamus by the GPI facilitates cortical motor areas and excessive movement, yet pallidal DBS and pallidotomy relieve dyskinesias and dystonia. In Parkinson's disease, tonic *inhibition* of the thalamus by the GPI impedes voluntary movements, but motor thalamic DBS and lesioning do not cause akinesia<br>Dopaminergic agents (levodopa, dopamine receptor agonists, catechol-O-methyl transferase inhibitors, and monoamine oxidase type B inhibitors): similar various motor dyskinesias[62]<br>Dopamine receptor agonist (apomorphine): profound akinesia[63] |

*Continued next page*

**Table I.** Contd

| Mechanism | Example(s) |
|---|---|
| 10. Multiple targets, same system, contemporaneous effects/interactions | Antidysrhythmic drugs: cardiac fast sodium channel inhibition (antidysrhythmic action) and cardiac potassium (hERG) channel inhibition (prodysrhythmic action)[64] |
| 11. Multiple targets, same system, time-dependent effects | Antidepressants (SSRIs): 5-HT uptake inhibition and 5-HT autoreceptor antagonism in diverse CNS sites associated with increased suicide risk when emerging from profound neurovegetative impairment early in therapy[9]<br>Xanthine oxidase inhibitors: precipitate gout early in therapy (perhaps via urate mobilization from tissue deposits, fluctuating serum uric acid concentration, or uric acid transport alteration) and later gout prevention (inhibition of intracellular uric acid production)[65,66] |
| 12. Multiple receptor targets, different systems, contemporaneous effects/interactions | Heart rate, stroke volume, and systemic vascular resistance affect blood pressure. The relative contributions of $\beta_1$ and $\beta_2$ adrenoceptor agonism by isoprenaline, for example, on each of these components may cause the blood pressure to rise, fall, or stay the same |
| 13. Effect not associated with primary target, antibody-mediated reaction | Heparin: heparin-platelet factor 4 IgG antibodies may trigger platelet aggregation and thrombus formation; thromboembolism despite thrombocytopenia[57]<br>Methylprednisolone succinate (parenteral): IgE antibodies with high specificity for the succinate moiety produce anaphylaxis and other hypersensitivity reactions[67,68] |
| 14. Systems level effects, response overcompensation | Highly active antiretroviral therapy: immune reconstitution inflammatory syndrome[69]<br>*Somogyi effect*: Fasting hyperglycaemia following hyperinsulinaemia-associated nocturnal hypoglycaemia[70] |
| 15. Systems level effects, altered function at a higher level | Digoxin: dynamic increase in left ventricular outflow obstruction in hypertrophic cardiomyopathy, reducing cardiac output[71,72]<br>Latanoprost (prostaglandin $F_{2\alpha}$ analogue): paradoxical increased inflammatory factors and intraocular pressure despite normally reducing inflammatory ocular hypertension by improving uveoscleral outflow[73] |

**DBS** = deep brain stimulation; **GPI** = globus pallidus interna; **hERG** = human ether-à-go-go-related gene; **SSRIs** = selective serotonin reuptake inhibitors.

(latanoprost-associated intraocular hypertension and isotretinoin-associated acne fulminans).[73,78]

It is thus useful to visualize the level at which a paradoxical effect occurs and to summarize graphically the underlying components in a particular biological network, as complexity increases from molecular pharmacology to cellular pharmacology and physiology, tissues, organs, and clinical outcome.[27] In these visualizations, which we call 'paradoxigrams', the term 'receptor' is used broadly to apply to subcellular aspects of molecular pharmacology (channels, enzymes, receptors, transporters, organelles, etc.). Figures 4a and 4b graphically summarize two distinct paradoxical reactions seen with digoxin: (i) ventricular outflow obstruction, reduced CO, and worsening clinical symptoms following digoxin administration in hypertrophic cardiomyopathy; and (ii) induction of potentially lethal tachydysrhythmias following digoxin administration for ventricular rate control in atrial tachycardia. A particular modifying factor influencing the 'initial conditions' (a distinctive phenotypic expression with anatomical consequence in hypertrophic cardiomyopathy) is present in the former example. These paradoxical reactions occur at clinically relevant, higher systems levels, even though the alterations at one systems level (inhibition of the sodium-potassium adenosine triphosphatase) are well known and anticipated.

### 2.3 Compendium of Paradoxical Drug Reactions

A Compendium of Paradoxical Drug Reactions is provided as SDC, and the reader is encouraged to examine this in conjunction with this

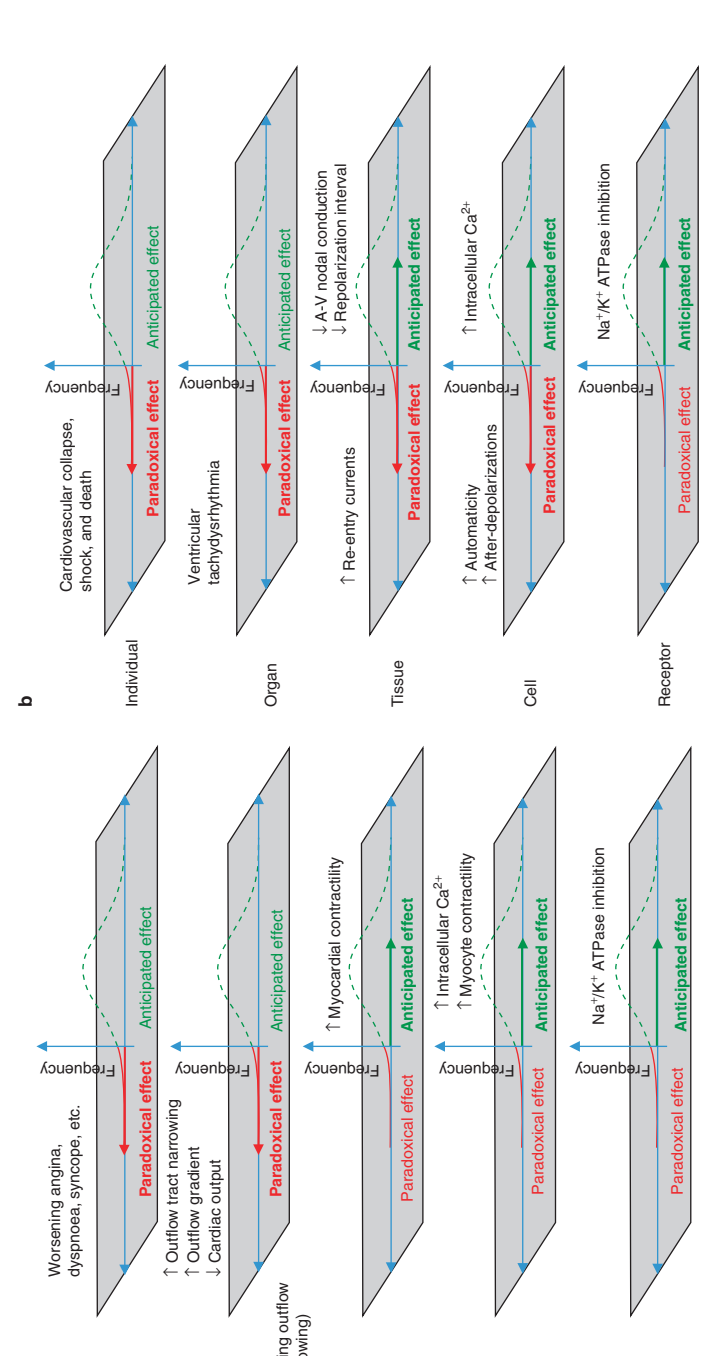


**Fig. 4.** Paradoxical reactions may arise at different systems levels. (**a**) Digoxin administration in hypertrophic cardiomyopathy. Digoxin functions as expected at the receptor and cell levels, yet organ function is compromised and clinical symptoms worsen via outflow tract narrowing. (**b**) Digoxin administration for ventricular rate control in atrial tachycardia. $Na^+/K^+$ ATPase inhibition increases intracellular calcium concentrations, increasing automaticity and promoting abnormal after-depolarizations. Atrioventricular nodal conduction is decreased via myocardial tissue depression and directly and indirectly mediated increased parasympathetic (vagus) tone, reducing supraventricular control of ventricular rate. Ectopic ventricular events, in the setting of increased ventricular myocardial excitability, automaticity, or accelerated ventricular pacemakers may then engender ventricular re-entry currents and ventricular tachydysrhythmias. In these visualizations, the term 'receptor' is used broadly to apply to subcellular aspects of molecular pharmacology. **ATPase** = adenosine triphosphatase; **A-V** = atrioventricular; ↑ indicates increased; ↓ indicates decreased.

**Table II.** Some examples of paradoxical and bidirectional drug effects in different pharmaceutical or systems classes

| Pharmaceutical or systems class | Examples |
|---|---|
| Antibiotics and immunomodulators | |
| Antibiotics | Chemotherapy for borreliosis, leptospirosis, Q fever, syphilis, mycobacteria, and tick- and louse-borne relapsing fever: reproduction and worsening of infectious symptoms (*Jarisch-Herxheimer reaction*)[79-81]<br>Highly active antiretroviral therapy: immune reconstitution inflammatory syndrome worsening clinical or radiological disease[69,82] |
| Immune and inflammatory modulators | Systemic glucocorticosteroids: hypersensitivity reactions[68,83]<br>TNFα antagonists for psoriasis: paradoxical psoriaform lesions[84-86] |
| Antineoplastic agents and carcinogens | Chemo- and radiation therapy: secondary malignant neoplasms[87]<br>Arsenic: pro-malignant (in skin, bladder, and lung),[88] as well as therapy for acute promyelocytic leukaemia and other malignancies (as $As_2O_3$)[89] |
| Cardiovascular system | |
| Antidysrhythmic drugs | Ventricular antidysrhythmic drugs: prodysrhythmia[54,64]<br>Isoprenaline (isoproterenol): positive (excitatory) chronotropy to control *torsades des pointes* (a ventricular tachydysrhythmia)[90] |
| Antihypertensive drugs and vasodilators | Centrally-acting $\alpha_2$-adrenoceptor and imidazoline $I_1$-receptor agonists (methyldopa, clonidine, guanabenz, moxonidine): hypertension[59,76]<br>Thiazides: antidiuresis in diabetes insipidus[14]<br>Vasodilators for angina: cardiac 'steal', reduces regional perfusion, and induces symptoms[91,92] |
| Drugs for congestive heart failure | Antihypertensives and negative inotropes (ACE inhibitors, angiotensin II receptor antagonists, hydralazine, β-blockers): bidirectional blood pressure effects and improved morbidity and mortality[13,93] |
| Lipid-modifying drugs | Fibrates (bezafibrate, ciprofibrate and fenofibrate): detrimental lipid profiles[94,95]<br>Ezetimibe: hyperlipidaemia[96] |
| Inotropes and chronotropes | Isoprenaline: bradycardia[45]<br>Epinephrine: hypotension[97]<br>β-blockers and calcium channel blockers: improved cardiac output in hypertrophic cardiomyopathy[98] |
| Vasoconstrictors | Ergot alkaloids (methylergonovine and dihydroergotamine): vasoconstriction or vasodilatation[99]<br>Vasopressin: hypotension[100] |
| Nervous system | |
| Anaesthetics | Inhalational anaesthetics: CNS excitation; hyperalgesia[101,102]<br>Ketamine, propofol: agitation[103] |
| Antiepileptic drugs | Benzodiazepines, barbiturates, hydantoins and others: seizure exacerbation or triggering[104-106] |
| Hypnosedatives | Anticholinergics, antihistamines, antispasmodics, barbiturates, benzodiazepines, bromides, chloral hydrate, ethanol, GHB, non-benzodiazepine hypnotics, opioids: CNS excitation[107-112]<br>Opioids: opioid-induced hyperalgesia[113,114] |
| Psychotropic drugs | Antidepressants: increased suicidality[9]<br>Antipsychotics: psychotic symptom exacerbation[115] |
| Peripheral nervous system | Acetylcholinesterase inhibitors: competing parasympathetic and sympathetic effects[116]<br>Capsaicin: postherpetic neuralgia relief[117] |
| Movement disorders | Dopaminergic agents (levodopa, dopamine receptor agonists, catechol-O-methyl transferase inhibitors and monoamine oxidase type B inhibitors: various adverse motor dyskinesias[62] |
| Endocrine system and metabolism | |
| Acid-base physiology | Exogenous sodium lactate: metabolic acidaemia[118]<br>Exogenous bicarbonate: intracellular acidosis[58] |
| Bone metabolism agents | Parathyroid hormone: bone resorption or deposition[119]<br>Bisphosphonates: increased femoral fracture prevalence; osteonecrosis[120,121] |
| Electrolytes | Hypertonic saline: hyponatraemia[122]<br>Magnaesium hydroxide: hypomagnesaemia[123] |

*Continued next page*

**Table II.** Contd

| Pharmaceutical or systems class | Examples |
|---|---|
| Glycaemic agents | Insulin: hyperglycaemia (*Somogyi effect*)[70]<br>Antiglycaemics: paradoxical treatment-related neuropathy and retinopathy[124] |
| Steroid hormones | RU486: increased and reduced corpus luteal progesterone secretion[125]<br>Dexamethasone suppression: increased cortisol[126] |
| Thyroid agents | Iodine: hyperthyroidism (*Jod–Basedow effect*) or hypothyroidism[127,128]<br>Lithium: goitre, hypothyroidism, thyroiditis, and thyrotoxicosis[129] |
| Antihyperuricaemics | Xanthine oxidase inhibitors: gout flares[65,66]<br>Urate oxidases: gout flares[130] |
| Gastrointestinal system | Opioids: diarrhoea ('narcotic bowel syndrome')[42]<br>Cholecystokinin or ceruletide: increased sphincter of Oddi activity[131] |
| Haematological system | Erythropoietin: erythrocyte aplasia[132]<br>Vitamin K antagonists: hypercoagulability[57]<br>Platelet adenosine diphosphate receptor ($P2Y_{12}$) antagonists: systemic or intrarenal platelets aggregations (thrombotic thrombocytopenic purpura)[77] |
| Respiratory system | Short- and long-acting $\beta_2$-agonists: increased risk of COPD- and asthma-related death[133-135]<br>Oxygen: brain, pulmonary, myocardial, renal, and retinal damage, and increased neonatal mortality[136] |
| Skin | High-intensity long-wave ultraviolet light and 8-methoxypsoralen (PUVA): hypopigmentation[137]<br>Histamine$_1$-receptor antagonists: worsening idiopathic urticaria[138-140] |

**ACE** = angiotensin-converting enzyme; **COPD** = chronic obstructive pulmonary disease; **GHB** = gamma-hydroxybutyric acid; **TNFα** = tumour necrosis factor-α.

paper. The Compendium provides an extensive review of paradoxical and bidirectional clinical examples from diverse pharmacological classes (some of these are listed in table II). It also offers examples from clinical toxicology in which overdose and non-pharmacological exposures produce paradoxical or bidirectional effects, in which similar toxicological reactions are seen in xenobiotic overdose or withdrawal, and in which antidotes have paradoxical or bidirectional effects (e.g. those in table III).

## 3. Conclusions

Paradoxical and bidirectional xenobiotic reactions complicate the assessment of adverse

**Table III.** Some paradoxical and bidirectional drug effects in toxicology

| Toxicological considerations | Examples |
|---|---|
| Overdose with paradoxical or bidirectional effects | Antipsychotic drugs: hypothermia or hyperthermia[141]<br>Isoniazid: CNS excitation (seizures) or depression (coma)[142,143]<br>Methylxanthines, monoamine oxidase inhibitors, nicotine: hypertension or hypotension[144,145]<br>Salicylates: hyperthermia[146] |
| Non-pharmacological exposures with paradoxical or bidirectional effects | Carbon monoxide, hydrogen sulfide, carbon disulfide, hydrocarbons: agitation or sedation[147-152]<br>Organophosphorus pesticides: meiosis or mydriasis, bradycardia or tachycardia, and hypertension or hypotension[60]<br>PNU, alloxan: hypoglycaemia or hyperglycaemia[153] |
| Similar toxicity in overdose and withdrawal | Baclofen: seizures[154,155]<br>Opioids: pulmonary oedema[156-158]<br>Serotonin reuptake inhibitors: agitation and restlessness[159-161] |
| Antidotes with paradoxical or bidirectional effects | Dextrose: hypoglycaemia in sulfonylurea overdose[12,162]<br>Methylthioninium chloride: worsening methaemoglobinaemia[163,164]<br>Protamine sulfate: anticoagulation[165] |

**PNU** = (N-3 pyridylmethyl-N′-4 nitrophenyl urea, Vacor®).

reactions, pharmacovigilance, and clinical management. An appreciation of complex systems and systems-level properties provides a useful basis for understanding these reactions. Clinical acceptance of paradoxical reactions will depend on a benefit-harm assessment of their nature, type, and frequency, compared with the advantages of the drug. Overdose or non-pharmaceutical xenobiotic exposure may also impart a spectrum of paradoxical findings. Certain antidotes must be used carefully to avoid paradoxical detrimental reactions. We hope that the Compendium, for which we anticipate interval updates, will serve as a useful resource in basic and clinical pharmacology and toxicology.

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The use of trade names and/or commercial products in this review is for identification purposes only and constitutes neither a recommendation nor an endorsement for use by the authors, the New York University School of Medicine, the New York City Poison Control Center, New York Medical College, Brunel University, or the University of Oxford. Off-label uses of pharmaceuticals, xenobiotics, and antidotes are referred to in this review. This is for discussion purposes only and does not constitute endorsement of off-label use by the authors, the New York University School of Medicine, the New York City Poison Control Center, New York Medical College, Brunel University, or the University of Oxford.

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