Drug Safety

Paradoxical and Bidirectional Drug Effects

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Supplemental Digital Content

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1. Introduction

In this Compendium we provide a list of paradoxical and bidirectional drug effects. It is generally organized (with some exceptions) first by body system and then within each system by drug class, physiological locus, or phenotype. The paradoxical and bidirectional drug effects may be a therapeutic drug class effect or limited to individual drugs. We also report paradoxical or bidirectional effects in intentional or unintentional overdose, poisoning, and toxicological antidotes. We have included cases in which causality may or may not be firmly established. Where definitive possible mechanisms have been proposed or established, they are supplied. When examples have been used to portray particular paradoxical mechanisms in the corresponding manuscript, they are reproduced below, in order to provide a complete reference tool.

2. Examples in drug therapy

2.1. Antibacterial drugs and immunomodulators

2.1.1. Antibacterial drugs

(a) Beyond a certain concentration, the efficacy of antibiotics *in vitro* is reduced in diverse bacteria, fungi, and parasites. This effect, the *Eagle phenomenon*, has been demonstrated *in vivo* with penicillins and echinocandins.[1-3] Bacteriostatic antibiotics may paradoxically induce resistance to endogenous cationic antimicrobial peptides and immune clearance.[4]

(b) The *Jarisch-Herxheimer reaction* may follow chemotherapy for borreliosis, leptospirosis, Q fever, syphilis, mycobacterial infection, and tick- and louse-borne relapsing fever.[5-7] Release of endotoxin-like material from dying organisms and increased cytokines may produce fever,
rigors, hypotension, and worsening symptoms of the infection.

(c) Perceived antibiotic failure because of recurrent pyrexia due to an antibiotic (drug fever) and not an infection is described with sulfonamides, beta-lactams, vancomycin, and others.[8,9]

(d) Antibacterial drug therapy for gut infections may be complicated by altered flora and subsequent infection with Clostridium difficile.[10,11]

(e) Controversy surrounds antibiotic administration in enterohaemorrhagic E. coli infections (e.g. O157:H7) and salmonellosis. Although one meta-analysis did not confirm a risk, antibiotics (particularly below minimum inhibitory concentrations) may promote verocytotoxin production and release, and increase the infectious complications (haemolytic–uraemic syndrome).[12,13] Similar controversy surrounds salmonellosis; treatment might prolong faecal shedding and increase the risk of relapse without improving symptoms.[14]

(f) While highly active antiretroviral therapy (HAART) permits immunological recovery, immune reconstitution inflammatory syndrome (IRIS) may develop in Cryptococcus, Histoplasma, Mycobacterium, Pneumocystis, Toxoplasma and herpesvirus infections. IRIS, associated with better virological responsiveness, may cause new or worsening clinical or radiological disease.[15-17]

(g) An analogous “paradoxical reaction” has been described in immunocompetent patients without HIV infection with mycobacterial infections, despite effective antimycobacterial therapy.[18-20] CNS and pleural involvement may be pronounced, and new anatomical lesions may appear.[21]
2.1.2. *Immune and inflammatory modulators*

(a) **Systemic glucocorticosteroids** alleviate allergic reactions and reactive airway disease. However, they themselves may rarely cause life-threatening hypersensitivity with IgE antibodies highly specific for succinate moieties.[22,23]

(b) **Tumour necrosis factor-alpha (TNFα) antagonists** (infliximab, etanercept, and adalimumab) are normally withdrawn in patients with active tuberculosis, from concern for disease progression. On withdrawal, reconstituted TNF-dependent inflammation may lead to paradoxical clinical deterioration (worsening infiltrate), despite improved microbiological eradication.[18]

(c) **TNFα antagonists** may also cause paradoxical psoriaform lesions.[24-26] Therapy with other antipsoriasis agents, such as the purine analogue fludarabine, which induces profound and prolonged immunosuppression, may also worsen the disease.[27]

(d) **Immunosuppressants**, such as ciclosporin and tacrolimus, may paradoxically activate immune system components, including IgG.[28]

(e) In abdominopelvic operations, **bioabsorbable sodium hyaluronate and carboxymethylcellulose** mitigate adhesion formation; isolated, severe postoperative inflammatory reactions with extensive dense adhesions are reported.[29]

2.2. *Antineoplastic drugs and carcinogens*

(a) **Carcinogens** may produce a “J” or “U” shaped dose-response curve, and antineoplastic drugs may enhance tumour cells proliferation in low concentrations.[30]

(b) **Metals** may produce varied degrees of paradoxical responsiveness, depending on concentration, formulation, and premorbid state. For example, arsenic consumption in drinking water has been causatively linked to skin, bladder, and lung cancer,[31] but As$_2$O$_3$ is effective
therapy for acute promyelocytic leukaemia and other malignancies.[32]

c) “Radiation hormesis” is associated with unanticipated apparent benefit at low doses.[33]
Various adaptive responses, including enhanced detoxification and excretion, altered gene expression, cell cycling, DNA repair, apoptosis, and augmented immune functions, have been proposed to explain this.[34]

d) Radiation is also reported to induce malignant transformation in benign tumours, such as craniopharyngioma.[35]

e) Neoadjuvant chemotherapy for the purpose of symptomatic improvement from bulky disease may result in clinical deterioration from fibrosis and stricture, despite pathological and radiological evidence of reduced neoplastic burden.[36]

f) One confounding issue confronting treatment for glioblastoma is early radiographic disease progression following radiotherapy or chemoradiotherapy. This may represent pseudoprogression (due to tumour vascular injury, vasogenic edema, and treatment-related pro-inflammatory effects) or actual early disease progression.[37]

(g) Effective killing of primary neoplasms by radiation or chemotherapy also risks “bystander” mutagenesis. Second malignant neoplasms in childhood cancer survivors approaches 8% incidence at 30 years.[38]

2.3. Cardiovascular system

2.3.1. Antidysrhythmic drugs

(a) Ventricular antidysrhythmic drugs may be prodysrhythmic, worsening pre-existing dysrhythmias or inducing others. Since antidysrhythmic drugs function by suppressing automaticity or triggered activity, by prolonging the action potential, or by prolonging the
effective refractory period, it is not surprising that phase delay effects may occur, leading to ventricular dysrhythmias.\(^{[39]}\)

(b) Dysrhythmias may also occur in antidysrhythmic drugs that slow atrioventricular nodal conduction in patients with accessory pathways, favouring the alternative conduction conduit.

(c) Procainamide can also act as a pro-dysrhythmic via the class III (potassium channel) effects of the metabolite acecainide (\(N\)-acetylprocainamide), which may conflict with class Ia (sodium channel) antidysrhythmic effects of the parent, particularly in renal insufficiency.\(^{[40]}\)

(d) Cardiac glycosides (e.g. digoxin) restrain atrial tachydysrhythmias. Sodium-potassium pump inhibition leads to increased intracellular calcium concentrations. In excess, despite persistent atrioventricular conduction block, cardiac glycosides may promote atrial flutter development by shortening the atrial effective refractory period, and increased ventricular automaticity may cause multifocal ventricular excitability and dysrhythmias. Atrial fibrillation may occasionally worsen.\(^{[41]}\)

(e) Paradoxical inhibition in oscillatory systems – reduced excitability by excitatory stimulation – occurs when a stimulus falls earlier in a cycle, lengthening the oscillation period.\(^{[42]}\) While originally applied to neural systems, the same principle in autorhythmic cardiac cells underlies pharmacological treatment to gain control of torsades des pointes with infusions of the positive (excitatory) chronotrope isoprenaline (isoproterenol). Isoprenaline also has been utilized to induce idiopathic ventricular tachycardia intentionally.\(^{[43]}\)

### 2.3.2. Antihypertensive drugs and vasodilators

(a) The preload sensitivity of the right ventricle may result in standard, normally beneficial therapies for myocardial infarction (diuretics, nitrates, opioids, ACE inhibitors, and beta-
blockers), paradoxically worsening the clinical effects of right-sided myocardial infarction, leading to haemodynamic compromise.[44,45] However, in the appropriate patient, despite their impaired cardiac function by a negative inotropic effect in systole, beta-blockers may improve overall cardiac function via a lusitropic effect in diastole. Beta-adrenergic receptor antagonists with intrinsic sympathomimetic activity, despite their negative chronotropic and inotropic activity, provide peripheral vasoconstriction, and bronchoconstriction in low sympathetic states.[46] Partial beta-adrenoceptor receptor agonists (e.g. xamoterol) may act as functional agonists when sympathetic nervous system activity in low or as antagonists when activity is high.[47]

(b) Methyldopa, clonidine, guanabenz, and centrally-acting antihypertensive drugs with presynaptic $\alpha_2$-adrenoceptor agonist effects may produce early hypertension from peripheral effects; tachycardia and bradycardia are reported.[48]

(c) Other imidazoline I$_1$-receptors agonists such as moxonidine may produce similar early paradoxical hypertension, particularly in overdose.[49]

(d) Sodium nitroprusside produces rapid vasodilatation by nitric oxide release. During prolonged infusions or after nitroprusside breakdown with light exposure, the release of cyanide groups may produce thiocyanate or cyanide toxicity, inducing paradoxical refractory rises in blood and intracranial pressure.[50]

(e) Vasodilators prescribed for angina (or cardiac imaging) may inadvertently induce cardiac “steal” and angina. Dilating normal vessels diverts blood from less-responsive diseased coronary vasculature and reduces regional perfusion.[51,52]
(f) Papaverine hydrochloride, a direct smooth muscle vasodilator, has been used intra-arterially to treat cerebral vasospasm refractory to medical and surgical therapy. Intra-arterial papaverine may produce paradoxical recurrence or persistent and worsening vasospasm.

(g) Rare adverse effects were reported when bromocriptine was used to suppress post-partum lactation. Bromocriptine appeared to cause vasospasm, a paradoxical reaction, given its primary vasodilatory action.

(h) Thiazides provide paradoxical antidiuretic benefit in the treatment of diabetes insipidus. Theories include increased renal sodium excretion which causes extracellular volume contraction with subsequent lowered GFR and increased proximal tubular sodium and water reabsorption, as well as water resorption distal to the proximal tubule.

(i) Latanoprost, a prostaglandin F\textsubscript{2α} analogue, may paradoxical increased inflammatory factors and intraocular pressure despite normally reducing inflammatory ocular hypertension by improving uveoscleral outflow.

2.3.3. Drugs for congestive heart failure (CHF)

(a) Acute therapy for CHF is complicated by the detrimental acute and chronic effects of positive inotropic drugs aimed at improving cardiac output. For example, dobutamine may adversely increase myocardial oxygen consumption and cause dysrhythmias, worsening output and precipitating cardiac arrest.

(b) Nesiritide (recombinant B-type natriuretic peptide), introduced for acute CHF, was associated with bidirectional effects in glomerular filtration rate (GFR). Direct effects (afferent renal arteriole dilatation and efferent renal arteriole constriction, increasing intra-glomerular pressure and GFR) competed with indirect effects (lowered systemic blood pressure, reducing renal blood
(c) Hypotension is a predictor of poor prognosis in patients with CHF. However, medications that lower blood pressure or impair cardiac output (ACE inhibitors, angiotensin II receptor antagonists, hydralazine, and beta-blockers) may have bidirectional effects on blood pressure and improve morbidity and mortality. For example, in the CHARM study, angiotensin II receptor antagonists increased baseline blood pressures below 100 mmHg, an effect that was reversed above 100 mmHg.

(d) While hydrochlorothiazide is used to mitigate fluid overload in CHF, pulmonary oedema may complicate therapy. The effect occurs predominantly in women, and an immune aetiology is thought to underlie intrapulmonary sequestration of leukocytes and acute lung injury.

2.3.4. Lipid-modifying drugs

(a) Therapy with fibrates (bezafibrate, ciprofibrate, and fenofibrate) has been associated with adverse effects on lipid profiles, particularly lowered HDL cholesterol.

(b) In a prematurely terminated trial, ezetimibe not only reduced high-density lipoprotein cholesterol, but also paradoxical increased carotid intima-media thickness. Hyperlipidaemia was also reported.

2.3.5. Inotropes and chronotropes

(a) The relative contributions of cardiac and peripheral non-selective beta₁ and beta₂ adrenoceptor agonism on heart rate, stroke volume, and systemic vascular resistance, as well as various systemic baroreflex functions, may cause the blood pressure to rise, fall, or stay the same. For example, isoprenaline produces paradoxical bradycardia in up to 7% of patients.
(b) **Epinephrine** (adrenaline) administration under rare circumstances may cause hypotension.\[^{70}\]

(c) **Terbutaline** is normally used for tocolysis and to facilitate external cephalic version, although beta-adrenoceptor agonists inhibit myometrial contraction; rare cases of paradoxical maternal hypertonus have occurred.\[^{71}\]

(d) **Beta-blockers** and **calcium channel blockers** may reduce cardiac output, decreasing rate or stroke volume. However, in hypertrophic cardiomyopathy, prolonged diastolic filling time reduces left ventricular outflow gradients and improves overall myocardial performance, including cardiac output.\[^{72}\]

(e) Opposite effects are seen with use of **digoxin** and other inotropes in hypertrophic cardiomyopathy. Augmented contractility produces dynamic increases in left ventricular outflow obstruction and reduced cardiac output.\[^{73,74}\]

(f) **Atropine** is generally avoided in the treatment of bradycardia in heart transplant patients due to donor heart denervation. However, dose-independent paradoxical bradycardia, atrioventricular block or sinus arrest are described.\[^{75}\] Explanations based on muscarinic receptor subtype expression and responsiveness remain hypothetical.

### 2.3.6. Vasoconstrictors

(a) In shock, **peripheral vasoconstrictors** are used to remedy inadequate blood pressure (a surrogate for perfusion). In certain shock states vasoconstrictors increase vascular tone but reduce cardiac output and regional blood flow, especially in cutaneous, splanchnic, and renal beds.\[^{76}\]
(b) Drug-mediated *peripheral vasoconstriction* may produce reflex bradycardia and reduced blood pressure, owing to the linked contributions of heart rate, stroke volume, and systemic vascular resistance.\cite{77,78}

(c) Paradoxical hypotension has been reported with *vasopressin* in the treatment of variceal bleeding.\cite{79}

(d) The vasoconstrictive properties of *ergot alkaloids* (*methylergonovine* and *dihydroergotamine*), serotonin receptor agonists, are exploited therapeutically in migraines.\cite{80} Depending on dose and pre-existing vascular tone, vasoconstriction or vasodilatation may occur.\cite{81}

(e) Acetylcholine affects vessel tone through vessel wall interactions and dilates normal blood vessels by releasing nitric oxide. Paradoxical vasoconstriction is induced in vessels denuded of endothelium and in atherosclerotic, angiographically abnormal coronary arteries.\cite{82}

2.4. Nervous system

2.4.1. Anaesthetics

(a) *Anaesthetics* disrupt memory formation, wakefulness, pain sensation and responses, and autonomic stability, while altering neuronal excitability, synaptic transmission, synchrony, and burst phenomena. These complex interactions underlie the apparent paradox depicted in classical anaesthesia constructs – excitation and central nervous system (CNS) stimulation in several “anaesthetic stages” before surgical (“stage III”) anaesthesia.\cite{83} Excitatory activity and EEG excitatory findings are also seen during emergence. Age and the particular anaesthetic agent play a role (e.g. relatively frequent emergence agitation in children given sevoflurane).\cite{84}
(b) Beyond central effects, **inhaled anaesthetics** may activate peripheral nociceptors and produce hyperalgesia.[85]

(c) Mirroring the actions of inhalational anaesthetics, **phencyclidine** produces a continuum of CNS effects from psychomotor depression (coma, catatonia, or stupor) to psychomotor excitement (agitation or combative/psychotic behaviour).[86]

(d) **Ketamine**, another NMDA receptor antagonist, and **propofol**, an NMDA antagonist and GABA<sub>A</sub> agonist, are commonly used in surgical or radiological procedures requiring sedation. Agitation has been described during both induction and recovery with these agents.[87]

(e) As an adjuvant therapy in patients with brain injury, **ketamine** has been considered both a neuroprotectant and a neurotoxin.[88]

2.4.2. **Antiepileptic drugs**

(a) **Antiepileptic drugs** suppress seizures by assorted mechanisms, including GABA channel agonism (benzodiazepines and barbiturates), increased GABA effects by inhibition of uptake (tiagabine) or catabolism (vigabatrin), inactivation of sodium channels (hydantoins), and inhibition of T-type Ca<sup>2+</sup> channels ( ethosuximide). Despite appropriate target serum concentrations, many antiepileptics have reportedly exacerbated existing seizure disorders or triggered new seizure types.[89-91] Various explanations include drug toxicity due to sedation or sleep impairment, drug-induced encephalopathy, inappropriate anticonvulsant choice, and inverse pharmacodynamic effects.[92]
2.4.3. Hypnosedatives

(a) This structurally diverse group includes anticholinergic drugs, antihistamines, antispasmodics, barbiturates, benzodiazepines, bromides, chloral hydrate, ethanol, gamma-hydroxybutyric acid (GHB), non-benzodiazepine hypnotics ( zaleplon, zolpidem, and zopiclone), and opioids. Orexinergic neurons around the perifornical and lateral hypothalamus, histaminergic cells in the tuberomammillary nucleus, noradrenergic cells in the locus caeruleus, serotonergic cells in the dorsal raphe nucleus, and cholinergic mesopontine neurons in the lateral dorsal tegmentum and pedunculopontine tegmentum contribute to arousal pathways in the hypothalamus and brainstem.\(^{[93]}\) Monoaminergic, orexinergic, and cholinergic neurons are most active during wakefulness, but have different activities during REM and non-REM sleep. Hypnosedative interference with these components may tilt the balance towards arousal or sedation.

(b) Drugs with anticholinergic effects ( atropine and hyoscine, cyclic antidepressants and antipsychotics) may have sedative or stimulant properties.\(^{[94]}\) Agitation, motor hyper-reactivity, sedation, and coma are seen in overdose.\(^{[95]}\)

(c) When antihistamines (including phenothiazine derivatives) have been used as hypnotics, a similar spectrum of sedation and paradoxical excitation is seen in adults and children – from somnolence, sedation, and coma to agitation, tremor, and convulsions.\(^{[96-98]}\)

(d) Short-acting barbiturates (e.g. methohexital) facilitate procedures, particularly in children.\(^{[99]}\) Methohexital’s paradoxical epileptogenic properties are used clinically to determine seizure foci by surface EEG and during intracarotid administration for evaluation of cerebral functional localization (Wada testing).\(^{[100]}\)
(e) Chloral hydrate may cause similar paradoxical excitation; one study reported excitement in 18% of children.\(^{[101,102]}\)

(f) Benzodiazepines are commonly used for anxiolysis, hypnosis, and procedural sedation. Several studies report adverse stimulatory reactions, including excitation, myoclonus, hallucinations, and aggressive and violent behaviour, which may persist for days because of active metabolites.\(^{[99,103]}\)

(g) The paradoxical stimulatory effects induced by some benzodiazepines, particularly midazolam, do not respond well to additional drug; stimulation may be mitigated by alternative agents or reversed by the benzodiazepine receptor antagonist flumazenil.\(^{[104,105]}\) Flumazenil, when used inappropriately in benzodiazepine-tolerant individuals, may provoke seizures.

(h) Ethanol may produce excitation and subsequent sedation. Owing to acute tolerance, ethanol potentially causes two differential states at identical concentrations, depending upon the position on the ascending or descending limb of the time versus blood alcohol concentration curve (the Mellanby effect).\(^{[106]}\)

(i) Ethanol has unrelated hormetic effects on the cardiovascular disease risk (“J-shaped curve”).\(^{[107]}\)

(j) The spectrum of intoxication by GHB and precursors undergoing \textit{in vivo} conversion (\textit{gamma}-butyrolactone and 1,4-butanediol) mirrors that from ethanol. Aggression, combative behaviour, and seizures, as well as bradycardia, respiratory depression, and coma are reported.\(^{[108]}\)

(k) Opioids normally cause CNS and respiratory depression, analgesia, and sedation. Certain opioids (pentazocine, propoxyphene, tramadol) or opioid metabolites (norpethidine) have a propensity for paradoxical neuropsychiatric excitation (including seizures) by sodium channel antagonism, serotonin receptor agonism, or other mechanisms.\(^{[109]}\)
(l) Some CYP2D6 isoforms metabolize codeine, hydrocodone, and oxycodone to morphine and derivatives at an “ultrarapid” rate, causing hypervigilance, anxiety, and insomnia.\cite{110}

(m) Opioid-induced hyperalgesia is increasingly recognized to complicate pain management. Paradoxical increases in pain sensitivity result from various proposed compensatory factors (NMDA receptor activation, increased spinal dynorphin content, spinal release of excitatory neuropeptides, and tonic activation of descending pain modulatory systems) and are additional to physiological dependence and tolerance.\cite{111,112} This paradoxical hyperalgesia may occur with agents with only partial agonist activity such as buprenorphine.\cite{113} To preclude opioid-induced hyperalgesia, ultra-low-dose opioid antagonists (naloxone and naltrexone) are used to preclude the loss of opioid potency and reverse hyperalgesia.\cite{114,115}

(n) Analgesia for chronic headache includes treatment with ergot alkaloids, triptans, opioids, non-steroidal anti-inflammatory drugs, and combination products, which may include paracetamol, caffeine, or barbiturates. Frequent headaches may predispose patients to medication-overuse headache. Treatment of this disorder paradoxically involves complete weaning from overused medications.\cite{116}

2.4.4. Psychotropic drugs

(a) In 2007 after reports of increased risks of suicidality, the FDA required a “black box warning” for over thirty antidepressants from diverse drug classes. This increased suicide risk appeared associated with emerging from profound neurovegetative impairment early in therapy.\cite{117}

(b) Antidepressant use has been associated with bidirectional metabolic disturbances (hypo- and hyperglycaemia),\cite{118} and autonomic dysfunction (hypertension and hypotension).\cite{119}
(c) Antipsychotic drugs are reported to paradoxically exacerbate psychotic symptoms, particularly in cases of dementia or Parkinson’s disease.\[120\]

(d) Levetiracetam, when used in bipolar disorder, produces stimulating positive or negative behavioural effects (enhanced energy, vigilance, and psychomotor activity versus loss of self-control, sleep disturbances, and aggression).\[121\]

(e) Attention deficit hyperactivity disorder (ADHD) causes inattention and hyperactivity in children and symptoms such as restlessness in adults. Stimulants such as methylphenidate and amphetamines increase the physiological effects of norepinephrine (noradrenaline) and/or dopamine and promote reduced motor activity and restlessness. Reversal of typical amphetamine sequelae (e.g. pupillary constriction) has been reported.\[122\] Clonidine has been used synergistically with methylphenidate to provide better control of ADHD, although some patients experience significantly worse symptoms, which resolve after clonidine withdrawal.\[123\]

(f) According to the Yerkes–Dodson Law, learning follows a U-shaped response to stress or motivational stimulation.\[124\] Some degree of stimulus improves learning; too much is counterproductive. As task difficulty increases, the optimal amount of stress or motivational stimulation decreases. Although data are conflicting, “performance enhancers” such as caffeine improve cognitive and motor performances at low doses but impair it or have no effect at higher doses.\[125-129\] The response of cognitive function to glucocorticoids is similarly bidirectionally U-shaped.

2.4.5. Peripheral nervous system

(a) The depolarizing neuromuscular blockers (e.g. suxamethonium), despite nicotinic neuromuscular receptor agonism, ultimately produce muscle paralysis by inactivating voltage-
gated sodium channels via desensitization block. Excess acetylcholine from organophosphorous or carbamate exposures may produce similar fasciculations followed by paralysis.\cite{130}

(b) Acetylcholinesterase inhibitors may produce competing parasympathetic and sympathetic effects in various systems, depending on relative contributions. This provides the rational basis for the use of acetylcholinesterase inhibitors in disorders of ganglionic synaptic transmission.\cite{131}

(c) Edrophonium, despite increasing parasympathetic nervous activity, has been can by used diagnostically to elicit ventricular tachycardia resistant to other induction methods.\cite{132}

(d) Despite agonism at transient receptor potential vanilloid 1 (TRPV1), the principal nociception transduction channel, capsaicin formulations are used to treat painful neuropathic conditions, such as postherpetic neuralgia. Increased sensitivity and increased pain sensation (sometimes requiring systemic analgesia) is ultimately followed by reduced TRPV1 expression as well as potential neurolysis of epidermal nerve fibers, providing relief.\cite{133}

2.4.6. Movement disorders

(a) Deep brain stimulation (DBS) or brain lesioning paradoxically improve the opposite pathologies of dystonia, levodopa-induced tardive dyskinesia, and parkinsonism.\cite{134} In dystonias, decreased tonic inhibition of the thalamus by the globus pallidus interna (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. Dopaminergic agents such as levodopa, dopamine receptor agonists, catechol-O-methyl transferase inhibitors, and monoamine oxidase type B inhibitors can all produce similar various motor dyskinesias.\cite{135}
(b) In contrast, dopamine receptor agonists such as apomorphine may result in profound akinesia;\textsuperscript{[136]} MK-458 (a D\textsubscript{2} receptor agonist) produced paradoxical gait freezing.\textsuperscript{[137]}

2.5. Endocrine system and metabolism

2.5.1. Acid-base physiology

(a) While exogenous sodium lactate normally would be expected to be converted to bicarbonate, in hepatorenal syndromes, metabolic acidaemia can paradoxically develop in patients provided lactate-buffered solutions.\textsuperscript{[138]} In these ill patients the liver is thought to shift from a net lactate consumer to an exporter due to hepatocyte hypoxia.

(b) Conversely, when used to promote alkalinization in severe acidaemia, exogenous bicarbonate reacts with acid to form water and large amounts of CO\textsubscript{2}. CO\textsubscript{2} has the capacity to diffuse intracellularly, whereupon reaction with intracellular water generates protons, producing paradoxical intracellular acidosis.\textsuperscript{[139]}

2.5.2. Bone metabolism agents

(a) Osteoclasts resorb bone and osteoblasts produce osteoid, which calcifies to form new bone. Parathyroid hormone (PTH) produces opposite effects, depending on the time course of administration: net bone loss (resorption) when provided continuously and net bone formation (deposition) when administered intermittently.\textsuperscript{[140]} PTH stimulates differentiation of mesenchymal stem cells to preosteoblasts, which ultimately become osteoblasts. PTH receptors on osteoblasts induce IL-6 production, which stimulates the production of osteoclasts and results in increased bone resorption during continuous PTH administration.
(b) Single annual high-dose oral colecitferol (vitamin D₃) worsens outcomes and increases the risk of falls and fractures.¹⁴¹

(c) Bisphosphonates treat osteoporosis and hypercalcaemia by inducing osteoclast apoptosis. Paradoxically, bisphosphonates may increase the prevalence of femoral fractures and produce osteonecrosis, particularly in the jaw.¹⁴²,¹⁴³ Proposed mechanisms are reduced bone resorption, bone turnover, and bone remodelling, promoting skeletal fragility.

(d) Fluoride is a bidirectional osteoblast mitogen – stimulating at low doses (enhancing growth, mineralization, and bone strength) and inhibitory at higher doses (poorly mineralized and mechanically defective bone).¹⁴⁴,¹⁴⁵ Fluoride incorporation hardens enamel to protect teeth from acid, dental caries, and demineralization. However, fluoride ingestion in the critical period before dental eruption is also associated with dental fluorosis, (mottled, pitted, and potentially damaged enamel), from replacement of hydroxyapatite by fluoroapatite.¹⁴⁶

2.5.3. Electrolytes

(a) Hypokalaemia is associated with respiratory muscle weakness, paralysis, and myocardial hyper-excitability, which may cause dysrhythmias. Excessively rapid correction of hypokalaemia with intravenous potassium chloride (KCl) risks respiratory paralysis, dysrhythmias, and cardiac arrest. Undiluted KCl may be instantaneously fatal. The R(–) isomer of salbutamol causes hypokalaemia by stimulating the Na+/K+ pump, while its S(+) isomer may cause hyperkalaemia.¹⁴⁷ Significant hypomagnesaemia produces respiratory muscle weakness, paralysis, and dysrhythmias. Excessively rapid correction with intravenous magnesium sulfate risks respiratory paralysis and dysrhythmias.
(b) While hypermagnesaemia following excess magnesium hydroxide ingestion is expected, laxative effects which promote diarrhea with excessive magnesium loss may induce paradoxical hypomagnesaemia.[148]

(c) Both hyponatraemia and hypernatraemia can cause seizures, altered consciousness, and coma. Reversing these effects involves hypertonic saline or solute-free water administration. However, central pontine and extrapontine myelinolysis complicate aggressive treatment of hyponatremia, producing encephalopathy or coma.[149] Rapid correction of hypernatraemia may cause cerebral oedema, associated seizures, as well as myelinolysis.[150]

(d) Hypertonic saline administration may increase sodium delivery to the loop of Henle. Enhanced renal tubular water reabsorption promotes persistent paradoxical hyponatraemia that resolves upon discontinuation of hypertonic saline.[151]

2.5.4. Glycaemic agents

(a) Fasting hyperglycaemia may paradoxically follow a period of nocturnal hypoglycaemia due to hyperinsulinaemia (Somogyi effect). The Somogyi effect is thought to be induced by counter-regulatory hormones that rapidly mobilize hepatic glucose stores and reduce peripheral insulin sensitivity.[152] Treating the morning hyperglycaemia with escalating evening insulin might prove harmful.

(b) Both hypoglycaemia and hyperglycaemia are associated with fluoroquinolones; gatifloxacin was withdrawn for this reason. Hypoglycaemia is presumed to occur by inhibition of ATP-sensitive potassium channels; secretion of histamine and adrenaline mediates hyperglycaemia.[153]

(c) Pentamidine may cause cytolytic pancreatic beta cell insulin release, leading to
hypoglycaemia, which may be followed by subsequent hyperglycaemia.[154]

(d) Streptozocin produces a triphasic response in experimental models. Initial hyperglycaemia with low insulin concentrations is followed within hours by severe hypoglycaemia with high insulin concentrations due to massive beta-cell necrosis. Pancreatic destruction may cause chronic, sometimes permanent, hyperglycaemia.[155]

(e) Normalization of blood sugar would be anticipated to mitigate or improve long-term tissue damage in diabetes. However, rapid correction in chronic hyperglycaemia may provoke or exacerbate neuropathy and retinopathy, possibly due to hypoglycaemic axonal degeneration or impaired perfusion.[156]

2.5.5. Steroid hormones

(a) Continuous provision of oestrogen and/or progesterone suppresses ovulation. In a time dependent fashion, oestrogens stimulate pituitary luteinizing hormone (LH) release, which triggers ovulation and increased progesterone concentrations to promote implantation. Continued oestrogens exposure in oral contraceptives or post-coital provision suppresses follicle-stimulating hormone (FSH) and LH surges and hinders ovulation/implantation. Luteinizing hormone-releasing hormone analogues are being explored for similar counter-fertility effects.[157]

(b) Other hormones, such as the progesterone receptor antagonist RU486, may both increase and reduce corpus luteal progesterone secretion.[158]

(c) The dexamethasone suppression test may produce paradoxical increases in cortisol in patients with Cushing’s syndrome.[159] In the primary pigmented nodular adrenocortical disease variant, it does so via glucocorticoid receptor-mediated effects on protein kinase A catalytic subunits.[160]
2.5.6. Thyroid agents

(a) Hypothyroidism due to iodine deficiency is treated with iodine. In a protective mechanism, the Wolff–Chaikoff effect, intracellular iodine inhibits the first step in thyroid hormone biosynthesis (incorporation into thyroglobulin).\textsuperscript{[161]} In paradoxical iodine-induced hyperthyroidism (the Jod–Basedow effect), this protective block does not occur, and subsequent excess thyroid hormone is produced. Other iodine-containing substances may do this (contrast dyes and amiodarone).\textsuperscript{[162]} Iodine excess may also cause hypothyroidism, generally in states that predispose to persistent iodine uptake, which prevents escape from the Wolff–Chaikoff effect.\textsuperscript{[161]}

(b) Amiodarone may cause either hypo- or hyperthyroidism because of multiple competing effects, which include the Jod–Basedow effect, blockade of thyroid hormone entry into cells, inhibition of type 1 and type 2 5'-deiodinase, reduced T3 binding to its receptors, thyroid cytotoxicity, and potentiation of thyroid autoimmunity.\textsuperscript{[163]} Non-autoimmune hyperthyroidism is more frequent in the setting of iodine deficiency.

(c) Radioactive iodine (\textsuperscript{131}I) to treat goitre has similarly caused paradoxical hyperthyroidism, presumably via \textsuperscript{131}I-induced release of TSH-receptor antigens and subsequent induction of anti-TSH receptor antibodies.\textsuperscript{[164]}

(d) Lithium inhibits thyroid hormone release and commonly causes goitre and hypothyroidism; long-term lithium therapy may worsen pre-existing autoimmune thyroid disease and may also induce a destructive granulomatous thyroiditis and thyrotoxicosis.\textsuperscript{[165]}
2.5.7. Antihyperuricaemics

(a) Xanthine oxidase inhibitors (allopurinol and febuxostat), which inhibit intracellular uric acid production and provide later gout prevention, may precipitate gout flares early in therapy.[166] Flares may occur even when administered after a gout attack has subsided. Greater serum uric acid reductions were correlated with an increased flare risk in one study.[166] Mechanisms may involve urate mobilization from tissue deposits, fluctuating serum uric acid concentrations, altered uric acid transport, or activation of previously precipitated urate crystals.[166-168] Rasburicase (recombinant urate oxidase) and pegloticase (PEGylated urate oxidase), which catalyse the conversion of urate to allantoin, are used to prevent and treat tumour lysis syndrome; in refractory gout, they too have induced paradoxical gout flares.[169]

2.6. Gastrointestinal system

(a) Opioids are normally constipating. In “narcotic bowel syndrome” chronic use leads to paradoxical diarrhoea, which improves upon narcotic withdrawal.[170] Overflow diarrhoea may also occur in narcotic bowel dysfunction due to mechanical faecal impaction.[171]

(b) In patients with biliary dyskinesia, intravenous injection of cholecystokinin or ceruletide reduces the pressure in the sphincter of Oddi. A paradoxical increase in sphincter activity may occur, in which case interventions such as papillotomy or balloon dilatation may be therapeutic.[172]

(c) In infectious diarrhoea antimitotility agents such as diphenoxylate/atropine may worsen or prolong illness and faecal shedding.[173]
(d) **Cannabinoids** (dronabinol, marijuana) are sometimes employed for relief of nausea and emesis. However, persistent use can induce a cyclical vomiting syndrome (cannabinoid hyperemesis), which resolves upon cannabinoid discontinuation.\[^{174}\]

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2.7. Haematological system

(a) **Vitamin K antagonists** may produce 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.\[^{175}\]

(b) In **heparin-induced thrombocytopenia type II**, heparin-platelet factor 4 IgG antibodies may trigger platelet aggregation and thrombus formation; thromboembolism occurs despite thrombocytopenia.\[^{176}\]

(c) In the “thrombin paradox”, **thrombolytic drugs** (streptokinase and to a lesser extent alteplase and retesplase) induce plasmin activation, subsequent thrombin activation, and procoagulant effects by plasmin-mediated activation of the contact system (kallikrein/factor XII).\[^{177}\] Life- or limb-threatening thrombotic thrombosis may occur.\[^{178}\]

(d) The platelet adenosine diphosphate receptor (P2Y\(_{12}\)) antagonists ticlopidine, clopidogrel, and prasugrel reduce platelet aggregation and arterial thrombosis. All have been reported to cause thrombotic thrombocytopenic purpura (systemic or intrarenal platelets aggregations causing thrombocytopenia and erythrocyte damage), with varying frequency.\[^{179,180}\] In many cases this is due to antibody-mediated ADAMTS13 deficiency.

(e) **Aspirin** reduces adverse coronary, neurological, and peripheral vascular conditions. Its paradoxical effect on bleeding time reflects competing effects of arachidonic acid metabolites. Vascular endothelium-derived prostaeyclin (PGL\(_{2}\)) inhibits platelet aggregation; platelet-derived
thromboxane A2 (TXA₂) promotes it. Inhibition of cyclo-oxygenase by aspirin prevents TXA₂-mediated platelet aggregation, but PGI₂ inhibition is prothrombotic. These effects are time-dependent. Platelet inhibition is permanent; endothelial PGI₂ production recovers.[181,182] In animals high-dose aspirin causes greater platelet deposition on vein grafts than low-dose aspirin, perhaps because of the secondary unintended adverse effect of reducing vessel wall PGI₂.[183]

(f) Diclofenac and flurbiprofen similarly increase platelet adhesion in a non-linear dose-dependent fashion.[184]

(g) Glycoprotein IIb-IIIa inhibitors (abciximab, eptifibatide, and tirofiban) are used in acute coronary syndromes to inhibit platelet aggregation. In certain individuals, paradoxical platelet activation and aggregation are reported[185], this may promote glycoprotein IIb/IIIa inhibitor-induced thrombocytopenia.

(h) Anaemia in patients with chronic kidney disease is treated with agents that stimulate erythropoiesis (epoetin alfa, methoxypolyethylene glycol-epoetin beta, and darbepoetin alfa). Erythropoietin reportedly caused paradoxical, rapid-onset erythrocyte aplasia due to production of antibodies that inhibited erythroid-colony formation.[186] The incidence fell after storage, handling, packaging, and formulation changes. Separately, it was anticipated that additional haemoglobin would reduce transfusion requirements and improve cardiovascular endpoints and survival, specifically in those with comorbid conditions, such as CHF. However, epoetins were linked with adverse thrombotic events, particularly at higher target haemoglobin concentrations (>13 g/dL).[187]

(i) At sufficiently high concentrations, the chelator deferiprone forms a stable, water-soluble 3:1 complex with ferric iron and has antioxidant activity. Lower concentrations generate incomplete
1:1 and 1:2 chelator-iron complexes, with unoccupied coordination sites that can paradoxically catalyze the formation of hydroxyl radicals and other reactive oxygen species. [188]

2.8. Respiratory system

(a) Short-acting beta₂ adrenoceptor agonists (SABAs) relieve exacerbations of reactive airway disease. SABAs or additives in the nebulizer solutions (e.g. disodium edetate) may cause paradoxical laryngospasm, worsening bronchoconstriction, and increased airway responsiveness. [189,190] Long-acting beta₂-agonists (LABAs) improve control of asthma symptoms and severe exacerbations. SABA and LABA monotherapy has been associated with an increased risk of COPD- and asthma-related death. [191-193] LABA monotherapy may increase the concentrations of brain-derived neurotrophic factor, which increases airway hyperresponsiveness and is inhibited by inhaled glucocorticoid co-therapy. [190]

(b) In severe asthma, volatile anaesthetics are sometimes used for bronchodilatation. However, on activation of the excitatory transient receptor potential-A1 ion channel, neurogenic bronchoconstriction, a severe cough reflex, and laryngospasm may occur. [85]

(c) Mucolytic cysteine derivatives (acetylcysteine, carbocysteine) have been prescribed as therapy for acute respiratory tract infections such as bronchitis, bronchiolitis, or productive cough. Marketing approval was withdrawn in several countries following reports of paradoxical respiratory distress and worsening respiratory symptoms, including bronchorrhea, dyspnoea, and cough aggravation, theorized to occur because of increased bronchial mucus flow induced by mucolytic drugs. [194]

(d) Persistent use of nasal decongestants with or without a preservatives has long been recognized to produce worsening symptoms (rhinitis medicamentosa). [195,196]
(e) High oxygen concentrations were once used to resuscitate neonates with birth asphyxia, in the belief that neurocardiopulmonary response and outcomes would improve. They are paradoxically detrimental, increasing oxidative stress; brain, pulmonary, myocardial, renal, and retinal damage; and neonatal mortality.[197] Similarly, adults undergoing resuscitation are given high oxygen concentrations to ensure oxygen delivery and minimize potentiating anoxic injury. However, in adults with non-traumatic cardiac arrest, hyperoxia was associated with a significantly higher in-hospital mortality than either normoxia or hypoxia.[198]

2.9. Skin

(a) Phototherapy with high-intensity long-wave ultraviolet light and 8-methoxypsoralen (PUVA) stimulates melanogenesis, produces diffuse tanning of normal skin, and has been used to treat vitiligo. The use of PUVA for mycosis fungoides and psoriasis has produced paradoxical hypopigmentation, histologically identical to vitiligo.[199]

(b) Urticaria and allergic dermatoses are treated with histamine (H₁) receptor antagonists. However, dimenhydrinate, diphenhydramine, cetirizine, hydroxyzine, levocetirizine, and loratadine have been associated with worsening of pre-existing idiopathic urticaria.[200-204]

(c) While mild cleansing is generally recommended for acne, excessive mechanical or chemical cleaning may worsen the clinical picture. Acne treatment with isotretinoin may occasionally produce clinical worsening and progression to acne fulminans, requiring systemic glucocorticoids.[205]
3. Examples in toxicology

3.1. Overdose

Intentional or unintentional overdose may magnify the spectrum of atypical outcomes. Overdose may overextend systems to collapse, and absorption may be significantly altered.\textsuperscript{[206,207]}

(a) Poisoning with \textit{monoamine oxidase inhibitors} produces hypertension, followed by profound hypotension when monoaminergic neurotransmitters are depleted.\textsuperscript{[208]}

(b) Similarly, methylxanthine (\textit{caffeine}, \textit{theophylline}, and \textit{theobromine}) toxicity may cause hypertension and subsequent hypotension.\textsuperscript{[209,210]}

(c) \textit{Nicotine} poisoning may cause a range of bidirectional signs, owing to competing ganglionic effects at nicotinic- type acetylcholine receptors (nAChRs) as well as the time course of the ingestion. Thus, miosis or mydriasis, bradycardia or tachycardia, hypertension or hypotension, tachypnoea or bradypnoea, and CNS sedation or agitation are reported following acute exposure.\textsuperscript{[211]}

(d) Seizures or coma are described in \textit{isoniazid} overdose.\textsuperscript{[212,213]}

(e) Centrally-acting agents such as \textit{lithium} may cause sedation or agitation.\textsuperscript{[214,215]}

(f) \textit{Salicylate} antipyretics may cause hyperthermia by uncoupling cellular respiration.\textsuperscript{[216]}

(g) \textit{Local anaesthetics} may cause CNS agitation and seizures by inhibiting inhibitory systems.\textsuperscript{[217]}

(h) \textit{Antipsychotic drugs} may cause hypothermia (via 5-HT\textsubscript{2a}, alpha\textsubscript{2}-adrenergic receptor, and other effects) or hyperthermia (neuroleptic malignant syndrome from excess dopaminergic antagonism).\textsuperscript{[218]}

(i) \textit{Ethanol} and \textit{general anaesthesia} may render humans poikilothermic; body temperature depends upon ambient environmental temperature.\textsuperscript{[219]}
3.2. Non-pharmacological exposures

Non-therapeutic xenobiotics may produce paradoxical or bidirectional effects.

(a) Organophosphorous pesticides may induce miosis or mydriasis, bradycardia or tachycardia, and hypertension or hypotension, depending upon sympathetic and parasympathetic contributions.[220]

(b) Exposure to carbon monoxide,[221,222] hydrogen sulfide,[223] carbon disulfide,[224] and hydrocarbons[225,226] may cause agitation or sedation.

(c) The rodenticide PNU (N-3 pyridylmethyl-N'-4 nitrophenyl urea, Vacor®) and alloxan, like pentamidine and streptozocin, are cytotoxic to pancreatic beta cells and have been associated with hypoglycaemia and hyperglycaemia.[227]

(d) Ciguatera fish poisoning produces a typical temperature dysaesthesia (hot and cold temperature sensation reversal), presumably due to excess voltage-gated sodium channel activity (binding site 5).[228,229]

(e) Veratrum alkaloids also bind voltage-gated sodium channels (at site 2), prolonging depolarization. Veratrum alkaloids were historically utilized to treat both CHF to improve cardiac output and as antihypertensives.[230,231] A stimulant effect on unmyelinated vagus afferent branches evokes the cardioinhibitory Bezold–Jarisch reflex, characterized by bradycardia, hypotension, and vasodilatation.[232] Severe decreases in cardiac output are reported both in therapeutic use and unintentional ingestion.[231,233] Site 2 sodium channel binding by grayanotoxins in Azalea, Kalmia, and Rhododendron species produces hypotension by a similar mechanism, although hypertension is rarely reported.[234]
(f) Other site 2 toxins such as *Aconitum* alkaloids were prescribed as cardiac stimulants in traditional Chinese Medicine for thousands of years due to their positive inotropy by prolonging sodium influx.\(^{[235-237]}\) Both prodysrhythmic and antidysrhythmic effects of *Aconitum* alkaloids are described.\(^{[238]}\) A narrow therapeutic window limits their use, as paradoxical negative inotropy occurs due to persistently impaired repolarization of sodium channels, which then become refractory to excitation, producing shock, or by induction of malignant dysrhythmias.\(^{[236]}\)

(g) *Datura* species and *Atropa belladonna* may produce the spectrum of paradoxical CNS effects seen with therapeutic anticholinergic drugs (see above).

3.3. Toxicity in overdose and drug withdrawal

Some xenobiotics produce similar reactions in excess or upon withdrawal.

(a) In the dyspnoeic patient with myasthenia and diaphragmatic weakness, the clinician must distinguish between cholinergic crisis (excess acetylcholinesterase inhibition) and myasthenic crisis (insufficient medication).\(^{[239]}\)

(b) Osler’s descriptions of opioid overdose-associated pulmonary oedema\(^{[240]}\) were later substantiated by clinical and forensic work.\(^{[241,242]}\) Inappropriate administration of opioid reversal agents to tolerant individuals (precipitated withdrawal) may also produce pulmonary oedema. The risk is minimized by ensuring normocapnia and titrating the reversal dose so as not to induce a catecholamine surge associated acute lung injury.\(^{[243]}\)

(c) The GABA\(_B\) receptor agonist baclofen produces seizures in overdose.\(^{[244]}\) After the development of tolerance, baclofen withdrawal produces seizures.\(^{[245]}\) Other hypnosedatives also cause neuronal excitation, agitation, aggression, and seizures in intoxication. These symptoms can also occur during withdrawal.
(d) In addition to akathisia and various movement disorders, acute cocaine intoxication can cause dystonias.[246,247] This effect is also described during cocaine withdrawal.[248] Restlessness and agitation can feature in both serotonin syndrome (serotonin toxicity) and after withdrawal of selective serotonin- or serotonin-norepinephrine reuptake inhibitors.[249-251]

3.4. Antidotes

Toxicological antidotes may induce paradoxical or bidirectional effects.

(a) Beta-blockers are generally recommended in unstable angina or non-ST elevation myocardial infarction.[252] Cocaine use may trigger acute coronary syndromes. However, clinical trials, cardiac catheterizations, case reports, and animal studies suggest harm from beta-blockers in cocaine intoxication, owing to unopposed alpha-adrenergic effects.[253-256] The harmful paradoxical coronary vasculature effects persist even when mixed alpha- and beta-adrenoceptor antagonists, such as labetalol, are substituted.[257]

(b) Sulfonylurea toxicity causes persistent hypoglycaemia. Rapid parenteral dextrose administration may promote recurrent hypoglycaemia and cycling of serum glucose concentrations.[258,259] Glucose distribution and uptake occur, and the competent pancreas responds to dextrose with an exaggerated insulin response during continued sulfonylurea exposure. For this reason, octreotide acetate is recommended in refractory hypoglycaemia from sulfonylureas or quinine.

(c) Multiple oxidizing agents produce methaemoglobinaemia, including amyl nitrite, benzocaine, dapsone, and quinine. The antidote, the mild oxidant methylthioninium chloride (methylene blue), is reduced to leukomethylene blue by methaemoglobin reductase when sufficient reduced nicotinamide adenine dinucleotide phosphate (NADPH) is available. Leukomethylene blue then
reduces methaemoglobin to haemoglobin. Methylthioninium chloride may paradoxically worsen methaemoglobinemia in patients given large doses or in those with inadequate NADPH, severe G6PD deficiency, or abnormal methaemoglobin reductase. Clinicians expect methylthioninium chloride to improve digital pulse oximetry (indicating resolving methaemoglobinemia); worsening pulse oximetry can occur from interference with device detection of transmitted red and infrared waves by methylthioninium chloride; this is pseudoparadoxical.

(d) Severe symptomatic lead toxicity generally mandates parenteral chelation therapy with dimercaprol (British Anti-Lewisite, BAL) and calcium disodium edetate (CaNa₂ EDTA). BAL is provided before CaNa₂EDTA in severe cases because CaNa₂EDTA may worsen lead encephalopathy, perhaps because of migration of mobilized lead into the brain. BAL is additionally used in mercury poisoning; however, it is not recommended for toxicity from organic mercury compounds, as brain mercury concentrations may increase, despite overall increased elimination. BAL is the primary chelating drug in acute arsenic poisoning, but it may adversely shift arsenic into the brain and testes.

(e) Paradoxically, chelation with succimer for lead concentrations between 0.96-2.12 μmol/L (20 and 44 μg/dL) worsened certain growth and cognitive performance measures.

(f) Protamine sulfate is used in heparin overdose and to reverse anticoagulation after coronary procedures. Excess protamine may act as an anticoagulant, adversely affecting clot initiation, clot kinetics, and platelet function.

(g) Pyridoxine counteracts the adverse effects of isoniazid in chronic administration (neuropathy) and in acute overdose [neuronal hyperexcitability (seizures) and depression (coma)]. Glutamic acid decarboxylase requires activated pyridoxine to generate inhibitory GABA from
glutamate. After massive acute doses (>100 g) or chronic large daily consumption, a permanent sensory neuropathy may paradoxically develop.\textsuperscript{[272,273]} Multiple neonatal intractable seizure types also respond to pyridoxine, which can rarely increase seizure frequency.\textsuperscript{[274]}

(h) Methotrexate toxicity is commonly treated with leucovorin, which bypasses the dihydrofolate reductase pathways inhibited by methotrexate. \textit{Glutamate carboxypeptidase} (glucarpidase) is a bacteria-derived metallo-enzyme that cleaves methotrexate into inactive DAMPA (4-amino-4-deoxy-10-methylpterio acid) and glutamate. Methotrexate toxicity has been treated with glucarpidase to reduce plasma methotrexate concentrations rapidly.\textsuperscript{[275]} Glucarpidase also inactivates the active leucovorin isomer, \textit{levo}-(6S)-leucovorin.\textsuperscript{[276]} Glucarpidase might paradoxically worsen an initial response to leucovorin rescue, owing to stereoselective destruction of leucovorin and its active metabolites.\textsuperscript{[277,278]} Providing the two antidotes several hours apart and continued leucovorin administration have been recommended actions.

(i) \textit{Flumazenil}, normally utilized to reverse benzodiazepine effects, has inverse agonist or partial agonist capacity at GABA\textsubscript{A} receptors.\textsuperscript{[279,280]} It paradoxically reduced aggression and hostility when given to patients with benzodiazepine dependence.\textsuperscript{[281]}

(j) \textit{Antihistamines} (e.g. diphenhydramine) are often used to treat antipsychotic drug-induced akathisia and movement disorders. However, diphenhydramine itself may produce acute dystonic reactions.\textsuperscript{[282,283]}

(k) \textit{N}-\textit{acetylcysteine} reduces clotting factor II, VII, and X activity, mildly increasing INR, despite the fact that it is designed to remedy paracetamol (acetaminophen) overdose complicated by hepatic failure and coagulopathy (increased INR).\textsuperscript{[284]}
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