

PRESCRIBED DRUGS AND NEUROLOGICAL COMPLICATIONS

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A treatment history is a fundamental part of the healthcare consultation. Current drugs (prescribed, over the counter, herbal remedies, drugs of misuse) and how they are taken (frequency, timing, missed and extra doses), drugs tried previously and reason for discontinuation, treatment response, adverse effects, allergies, and intolerances should be taken into account. Recent immunisations may also be of importance. This article examines the particular relevance of medication in patients presenting with neurological symptoms. Drugs and their interactions may contribute in part or fully to the neurological syndrome, and treatment response may assist diagnostically or in future management plans. Knowledge of medicine taking behaviour may clarify clinical presentations such as analgesic overuse causing chronic daily headache, or severe dyskinesia resulting from obsessive use of dopamine replacement treatment. In most cases, iatrogenic symptoms are best managed by withdrawal of the offending drug. Indirect mechanisms whereby drugs could cause neurological problems are beyond the scope of the current article—for example, drugs which raise blood pressure or which worsen glycaemic control and consequently increase the risk of cerebrovascular disease, or immunosuppressants which increase the risk of infection. Different categories of neurological syndromes will be considered.

CEREBROVASCULAR DISEASE

Prothrombotic drugs are the main consideration, with both arterial and venous effects.

Stroke

Current users of low oestrogen dose combined oral contraception (COC) have a small increased risk of ischaemic stroke, particularly in women with other risk factors; notably smoking, hypertension, and probably a history of migraine, and a modestly elevated risk of haemorrhagic stroke mainly in women older than 35 years of age. Former users of COC have no increase in risk of ischaemic or haemorrhagic stroke.

Women taking hormone replacement therapy (HRT) have a small increased risk of ischaemic stroke. In the women's health initiative study 16 608 postmenopausal women on combined HRT (oestrogen plus progesterone) were followed up for a mean of 5.6 years. There were 258 (151 on HRT and 107 on placebo) cases of stroke (79.8% ischaemic) with an estimated hazard ratio of 1.5 (nominal 95% confidence intervals (CI) 1.08 to 2.08) with adjustment for adherence. Other risk factors did not modify the effect of oestrogen plus progesterone on stroke risk. In the Danish nurse study, overall HRT exposure was not consistently associated with stroke, but there was a significant increased risk of stroke among hypertensive women on HRT.

Intracranial venous thrombosis

COC pills and androgens predispose to thrombotic conditions. Third generation COC containing desogestrel or gestodene, when compared to those preparations containing levonorgestrel (second generation), were found to have a relatively higher risk for venous thromboembolism in three studies. Consequently in October 1995 the Committee on Safety of Medicines warned of a twofold increase in venous thromboembolic disease with these preparations. Further studies failed to confirm this association. The Medicines Commission reviewed this issue in 1999. The risk of venous thromboembolism (VTE) is increased from 15 to 25 per 100 000 women years for third generation COC. The absolute risk remains very small and is much less than the risk of VTE in pregnancy.

Pelvic or leg vein thrombosis in conjunction with patent foramen ovale theoretically increases the risk of embolic stroke and may be a significant aetiology in cryptogenic stroke.

CEREBELLAR SYNDROMES

Ataxia, dysarthria, and nystagmus can be a consequence of phenytoin toxicity. Phenytoin has saturation non-linear kinetics. Once saturation is reached, a small increase in dose or interaction with another drug causes a significant increase in serum levels with potential toxic effects.

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Phenytoin induced cerebellar syndrome is dose related and reversible, but a long term treatment effect may arise due to cerebellar atrophy.

Lithium has a very narrow therapeutic range. Adverse effects including a cerebellar syndrome occur particularly with high plasma drug concentrations. A permanent cerebellar syndrome may result, particularly from overdose or with neuroleptic co-prescription. Lithium, cytokines, and neuroleptics may disrupt calcium homeostasis in Purkinje cells resulting in neurotoxicity.

Acute cerebellar syndromes can occur with the chemotherapy agents fluorouracil and cytarabine.

Aminoglycosides, amiodarone, barbiturates, carbamazepine, and piperazine can also induce cerebellar syndromes.

COGNITIVE IMPAIRMENT

Confusion, cognitive impairment, and hallucinations are manifestations of relatively reduced cholinergic activity (fig 1). Anti-parkinsonian medications, particularly anticholinergics and dopamine agonists, may induce such adverse effects that necessitate dose reduction although discontinuation is often required. Psychosis occurs more rarely. Cognitive impairment is also reported with valproate. Many drugs can cause confusional states including amphetamines, anticonvulsants, antidepressants, antituberculous drugs, antimalarials, anti-inflammatories, cardiac glycosides, diuretics, hypotensive agents, H₂ antagonists, neuroleptics, opiates, sympathomimetics, and sedatives. Agitation and confusion may be part of a withdrawal syndrome from drugs of addiction or alcohol. Central neurotoxicity can result from chemotherapy (particularly methotrexate, cytarabine, and ifosfamide used in the treatment of acute leukaemias) ranging from minor cognitive impairment to encephalopathy.¹

Serotonin syndrome

Serotonin syndrome is an acute iatrogenic drug induced condition, characterised by a triad of cognitive behavioural changes, autonomic instability, and neuromuscular

excitability.² It is caused by overstimulation of 5-hydroxytryptamine (5-HT) receptors. However, the clinical similarity between serotonin syndrome and neuroleptic malignant syndrome (an acute dopaminergic blockade) indicates a more complex reciprocal interplay in the balance between serotonergic and dopaminergic systems rather than a simple serotonergic excess or dopamine deficiency. Since serotonin excess inhibits dopamine secretion, there is clinical overlap in the two syndromes (table 1).

Different mechanisms of serotonin (5-HT) excess are summarised in table 2 and fig 2. The main causative drugs are selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs—for example, selegiline). The syndrome usually occurs after a dose increase or addition of a second serotonergic agent. Fortunately the risk of inducing this syndrome is low. For example, a serotonin interaction rate of 0.24% (11 of 4568 patients) was found in depressed Parkinson's disease patients already on selegiline and treated with an SSRI agent. Serotonin syndrome may result from interaction of St John's wort (*Hypericum perforatum*, a herbal remedy used in depression) and SSRIs. Theoretically the 5-HT agonists (the triptans) could cause serotonergic overstimulation, but the serotonin syndrome has been described only if triptans are combined with another serotonergic drug. The Radomski revised diagnostic criteria of serotonin syndrome is outlined in table 3. The diagnosis should be considered in patients who present with an acute confusional state with mild pyrexia, sweating, agitation, nausea, tremor, and diarrhoea. Symptoms typically occur rapidly after medication change, within two hours in 50% and 24 hours in 75% of cases. Neuromuscular excitability (myoclonus, rigidity, tremor) occurs in 50% and changes in mental state (usually excitation) occur in 40% of cases. Elevated serum creatine kinase, white cell count, hepatic transaminases, and lowered serum bicarbonate concentrations support the diagnosis. The serotonergic agent or agents must be discontinued. Supportive treatment should be given; ventilation and intensive care may be required in severe cases (40% require intensive care admission and 25% need intubation). Benzodiazepines have been used to reduce anxiety. Cyproheptadine (an antihistamine with antiserotonergic characteristics) and chlorpromazine (a 5-HT receptor antagonist neuroleptic) may be tried although their benefit is not proven. Deaths have been reported but the mortality rate is unknown.

Cholinesterase inhibitors

Cholinesterase inhibitors indicated for mild to moderate Alzheimer's disease may cause hypercholinergic effects, either central (excitation, agitation) or peripheral (bradycardia, gastrointestinal symptoms), via drug interactions with psychotropics or antiarrhythmics.

HEADACHE

Epidemiology studies show that medication is the cause of headache in up to 8% of patients. Headache is a side effect of many drugs,³ including vasodilators (nitrates, calcium antagonists, dipyridamole), sympathomimetic drugs, hypoglycaemic agents, anti-infective drugs, anti-inflammatories, antidepressants, H₂ antagonists, hormonal preparations, proton pump inhibitors, and anticonvulsants. The temporal relation of drug ingestion and symptom onset may implicate the drug as causative. However, headache is very common in the general population. In a one day point prevalence study

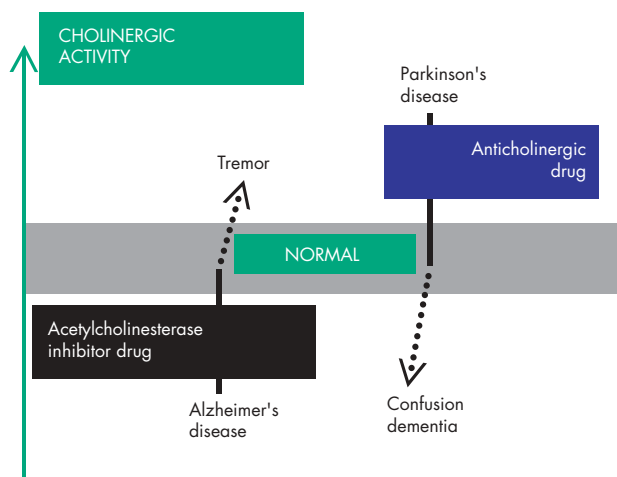


Figure 1 Conceptual diagram of acetylcholine system and disease and drug effects. Relative cholinergic excess in Parkinson's disease may be corrected by using anticholinergic drugs, but the risks of causing confusion and aggravating Parkinson's related cognitive impairment or dementia means that these drugs are less commonly prescribed today. Acetylcholinesterase inhibitor drugs, used to treat Alzheimer's disease, have an opposite effect, and have tremor among the list of side effects.

Table 1 Characteristics of serotonin syndrome and neuroleptic malignant syndrome

	Serotonin syndrome	Neuroleptic malignant syndrome
▶ Causative drugs	SSRIs, TCAs, MAOIs	Neuroleptics, metoclopramide, amoxapine (a TCA), sudden dopaminergic drug withdrawal
▶ Mechanism	5-HT receptor overstimulation	D2 receptor blockade
▶ Onset of symptoms	Within 24 hours	Within 7 days (longer with depot drugs)
▶ Symptoms	Autonomic, mental, neurological	Autonomic, mental, neurological
▶ Differentiating symptoms	Myoclonus, diarrhoea, nausea, shivering	Dysphagia, hypersalivation, incontinence
▶ Signs	Dilated pupils, myoclonus, hyperreflexia	Temp >38°C, akinesia, extrapyramidal rigidity
▶ Laboratory results	↑ WCC, ↑ CK	↑ WCC, ↑ ↑ CK
▶ Disease severity	Wide spectrum mild to severe	More severe—most cases require intensive care
▶ Serious complications	DIC, leucopenia, thrombocytopenia, seizures, multi-organ failure, rhabdomyolysis	DIC, acute renal failure, rhabdomyolysis, myocardial infarction, sepsis, cerebellar neuronal degeneration
▶ Main treatment	Discontinue causative drug(s); supportive	Discontinue causative drug(s); supportive
▶ Specific treatments	Benzodiazepines, cyproheptadine, chlorpromazine	Dopamine agonists, amantadine, carbidopa-levodopa, dantrolene
▶ Recovery	70% within 24 hours	2–14 days
▶ Mortality	Total of 23 deaths reported up to 1999	10–20% of cases

CK, creatine kinase; DIC, disseminated intravascular coagulation; 5-HT, 5-hydroxytryptamine (serotonin); MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants; WCC, white cell count.

11% of men and 22% of women had headache; ingestion of medication may therefore be coincidental. COC may cause new onset migraine or exacerbate existing migraine, and is contraindicated in patients with migraine with typical focal aura, severe migraine lasting over 72 hours despite treatment, and migraine treated with ergot derivatives.

Medication overuse headache

Chronic daily headache (CDH) associated with analgesic overuse, recently termed medication overuse headache (MOH) by the revised classification of the International Headache Society, was the most common reason for attending a specialist UK headache clinic. In the USA 50–80% of patients who presented with CDH used analgesics on a daily or near daily basis. The definition of medication overuse is based on the frequency and type of medication and not the absolute quantity. Use of triptans, ergotamine, opioids, or compound analgesics on 10 days or more a month and of simple analgesics on 15 or more days a month is defined as medication overuse. The mean duration until onset of analgesic overuse headache is shortest for triptans (1.7 years) compared to ergots (2.7 years) and analgesics (4.8 years). The mean frequency of dosing is lowest for triptans (18 doses per month), highest for analgesics (114 doses per month), with the ergots in the middle (37 doses per month).

Patients are often unaware that the very medication they are taking for headaches is perpetuating the problem. When these drugs are taken for conditions other than headache, MOH occurs rarely. Patients who are headache-prone and migraineurs are particularly susceptible to transformation

into MOH. Patients overusing analgesics invariably develop a daily tension-type headache, whereas only a third of patients overusing triptans develop daily tension-type headache; the remainder have either an increased frequency of migraine (40%), or a daily migraine-like headache (26%). Primary tension-type headache evolves to a constant headache, while in patients whose initial headache is migraine, two thirds evolve to daily tension-type daily headache, 13% daily migraine-like headache, and 23% have an increase in migraine frequency.

Overuse of a combination of medications and overlapping headache types complicate the situation in clinical practice. A recurrent rebound mechanism is likely, so reduction of the causative agent(s) with a view to discontinuation is needed. Initially, the headache may worsen and prophylactic agents may be used as a support, particularly antidepressants (tricyclics or SSRIs), especially when depression and anxiety co-exist. Sodium valproate, β blockers, and verapamil are alternative prophylactic drugs. The relapse rate reaches 40% within a year after previously successful drug withdrawal. Identifying patients at risk of developing MOH, warning them of the risk, and careful prescribing may have some preventive benefit.

Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) has an overall population incidence of 1 case per 100 000 per year, but is 19 times higher in obese young women age 24–44 years.

The typical presentation is of daily headaches, transient visual obscurations, and intracranial noises (described as buzzing, wind rushing, heartbeat in the ear). The modified Dandy diagnostic criteria are listed in table 4. Other causes of raised intracranial pressure should be excluded. Drug history, specifically of the combined contraceptive pill, tetracyclines, retinoids, vitamin A, and steroid withdrawal,⁴ should be sought. There are also reports of patients on mesalazine, indomethacin, and valproate developing IIH. However, most associations are based on uncontrolled and retrospective case reports or series; by contrast a study with sex and age matched controls found no evidence linking IIH to tetracyclines or oral contraceptive intake. Recent weight gain is a risk factor. Neurological examination is normal except for papilloedema and occasionally a sixth cranial nerve palsy and

Table 2 Mechanisms of serotonin overstimulation

Mechanism	Drugs
Drugs metabolised to serotonin or promoting serotonin release	Levodopa, lithium, MAOIs, tryptophan, trazodone, tetrabenazine
Inhibition of serotonin reuptake	SSRIs, TCAs, trazodone, tramadol, St John's wort, venlafaxine
Inhibition of serotonin metabolism	MAOIs (phenelzine, isocarboxid, selegiline), St John's wort
Postsynaptic receptor stimulation	Buspiron, triptans, lithium, carbamazepine

MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCAs, tricyclic antidepressants.

Table 3 Diagnostic criteria for serotonin syndrome

<ul style="list-style-type: none"> ▶ Increase in dosage or addition of a second serotonergic agent ▶ Plus 4 major symptoms or 3 major and 2 minor symptoms 	
Autonomic symptoms	
Major	
Fever	Tachycardia
Hyperhidrosis	Tachypnoea, dyspnoea
	Diarrhoea
	Hypo- or hypertension
Mental symptoms	
Major	
Confusion	Minor
Hypomania	Agitation, nervousness
Coma or altered consciousness	Insomnia
Neurological symptoms	
Major	
Rigidity	Minor
Myoclonus	Akathisia
Tremor	Impaired coordination
Hyperreflexia	Mydriasis
<ul style="list-style-type: none"> ▶ Exclusions No recent introduction or dose increase of neuroleptic Other causes (e.g. infective, metabolic, endocrine, toxic) excluded No similar symptoms attributed to psychiatric condition before introduction of serotonergic agent 	

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diplopia. Venous sinus occlusion should be excluded by computed tomographic venogram or magnetic resonance imaging. There is increased cerebrospinal fluid pressure demonstrated by lumbar puncture. The cerebrospinal fluid is of normal composition. Blindness is the primary morbidity occurring in 10% of patients. Management consists of weight reduction advice and diuretics. A short course of steroids, serial lumbar punctures, lumboperitoneal or

ventriculoperitoneal shunt, and optic nerve sheath fenestration are other treatment options.

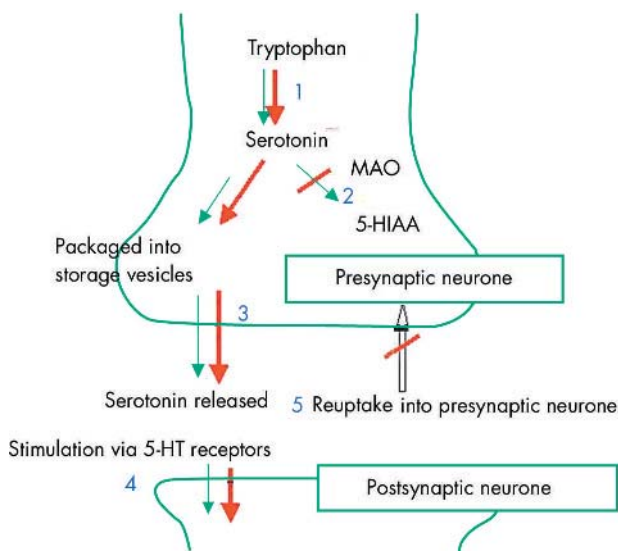
MOVEMENT DISORDERS

Drug induced movement disorders are common. In epidemiological studies between a third and a half of parkinsonism is caused by medication. Neuroleptics are particularly likely to induce movement disorders. In one prevalence study, 62% of patients on neuroleptics developed movement disorders, encompassing a mix of akathisia (31%), parkinsonism (23%), and tardive dyskinesia (32%). Extrapyramidal symptoms are associated to a lesser extent with all groups of antidepressants (tricyclics, monoamine oxidase inhibitors, and SSRIs), though this is based on case reports rather than controlled studies. The risk appears greater with the SSRIs than tricyclics. Complex interactions of dopamine, serotonin, and noradrenaline pathways between cortical structures and basal ganglia are involved.

Considering antidepressant treatment for patients with Parkinson's disease is complex. Depression affects at least a third of Parkinson's disease patients. Clinical experience is of significant benefit from antidepressants in selected patients, although some patients report worsened parkinsonism. A Cochrane systemic review concluded that there are insufficient data on the effectiveness and safety of antidepressant therapies in Parkinson's disease.

Akathisia

Akathisia (restlessness) may be induced by antidepressants, antipsychotics, antihistamines, calcium channel blockers,



- 1 Increased substrate
- 2 Inhibited serotonin metabolism
- 3 Increased release of serotonin into synaptic cleft
- 4 Postsynaptic receptor stimulation
- 5 Inhibited serotonin reuptake

Figure 2 Mechanisms of serotonin syndrome. Metabolism of tryptophan to serotonin and release and recycling in the synaptic system is shown. Sites of potential disruption from exogenous drugs, which may be involved in generating a serotonin syndrome, are numbered (see key). For further details see table 2 and text.

Table 4 Modified Dandy criteria for idiopathic intracranial hypertension

<ul style="list-style-type: none"> ▶ Signs and symptoms of raised intracranial pressure ▶ No localising features on neurological examination ▶ Normal neurodiagnostic studies except increased cerebrospinal fluid pressure on lumbar puncture ▶ Patient awake and alert ▶ No other cause of raised intracranial pressure
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carbamazepine, or metoclopramide. Akathisia is described as a sense of inner restlessness, a subjective need to move, such as shuffling of the legs, marching on the spot, pacing, rocking, or crossing/uncrossing the legs. It is a frequent and early side effect of antipsychotic treatment usually occurring within two weeks of initiation. If the offending drug cannot be stopped, propranolol or benzodiazepines may alleviate the symptoms.

Chorea

Chorea is an adverse effect of dopaminergic excess. Thus in patients with Parkinson's disease levodopa, dopamine agonists, and COMT (catechol-O-methyltransferase) inhibitors may all contribute. About half of Parkinson's disease patients treated with levodopa will develop motor complications of end-of-dose "wearing off", dyskinesia (chorea/dystonia), and "on-off" fluctuations within five years. Such motor complications are more common in young onset patients (100% after six years in cases developing Parkinson's disease before the age of 40 years).

Dopamine agonists are now a frequent choice of initial antiparkinsonian medication, based on strong evidence from many independent controlled studies that they delay the onset of motor complications and the need to initiate levodopa treatment for many months and even years. Selegiline is an alternative dopamine sparing agent which delays the need for levodopa by nine months. Reducing antiparkinsonian medication lessens dyskinesia but increases "off" time, and most patients prefer to maintain "on" time despite the dyskinesia. Amantadine has some antidyskinetic activity in levodopa induced motor complications. A small subgroup of Parkinson's disease patients use dopamine replacement excessively and compulsively, and take increasing quantities of dopamine replacement treatment despite severe drug induced dyskinesia and a cyclical mood disorder.

Anticonvulsant induced chorea is rare, but the risk increases with polytherapy perhaps caused by an additive or synergistic effect on central dopaminergic pathways; the combination of phenytoin and lamotrigine in particular predisposes to drug induced chorea. Other drugs such as amiodarone, amphetamines, antihistamines, anti-psychotics, oral contraceptives, and metoclopramide may cause chorea.

Tardive syndromes

Tardive syndromes are a group of delayed onset abnormal involuntary movement disorders induced by dopamine receptor blocking agents. Tardive dyskinesia (rhythmic involuntary movements of tongue, face, and jaw) is the best known and may occur even years after drug withdrawal. Tardive dystonia (usually of the face and neck), akathisia (which begins during neuroleptic treatment or within three months of discontinuation and persists for one month or more after drug discontinuation), tics (tardive Tourettism), myoclonus (of the neck or upper arms and particularly associated with high doses of neuroleptics), and tremor can also result from chronic antipsychotic use.⁵ These syndromes also occur with the newer atypical antipsychotics but the risk is lower. Informing and monitoring the patient may help to reduce malpractice claims that are common in the USA in this therapeutic area.

Onset of tardive dyskinesia within three months of drug exposure is possible but uncommon. Some improvement after withdrawal of the offending drug occurs in a third of cases, but complete recovery is rare. If antipsychotic treatment cannot be

Abbreviations

CDH: chronic daily headache
CK: creatine kinase
COC: combined oral contraception
COMT: catechol-O-methyltransferase
DIC: disseminated intravascular coagulation
GBS: Guillain-Barré syndrome
HRT: hormone replacement therapy
IIH: idiopathic intracranial hypertension
5-HT: 5-hydroxytryptamine (serotonin)
MAOIs: monoamine oxidase inhibitors
MOH: medication overuse headache
NMS: neuroleptic malignant syndrome
SSRIs: selective serotonin reuptake inhibitors
TCA: tricyclic antidepressants
VTE: venous thromboembolism

discontinued, substituting with an atypical agent or adding tetrabenazine may help (tetrabenazine is dopamine depleting and blocks postsynaptic dopamine receptors).

Acute dystonic reactions

Acute dystonic reactions can be induced by dopamine depleting drugs such as antihistamines, antipsychotics, antiemetics (domperidone, metoclopramide, prochlorperazine), tetrabenazine, and antimalarials. Domperidone and metoclopramide use is restricted in children and young adults (under 20 years) in whom acute dystonic reactions are more common. The dystonia usually occurs on the first day of drug exposure and affects the head, neck, and trunk muscles with neck retraction, tongue protrusion, trismus, and oculogyric crisis. Acute dystonic reactions are treated with anticholinergics (benztropine) or benzodiazepines.

Chronic dystonia

Chronic dystonia is associated with antiparkinsonian medication (levodopa and the dopamine agonists), phenytoin, phenobarbitone, and tetrabenazine. The dystonia of Parkinson's disease, typically early morning calf or foot cramps, is a "wearing-off" symptom which responds to dopamine agonists or levodopa.

Tremor

Tremor is caused by many drugs through several mechanisms (table 5). Drugs may enhance physiological tremor, typically a high frequency postural tremor. Dopamine depleting drugs cause a parkinsonian tremor—typically the 4–6 Hz "pill rolling" rest tremor. Drugs causing a cerebellar syndrome cause an intention tremor; withdrawal tremors follow discontinuation of drugs of dependence or alcohol.

Parkinsonism

Parkinsonism can be induced by dopamine depleting drugs contrasting with dopaminergic excess resulting in hallucinations, chorea, and dystonia (fig 3). Drug induced parkinsonism may be clinically indistinguishable from idiopathic Parkinson's disease. Although symptoms may be asymmetrical, a symmetrical presentation is more common than in idiopathic Parkinson's disease. Functional imaging using [123I]-FP-CIT (DaTSCAN, Nycomed Amersham, UK) single photon emission computerised tomography, a measure of presynaptic dopamine transporter system, differentiates drug

Table 5 Mechanisms of drug induced tremor

Enhanced physiological	Parkinsonian	Cerebellar	Withdrawal
Sympathomimetics	Neuroleptics	Lithium	Benzodiazepines
Bronchodilators	Metoclopramide	Phenytoin	SSRI—paroxetine
Theophylline	Prochlorperazine	Chemotherapy-5FU	Alcohol
Pseudoephedrine	Antidepressants	Chronic alcoholism	Opiates
Antidepressants	Calcium antagonists	Amiodarone	
Amiodarone	Sodium valproate		
Sodium valproate			

5FU, 5 fluorouracil; SSRI, selective serotonin reuptake inhibitor.

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induced parkinsonism (normal scan) from idiopathic Parkinson's disease (abnormal scan).

Drug induced parkinsonism is most commonly attributed to antipsychotics or prochlorperazine. Other implicated drugs are antidepressants, cinnarizine, metoclopramide, and tetra-benazine. Atypical antipsychotics are less likely to induce extrapyramidal adverse effects, ranked in the following order: clozapine < quetiapine < olanzapine = zispridone (though this excludes akathisia and neuroleptic malignant syndrome).⁶ Antipsychotic induced parkinsonism is treated with an antimuscarinic (less correctly anticholinergic), usually procyclidine, if the antipsychotic medication cannot be discontinued. Sodium valproate can induce reversible parkinsonism. There are reports of calcium channel blockers such as diltiazem and verapamil causing drug induced parkinsonism on rare occasions.⁵

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome (NMS) is caused by acute dopamine D₂ receptor blockade in the corpus striatum, hypothalamus, and spinal cord. It is an acute and severe form of drug induced parkinsonism with a mortality of around 10% caused by rhabdomyolysis, disseminated intravascular coagulation, and acute renal failure. Estimations of incidence vary between 0.02–3.2% of patients on neuroleptics. Dehydration is an important predisposing factor. NMS is characterised by hyperthermia, fluctuating level of consciousness, muscular rigidity (often axial), dystonia, autonomic dysfunction, and raised concentrations of muscle proteins (creatin kinase and myoglobin) (table 1). Several diagnostic criteria have been proposed; hyperthermia and muscle

rigidity are cardinal features.⁷ Drugs causing parkinsonism may all produce NMS (particularly antipsychotic drugs, with a delay in onset for depot preparations), but withdrawal, particularly if rapid, of antiparkinsonian medication—especially levodopa—is also a trigger mechanism, as is a rapid switch of dopamine agonists.

Treatment involves stopping the causative agent (and lithium if the patient is taking this) and supporting with intravenous fluids, antipyretics, and a cooling blanket. Several case reports demonstrate effective use of specific treatment such as dopamine agonists, levodopa, amantadine, or dantrolene. Recovery usually occurs within 2–14 days.

NERVE AND MUSCLE

Peripheral neuropathy

Peripheral neuropathy may be a complication of chemotherapy.¹ Plant alkaloids, interferons, antimetabolites, taxanes, and platinum based compounds are particularly implicated. Chemotherapy induced neuropathy is sensory, related to cumulative dose or dose intensities, and is usually delayed, appearing weeks after initiation of treatment.⁸ Neurotoxicity induced by the vinca alkaloids commonly manifests as peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation. Several antibiotics can induce peripheral neuropathy: the penicillins, sulfonamides, chloramphenicol, colistin, metronidazole, and dapsone.⁹ The antituberculous drug isoniazid can cause pyridoxine deficiency neuropathy. Co-existing diabetes, alcohol dependence, chronic renal failure, malnutrition, or HIV infection increase the risk but can be prevented by co-prescribing pyridoxine. Paradoxically, pyridoxine itself is implicated as causing neuropathy in high doses. The Royal Pharmaceutical Society of Great Britain recommends that pharmacists advise customers of this risk for products with more than 10 mg/day of pyridoxine. Other antituberculous drugs (ethambutol and ethionamide) can also induce neuropathy.

Other drugs, including phenytoin, disulfiram (antabuse), and hydralazine, may also cause neuropathy.

Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) occurs more often than expected after hepatitis B vaccine, but there is no conclusive epidemiological association and the preventive benefits for those at risk of hepatitis B outweigh the risk of neurological adverse effects. An increased risk of acute GBS (relative risk 4.3, 95% CI 3.0 to 6.4) and severe GBS (relative risk 8.5, 95% CI 3.7 to 18.9) occurs after influenza vaccine in comparison to an adult tetanus–diphtheria vaccine control group.

Neuromuscular blockade

Neuromuscular blockade has been associated with the use of tetracyclines, polymyxins, clindamycin, aminoglycosides,

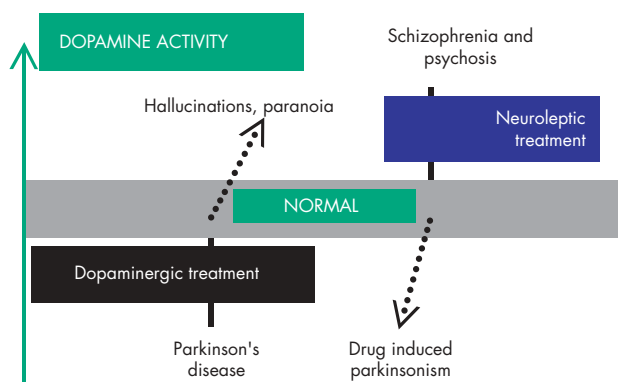


Figure 3 Conceptual diagram of dopaminergic system and disease and drug effects. Treatment to replace deficient dopamine or otherwise stimulate the dopaminergic system in Parkinson's disease may cause hallucinations and paranoia, a form of drug induced psychosis. Schizophrenia patients treated with neuroleptics may develop a movement disorder, such as tremor, parkinsonism, or tardive dyskinesia.

phenytoin, lithium, and chlorpromazine. These drugs should be avoided in patients with myasthenia gravis. Penicillamine and β blockers can rarely cause a myasthenia-like syndrome.

Myopathy

Muscle pain or weakness affects 1–5% of patients on statins. In an in-vivo culture system, skeletal muscle cytotoxicity of statins was ranked: cerivastatin > fluvastatin > simvastatin/atorvastatin/pravastatin. Cerivastatin was withdrawn worldwide in 2001 because of myotoxicity. It has a different pharmacokinetic profile and a 16–80 times higher risk of rhabdomyolysis than other statins. The fibrate gemfibrozil increases plasma statin concentrations, increasing the risk of myopathy, and should not be co-prescribed with a statin.

The oral retinoids used for psoriasis may cause atypical musculoskeletal symptoms. The vinca alkaloids used to treat acute leukaemias, lymphomas, and some solid tumours can cause motor weakness. If there is increasing motor weakness the drug should be discontinued.

OPTIC NEURITIS

Optic neuritis and retrobulbar neuritis may be caused by chloramphenicol, the antituberculous drugs (ethambutol and isoniazid), and alpha interferon. Visual acuity should be tested before commencing ethambutol and treatment stopped if visual symptoms develop. Loss of visual acuity, colour blindness, and reduced visual fields develop. Ethambutol induced ocular toxicity is dose related and more common in patients with renal insufficiency. Early discontinuation of the drug results in recovery of eyesight.

Isotretinoin (used to treat acne), amiodarone, and the platinum antineoplastic agents cisplatin and carboplatin can also cause optic neuritis.

Demyelination and vaccines

Despite several case reports of onset or relapse of demyelinating disease after vaccination, a case-control study failed to show any such association after immunisation against hepatitis B, influenza, tetanus, measles, or rubella. The National Institute for Clinical Excellence recommends that patients with demyelinating disease should be offered influenza vaccine.

SEIZURE DISORDERS

Lower seizure threshold

Many drugs are epileptogenic including analgesics (for example, non-steroidal anti-inflammatory drugs, tramadol, diamorphine, pethidine), antibiotics (penicillins, cephalosporins, quinolones), antidepressants, anticholinergics, antiemetics, antihistamines, antimalarials, antipsychotics, antispasmodics, amphetamines, baclofen, bupropion, chemotherapy (vincristine), cholinesterase inhibitors, cyclosporine, isotretinoin, oral contraceptives, and theophyllines. Clozapine, tricyclic antidepressants, and lithium in particular may precipitate drug induced seizures.¹⁰ The newer psychotropic agents appear to have a low risk of inducing seizures.¹⁰ Bupropion, a monocyclic antidepressant used as a smoking cessation aid, provokes seizures in 1 in 1000 patients. Various Chinese herbal remedies, Indian traditional remedies, and red flower oil may cause seizures.

Withdrawal seizures

Withdrawal seizures typically occur within a few days of suddenly stopping a drug (for example, barbiturates, benzodiazepines, baclofen) which has been taken for a prolonged period.

Drug interactions

The anticonvulsants are particularly susceptible to drug interactions as many are both substrates and inhibitors of cytochrome P450 (CYP450) isoenzymes.¹⁰ A decrease in the antiepileptic drug concentration via pharmacokinetic drug interactions may precipitate seizures. Anticonvulsants can interact with, for example, alcohol, analgesics, antibacterials, anticoagulants, antidepressants, antimalarials, antipsychotics, antivirals, bupropion, cytotoxics, lithium, oestrogens, progesterones, ulcer healing drugs, and other anticonvulsants.

CONCLUSION

A wide spectrum of neurological presentations may be caused or precipitated by drugs, both prescribed and non-prescribed. This can be at first presentation, or in cases with already established neurological disease. Doctors have a responsibility in preventing iatrogenic symptoms by careful prescribing, and in identifying drug induced syndromes. Failure to consider a drug induced cause may lead to inappropriate investigations and management. An accurate drug history remains an essential component of the consultation, as this can explain several of the clinical presentations seen in the clinic or acute neurology ward.

REFERENCES

- 1 Verstappen CC, Heimans JJ, Hoekman K, *et al.* Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. *Drugs* 2003;**63**:1549–63.
 - 2 Ener RA, Meglathery SB, Van Decker WA, *et al.* Serotonin syndrome and other serotonergic disorders. *Pain Med* 2003;**4**:63–74.
 - 3 Toth C. Medications and substances as a cause of headache: a systematic review of the literature. *Clin Neuropharmacol* 2003;**26**:122–36.
 - 4 Griffin JP. A review of the literature on benign intracranial hypertension associated with medication. *Adverse Drug React Toxicol Rev* 1992;**11**:41–57.
 - 5 Rodnitzky RL. Drug-induced movement disorders. *Clin Neuropharmacol* 2002;**25**:142–52.
 - 6 Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. *CNS Drugs* 2002;**16**:23–45.
 - 7 Pelonero AL, Levenson JL, Pandurangi AK. Neuroleptic malignant syndrome: a review. *Psychiatr Serv* 1998;**49**:1163–72.
 - 8 Visovsky C. Chemotherapy-induced peripheral neuropathy. *Cancer Invest* 2003;**21**:439–51.
 - 9 Snively SR, Hodges GR. The neurotoxicity of antibacterial agents. *Ann Intern Med* 1984;**101**:92–104.
 - 10 Lee KC, Finley PR, Alldredge BK. Risk of seizures associated with psychotropic medications: emphasis on new drugs and new findings. *Expert Opin Drug Saf* 2003;**2**:233–47.
- **Detailed neurological review of central and peripheral effects.**
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- **Covers the various categories of cancer drugs associated with neuropathy, including time course.**
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- **Long article, but worthwhile reading, which makes clear the importance of drug history in patients presenting with collapse/seizure.**