

Antiparkinsonian agents

Medicines that restore dopaminergic signalling in the striatum by supplying dopamine's precursor, by stimulating the dopamine receptor directly, or by blocking the enzymes that dispose of levodopa and dopamine, with a small antimuscarinic group that works on the opposite side of the same balance.

Online guide: <https://www.medguideglobal.com/pharmacology/central-nervous-system/antiparkinsonian-agents>

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Quick revision

One Liner: Dopamine cannot be given as a medicine, so the whole class is built around getting its precursor into the brain and then defending it from the enzymes and the passage of time.

1. Dopamine is useless as a treatment because it does not cross the blood-brain barrier; its precursor levodopa does, and is presumed to be converted to dopamine in the brain. [1]
2. Levodopa taken orally is rapidly decarboxylated to dopamine in extracerebral tissues, so only a small portion of a given dose is transported unchanged to the central nervous system. [1]
3. Carbidopa inhibits that peripheral decarboxylation, does not itself cross the blood-brain barrier, and thereby makes more levodopa available for transport to the brain. [1]
4. Benserazide is the other peripheral decarboxylase inhibitor; with levodopa it forms co-beneldopa, sold as Madopar, and it blocks conversion outside the brain in the same way. [2]
5. Sustained levodopa treatment brings motor complications: a wearing-off effect at the end of the dosing interval, and dyskinesias that may themselves force the dose down. [1]
6. Dopamine agonists cause impulse control disorders including pathological gambling, hypersexuality, compulsive eating and compulsive shopping. [4][13]
7. Patients on dopaminergic drugs have fallen asleep without warning while operating a motor vehicle, sometimes causing accidents, which makes this a fitness-to-drive question. [4][3]
8. MAO-B inhibition blocks the catabolism of dopamine and so increases the net amount available, but selegiline and rasagiline carry long serotonergic and opioid contraindication lists. [6][7]
9. Among the COMT inhibitors only tolcapone carries a boxed warning for fatal fulminant liver failure and a defined transaminase monitoring schedule, which is why it is reserved. [10]
10. Antimuscarinics such as trihexyphenidyl are licensed both for parkinsonism and for extrapyramidal disorders caused by antipsychotic medicines. [11]

Overview

1. Parkinson's disease is a failure of dopaminergic transmission, and every agent here addresses that failure from a different angle. The oldest and still the most effective approach is replacement, but dopamine itself cannot be used: its label-recorded ineffectiveness in Parkinson's disease is attributed to the fact that it does not cross the blood-brain barrier. Levodopa, the metabolic precursor of dopamine, does cross it and is presumably converted to dopamine within the brain, which is the entire reason the precursor rather than the transmitter is the drug. [1]
2. Levodopa given by itself is mostly wasted. Taken orally it is rapidly decarboxylated to dopamine in extracerebral tissues, so only a small portion reaches the central nervous system, and the dopamine generated outside the brain is what produces the vomiting. Adding an inhibitor of aromatic amino acid decarboxylase that cannot enter the brain solves both problems together: carbidopa inhibits decarboxylation of peripheral levodopa, does not cross the blood-brain barrier, does not affect levodopa metabolism within the central nervous system, and leaves more levodopa available for transport to the brain, with less nausea than levodopa alone. Benserazide performs the same job in the combination marketed as co-beneldopa. [1][2]

3. Most of the rest of the class exists because levodopa's benefit becomes unstable over years. A wearing-off effect appears at the end of the dosing interval and dyskinesias emerge, so adjuncts are added to smooth the plasma curve or to act independently of it. Dopamine agonists stimulate the receptor without needing conversion; MAO-B inhibitors block the catabolism of dopamine already formed; and COMT inhibitors block the alternative methylation route, with entacapone licensed specifically for end-of-dose wearing-off. [1][8][6]

4. Two safety themes dominate teaching on this class. The first is behavioural: dopamine agonists carry impulse control disorders and episodes of sudden sleep as label warnings, not as curiosities, and UK regulators treat pathological gambling and increased libido as class effects that are generally reversible when the dose is reduced or the drug stopped. The second is that dopaminergic treatment is never withdrawn abruptly, because a symptom complex resembling neuroleptic malignant syndrome has been reported with rapid dose reduction or withdrawal of these agents. [13][4][1]

Classification and drug examples

Intro: Grouped by where each agent intervenes on the dopamine pathway: supplying the precursor, protecting it in the periphery, stimulating the receptor, or blocking the two enzymes that break dopamine and levodopa down. The antimuscarinics sit apart because they work on the opposing cholinergic arm rather than on dopamine at all.

1. Name: Levodopa with a peripheral decarboxylase inhibitor

1. Note: The reference treatment and the most important entry on this page. Levodopa is not given alone in practice, because an inhibitor that cannot enter the brain redirects the dose there instead of into peripheral dopamine.

1. Name: Levodopa

L-dopa

1. Route: Oral

1. Note: The metabolic precursor of dopamine, and the reason this class works at all. Administration of dopamine is ineffective in Parkinson's disease apparently because it does not cross the blood-brain barrier, while levodopa does. [1]

2. Name: Carbidopa with levodopa

1. Co-careldopa

2. Sinemet

2. Route: Oral

2. Note: Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system, so administration of carbidopa with levodopa makes more levodopa available for transport to the brain, and the incidence of levodopa-induced nausea and vomiting is less with the combination product. [1]

3. Name: Benserazide with levodopa

1. Co-beneldopa

2. Madopar

3. Route: Oral

3. Note: The combination used across much of Europe and the UK. Benserazide stops levodopa from being changed to dopamine in the rest of the body, which reduces side effects such as feeling sick and a fast heartbeat. [2] [1]

2. Name: Dopamine receptor agonists

2. Note: Agents that stimulate the receptor directly and so need no enzymatic conversion. They share a distinctive behavioural profile: impulse control disorders, sudden onset of sleep, hallucinations and orthostatic effects.

1. Name: Ropinirole

1. Route: Oral

1. Note: A non-ergoline agonist whose effect is attributed to its ability to stimulate dopamine D2 receptors within the caudate-putamen. Licensed for Parkinson's disease and for moderate-to-severe primary restless legs syndrome, and metabolised principally by CYP1A2. [3]

2. Name: Pramipexole

2. Route: Oral

2. Note: A nonergot agonist with full intrinsic activity at the D2 subfamily, binding with higher affinity to D3 than to D2 or D4 receptor subtypes. Urinary excretion is the major route of elimination, with about 90% of a dose recovered in urine almost all as unchanged drug. [4]

3. Name: Rotigotine

Neupro

3. Route: Transdermal patch

3. Note: A transdermal system that provides continuous delivery of a non-ergoline agonist for 24 hours following application to intact skin. Application site reactions are its characteristic problem, and it contains sodium metabisulfite, which can provoke allergic-type reactions in susceptible people. [5]

4. Name: Apomorphine

4. Route: Subcutaneous

4. Note: Named by UK regulators among the dopamine agonists used in Parkinson's disease that share the class risk of pathological gambling, increased libido and hypersexuality. [13] [3][4]

3. Name: Monoamine oxidase type B inhibitors

3. Note: Agents that block the enzymatic breakdown of dopamine and so raise the amount available. Their interaction lists are considerably longer than their symptomatic benefit would suggest.

1. Name: Selegiline

L-deprenyl

1. Route: Oral

1. Note: Indicated as an adjunct where a patient already on levodopa with carbidopa shows deterioration in the quality of response, and its label states there is no evidence from controlled studies of benefit in the absence of concurrent levodopa. Its selectivity for MAO type B holds only at the recommended dose. [6]

2. Name: Rasagiline

Azilect

2. Route: Oral

2. Note: A selective, irreversible MAO-B inhibitor that produces an increase in extracellular levels of dopamine in the striatum. Its metabolism by CYP1A2 makes ciprofloxacin a clinically important interaction. [7] [6][7]

4. Name: Catechol-O-methyltransferase inhibitors

4. Note: Adjuncts that block the methylation of levodopa to 3-O-methyldopa, sustaining its plasma level. They are given only alongside levodopa, and they differ from one another mainly in hepatic risk.

1. Name: Entacapone

Comtan

1. Route: Oral

1. Note: Licensed as an adjunct to levodopa and carbidopa to treat end-of-dose wearing-off. Its label states plainly that entacapone has no antiparkinsonian effect of its own, and in clinical studies the majority of patients required a decrease in daily levodopa dose once it was added. [8]

2. Name: Opicapone

Ongentys

2. Route: Oral

2. Note: A selective and reversible COMT inhibitor indicated as adjunctive treatment to levodopa and carbidopa in patients experiencing off episodes. Non-selective MAO inhibitors are contraindicated with it, while selective MAO-B inhibitors can be used concomitantly. [9]

3. Name: Tolcapone

Tasmar

3. Route: Oral

3. Note: Increases the relative bioavailability of levodopa by approximately twofold, but carries a boxed warning for

potentially fatal acute fulminant liver failure and is therefore reserved for fluctuating patients not responding satisfactorily to, or not appropriate candidates for, other adjunctive therapies. [10] [8][9]

5. Name: Central antimuscarinic agents

5. Note: The oldest group, in use long before levodopa. Their value now lies mainly in tremor and in extrapyramidal disorders caused by antipsychotic medicines, and they are badly tolerated by older patients.

1. Name: Procyclidine

Kemadrin

1. Route: Oral

1. Note: The antimuscarinic used most often in UK practice for drug-induced extrapyramidal symptoms. Its anticholinergic activity is recognised even outside its own labelling: the paroxetine label reports that paroxetine raised steady-state procyclidine concentrations and directs that the procyclidine dose be reduced if anticholinergic effects are seen. [12]

2. Name: Trihexyphenidyl

1. Benzhexol

2. Artane

2. Route: Oral

2. Note: Licensed as an adjunct in the treatment of all forms of parkinsonism and for control of extrapyramidal disorders caused by central nervous system drugs such as the dibenzoxazepines, phenothiazines, thioxanthenes and butyrophenones. Geriatric patients, particularly over the age of 60, frequently develop increased sensitivity to drugs of this type. [11] [11]

Mechanism of action

Summary: One target, five ways of reaching it. The striatum is short of dopamine; levodopa supplies the precursor that can cross into the brain, a peripheral decarboxylase inhibitor protects that supply on the way, agonists bypass the synthesis step altogether, and the MAO-B and COMT inhibitors remove the two enzymes that would otherwise dispose of dopamine and levodopa. The antimuscarinics do none of this and instead damp the cholinergic side of the same circuit.

Target: Striatal dopamine receptors, approached through precursor supply, direct receptor stimulation, or inhibition of the enzymes that metabolise levodopa and dopamine

Cidal Static: Symptomatic replacement rather than disease-modifying

Kill Kinetics: Benefit tracks plasma levodopa and receptor occupancy, which is why the response fluctuates as concentrations fall

1. Step: 1

1. Title: Precursor loading across the blood-brain barrier

1. Detail: Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. Levodopa, the metabolic precursor of dopamine, does cross it, and is presumably converted to dopamine in the brain. That single pharmacokinetic difference is why the precursor is the medicine. [1]

2. Step: 2

2. Title: Blocking decarboxylation outside the brain

2. Detail: When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues, so only a small portion of a given dose is transported unchanged to the central nervous system. Carbidopa inhibits that peripheral decarboxylation, does not cross the blood-brain barrier, and does not affect the metabolism of levodopa within the central nervous system. Benserazide stops levodopa being changed to dopamine in the rest of the body in the same way. [1][2]

3. Step: 3

3. Title: Direct stimulation of the dopamine receptor

3. Detail: Ropinirole is a non-ergoline dopamine agonist whose antiparkinsonian effect is related to its ability to

stimulate dopamine D2 receptors within the caudate-putamen. Pramipexole is a nonergot agonist with full intrinsic activity at the D2 subfamily, binding with higher affinity to D3 than to D2 or D4 subtypes, and rotigotine delivers the same kind of stimulation continuously through the skin. [3][4][5]

4. Step: 4

4. Title: Preventing the breakdown of dopamine by MAO-B

4. Detail: Inhibition of monoamine oxidase type B blocks the catabolism of dopamine and so increases the net amount available. Rasagiline is a selective, irreversible MAO-B inhibitor that produces an increase in extracellular dopamine in the striatum, and selegiline acts as a selective type B inhibitor only while it is kept within its recommended dose range. [6][7]

5. Step: 5

5. Title: Closing the alternative COMT route

5. Detail: COMT catalyses the methylation of levodopa to 3-methoxy-4-hydroxy-L-phenylalanine, better known as 3-O-methyldopa. Plasma levels of that metabolite are markedly and dose-dependently decreased by a COMT inhibitor, while levodopa levels become greater and more sustained, producing more constant dopaminergic stimulation in the brain. Tolcapone raises the relative bioavailability of levodopa roughly twofold, and opicapone raises peak and overall levodopa exposure by 43% to 44% and 62% to 94% respectively. [8][10][9]

6. Step: 6

6. Title: Damping the cholinergic arm instead

6. Detail: Trihexyphenidyl exerts a direct inhibitory effect upon the parasympathetic nervous system, and this antimuscarinic action is used both as an adjunct in all forms of parkinsonism and to control extrapyramidal disorders caused by central nervous system drugs. It restores nothing dopaminergic, which is why the group helps tremor more than it helps bradykinesia. [11]

Major clinical uses

1. Drug: Carbidopa with levodopa

1. Organism: Not applicable

1. Indication: Parkinson's disease, post-encephalitic parkinsonism, and symptomatic parkinsonism following carbon monoxide or manganese intoxication

1. Line: reference treatment

1. Note: The indication is broader than idiopathic disease alone. The label also advises that a wearing-off effect may sometimes occur at the end of the dosing interval, which is the origin of most of the adjunctive prescribing in this class. [1]

2. Drug: Ropinirole

2. Organism: Not applicable

2. Indication: Parkinson's disease and moderate-to-severe primary restless legs syndrome

2. Line: first-line agonist

2. Note: Its label carries the instruction that treatment should ordinarily be discontinued if a patient develops significant daytime sleepiness or episodes of falling asleep during activities requiring active participation, such as driving. [3]

3. Drug: Pramipexole

3. Organism: Not applicable

3. Indication: Signs and symptoms of idiopathic Parkinson's disease, and moderate-to-severe primary restless legs syndrome

3. Line: first-line agonist

3. Note: In restless legs syndrome the label describes augmentation, meaning earlier onset of symptoms in the evening or even the afternoon, an increase in symptoms, and spread to involve other extremities. [4]

4. Drug: Rotigotine

4. Organism: Not applicable

4. Indication: Parkinson's disease, and moderate-to-severe primary restless legs syndrome
4. Line: agonist, transdermal route
4. Note: The patch route is what distinguishes it, since delivery continues for a full day after application and does not depend on swallowing, which matters where oral intake is unreliable. [5]
5. Drug: Selegiline
5. Organism: Not applicable
5. Indication: Adjunct in parkinsonian patients on levodopa with carbidopa who show deterioration in the quality of their response
5. Line: adjunct only
5. Note: Its licensed role is strictly additive. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy, and patients may need their levodopa reduced once it is started. [6]
6. Drug: Rasagiline
6. Organism: Not applicable
6. Indication: Treatment of Parkinson's disease, as monotherapy or as an adjunct
6. Line: monotherapy or adjunct
6. Note: Used as an adjunct to levodopa it may cause dyskinesia or potentiate dopaminergic side effects and exacerbate pre-existing dyskinesia, so the levodopa side of the regimen often has to be revisited. [7]
7. Drug: Entacapone
7. Organism: Not applicable
7. Indication: End-of-dose wearing-off in Parkinson's disease, as an adjunct to levodopa and carbidopa
7. Line: adjunct only
7. Note: The clearest illustration in the class of an adjunct that treats a complication rather than the disease: it is licensed for the wearing-off phenomenon itself and has no antiparkinsonian effect of its own. [8]
8. Drug: Opicapone
8. Organism: Not applicable
8. Indication: Adjunctive treatment to levodopa and carbidopa in patients with Parkinson's disease experiencing off episodes
8. Line: adjunct only
8. Note: A once-daily COMT inhibitor without the hepatic monitoring requirement that constrains tolcapone; dyskinesia was the commonest problem, occurring in 20% of treated patients in its trials. [9]
9. Drug: Tolcapone
9. Organism: Not applicable
9. Indication: Adjunct to levodopa and carbidopa in idiopathic Parkinson's disease, restricted to fluctuating patients unsuited to other adjuncts
9. Line: restricted reserve
9. Note: Its own label narrows its indication on safety grounds, and directs that a patient who fails to show substantial clinical benefit within three weeks of starting should be withdrawn from it. [10]
10. Drug: Trihexyphenidyl
10. Organism: Not applicable
10. Indication: Adjunct in all forms of parkinsonism, and control of extrapyramidal disorders caused by central nervous system drugs
10. Line: older agent, selected cases
10. Note: The named culprit drug groups are the dibenzoxazepines, phenothiazines, thioxanthenes and butyrophenones, which is why this agent appears far more often on psychiatric wards than in movement disorder clinics. [11]

Pharmacokinetics

1. Drug: Levodopa with carbidopa
 1. Route: Oral
 1. Absorption: Oral, and sensitive to the fate of levodopa in extracerebral tissues
 1. Csf Penetration: Levodopa crosses the blood-brain barrier; carbidopa does not
 1. Metabolism: Rapid decarboxylation to dopamine outside the brain unless that step is inhibited
 1. Elimination: Hepatic and peripheral metabolism
 1. Half Life: Short, which is the origin of end-of-dose wearing-off
 1. Dose Adjust: Pyridoxine may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation, and carbidopa inhibits that action of pyridoxine [1]
2. Drug: Ropinirole
 2. Route: Oral
 2. Absorption: Oral
 2. Csf Penetration: Not applicable
 2. Metabolism: CYP1A2 is the major cytochrome P450 enzyme involved
 2. Elimination: Hepatic
 2. Half Life: Approximately 6 hours
 2. Dose Adjust: Oral clearance is 47 litres per hour, and inhibitors of CYP1A2 raise exposure [3]
3. Drug: Pramipexole
 3. Route: Oral
 3. Absorption: Oral
 3. Csf Penetration: Not applicable
 3. Metabolism: Minimal; recovered largely as unchanged drug
 3. Elimination: Renal, with about 90% of a dose recovered in urine
 3. Half Life: About 8 hours in healthy volunteers and 12 hours in elderly volunteers
 3. Dose Adjust: Renal function governs exposure, and the longer half-life in older people matters [4]
4. Drug: Rotigotine
 4. Route: Transdermal
 4. Absorption: Continuous delivery for 24 hours following application to intact skin
 4. Csf Penetration: Not applicable
 4. Metabolism: Hepatic
 4. Elimination: Hepatic and renal
 4. Half Life: Governed by the patch rather than by an oral dosing interval
 4. Dose Adjust: Sudden discontinuation or dose reduction can be followed by hyperpyrexia and confusion [5]
5. Drug: Rasagiline
 5. Route: Oral
 5. Absorption: Oral
 5. Csf Penetration: Not applicable
 5. Metabolism: CYP1A2 is the major isoenzyme involved in its metabolism
 5. Elimination: Hepatic
 5. Half Life: Short, though enzyme inhibition is irreversible so the effect outlasts the drug
 5. Dose Adjust: Plasma concentrations may rise up to twofold with ciprofloxacin [7]
6. Drug: Selegiline
 6. Route: Oral
 6. Absorption: Oral
 6. Csf Penetration: Not applicable

- 6. Metabolism: Hepatic, to N-desmethylselegiline, L-amphetamine and L-methamphetamine
- 6. Elimination: Hepatic
- 6. Half Life: Short, with irreversible enzyme inhibition outlasting it
- 6. Dose Adjust: Two of its principal metabolites have pharmacological actions of their own [6]
- 7. Drug: Tolcapone
- 7. Route: Oral
- 7. Absorption: Oral
- 7. Csf Penetration: Not applicable
- 7. Metabolism: Hepatic
- 7. Elimination: Hepatic
- 7. Half Life: Short
- 7. Dose Adjust: Raises the relative bioavailability of levodopa by approximately twofold, so the levodopa side of the regimen usually needs review [10]
- 8. Drug: Opicapone
- 8. Route: Oral
- 8. Absorption: Oral, with a food-free interval required around administration
- 8. Csf Penetration: Peripheral action only
- 8. Metabolism: Hepatic
- 8. Elimination: Hepatic
- 8. Half Life: The duration of COMT inhibition greatly outlasts plasma exposure, allowing once-daily use
- 8. Dose Adjust: Avoided in severe hepatic impairment of Child-Pugh class C [9]
- 1. This page gives no dose regimens. Choosing, titrating and monitoring any of these medicines belongs to the treating clinician working from a current prescribing reference, because it depends on disease stage, age, cognition, comorbidity and everything else already prescribed.
- 2. The COMT inhibitors have no pharmacology worth learning in isolation; what matters is the shape they give to the levodopa concentration curve and how much less levodopa is then needed. [8][10]
- 3. Ropinirole and rasagiline both depend on CYP1A2, so a single inhibitor of that enzyme can raise the exposure of either drug substantially. [3][7]

Adverse effects

- 1. Effect: Nausea and vomiting
 - 1. Detail: Generated by dopamine formed outside the brain, which is why the incidence of levodopa-induced nausea and vomiting is less with the carbidopa combination than with levodopa given alone. Benserazide reduces the same effects in the European combination. [1][2]
- 2. Effect: Somnolence and daytime sleepiness
 - 2. Detail: Common across the dopaminergic agents and, at its extreme, becomes the sudden sleep episodes described in the serious column. Falling asleep during activities of daily living has been reported with levodopa preparations and with each of the agonists. [1][3][5]
- 3. Effect: Orthostatic hypotension and syncope
 - 3. Detail: Syncope, sometimes associated with bradycardia, was observed with ropinirole in patients with Parkinson's disease and in those treated for restless legs syndrome. Hypotension, both orthostatic and non-orthostatic, with syncope occurred in 5% of patients given opicapone. [3][9]
- 4. Effect: Dyskinesia
 - 4. Detail: Levodopa alone, and the carbidopa combination, are both associated with dyskinesias, and their occurrence may require the dose to be reduced. Adjuncts make this worse rather than better: entacapone may cause or exacerbate pre-existing dyskinesia, and dyskinesia occurred in 20% of patients treated with opicapone. [1][8][9]
- 5. Effect: Antimuscarinic effects with the anticholinergic group

5. Detail: Dryness of the mouth, blurring of vision, dizziness and mild nausea were reported in 30% to 50% of patients on trihexyphenidyl, together with constipation and urinary hesitancy or retention. [11]

6. Effect: Diarrhoea with COMT inhibitors

6. Detail: Diarrhoea developed in 10% of patients on entacapone against 4% on placebo. With tolcapone it reached 16% and 18% on the two regimens studied against 8% on placebo, was regarded as severe in 3% to 4%, and typically presented six to twelve weeks after starting. [8][10]

1. Effect: Impulse control disorders

1. Detail: Cases of pathological gambling, hypersexuality, compulsive eating including binge eating, and compulsive shopping have been reported with dopamine agonist therapy. UK regulators regard pathological gambling and increased libido including hypersexuality as rare class effects of dopamine agonists, generally reversible on reduction of the dose or discontinuation of treatment.

1. Action: Because patients may not recognise these behaviours as abnormal, labels direct prescribers to ask specifically about new or increased gambling urges, sexual urges, uncontrolled spending and compulsive eating; any change of treatment is a matter for the treating clinician. [4][13][3]

2. Effect: Falling asleep during activities of daily living

2. Detail: Patients treated with pramipexole have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. With levodopa preparations, sudden onset of sleep has been reported as long as one year after treatment began.

2. Action: The ropinirole label states that the drug should ordinarily be discontinued if significant daytime sleepiness or episodes of falling asleep develop during activities that require active participation. [4][1][3]

3. Effect: Fulminant hepatic failure with tolcapone

3. Detail: Its boxed warning reports that as of May 2005 three cases of fatal fulminant hepatic failure had been reported from more than 40,000 patient years of worldwide use, an incidence that may be ten to a hundred times higher than the background rate.

3. Action: The label requires that the drug not be used until the risks have been fully discussed and the patient has given written acknowledgement, and directs transaminase measurement at baseline and every two to four weeks for the first six months. [10]

4. Effect: Hallucinations and psychotic-like behaviour

4. Detail: In three double-blind placebo-controlled trials in early Parkinson's disease, hallucinations occurred in 9% of patients receiving pramipexole against 2.6% on placebo. Postmarketing reports for rasagiline describe new or worsening mental status and behavioural changes that may be severe, including psychotic-like behaviour.

4. Action: A dopaminergic burden problem rather than a single-drug one, so the whole regimen is reviewed together; the decision rests with the treating clinician. [4][7][8]

5. Effect: Neuroleptic malignant syndrome on withdrawal

5. Detail: Sporadic cases of a symptom complex resembling neuroleptic malignant syndrome have been reported with dose reduction or withdrawal of levodopa preparations. Four such cases were reported in tolcapone trials on abrupt withdrawal or dose lowering, and the same complex has followed rapid reduction of entacapone.

5. Action: This is the reason nothing in the class is stopped abruptly; patients are observed carefully when a dopaminergic dose is reduced, especially where a neuroleptic is also being given. [1][10][8]

6. Effect: Dopamine agonist withdrawal syndrome

6. Detail: Insomnia, apathy, anxiety, depression, fatigue, sweating and pain have been reported during taper or after discontinuation of dopamine agonists including ropinirole. It is distinct from the neuroleptic malignant picture and does not respond to levodopa.

6. Action: Relevant whenever an agonist is being reduced, including reductions made because of impulse control problems. [3]

7. Effect: Rhabdomyolysis with entacapone

7. Detail: Cases of severe rhabdomyolysis have been reported after the approval of entacapone, an uncommon but

recognised postmarketing signal for this adjunct.

7. Action: Considered where an unexplained rise in creatine kinase or muscle pain appears in a patient on the drug. [8]

1. Drug: Rotigotine

1. Effect: Application site reactions, which occurred more often than with placebo in the dose-response studies; weight gain frequently associated with peripheral oedema, suggesting the patch may cause fluid retention in some patients; and sodium metabisulfite content, which can cause allergic-type reactions including anaphylactic symptoms in susceptible people. [5]

2. Drug: Pramipexole

2. Effect: Augmentation in restless legs syndrome, meaning earlier onset of symptoms in the evening or afternoon, an increase in their intensity, and spread to other extremities. [4]

3. Drug: Selegiline

3. Effect: Amphetamine and methamphetamine appear among its principal metabolites and have pharmacological actions of their own, which contributes to insomnia and to exacerbation of levodopa-associated effects. [6]

4. Drug: Tolcapone and entacapone

4. Effect: Both discolour the urine; with entacapone the label describes a brownish-orange change that is not clinically relevant, and urine discoloration was reported by 7% of patients on the higher tolcapone regimen. [8][10]

5. Drug: Trihexyphenidyl

5. Effect: Incipient glaucoma may be precipitated, so gonioscope evaluation and close monitoring of intraocular pressures at regular periodic intervals are directed. Delusions, hallucinations, mental confusion, agitation and disturbed behaviour are described, and sensitivity rises after the age of sixty. [11]

6. Drug: Opicapone

6. Effect: Impulse control disorders occurred in 1% and hallucinations in 3% of treated patients, showing that the behavioural liabilities of dopaminergic treatment follow the adjuncts as well as the agonists. [9]

Contraindications, precautions and interactions

1. Nonselective monoamine oxidase inhibitors are contraindicated for use with carbidopa and levodopa, and the combination is also contraindicated in narrow-angle glaucoma and in known hypersensitivity to any component. [1]

2. Rasagiline is contraindicated with meperidine, tramadol, methadone and propoxyphene because of the risk of serotonin syndrome, with dextromethorphan because of the risk of psychosis or bizarre behaviour, and with other MAO inhibitors because of the risk of non-selective MAO inhibition and hypertensive crisis. [7]

3. Selegiline is contraindicated for use with meperidine, and its label notes that this contraindication is often extended to other opioids. [6]

4. Concomitant use of opicapone with non-selective MAO inhibitors is contraindicated, although selective MAO-B inhibitors can be used alongside it. [9]

1. Tolcapone is not a routine adjunct. Its label restricts it to patients with symptom fluctuations who are not responding satisfactorily to, or are not appropriate candidates for, other adjunctive therapies, and directs withdrawal if no substantial clinical benefit appears within three weeks. [10]

2. Driving and operating machinery is a live question for every patient on a dopaminergic drug, because sudden sleep has occurred without prior warning of sleepiness and, with levodopa preparations, as long as a year after treatment started. [1][4]

3. Dopaminergic treatment is not stopped or reduced abruptly, because a neuroleptic malignant syndrome-like complex has followed rapid dose reduction or withdrawal, and patients should be observed carefully when a levodopa dose is reduced, especially if a neuroleptic is being given. [1][10]

4. Antimuscarinics are a poor choice in older patients, in whom sensitivity to this drug type increases markedly after the age of sixty and confusion, delusions and hallucinations are described. [11]

5. Antiparkinson agents do not relieve tardive dyskinesia and in some instances may aggravate it, which separates that movement disorder sharply from drug-induced parkinsonism. [11]

6. Foods containing a very large amount of tyramine are avoided on rasagiline because of the potential for large increases in blood pressure, and selegiline's label explains the underlying mechanism: gut and liver MAO, mainly type A, normally protects against exogenous amines in what is called the cheese reaction. [7][6]
1. With: Selective serotonin reuptake inhibitors and tricyclic antidepressants
1. Effect: Serious and sometimes fatal reactions have been reported when selegiline is combined with fluoxetine, sertraline or paroxetine, and its label directs that at least fourteen days elapse between stopping selegiline and starting a tricyclic or an SSRI. [6]
2. With: Ciprofloxacin and other CYP1A2 inhibitors
2. Effect: Rasagiline plasma concentrations may increase up to twofold with ciprofloxacin, because CYP1A2 is the major isoenzyme involved in its metabolism; ropinirole depends on the same enzyme. [7][3]
3. With: Paroxetine and procyclidine
3. Effect: Daily paroxetine raised steady-state procyclidine exposure appreciably, with the trough concentration rising by 67%, and the paroxetine label directs that the procyclidine dose be reduced if anticholinergic effects are seen. [12]
4. With: Pyridoxine (vitamin B6)
4. Effect: Pyridoxine may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine, which is why the interaction matters far less with the modern combination products. [1]
5. With: Antipsychotic medicines
5. Effect: Extrapyramidal disorders caused by dibenzoxazepines, phenothiazines, thioxanthenes and butyrophenones are themselves an indication for an antimuscarinic, and the levodopa label separately warns that patients receiving a neuroleptic need particular care when a dopaminergic dose is reduced. [11][1]
6. With: Levodopa combined with an adjunct
6. Effect: Adding an adjunct usually means revisiting the levodopa itself: most patients in the entacapone studies required a decrease in daily levodopa dose, and selegiline's label anticipates the same need after it is started. [8][6]

Comparison tables

1. Title: Where each group intervenes, and what it costs
1. Caption: Position on the dopamine pathway predicts both the benefit and the characteristic problem. Selection among them belongs to the treating clinician.
1. Key: group
1. Label: Group
1. Is Row Header: true
2. Key: action
2. Label: Point of action
3. Key: role
3. Label: Role in treatment
4. Key: signature
4. Label: Signature problem
1. Group: Levodopa with carbidopa or benserazide
1. Action: Supplies the precursor that crosses into the brain, protected from peripheral decarboxylation
1. Role: The reference treatment for Parkinson's disease
1. Signature: Motor complications over time: wearing-off at the end of the dosing interval, and dyskinesia [1][2]
2. Group: Dopamine agonists
2. Action: Stimulate the dopamine receptor directly, needing no conversion
2. Role: Used alone early on or added to levodopa
2. Signature: Impulse control disorders, sudden sleep episodes and hallucinations [4][3]
3. Group: MAO-B inhibitors

- 3. Action: Block the catabolism of dopamine already present
- 3. Role: Modest monotherapy or adjunct where the levodopa response has deteriorated
- 3. Signature: Serotonergic and opioid contraindications out of proportion to the benefit [6][7]
- 4. Group: COMT inhibitors
- 4. Action: Block methylation of levodopa to 3-O-methyldopa, sustaining its plasma level
- 4. Role: Adjunct only, aimed squarely at wearing-off and off episodes
- 4. Signature: Diarrhoea, urine discolouration, worsened dyskinesia, and hepatotoxicity in tolcapone's case [8][10]
- 5. Group: Central antimuscarinics
- 5. Action: Inhibit the parasympathetic side of the same circuit rather than raising dopamine
- 5. Role: Tremor, and extrapyramidal disorders caused by antipsychotic drugs
- 5. Signature: Dry mouth, blurred vision, urinary retention and confusion, worst in the old [11]
- 2. Title: The three COMT inhibitors side by side
- 2. Caption: All three do the same biochemistry; only one of them requires a liver monitoring programme, and that difference decides where each is used.
- 1. Key: drug
- 1. Label: Drug
- 1. Is Row Header: true
- 2. Key: licence
- 2. Label: Licensed role
- 3. Key: liver
- 3. Label: Hepatic requirement
- 4. Key: place
- 4. Label: Place in practice
- 1. Drug: Entacapone
- 1. Licence: Adjunct to levodopa and carbidopa for end-of-dose wearing-off
- 1. Liver: No routine transaminase monitoring programme in its label
- 1. Place: The everyday COMT inhibitor; taken with each levodopa dose and with no antiparkinsonian action alone [8]
- 2. Drug: Opicapone
- 2. Licence: Adjunct to levodopa and carbidopa in patients with off episodes
- 2. Liver: No hepatotoxicity warning; avoided in Child-Pugh class C impairment
- 2. Place: The once-daily option, with non-selective MAO inhibitors contraindicated alongside it [9]
- 3. Drug: Tolcapone
- 3. Licence: Restricted adjunct for fluctuating patients unsuited to other adjuncts
- 3. Liver: Boxed warning for fatal fulminant liver failure; transaminases at baseline and every two to four weeks for six months
- 3. Place: Reserve only, used after a documented discussion of the hepatic risk [10]

High-yield exam pearls

- 1. Pearl: Dopamine is ineffective in Parkinson's disease apparently because it does not cross the blood-brain barrier, whereas its precursor levodopa does.
- 1. Why: It is the single most asked question about this class, and it explains why a precursor rather than the transmitter itself is the drug. [1]
- 2. Pearl: Carbidopa works precisely because it cannot get into the brain; it inhibits peripheral decarboxylation without affecting levodopa metabolism within the central nervous system.
- 2. Why: Candidates routinely invert this and describe carbidopa as a central booster, which reverses the whole logic of the combination. [1]
- 3. Pearl: Entacapone has no antiparkinsonian effect of its own, and most patients in its studies needed their daily

levodopa dose reduced once it was added.

3. Why: It fixes the idea that a COMT inhibitor is a pharmacokinetic modifier of levodopa rather than a treatment in its own right. [8]

4. Pearl: Selegiline has no demonstrated benefit in controlled studies in the absence of concurrent levodopa, and its indication is limited to patients whose levodopa response has deteriorated.

4. Why: The licensed wording is narrower than most students assume, and the restriction is examinable in its own right. [6]

5. Pearl: Pramipexole binds with higher affinity to D3 than to D2 or D4, while ropinirole's effect is attributed to stimulation of D2 receptors within the caudate-putamen.

5. Why: Receptor detail is the usual way agonists are distinguished in written papers, and both statements come straight from the labels. [4][3]

6. Pearl: Tolcapone alone among the COMT inhibitors carries a boxed warning for fatal fulminant liver failure, with three deaths reported from more than 40,000 patient years as of May 2005.

6. Why: The contrast with entacapone and opicapone, neither of which carries such a warning, is the point of the comparison. [10][8][9]

7. Pearl: Impulse control problems on dopamine agonists are generally reversible upon reduction of the dose or discontinuation of treatment.

7. Why: Reversibility is what makes asking the question worthwhile, and it is the detail candidates most often omit. [13]

8. Pearl: Pyridoxine can reverse the effects of levodopa by increasing aromatic amino acid decarboxylation, and carbidopa inhibits that action of pyridoxine.

8. Why: A classic historical interaction that also tests whether the peripheral decarboxylation story has really been understood. [1]

Common exam traps

1. Trap: Suggesting that dopamine could be given directly if only the dose were high enough.

1. Correction: No dose helps, because the barrier is anatomical rather than one of quantity; dopamine does not cross into the brain, which is why the precursor is used instead. [1]

2. Trap: Describing carbidopa as an agent that increases levodopa's effect inside the brain.

2. Correction: It acts only outside the brain. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system; the central gain is indirect, through more levodopa surviving the journey. [1]

3. Trap: Treating all three COMT inhibitors as interchangeable.

3. Correction: Only tolcapone carries a boxed warning for acute fulminant liver failure and a scheduled transaminase programme, which is exactly why entacapone and opicapone are used freely and it is not. [10][9]

4. Trap: Recording impulse control disorders as an unusual idiosyncrasy rather than a labelled warning.

4. Correction: Pathological gambling, hypersexuality, compulsive eating and compulsive shopping appear in the agonist labels, and UK regulators advise that patients are warned about them before treatment starts. [4][13]

5. Trap: Stopping a dopaminergic medicine suddenly when a patient is admitted, is nil by mouth, or develops a side effect.

5. Correction: A symptom complex resembling neuroleptic malignant syndrome has followed dose reduction or withdrawal of these agents, so any reduction is made deliberately and under observation. [1][10]

6. Trap: Reaching for an antimuscarinic when an antipsychotic-treated patient develops abnormal movements.

6. Correction: It depends entirely on which movement disorder it is. Antimuscarinics are indicated for drug-induced extrapyramidal disorders, but antiparkinson agents do not relieve tardive dyskinesia and may aggravate it. [11]

Self-test questions

1. Question: Why is levodopa given rather than dopamine itself in Parkinson's disease?

1. Dopamine does not cross the blood-brain barrier, whereas levodopa does
2. Dopamine is destroyed by gastric acid, whereas levodopa is not
3. Dopamine has no affinity for striatal dopamine receptors
4. Levodopa is a more potent agonist at the D3 receptor

1. Explanation: The label states that administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier, while levodopa, the metabolic precursor of dopamine, does cross it and is presumably converted to dopamine in the brain. [1]

2. Question: What is the pharmacological reason for combining levodopa with carbidopa?

1. Carbidopa inhibits decarboxylation of levodopa in the periphery and does not itself enter the brain
2. Carbidopa inhibits catechol-O-methyltransferase in the brain
3. Carbidopa is a dopamine agonist that supplements the levodopa effect
4. Carbidopa slows gastric emptying so that levodopa is absorbed more evenly

2. Explanation: Carbidopa inhibits decarboxylation of peripheral levodopa, does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system, so more levodopa is available for transport to the brain and nausea and vomiting are less frequent than with levodopa alone. [1]

3. Question: A patient on a dopamine agonist for Parkinson's disease has begun gambling heavily and spending money uncontrollably. How should this be understood?

1. A recognised class effect of dopamine agonists that is generally reversible on dose reduction or withdrawal
2. An unrelated psychiatric illness with no bearing on the medicines
3. An early sign of levodopa-induced dyskinesia
4. A withdrawal phenomenon seen only when an agonist is being tapered

3. Explanation: Pathological gambling, hypersexuality, compulsive eating and compulsive shopping have been reported with dopamine agonist therapy, and UK regulators describe pathological gambling and increased libido as rare class effects that are generally reversible upon reduction of the dose or discontinuation of treatment. [4][13]

4. Question: Which COMT inhibitor carries a boxed warning for potentially fatal acute fulminant liver failure?

1. Tolcapone
2. Entacapone
3. Opicapone
4. Carbidopa

4. Explanation: The tolcapone label carries a boxed warning for potentially fatal acute fulminant liver failure and directs transaminase measurement at baseline and every two to four weeks for the first six months of therapy; entacapone and opicapone carry no equivalent warning. [10][9]

5. Question: Which statement about entacapone is correct?

1. It has no antiparkinsonian effect of its own and must be given with levodopa
2. It is effective as monotherapy in early Parkinson's disease
3. It requires transaminase monitoring every two weeks for six months
4. It acts by irreversibly inhibiting monoamine oxidase type B

5. Explanation: The label states that entacapone should always be administered in association with levodopa and carbidopa and that entacapone has no antiparkinsonian effect of its own; it is licensed for end-of-dose wearing-off rather than as a primary treatment. [8]

6. Question: A patient stabilised on rasagiline needs an antibiotic. Which agent most warrants caution because of an interaction with rasagiline?

1. Ciprofloxacin
2. Amoxicillin
3. Nitrofurantoin
4. Doxycycline

6. Explanation: CYP1A2 is the major isoenzyme involved in rasagiline metabolism, and the label reports that rasagiline

plasma concentrations may increase up to twofold when ciprofloxacin is given with it. [7]

7. Question: An older patient on an antipsychotic develops rigidity and a resting tremor. Which agent is licensed for this drug-induced problem?

1. An antimuscarinic such as trihexyphenidyl
2. A COMT inhibitor such as opicapone
3. An MAO-B inhibitor such as rasagiline
4. A transdermal dopamine agonist such as rotigotine

7. Explanation: Trihexyphenidyl is indicated for the control of extrapyramidal disorders caused by central nervous system drugs such as the dibenzoxazepines, phenothiazines, thioxanthenes and butyrophenones, although sensitivity to this class of drug increases after the age of sixty. [11]

8. Question: Which of these is the correct description of selegiline's licensed place in treatment?

1. An adjunct for patients on levodopa with carbidopa whose response has deteriorated, with no evidence of benefit without levodopa
2. First-line monotherapy for newly diagnosed Parkinson's disease
3. A treatment for tardive dyskinesia caused by antipsychotic drugs
4. A peripheral decarboxylase inhibitor given with levodopa

8. Explanation: Selegiline is indicated as an adjunct in the management of parkinsonian patients being treated with levodopa and carbidopa who exhibit deterioration in the quality of their response, and its label states there is no evidence from controlled studies of any beneficial effect without concurrent levodopa therapy. [6]

Frequently asked questions

1. Question: Why can dopamine not simply be given as a medicine?

1. Answer: Because it never reaches the tissue that needs it. The carbidopa and levodopa label records that giving dopamine is ineffective in Parkinson's disease apparently because it does not cross the blood-brain barrier. Levodopa is the metabolic precursor of dopamine and does cross, and is presumably converted to dopamine in the brain, so the pharmacological trick of the whole class is to deliver a molecule that can make the journey and then let the brain finish the synthesis. [1]

2. Question: Why is levodopa always paired with carbidopa or benserazide?

2. Answer: Because levodopa given alone is largely converted before it arrives. Taken orally it is rapidly decarboxylated to dopamine in extracerebral tissues, so only a small portion is transported unchanged to the central nervous system, and the peripheral dopamine causes vomiting. Carbidopa inhibits that peripheral decarboxylation without entering the brain, so more levodopa is available for transport there and less nausea results; benserazide does the same job in co-beneldopa. [1][2]

3. Question: What are wearing-off and dyskinesia, and why do they matter so much?

3. Answer: They are the motor complications that accumulate on long-term levodopa. The label advises that a wearing-off effect may sometimes occur at the end of the dosing interval, meaning the benefit fades before the next dose is due, and it separately notes that levodopa is associated with dyskinesias whose occurrence may require the dose to be reduced. Most of the adjunctive drugs on this page exist to smooth that curve, which is why entacapone's licence names end-of-dose wearing-off explicitly. [1][8]

4. Question: Why is tolcapone restricted when entacapone and opicapone are not?

4. Answer: Hepatic risk, and nothing else. Tolcapone's boxed warning describes potentially fatal acute fulminant liver failure, with three fatal cases reported from more than 40,000 patient years as of May 2005, an incidence that may be ten to a hundred times the background rate. Its label requires written acknowledgement from the patient that the risks were explained and a transaminase schedule through the first six months. The other two block the same enzyme without carrying such a warning. [10][8][9]

5. Question: How do antipsychotics fit into a page about antiparkinsonian drugs?

5. Answer: They sit on the opposite end of the same receptor. Antipsychotic medicines produce extrapyramidal

disorders that mimic Parkinson's disease, and the trihexyphenidyl label lists the dibenzoxazepines, phenothiazines, thioxanthenes and butyrophenones as the causes it is licensed to counteract. That is why an antimuscarinic often appears on a psychiatric prescription chart, and the class detail belongs on the typical antipsychotics page rather than here. [11]

6. Question: Can any of these medicines be stopped quickly if a side effect appears?

6. Answer: No, and that is a safety point in its own right. Sporadic cases of a symptom complex resembling neuroleptic malignant syndrome have been reported with dose reduction or withdrawal of levodopa preparations, four such cases appeared in the tolcapone trials on abrupt withdrawal, and agonists have their own withdrawal picture of insomnia, apathy, anxiety, depression, fatigue, sweating and pain. Any reduction is planned and supervised by the treating clinician. [1][10][3]

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