Question 40
Which one of the following is least likely to improve the “on-off” phenomenon in a patient with Parkinson’s disease currently treated sixth-hourly with levodopa/carbidopa and selegiline?

A. Reducing the time between doses of levodopa/carbidopa
B. Introduction of a dopamine agonist
C. Introduction of a catechol-O-methyltransferase (COMT) inhibitor
D. Increasing each dose of levodopa/carbidopa
E. Introduction of a sustained-release form of levodopa/carbidopa

Answer:

Learning Issues:
1) Parkinson’s disease
2) Treatment and side effects

**Parkinson’s Disease (PD)**
- Bradykinetic neurodegenerative movement disorder
- Peak age onset >60 years old
  - Males > females

- **Cardinal features:** (need 2 out of 4 for dx)
  - Rigidity
  - Bradykinesia
  - Rest tremor (present in >85%)
  - Gait disturbance

- **Other features:**
  - Anosmia
  - Autonomic dysfunction (may also be treatment related)
  - Psychiatric features (depression, dopamine-related hallucinations)
  - Sleep disturbance
  - Dementia
  - Dyskinesia and motor fluctuation (Levodopa related)

- **Subtypes**
  - Idiopathic (75%)
  - Genetic/familial clusters (<5%)
  - Others eg other neurodegenerative disease/drugs/CVA

- **Pathology (degree relates well with motor symptoms and dementia)**
  - **Degeneration of dopaminergic pathways** (dopamine deficiency) and cholinergic sensitivity in basal ganglia
  - Neurons accumulate alpha synuclein protein -> Lewy bodies (especially olfactory and brainstem to midbrain)
  - Brain atrophy (limbic/paralimbic structures; anterior cingulate gyrus)

A few general statements about PD:
- An early onset resting tremor especially if unilateral suggests idiopathic PD
- Early onset cognitive decline, neuropsychiatric symptoms or autonomic dysfunction suggests syndromes with Parkinsonian features – usually earlier age of onset and less responsive to levodopa
- Drug induced parkinsonism (mainly neuroleptics, metoclopramide, manganese, CO) closely resembles idiopathic except the tremor is generally less prominent. This often resolves with drug cessation – if it persists, the patient may already have been in the process of developing PD
- Diffuse Lewy body dementia (DLB) closely associated with PD, there is controversy whether it is a spectrum of disease
  o However tend to have action rather than rest tremor
  o Rapidly fading response to levodopa
  o Marked early neuropsychiatric features

**Treatment**

**PHARMACOLOGICAL**

**Symptomatic**

1) \( \uparrow \) dopamine supply
   - Levadopa + carbidopa / benserizide

2) Dopamine agonist
   - Direct stimulation of dopamine receptors

3) \( \downarrow \) metabolism of dopamine
   - MAO inhibitors
   - COMT inhibitors

4) Anticholinergics

**Neuroprotective**

Mostly experimental
- MAO inhibitor selegiline (showing promise but conflicting data)
- Chronic NSAIDS
- Oestrogen in post-menopausal women
- Coenzyme Q10 (anti-oxidant)
- Minocycline (antibiotic)

### DRUGS AND SIDE EFFECTS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM</th>
<th>SIDE EFFECTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levadopa/ Carbidopa</td>
<td>Can be used 1st line</td>
<td>Nausea</td>
</tr>
<tr>
<td>(Sinemet)</td>
<td>Levadopa: Precursor of dopamine which crosses BBB</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Levadopa/ Benzaseride</td>
<td>Carbidopa/ benzaseride: Peripheral decarboxylase inhibitor which prevents</td>
<td>Headaches</td>
</tr>
<tr>
<td>(Madopar)</td>
<td>peripheral conversion to dopamine in systemic circulation</td>
<td>Somnolence</td>
</tr>
<tr>
<td><strong>Sustained release</strong></td>
<td>Start with small doses TDS with meals</td>
<td>( \uparrow ) homocysteine - ( \uparrow ) risk hip #</td>
</tr>
<tr>
<td>formulations</td>
<td></td>
<td>In older patients</td>
</tr>
<tr>
<td>available but less</td>
<td></td>
<td>- Hallucinations/ delusions</td>
</tr>
<tr>
<td>completely absorbed</td>
<td></td>
<td>- Confusion</td>
</tr>
<tr>
<td>so need 30% more</td>
<td></td>
<td>- Agitation</td>
</tr>
<tr>
<td>to achieve same</td>
<td></td>
<td></td>
</tr>
<tr>
<td>response</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>With dementia:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>start with smaller</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>doses due to</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>( \uparrow ) susceptibility to psychiatric complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Most with idiopathic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>Good response</td>
<td></td>
</tr>
<tr>
<td>- if no/minimal response with moderate doses, reconsider dx or revise it</td>
<td></td>
<td></td>
</tr>
<tr>
<td>to other subtype eg MSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Long term use:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Within 5-10 years,</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>up to 50% develop</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>motor fluctuations,</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>dyskinesias and</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>dystonia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concerns re neurotoxic effects of levadopa in vitro</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Dopamine agonists**

Can be used 1st line and monotherapy but most will need levadopa in a few years (OR) adjunctive in advanced PD where

Similar to levadopa
Peripheral oedema common
| **Bromocryptine**  
| **Cabergolide**  
| **Pergolide**  
| **Pramipexole**  
| **Ropinirole**  
| **Apomorphine** (used IV as rescue therapy) | there is ↓ levodopa response and ↑ levodopa complications  
Direct stimulation of dopamine receptors  
- No need conversion  
- No competition with other amino acids for gut absorption  
- Longer duration of action | in chronic use (rare in those using levodopa alone)  
- ↓ PRL  
“Sleep attacks” with pramipexole  
**Valvular heart disease with pergolide and cabergoline**  
(secondary activation of serotonin receptors activation and overgrowth) so they should be avoided  
Ergot-related side effects rare  
- Raynaud  
- Erythromelalgia  
- Retriperitoneal/pulmonary fibrosis  
↑ risk of impulse control disorders eg pathological gambling |
| **MAO-B inhibitors**  
| **Selegiline**  
| **Rasagiline** | Can be used as monotherapy in very early PD  
Combination of selegiline and levodopa produces better Sx control than levodopa monotherapy  
Slows oxidative metabolism of dopamine thus may ↑ levodopa-induced side effects eg dyskinesia and psychiatric effects | Nausea  
Headache  
Insomnia  
Worsen side effects of levodopa  
**Confusion in elderly (very common)**  
Avoid simultaneous SSRI or TCA |
| **COMT inhibitors**  
| **Entacapone**  
| **Tolcapone** | Levodopa extenders thus useless as monotherapy  
- ↓ peripheral methylation of levodopa (entacapone)  
- ↓ central methylation of levodopa (tolcapone) | From ↑ dopaminergic effects thus nausea  
Hallucinations  
Confusion  
Dyskinesia  
Postural hypotension  
Orange urine  
Abnormal LFTS and hepatotoxicity (only tolcapone) |
| **Anticholinergics**  
| **Benztropine** | Dopamine depletion produces state of cholinergic sensitivity so cholinergic drugs exacerbate PD symptoms and | Memory impairment  
Confusion |
<table>
<thead>
<tr>
<th>(Cogentin)</th>
<th>Trihexyphenidyl (Artane)</th>
<th>anticholinergics improve symptoms</th>
<th>Antimuscarinic effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Useful as monotherapy in age &lt; 70 with mainly tremor but no gait problems or significant akinesia</td>
<td>- Dry mouth&lt;br&gt;- Blurred vision&lt;br&gt;- Ur retention/constipation&lt;br&gt;- Impaired sweating&lt;br&gt;- Tachycardia</td>
</tr>
</tbody>
</table>

**Amantadine**

Antiviral, mechanism uncertain
- Antimuscarinic agent
- Weak dopamine agonist
- Glutamate antagonist

Use to treat dyskinesias

Elimination depends on renal clearance so **dose reduce in renal impairment**

Usually transient and modest effect for early/mild PD

Of little benefit adding to levodopa but great effect with levodopa added to amantadine

**NON-PHARMACOLOGICAL**

Exercise
Education/ counselling

**SURGICAL**

- Deep brain stimulation and paiidotomy/ thalmotomy/ subthalmotomy
- Patient selection crucial
- **Symptoms that do not respond to levodopa generally do not improve** (eg postural instability, hypophonia, drooling)
- Major indications
  - Idiopathic PD (atypical PD does not have a good response)
  - Good levodopa response
  - Significant, severe symptoms
  - Minimal cognitive impairment

**Motor fluctuations**

- “On-Off” phenomenon/ alterations
- Usually in **advanced** PD
- Noticed < 4 hours post dose of levodopa

- Management:
  - ↑ dose of levodopa IF on a small dose and not having other side effects
  - Shorten interdose interval (more effective, but some may experience “all or nothing” with small doses: in advanced disease the pharmacological threshold is higher)
  - SR (Need to ↑ dose 30% - some studies showed no ↓ “Off” time)
  - Addition of 2nd drug
- Dopamine agonist to “Off” time (bromocriptine ineffective, others equal efficacy though cabergoline ↑ dyskinesia)
- COMT inhibitors (clinical effect immediate)
- MAO-B inhibitors (seligine on “Off” time modest, resiligine better)
  - Anticholinergics and amantadine NOT helpful in motor fluctuations
  - H-Pylori eradication (improved levodopa absorption)

- Unpredictable freezing
  - Sudden immobilisation for minutes -> falls
  - Not medication related
  - Resistant to treatment

- Some occasionally fail to turn “On” following a dose of levodopa
  - Known as “No On” response
  - May be due to ↓ gastric motility and poor absorption
  - Or due to prolonged “Off” time
  - Can treat with prokinetic agent eg domperidone (D2 antagonist but does not cross BBB so does not worsen PD symptoms like metoclopramide)

**Dyskinesia**
- Involuntary abnormal movements
- May be choreic or dystonic, affecting face, trunk, extremities and respiratory muscles
- Or when severe, can be myoclonic or ballistic and interfere with movement
- Often well-tolerated
- Happens when patient is “On” and during “peak dose” (60-90 minutes post-dose), may have a diphasic pattern
- Direct effect of levodopa – especially common in those with young onset PD
- Affects up to 40% by 5 years and ↑ with duration of treatment

- Management
  - Avoid SR formulations
  - ↓ levodopa dose as much as possible
  - Try adding dopamine agonist and ↓ levodopa dose
  - Amantadine (short term benefit)
  - Clozapine (but watch for agranulocytosis)
  - Olanzepine (but may have unacceptable ↑ PD symptoms and “Off” time)

**Dystonia**
- Sustained abnormal postures mainly affecting limbs but also face, neck and trunk
- During “Off” period
- Can be painful eg early AM foot twisted in abnormal posture due to withdrawal from treatment
- Or as akathisia (motor restlesseg restless legs) a few hours after PM dose of levodopa

- Management
  - Take SR before sleep
  - Levodopa or dopamine agonist 1st thing in the morning/ middle of the night
  - Avoid taking levodopa with high protein meals

**Non-motor symptoms**
- Depression: antidepressants eg SSRIs and ECT very effective
- Psychotic features/ confusion: stop amantadine and anticholinergics 1st then consider simplification of drug regime in the following order: selegiline, nocturnal doses of dopamine agonist, sustained release formulations, daytime doses of dopamine agonists and finally daytime levadopa
  o If doing this worsens PD – atypical antipsychotics (quetiapine the best, clozapine also good but risk of agranulocytosis)
  o Risperidone and olanzepine tend to worsen PD symptoms
  o Some evidence suggest anti-cholinesterase inhibitors may be useful in those with dementia

Back to the question:
The patient is on QID levadopa/ carbidopa + MAO-B inhibitor selegiline and experiencing motor fluctuations – suggesting advanced disease.

All options are aiming towards either increasing the dose or duration of effect of dopamine, however ↑ dose of levadopa is the least effective so the answer is D.