DIAMOND
L E W Y

The U.S. Based

DIAMOND Lewy™ Management Toolkit

Management Overview and Symptom Management Summaries

LBDA
LEWY BODY DEMENTIA ASSOCIATION

Lewy body dementia: Management Overview

- Identify key problems under domain headings such as cognition; gait, balance and movement; hallucinations; fluctuations; behavior and mood; sleep, and autonomic system dysfunction.
- Establish which problems have high priority for treatment.
- Discuss benefits and risks of treatment.
- Be aware that symptom response is variable and that benefits in one might be at the cost of worsening of others
- Individual treatments may have global benefits e.g. cholinesterase inhibitors.

COGNITIVE

Non-pharmacological

- cognitive stimulation, use of memory aids, increased social interaction and stimulation, and exercise.

Pharmacological

- **Cholinesterase inhibitors** first-line.
- **Memantine** second line.

NEUROPSYCHIATRIC

Psychosis

- Non-pharmacological includes orientation, validation, reassurance, distraction.
- May respond to **cholinesterase inhibitors** especially visual hallucinations.
- Be cautious in the use of antipsychotics.
- **Quietiapine and clozapine** are least apt to worsen parkinsonism. ⚠

Mood

- Use of **social interventions** may enhance mood.
- SSRIs or SNRIs first line ⚠
- Avoid agents with significant anti-cholinergic side effects.
  Avoid antipsychotics for non-psychotic mood disorders

SLEEP

Insomnia

- Work on **sleep hygiene.**
- **Review all medications** that could be affecting sleep.
- **Melatonin** 1 hour prior to bedtime

⚠ **Cautious consideration for other sleep aids**

REM-sleep behavior disorder

- Consider **non-pharmacological** as first-line and only treat if troublesome.
- **Melatonin is first line**

⚠ **Clonazepam** may help although **possible** side effects

Motor related sleep disturbances

- May be improved with long-acting levodopa.

Other

Evaluation for OSA

AUTONOMIC

Orthostatic hypotension

- **non-pharmacological** management e.g. compression stockings, fluid/salt intake, stand slowly.
- pharmacological e.g. fludrocortisone, midodrine, droxidopa

✕ Reduce/remove exacerbating drugs e.g. antihypertensives.

Constipation

- **Hydration and fiber intake.**
- **Stool softeners or mild laxatives like polyethylene glycol**

Gastroparesis

- **Non-pharmacological: smaller, more frequent meals**

X Avoid using metoclopramide.

Urinary dysfunction

- **Non-pharmacological** first-line e.g. pads, sheath catheter etc.

Pharmacological: based on etiology. Consideration for referral to Urology. Agents like, Mirabegron can be considered. Botox may be considered for overactive bladder. Avoid centrally acting anticholinergics.

Sexual dysfunction

⚠ **Phosphodiesterase-5 inhibitors** may be considered with caution in men

Sialorrhea

✕ Anticholinergics should not generally be used

- **Botulinum toxin injections** to salivary glands is an effective treatment

MOTOR

- Preferred pharmacological treatment of parkinsonism in LBD is **levodopa monotherapy.**
- Use **minimal dose** needed for benefit.

Monitor for potential neuropsychiatric side effects, if present:

X Withdraw in order, one at a time: anticholinergic drugs, amantadine, selegiline, dopamine agonists and catechol-O-methyltransferase inhibitors.

- Remember that LBD patients may exhibit exaggerated responses to medications.
- Severe antipsychotic sensitivity can occur in up to 50% of patients therefore use antipsychotic agents with caution.
- Review the need for drugs which can affect brain function and/or cause sedation and falls (see Beers List).
- Minimize anticholinergic burden as this may worsen cognition and behavior, and counteract cholinesterase inhibitors.

Cognitive Symptoms

General Principles

- Establish the presence of significant cognitive difficulties warranting treatment. Impairments in cognition can fluctuate and may relate to:
  - **memory**
  - **attention**
  - **executive functioning**
  - **visuoperceptual abilities**
  - **disorganized speech/communication**.
- Evidence of cognitive difficulties should be obtained from reports by the **patient** and an informed **carer,** and from the results of **formal cognitive testing**.
- Cognitive **fluctuations**, while intrinsic to LBD, may also be a feature of **delirium**. Therefore, exclusion of the latter is important.
- Other factors causing or aggravating cognitive decline should also be excluded.
- **Non-pharmacological approaches** to managing cognitive impairments include cognitive stimulation, use of memory aids, increased social interaction and stimulation, and exercise.

Cholinesterase Inhibitors

- Choice will be influenced by previous experience, ease of administration, dose titration regime and side effect profile.
- Donepezil and rivastigmine are similarly effective in DLB.
- There is more evidence for the benefits/effectiveness of rivastigmine in PDD.
- There is less evidence for the use of galantamine in LBD.

- Before starting Cholinesterase Inhibitors (ChEIs)
  - Check for clinically significant cardiovascular disease, particularly orthostatic hypotension, syncope or pre-syncope or cardiac dysrhythmia / conduction disturbance or bradycardia.
  - Consider carrying out an ECG before ChEI, particularly if there is a history of cardiac issues and/or autonomic dysfunction.
  - Cardiology referral should be made in cases of uncertainty including decisions regarding fitting of pacemakers.

- Cholinesterase inhibitors are best **titrated to the maximum tolerated dose** and maintained at this level. For example:
  - **Donepezil**: 5mg once daily for 4 weeks, increased to 10mg daily if no significant side effects occur.
  - **Rivastigmine (oral)**: 1.5 mg twice daily for 4 weeks, increased to 3 mg twice daily ideally. Dose can be increased up to 4.5 mg twice daily going up to 6 mg twice daily if no significant side effects occur.
  - **Rivastigmine patch:** 4.6 mg/24 hours for 4 weeks, increased to 9.5mg/24 hours with a further increase to 13.3 mg/24hours if no significant side effects. May have advantages in patients with swallowing difficulties, gastrointestinal side-effects in response to oral agents, compliance issues, or if there is a history of significant response variation to oral dosing.
  - **Galantamine:** 8mg/day increased to the initial maintenance dose of 16mg/day after a minimum of 4-6 weeks. A further increase of 24mg/day of galantamine can be attempted after 4 weeks at 16mg/day if no significant side effects occur.

- Assessing response and deciding about continuation:
  - Global and behavioural/psychiatric baseline symptoms should be documented.
  - Assess outcome after 3-6 months on maximum tolerated dose (be aware that some patients may take longer to respond). Once optimized, treatment should be continued for as long as the patient/carer/clinician consensus is that there are positive benefits.
  - If/when discontinued, ChEIs should be withdrawn gradually as there are reports of a rebound worsening of symptoms.
  - Strategies for non-response or poor tolerance to one ChEI include switching to another ChEI.

- **Adverse effects**
  - Gastrointestinal symptoms (ie, diarrhea, nausea, loss of appetite)
  - May lower threshold for seizures
  - Bradycardia
  - **Adverse effects may improve with dose reduction**.

Memantine

- **Consider as:**
  - Monotherapy if cholinesterase inhibitors are not tolerated or contra-indicated.
  - In combination with cholinesterase inhibitors, particularly if the effectiveness of the cholinesterase inhibitor is limited or is declining, or the disease is becoming more severe.
  - However, no clear evidence in LBD.
- **Dose and titration**
  - Start at 5 mg daily and increase by 5 mg per week to a maximum of 20 mg daily if tolerated.
  - In patients with an estimated glomerular filtration rate (eGFR) of <50ml/min, dose adjustments maybe required.
- **Adverse effects**
  - Side effects of memantine include gastrointestinal symptoms, confusion, somnolence, hypertension and dizziness.
  - Be cautious in prescribing memantine to individuals with a history of **seizures**, or poor **renal function**.
  - May enhance the effects of **dopaminergics**/**selegiline**, and be toxic when given with **amantadine**.

- **Assessing response and deciding about continuation**
  - Record **baseline cognitive** performance using a preferred scale.
  - **Global** and **behavioral / psychiatric baseline** symptoms should also be documented.
  - Assess outcome after **3-6 months** on maximum tolerated dose (be aware that some patients may take longer to respond). Cognitive, global and other domain assessments may be used to support this.
  - Once optimized, treatment should be continued for as long as the patient/carer/clinician **consensus is that there are positive risk/benefits**.
  - Due to the progressive nature of LBD it is likely that global/behavioural/cognitive measures will eventually fall below baseline levels but this alone should not be taken as lack of continuing response.
  - Potential benefit for use of acetelcholinesterase inhibitors on visual hallucinations and cognitive fluctuations.

Motor Symptoms

Dementia with Lewy bodies

General Principles

- Establish the **presence of significant motor difficulties (**e.g., tremor, slowness, stiffness, walking, balance, falls) which are impairing function and warrant treatment.
- **Exclude other factors** which may be a cause of a worsening of motor function e.g. antipsychotic use, osteoarthritis.
- Be aware that parkinsonian symptoms **may be less treatment-responsive** in DLB than in Parkinson's disease.
- Additionally, medications for parkinsonism may cause more unwanted side effects (e.g. worsening of hallucinations) in DLB than in PD.

Treatment

- The preferred pharmacological treatment of parkinsonism in LBD is **levodopa monotherapy** (carbidopa/levodopa)**.**
- Use the **minimal levodopa dose** required for benefit.
- Start low, and increase dose slowly: typical initiation doses are lower than in Parkinson's disease (e.g. 50mg (expressed as levodopa) taken 1-3 times daily).
- Monitor closely for **side effects,** including psychosis, postural hypotension, sedation, nausea and vomiting.

- Physical therapy may help with freezing of gait, gait re-education, improvement in balance, power and flexibility, enhanced mobility to decrease the risk of falls and improve functional independence.
- Occupational therapy assessment and home adaptations can help reduce the impact of motor difficulties and reduce falls risk.
- Consider **speech and language therapy** referral for motor related speech and swallowing problems.
- In LBD cognitive impairment and other comorbid symptoms can diminish engagement with therapy but outcomes may still be positive. Inclusion and training of the care partner can help support therapy outcomes.
- Encourage safe exercise within the abilities of the individual.
- Given increased falls risk in LBD vitamin D supplementation and bone mineral density screening should be considered if appropriate.

Parkinson's disease dementia

General Principles

- The **general principles are similar** to those for DLB but PDD patients are typically taking or have been on one or more anti-parkinsonian agents during the course of their PD.
- Management decisions are therefore typically around **dose reduction/cessation or optimization.**

Treatment

- A gradual and systematic **simplification of the antiparkinsonian drug regimen** is often necessary to balance neuropsychiatric symptoms vs. motor benefits.
- Where anti-parkinsonian drugs are being altered, this should be done in **close collaboration with the original prescriber** of the medicines where possible.
- **Withdraw (in following order) one at a time:**
  - anticholinergic drugs
  - amantadine
  - selegiline
  - dopamine agonists and
  - catechol-O-methyltransferase inhibitors.

Neuropsychiatric Symptoms

General Principles

- Establish the **presence, severity and impact** of significant neuropsychiatric symptoms warranting treatment. These may include **visual hallucinations, hallucinations in other modalities, delusions and apathy.**
- **Consider trial of non-pharmacological strategies first (ie, validation, orientation)**
- Obtain **collateral history** for symptoms from reports of the patient and an informed caregiver Systematic **rating scales** may be helpful.
- **Other factors causing or aggravating** mood and behavior disturbance should be excluded e.g. physical illness, pain or discomfort, environmental precipitants, agitation & aggression, depression & anxiety.

Cholinesterase Inhibitor use

- Consider as a first line treatment.
- Choice will be influenced by previous experience, ease of administration, dose titration regime and side effect profile.
- Donepezil and rivastigmine are similarly effective in DLB.
- There is more evidence for the benefits/effectiveness of rivastigmine in PDD.
- There is less evidence for the use of galantamine in LBD.

- Before starting Cholinesterase Inhibitors (ChEIs)
  - Check for clinically significant cardiovascular disease, particularly orthostatic hypotension, syncope or pre-syncope or cardiac dysrhythmia / conduction disturbance or bradycardia.
  - Consider performing an ECG before ChEI, particularly if there is a history of cardiac issues and/or autonomic dysfunction.
  - Cardiology referral should be made in cases of uncertainty regarding cardiac co-morbidities that may impact safety of these agents.

- Cholinesterase inhibitors are best **titrated to the maximum tolerated dose** and maintained at this level.
  - **Donepezil**: 5mg once daily for 4-6 weeks, increased to 10mg daily if no significant side effects occur.
  - **Rivastigmine (oral)**: 1.5 mg twice daily for 4 weeks, increased to 3 mg twice daily ideally. Dose can be increased up to 4.5 mg twice daily going up to 6 mg twice daily if no significant side effects occur.
  - **Rivastigmine patch:** Dosing and titration is typically 4.6 mg/24 hours for 4 weeks, increased to 9.5 mg/24 hours with a further increase to 13.3 mg/24hours if no significant side effects. May have advantages in patients with swallowing difficulties, gastrointestinal side-effects in response to oral agents, compliance issues, or if there is a history of significant response variation to oral dosing.
  - **Galantamine:** 8mg/day increased to the initial maintenance dose of 16mg/day after a minimum of 4-6 weeks. A further increase of 24mg/day of galantamine can be attempted after 4 weeks at 16mg/day if no significant side effects occur.

- **Assessing response and deciding about continuation:**
  - Global and behavioral / psychiatric baseline symptoms should be documented.
  - Assess outcome after 3-6 months on maximum tolerated dose (although some patients neuropsychiatric symptom improvement may be judged earlier).Once optimized treatment should be continued for as long as the patient/carer/clinician consensus is that there are positive benefits.
  - If/when discontinued, ChEIs should be withdrawn gradually as there are reports of a rebound worsening of symptoms.
  - Strategies for non-response or poor tolerance to one ChEI include switching to another ChEI.

- **Adverse effects** include gastrointestinal symptoms, postural hypotension, urinary frequency, hyper-salivation, watery eyes, runny nose and worsening of extrapyramidal motor symptoms, particularly fine tremor. Adverse effects may improve with dose reduction.

Antipsychotic use

- There should be a full discussion with the person with dementia and/or caregivers about the possible benefits and risks of antipsychotic treatment. This should be documented in medical records.
- Watch for severe antipsychotic sensitivity reactions.
- **Be aware of the increased risk of mortality and morbidity associated with the use of antipsychotics in dementia and Parkinson's disease.**
- Identify target symptoms and monitor these regularly.
- Watch for worsening of cognition and more subtle deteriorations in motor function.
- **The only antipsychotics with better tolerability in parkinsonism are quietiapine and clozapine.** As a result, these are the only antipsychotics used in LBD by experts.
- While not FDA approved in LBD, pimavanserin may be considered.
- The lowest possible dose should be initiated and then titrated upwards.
- Treatment should be regularly reviewed.

Specific symptoms

- **Visual hallucinations**
  - Not all visual hallucinations need treating as in some the hallucinations may be regarded neutrally or sometimes even comforting/pleasurable.
  - Simple explanation of visual symptoms as a consequence of impaired visual processing may allay fears and avoid the need for medication.
  - Interventions such as removing cushions, patterned curtains and other stimuli that might precipitate visual misinterpretations can be helpful, as is provision of good lighting.
  - ChEI are a first line pharmacological treatment for visual hallucinations in LBD. If these are ineffective a trial of an antipsychotic agent may need to be considered.
- **Delusions**
  - Delusions of misidentification, jealousy and paranoia can occur.
  - They are often associated with visual hallucinations and may improve with ChEI (first line) and antipsychotics (second line).
- **Apathy**
  - Providing adequate environmental stimulation may help reduce apathy and it may also improve with a ChEI. There is no evidence to support the use of psychostimulants.
- **Depression and Anxiety**
  - Consider use of social interventions to enhance mood.
  - Avoid antidepressants with significant anti-cholinergic side effects such as tricyclics.
  - Evidence for antidepressant drug efficacy and tolerability in LBD is limited. Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors have an evidence base in Parkinson's disease.
  - While there is no evidence base, ChEI may help some particularly if there is an apathy component.
- **Agitation and Aggression**
  - Often multi-factorial in cause: identify the relevant antecedent and perpetuating factors and treat as appropriate.
  - Sometimes, if driven by hallucinatory and other psychotic symptoms, agitation and aggression may improve when these are treated with a ChEI first line; anti-psychotics second line.
  - There is currently no evidence for efficacy of other medications in treating agitation or aggression in LBD.

Sleep Disturbances

Excessive daytime sleepiness

- Document the frequency and occurrence of daytime sleepiness. Sleep scales may be helpful.
- Give advice on sleep hygiene and treat any sleep disturbances.
- Exclude physical and medication causes.
- Exercise may help. Activities to promote stimulation.
- There are no specific pharmacological interventions but cholinesterase inhibitors may improve sleepiness in some. Stimulants, if used, should be prescribed by a specialist experienced in their use.

Restless legs syndrome (RLS)

- Be aware may be due to other factors e.g. anemia, diabetes or renal dysfunction. **In particular clinicians should consider checking ferritin levels** in appropriate patients, and in those with values < 50 ug/mL, to recommend oral iron replacement therapy for at least two to three months.
- Some medications e.g. antidepressants, antipsychotics and anti-emetics may exacerbate RLS.
- Regular exercise may help, but may exacerbate RLS for some.
- Avoid smoking.
- **Pharmacological treatments** include:
  - Dopamine replacement therapy
  - Gabapentin

  A **high degree of caution** needs to be applied if using these drugs given their potential for side effects.

Motor-related sleep disturbances

- Nocturnal extrapyramidal symptoms may be improved using long-acting dopamine replacement preparations prior to going to bed.
- Be aware though of their propensity to cause side effects e.g. neuropsychiatric.

Sleep apnea

- Be **aware of risk factors** (loud disruptive snoring, overweight, male, smoker, on sedatives, alcohol use, reflux and anatomical considerations e.g. collar size >43 cm or 17 inches).
- If suspicion of sleep apnea, consider referral to a sleep specialist
- Continuous positive airways pressure (CPAP) treatment in confirmed sleep apnea can improve nocturnal sleep, cognition and daytime sleepiness.

REM sleep behavior disorder

- Consider and exclude potential mimics e.g. obstructive sleep apnea
- **Consider non-pharmacological strategies as a first line, for example:**
  - placing bed on floor,
  - removing potentially dangerous objects and put padding around sharp/firm objects,
  - bed partners sleep separately etc.
- **Pharmacological treatments**
  - Melatonin is generally first line given benign side effect profile. 1 mg to 12 mg per day taken 1 hour before bedtime.
  - Second line, consider Clonazepam 0.25 mg – 0.5 mg (up to 1 mg) per day taken 30 minutes before bedtime. Be aware of side effects esp. increased risk of falls/worsening cognition.
- Be aware some medications may exacerbate REM sleep behavior symptoms.

Insomnia & sleep fragmentation

- Advise on good **sleep hygiene**:
  - avoidance of stimulants in late afternoon/evening e.g. caffeine
  - avoid alcohol in the evening
  - establish regular pattern of sleep
  - have comfortable bedding and temperature
  - restrict daytime naps, and
  - exercise regularly.
- **Review of all medication** (including over the counter) and avoid any drugs that may affect sleep or alertness,or may interact with other medication.
- Treat nocturia if a cause is identified. **Avoid anticholinergics** if possible.
- Melatonin 1 to 10 mg before bedtime may help some with subjective sleep disturbance.
- Caution with use of other sleep aids.

Autonomic Symptoms

Urinary Dysfunction

- **Non-pharmacological (first line) treatment of urinary incontinence**
  - **Regular, prompted, voiding** with use of incontinence pads may be helpful.
  - Consider **referral** to urology if symptoms are particularly troublesome or have never been previously investigated.
- **Pharmacological treatment of urinary incontinence**
  - **Avoidance or reduction in diuretics** may help if no contraindications.
  - Be aware that cholinesterase inhibitors can precipitate urgency and urge incontinence.
  - **Avoid: Bladder anticholinergics** particularly the use of agents which have a significant centrally acting effect such as oxybutynin and tolterodine.
  - Intravesical botulium toxin may have a positive effect on neurogenic detrusor overactivity in those intolerant of anticholinergics.
  - Mirabegron, a β3 adrenergic agonist (25-50 mg per day) may be an alternative to anticholinergics for bladder overactivity.

Male sexual dysfunction

The use of phosphodiesterase-5 inhibitors such as sildenafil can be considered for erectile dysfunction; prescribe with caution if the patient has postural / orthostatic hypotension.

Excessive sweating

- Wear loose fitting/natural fiber clothing and use natural light cotton bedding if there are significant night sweats. Antiperspirants can help some.
- Utilize clip-on fans or ceiling fans during sleep
- Avoid foods and situations which trigger sweating e.g. alcohol, spicy foods, hot rooms.
- Ensure adequate fluid intake to replace losses.
- Alteration to the dopamine replacement regimen may sometimes help if associated with “OFF” motor state.

Constipation

- Check there has been no significant changes in bowel habits (such as per rectum bleeding, weight loss and/or anemia) which may indicate other causes.
- Give advice on increasing fluid and fiber intake, as well as exercise.
- If possible avoid constipating medications (e.g. opiates and some anti-parkinsonian drugs).
- Stool softeners can be helpful if stools are very hard.
- Mild suppositories such as glycerin may help also bowel emptying.
- Laxatives can be used, if required e.g.
  - Senna (7.5-15 mg at night); senna tea may work for some
  - Bisacodyl (5-10 mg at night)
  - Sodium docusate (50-400 mg in divided doses each day)
  - Bulk forming / osmotic laxatives e.g. polyethylene glycol.
- Lubiprostone is a second line treatment: 24 mcg twice daily.

Sialorrhea

- Speech and language therapist input can be helpful.
- Use of sugar free chewing gum or hard candy may help some.
- Anticholinergics should not be used if possible.
- Botulinum toxin injections to salivary glands is an effective treatment.
- Clonidine 150 mcg per day is an alternative option but can aggravate orthostatic hypotension and precipitate daytime somnolence.
- Glycopyrrolate 1–2 mg twice or three-times daily is a second line option.

Gastroparesis

- Be aware that dopaminergic medications can exacerbate gastroparesis.
- Advise the patient to have small and frequent meals and drink during meals. Avoidance of high fat foods may also help as well as walking after meals.
- Avoid using metoclopramide given its central dopamine antagonist effect.
- Giving levodopa in solution may help with patients with significant motor fluctuations and delayed gastric emptying.
- Alternatively, for some patients with delayed gastric emptying, their motor fluctuations may be improved through jejunal administration of levodopa.

Orthostatic hypotension

- Review medication list for antihypertensive regimens and confer with PCP/cardiologist about reducing hypertensives.
- Medications (e.g. levodopa, dopamine agonists, antihypertensives, antidepressants, alpha-adrenergic blockers, sildenafil), dehydration, cardiac disease, fever and anemia may cause or exacerbate orthostatic hypotension.
- Orthostatic hypotension may manifest at particular times e.g. at mealtimes, when taking alcohol, in early morning, during defecation or micturition, and/or with physical activity.
- If there is **significant dizziness, falls or episodes of loss of consciousness**, **consider a referral** to a falls/ syncope clinic.

- **Non-pharmacological principles (first line)**
  - Advise the patient to stand slowly
  - Raising the head of the bed may help with morning orthostatic hypotension.
  - Slight increases in salt intake may help some
  - Consider use of compression stockings or abdominal binders
  - Increase fluid intake – usual advice is 2 quarts, in total, daily.

- Potential **pharmacological therapies**
  - Fludrocortisone (50-300 mcg/ day). Titrate slowly and monitor electrolytes
  - Midodrine (2.5-10 mg bid). Monitor hepatic and renal function
  - Droxidopa (start at 100mg TID).
  - Note: these medications for orthostatic hypotension may cause severe supine hypertension and thus regular monitoring of blood pressure is needed.

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