

Practical Treatment of Lewy Body Disease in the Clinic: Patient and Physician Perspectives

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ABSTRACT

This article describes the practical considerations in the clinical medical treatment in dementia with Lewy body (DLB) patients. It is illustrated with the voice of a DLB sufferer and his wife. According to our experience, emanating from a 15 year collaboration between a doctor and a nurse at a memory clinic, there are several possible therapeutical entrances. However, the order in which the medication is introduced is of great importance to avoid aggravation of other DLB symptoms. We start the treatment with cholinesterase inhibitor and memantine, and; thereafter, we treat the most disturbing symptom. Thereafter, we consider if orthostatic hypotension is present and treat it. In the treatment of depression and anxiety it is beneficial to use agents affecting both noreadrenalin and serotonin. Dysphagia may be lethal but can be improved with carbohydrate drinks. These and other aspects are commented upon from our experience and are also reflected in relation to studies evaluating the existing level of evidence.

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INTRODUCTION

In a meta-analysis of pharmacological treatments of Lewy body dementia, Stinton et al. concluded that “high-level evidence related to pharmacological strategies for managing Lewy body dementia is rare”, and that the patients’ and caregivers’ opinions about pharmacological strategies have not been investigated (2015) [14].

Our dementia with Lewy bodies (DLB) patients at the memory clinic, Skane University Hospital, Sweden all participate in a specially designed follow-up programme involving yearly visits with a nurse and physician that include cognitive testing, blood pressure measurements, electrocardiogram (ECG) and Neuropsychiatric Inventory (NPI). Some of these patients are also included in programs with a wider range of investigations involving the cerebro-spinal fluid (CSF), positron emission tomography (PET) and magnetic resonance imaging (MRI). In between these visits we are available for telephone consultations.

Here, we want to present experiences of our treatment strategies in DLB developed during 15 years of cooperation between the same doctor and nurse, and also illustrate it with the

voice a patient and his wife. Informed consent was obtained from all patient(s) for being included in the study.

WRITTEN DESCRIPTION OF THE ILLNESS FROM THE WIFE OF THE PATIENT (TRANSLATED)

“The first time I noticed that my husband was ill, he was 79 years old. He had come home late from a business meeting and damaged his car driving it right into the wall of the garage. He was very tired and went straight to bed. The day after, he told me that he had been obliged to stop on the highway to sleep in the car in order to be able to drive all the way home. I was worried and made an appointment with a doctor for him. The conclusion after the consultation was that he was stressed and ‘burned out’. He became worse and worse. On several occasions I had to call 911 because I suspected he suffered a stroke! On his third time at the emergency unit, we met a doctor who took the symptoms seriously and conducted an investigation. After a week at the hospital my husband was discharged with the diagnosis ‘Dementia NOS’. He could not walk without a walking frame, he fell when he got up at night and could not sit on the toilet without support. He was so tired and just wanted to lie in his bed. It did not get better. I thought it was hopeless”.

The wife also told us that after several months, the solution seemed to be a nursing home. “But then we managed to get an appointment at the Memory Clinic with a doctor and a nurse. Step by step, the medication was changed and new drugs were added. A low blood pressure in the standing position was also found. In parallel with the medication changes and dose escalations, my husband was instructed to walk outside every day, initially for 10 min. He was also instructed to rest in the afternoons and before undertaking strenuous activities. They explained that the disease (DLB) fluctuates, and that a decline does not necessarily mean a permanent deterioration, but that with rest he will return to his starting position. Today, three years later, I must say he is well. We can travel with our children and

grandchildren, he is back on the board of his company. But we know that we have to prepare and ‘pay’ by resting before and after undertaking more unusual activities. When the tiredness hits him, I no longer get scared. I let him rest and have confidence in the experience that he will get better again, and he does”.

THE PATIENT’S EXPERIENCE OF THE TREATMENT, BASED ON AN INTERVIEW

“Following treatment, I feel that the joy of living has returned. I have become better. I have gotten my life back! I have always asked much of myself but with this disease I have had to learn to listen to my body. I still think it is annoying, however, when I forget names and the TV programs I have watched. Nowadays I can travel alone by airplane and participate in the board meetings of my company, but I have to prepare myself by sleeping almost 2 days and nights before the meeting and at lunch-time during the meeting. I have become generally stronger and walk 30–40 min daily. The incentive for me to cope with my disease is to be able to continue to lead my company. I would never have been able to manage all this without my wife, who takes such good care of me. I used to have a lot of unpleasant dreams, nightmares, but they have disappeared. As have the figures I used to see during daytime. I never see them nowadays. The most disturbing symptom for me is the immense tiredness which makes me feel as if my brain is not catching up. But compared to where I could have been—I have gotten my life back!”

COMMENTS ON THE EXPERIENCES OF THE WIFE AND PATIENT

The patient expresses gratitude towards his wife and the work she puts into their lives; this reflects good insight of the DLB patient. We have often speculated about the great engagement of the wives of our DLB patients (who are in a great majority men) and have come to a plausible conclusion. The patients are often

unchanged in the fundamental areas of their personality and behaviour, have preserved insight into their illness, and are therefore almost always very grateful for help from their caregivers. This makes it easier for the caregivers to manage throughout the disease, despite heavy physical and working moments, getting up several times during the night and having their social lives restricted. It also minimizes feelings of loneliness for the caregiver. Our patient has a very strong interest in his company and wishes to continue working, which motivates him to meticulously follow all advice in order to get better.

SUCCESSFUL PHARMACOLOGICAL TREATMENT BASED ON OUR CLINICAL EXPERIENCE WITH DLB PATIENTS

Cholinesterase Inhibitor and Memantine

According to our experience, it is of utmost importance to consider the sequence in which the medication is introduced to the patient. We start medication with rivastigmine and memantine and, thereafter, the most troublesome symptom is considered and treated specifically. If treatment does not commence with rivastigmine or memantine, side effects from medication directed at a single symptom can provoke symptoms of the DLB disorder itself, including symptoms that have yet to appear clinically. For example, if you start with L-dopa treatment to alleviate Parkinsonism, nightmares [or REM sleep behaviour disorder (RBD)] and visual hallucinations can be enhanced; it may also have a negative effect on the blood pressure, thereby aggravating the general state of the patient. If you start treatment by trying to reduce the visual hallucinations with any kind of neuroleptic, you may risk the life of the patient because of possible neuroleptic hypersensitivity, or at the very least worsen the parkinsonism as well as lower the blood pressure. For our patient rivastigmine was initially prescribed, and increased stepwise to the highest dose at 13.3 mg/24 h. In parallel

with increases in the rivastigmine, memantine was introduced. Due to decreased kidney function, the memantine dose was maintained at 5 mg daily.

It is beneficial to try to reach as high a maintenance dose as possible from the beginning. Increasing rivastigmine at later stages of the disease is neither theoretically nor practically fruitful. We usually use rivastigmine due to the possibility of bandage administration, since swallowing difficulties due to pharyngeal dysphagia is eventually seen in a large proportion of these patients [9].

Using acetylcholinesterase inhibitors to ‘economize’ with acetylcholine usually improves the visual hallucinations. We also aim to introduce memantine early. In older patients with reduced expected life span, and for whom visual hallucinations are not a main problem, it may be efficient to start with memantine since this titration is faster (1 month compared to maybe 6 months with cholinesterase inhibitors), and thereafter introduce rivastigmine to ensure that the sufferer gets a chance to benefit from the treatment. We have, together with researchers from Norway and England, shown that memantine improves DLB patients globally by improving their quality of life, reducing RBD as well as improving cognition (mental speed) [1, 7, 8, 18]. In clinical practice improvement in some patients’ motor functions can be striking; however, this clinical experience was not confirmed in our study or in the review by Stinton et al. [14].

Treat the Most Disturbing Symptom

Once rivastigmine and memantine are in place, we can start treating what the patient (and the caregiver) consider to be their worst problem. This may vary between patients and also for the same patient over time. We find it helpful to use the Neuropsychiatric Inventory (NPI) [4], to determine a symptom profile and decide on the sequence of treatment. For example, if hallucinations and delusions dominate, this would suggest a particular sequence of treatment that would differ if depression and apathy were to

dominate. Important symptoms and signs are listed below.

Parkinsonism

If Parkinsonism is the worst problem, a low dose of L-dopa can now be trialled, up to a total dose of 300–500 mg/day, especially if we estimate that the cognitive reserve is sufficient. We recommend never using dopamine agonists or catechol-O-methyl transferase (COMT)-inhibitors for these patients. Doing so will most likely deteriorate their condition with more easily induced confusional episodes, visual hallucinations and wild dreams. Many DLB patients also benefit from physical training, which seems to maintain their motor functions and postpone worsening. Our patient improved in motor function with memantine, which made it possible for him to undertake and increase the recommended physical activity. Overall, daily physical activity improved his motor function, but after 2 years a low dose of L-dopa was added, which reduced stiffness in the muscles. The cognitive reserve in our patient was estimated to be high with a Minimental State Examination (MMSE) score of 24. We also changed selective serotonin reuptake inhibitors (SSRI) to Serotonin–norepinephrine–reuptake-inhibitor (SNRI) partly to reduce Parkinsonism.

RBD

If the most disturbing symptom is RBD with acting out of wild dreams, we usually try mirtazapine, especially if there is a concomitant depressive component. We try starting with a 30 mg dose from the beginning, since the reduced wakefulness would otherwise be enhanced. However, sometimes the sleep component is the target of treatment, in which case 15 mg is used, carefully informing the patient and caregiver about this potential effect. We often have to complement this treatment with melatonin 2 mg, and in exceptional cases clonazepam 1–2 mg. A disadvantage with clonazepam, however, is a further lowering of the blood pressure. In our patient rivastigmine reduced the hallucinations as well as the nightmares, which may illustrate how the

nightmares (RBD) interact with nightly hallucinations. Later, at a time of unexpected psychological pressure for our patient, the nightmares returned and were more typical of RBD. They were then treated with mirtazapine 15 mg, since he also experienced difficulties falling asleep at night.

Fluctuating Cognition

Variations in attention and wakefulness are very often expressed as tiredness: sleeping many hours at night and still needing more than 2 h sleep during daytime. Episodic confusion is also part of this core criterion. It is difficult to treat the ‘unnatural tiredness’, often the most distressing symptom these patients experience. Rivastigmine can assist but is not enough for most patients. Increasing the orthostatic blood pressure may help some patients. To try to reduce the overwhelming tiredness in our patient, we tried modafinil 50 mg on two occasions. It was not a pleasant experience for him: he felt out of control, happened to push a vase over the table, moved too quickly and stumbled, and could not control his temper (became irritated and angry).

In an uncontrolled and small preliminary study of modafinil and armodafinil, an effect was seen on attention and global mental status, but was contradicted in a case report where exacerbation of agitation and psychosis were described [13, 17]. None of the rather few patients we have tried to treat with modafinil have responded positively. An alternative is the non-pharmacological approach of treating deficient attention and wakefulness by planning activities and rest periods in advance, by informing patients that they have to “pay” for unusually strenuous activities with increased tiredness and a need to sleep extra hours. One way of preventing confusional episodes and tiredness is to plan for a regular rest in the afternoons and not to force the patient to stay awake so as to fit into ‘normal’ sleeping hours later. Most often forced wakefulness will result in confusional episodes. This strategy was practised and stressed by both the patient and his wife as crucial for his improved state.

Depression and Anxiety

If depression is the most troublesome symptom, it is important to remember that DLB sufferers most likely have a more noradrenalin dominated deficiency instead of a serotonergic deficiency, at least according to the neuropathological reports of DLB cases which frequently describe very few cells in the locus coeruleus. With this in mind, venlafaxine 75–150 mg is an alternative strategy, sometimes combined with mirtazapine. Our patient was already on citalopram for depression when he came to us. We sometimes see that this strategy worsens the motor function and therefore prefer SNRI. Mirtazapine 15 mg and melatonin 2 mg were introduced to improve sleep patterns and to further reduce depressive tendencies. Later, venlafaxin 75 mg replaced citalopram and mirtazapine.

The same medication, mirtazapine and/or venlafaxin, is the basal treatment for anxiety. Oxazepam is often used concomitantly with antidepressants in anxiety in other disorders, but may in DLB patients aggravate orthostatic hypotension and induce falls, and should be avoided if possible.

Orthostatic Hypotension

If the blood pressure is low and orthostatic (declines more than 20 mmHg systolic or 10 mmHg diastolic while in the supine position within three minutes of standing), midodrine is most often the drug of choice. The starting dose is 2.5 mg 1–2 times daily, never given after 18:00 to avoid nightly hypertension. The maintenance dose can be as high as 30 mg daily. To plan the timing of the dose, we perform a 24 h blood pressure measurement before starting treatment. It is also beneficial to combine the treatment with compression stockings and provide widely available information about how to rise from a lying to standing position (sitting on the bedside, flexing and extending the feet), how to avoid lowering the blood pressure while standing in line (crossing the legs) and how to help the baroreceptors (sleeping with an extra cushion under the head at night). These actions often improve the global

well-being of the patient. We have seen DLB patients improve from 15 to 25 points on the MMSE, just by reducing blood pressure lowering medication. Therefore, before introducing agents that increase blood pressure, antihypertensives or medications with hypotension as a side effect will have to be reduced. Treating orthostatic hypotension is important as it could be a negative prognostic factor for DLB [16]. It is also important to emphasize that classical orthostatic symptoms and signs may not be present. As many as 50% of patients do not report any of the typical orthostatic symptoms like dizziness, blurred vision, or feelings of fainting [2]. This means that blood pressure measurements must be undertaken in all patients when DLB is suspected.

Our patient exhibited low and orthostatic blood pressure but no falls or signs of dizziness. So midodrine was added to the medication, which probably contributed to his general improvement. Repeated orthostatic 24 h blood pressure measurements were performed, and the dose of midodrine was adjusted to appropriate time points, and eventually terminated due to increased blood pressure which is not common, however.

Listed below are other common symptoms during the course of the DLB disease. While none of these symptoms affected our patient, who is the focus of this study, they were monitored during his visits, as is routine with all our patients.

Dysphagia

In one of our studies we showed that DLB patients have pharyngeal dysphagia, which puts them at risk of aspiration [11]. Very often this is noted as coughing at night or experiencing a feeling of food getting stuck in the throat without being able to clear it. As mentioned above, this dysphagia could be alleviated by a simple measure—drinking carbohydrate fluid [9]. However, our patient has been recommended to drink carbohydrate fluid, together with food and medicine, since this action does not have to be based on an established pharyngeal dysphagia diagnosis.

Nocturia

A symptom that is difficult to treat and often leads to a situation where continuing to live at home with the partner is precluded, is frequent nightly micturition. The partner is often exhausted by not getting enough sleep. Some of our patients have a good response to mirabegron. Anticholinergic medication should be avoided since acetylcholine deficiency is one of the main neurochemical features of DLB, which limits treatment possibilities. Some of our patients have successfully used desmopressin in low doses.

Hypersalivation

With the basic rivastigmine treatment there might be an amplification of hypersalivation, already a Parkinsonian symptom of the DLB disorder. Hypersalivation can be socially demanding. In several cases we have seen a beneficial effect from Botox injections in the salivary glands. For those who only suffer from hypersalivation during the night with soaked pillows, drops of atropine under the tongue have been helpful.

Hypophonia

A Parkinsonistic symptom which sometimes affects social life is hypophonia. It can be alleviated by auxiliary means such as voice reinforcers.

The actual treatment of our patient is described in Table 1.

Reflection on the Prognostic Factors and the Course of the Disease

To be able to plan the treatment, it is also valuable to reflect on prognostic factors and the course of the disease.

Clinical Prognostic Factors

Throughout the years we have tried to understand what factors affect prognosis and how intense the treatment can be for the individual. Having a larger cognitive reserve or capacity with relatively better scores on the MMSE may signal a more favourable prognosis and possibly permit faster uptitration of the medication. We

have seen in our studies that in patients with MMSE scores of 16–18, there is a steeper decline and DLB patients survive for a shorter time compared with Alzheimer patients) [16]. However, a large European retrospective DLB study did not find that the deterioration measured by MMSE was different for DLB compared with AD patients [6]. We and others have also seen that patients with mixed pathologies, DLB and Alzheimer, and lower beta-amyloid and higher tau levels in the CSF, signal worse prognosis [3, 10], as does a more pronounced orthostatic blood pressure reaction [16].

The course of the disease. We have learned that longer and more pronounced unexpected deteriorations are not part of the natural course for DLB patients. In these situations, we should rather search for additive, treatable somatic factors, like infections. On innumerable occasions, we have managed to reverse deterioration by treating a urinary infection, and the patient has returned to the status quo. On one occasion, a patient was moved from hospice back to her usual residence after proper treatment of an infection.

Actively Query Particular Symptoms and Signs

We have noted that many DLB symptoms and signs, such as visual hallucinations, are rarely reported voluntarily by sufferers or their carers. Most probably, this depends on the insight that patients have, as such phenomena suggest something is wrong with them, maybe psychiatrically; therefore, they avoid disclosure, at least in the earlier stages of the disease. One strategy to get information about the hallucinations is to start talking about dreams and nightmares, and inform them that many DLB patients in fact believe the persons in their dreams may remain in their consciousness the day after, and that this experience is not a sign of a psychiatric illness but an expression of the DLB disorder.

‘Wild dreams’ or RBD, which may no longer be present when other symptoms appear, is another symptom that has to be actively queried. RBD may be a very early sign, and can

Table 1 Changes of medication over time to alleviate experienced symptoms and introduce basic treatment of Lewy body dementia in the patient discussed in the paper

| Year | MMSE score | Aim | Worst problem | Medication (dose) | Result |
|---|------------|--------------|---|---|-------------------------------------|
| Many years prior | | | 'Burnout syndrome' | Citalopram (40 mg) | |
| 2012 | 24 | | Memory problems | Donepezil (10 mg) | |
| 2014 DLB diagnosed at the Memory Clinic | 24 | | Nightmares (RBD) | Mirtazapine (15 mg) Melatonin (2 mg) | Improvement |
| 2014 Jun | | Basal DLB | Stiffness | Memantine (5 mg) L-dopa (50 mg + 0 + 50 mg) | |
| 2014 Jul | | Basal DLB | | Donepezil, changed to Rivastigmine patch (4.6 mg/24 h) | Marked improvement No nightmares |
| 2014 Aug | | Basal DLB | | Increase rivastigmine (9.5 mg/24 h) | |
| 2014 Sep | | | 24 h BP: frequent recordings below 100 mmHg systolic | Start etilefrin Midodrine | No effect on BP |
| 2014 Nov | | Basal DLB | | Midodrine 5 mg (½ + ½ + 0) Increase rivastigmine 11.3 mg/24 h | BP improved |
| 2015 Jan | | | Very tired, sleeps a lot | 10 min walks daily | Continuous improvement |
| 2015 May | | SSRI to SNRI | Low BP, standing 85/60 | Citalopram (20 mg +) venlafaxin (37.5 mg) Midodrine increased (5 mg 1 + 1+0) | |
| 2015 Dec | | | Increased stiffness No nightmares Difficulties falling asleep | L-Dopa increased (50 mg + 100 mg + 50 mg) Melatonin paused Tries his wife's zopiclone (7.5 mg)! | Good effect! |
| 2016 Jan | 28 | | BP increased 168/106 standing 139/85, 150/96 Worse balance | Midodrine stopped Increase L-dopa (100 mg × 3) | |

Table 1 continued

| Year | MMSE score | Aim | Worst problem | Medication (dose) | Result |
|----------|------------|--------------|--------------------------------|---|---|
| 2016 Nov | 29 | | | Amlodipine by GP | BP: supine 139/93 Standing 125/9, 117/89 |
| 2017 May | 27 | | Increased unbearable tiredness | Modafinil (50 mg once) | Confusion |
| 2017 Oct | | SSRI to SNRI | | Citalopram (20 mg) changed to venlafaxine (75 mg) | |

appear as early as 5–10 years before other symptoms. We have one patient who experienced RBD 40 years before the rest of the disorder appeared. Many of the wives of my patients experience RBD as shameful that their husbands “turn into monsters at night time” and therefore do not voluntarily report possible RBD.

Disordered attention and wakefulness, expressed by many hours of sleep during the night, often 12–14 h, also has to be queried. The reason for its under-reporting may be that the sufferers often need their carers’ full attention when they are awake; therefore, while the DLB patient is asleep their carers take the opportunity to fulfil household tasks. It is also more difficult for carers and other surrounding people to understand that something is wrong since many DLB patients are intellectually well-preserved, especially with respect to memory. Many of the patient’s incapacities are blamed on motor dysfunction, Parkinsonism, even if visuospatial inability or deficient execution may be equally important reasons. Examples of visuospatial dysfunction are difficulties with sitting straight on a chair, putting on clothes, serving a drink and managing domestic appliances. Difficulties with handling numbers in all sort of situations are also typical. A university teacher of mathematics came to the clinic because he could not help his 8-year-old

grandson with his school maths; this was his very first symptom. Therefore, visuospatial disability and difficulties with maths and numbers have to be actively queried.

CONCLUSION

In conclusion, DLB is a neurocognitive disorder even if the patient’s memory is relatively spared, which often misleads on initial presentation. Parkinsonism without tremor means we have to physically examine the patient to be able to establish Parkinsonism. DLB patients and their carers may not report visual hallucinations, disturbed REM sleep or deficient attention with many hours of sleep during the night. This puts demands on the health care professionals to be informed about DLB and to ask the right questions. DLB is underdiagnosed, and should constitute up to 24.4% of all dementia cases [5], but is reported only in 3% of the patients in the Swedish dementia registry. This is regretful, as correct treatment may significantly improve the quality of life of these patients.

Among the different cholinergic pharmacological agents evaluated by Stinton et al. [14], we use rivastigmine which has had beneficial effects and rarely adverse events according to

our experience; although these events were mentioned in their review. Memantine is described as being well tolerated but with few benefits, the latter in contrast to our clinical experience. This might be due to the fact that we start memantine treatment at an earlier stage of the disease compared to the studies. Of the substances found by the study to have an effect, we routinely use levodopa and sometimes a low dose of clozapine and clonazepam, but we have yet to see any positive effect from modafinil. Our clinical experience is consistent with study findings that selegiline, olanzapine, quetiapine, risperidone and citalopram do not appear to be effective in the treatment of DLB.

As our patient and his wife described above, there are possibilities for great improvement. We have throughout the years seen patients who were moved from dementia to non-dementia wards in nursing homes, patients who were able to move back home from a nursing home. One patient at a nursing home, for example, managed to call an estate agent and bank and bought an apartment for himself since he did not enjoy his room at the nursing home. Similarly, our patient in this article was able to get back on the board of his company instead of being placed in a nursing home.

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Compliance with Ethics Guidelines. Informed consent was obtained from all participants for being included in the study.

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