Optimising the Design of Dementia with Lewy Bodies Trials

PEER REVIEWED

Dementia with Lewy bodies (DLB) is a neurodegenerative disorder characterised by parkinsonism and cognitive impairment but may also manifest multiple symptoms of dysautonomia, rapid eye movement (REM) sleep behaviour disorders, hallucinations, and cognitive fluctuations. Although well described for several decades, DLB remains a diagnostic challenge due to the clinicopathological overlap with other neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease dementia (PDD) and frontotemporal degeneration (FTD)[1]. Unfortunately, current diagnostic criteria have notoriously meagre sensitivity (between 12 % and 32 %) and it is estimated that approximately 78 % of patients receive a non-DLB diagnosis initially[1].

Additionally, patients and caregivers will often view DLB as a purely cognitive disease, and consequently will not volunteer non-cognitive symptoms as they believe these are of little consequence. Other non-cognitive symptoms such as autonomic and sleep behaviour disorders may also go under-recognised by patients. This may explain why DLB remains an under-recognised disease, despite being the third most common form of dementia. DLB reportedly accounts for at least 4 % of dementia diagnoses[2] but the true prevalence may be closer to 20-30 % of all dementias[3-4]. This manuscript will review the current literature on DLB controlled clinical trials and suggest optimal inclusion criteria, study parameters and outcome measures to help improve the design of DLB studies and ultimately increase signal detection.

Prior Clinical Studies of DLB

Surprisingly, there have only been four randomised, placebo controlled, published interventional trials assessing two drugs to treat DLB or PDD from which to glean clinical data to date. The table below summarises the relevant characteristics and accompanying metrics of those four trials.

All of these studies were performed between 2005 and 2014 in Europe, Japan and Canada. Interestingly, since the establishment of formal clinical trial registries such as clinicaltrials.gov, none of the placebo controlled clinical studies in DLB have been conducted at sites in the United States. Studies were relatively small in scope, ranging from 72 to 199 subjects overall, with durations ranging between 12 and 36 weeks. Of note, for the memantine studies[5-6] which included patients with both DLB and PDD, the recruitment rate was roughly double that of the donepezil studies[7-8] which enrolled DLB patients alone. All studies were designed to capture symptomatic drug effects in subjects with DLB or PDD.

	Memantine[5]	Memantine[6]	Donepezil[7]	Donepezil[8]
Study period	2005-2008	2007-2009	2007-2010	2011-2013
Population	PDD or DLB	PDD or DLB	probable DLB	probable DLB
Total number of patients DLB/PDD	72 (40;32)	199 (121;78)	140**	142
MMSE range	>12	10-24	10-26	10-26
Drug exposure	24 weeks	6 months	12 weeks	12 weeks + 36 weeks
Primary endpoint	CGIC;	#ADCS-CGIC; ADCS-ADL23	#CIBIC+; NPI*	MMSE; NPI-2
Secondary endpoints	MMSE; NPI, DAD; CST; UPDRS-3	NPI-12; ZBI; UPDRS-3	WMS-R; MMSE; ZBI; UPDRS-3	NPI-10; UPDRS-3; ZBI
Participating countries	Norway, Sweden, UK	EU	Japan	Japan
Total number of sites	4	30	48	72
Randomisation period (m)	36	23	28	14
Randomisation rate (p/m/s)	0.5 (DLB 0.22)	0.29 (0.11 DLB)	0.10	0.14
Screen failure rate	45.5%	Not provided	16.2%	11.8%
Attrition rate	22.2%	20.1%	11.5%	21.8%
SAE rate	Not given	12.5%	7%	7%

ADAS-cog = Alzheimer's Disease Assessment Scale-cognitive domain; ADCS-CGIC= Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change; CIBIC+ = Clinical Interview Based on Impression of Change; NPI=Neuropsychiatric Inventory; DAD = Dementia Assessment Disability; ADL = Activities of Daily Living; CDR=Cognitive Drug Research; CST=Cognitive Speed Test; VFT=Verbal Fluency Test; WMS-R = Wechsler Memory Scale; UPDRS-3 = Unified Parkinson's Disease Rating Scale – third item; ZBI =Zarit Burden Interview. *Original 10 items of NPI was enhanced with sleep and cognitive fluctuations assessment. **Initially planned sample size of 160 was reduced due to recruitment difficulties. # Primary endpoint was not formally defined.

Ensuring the Enrolment of Appropriate Patients

DLB represents a diagnostic conundrum and ensuring that the appropriate population of DLB patients are enrolled represents the foremost challenge of controlled clinical investigations at this time. DLB is most commonly associated with PDD and many researchers believe that the two diseases are simply different expressions of the same underlying disorder related to alpha synuclein dysfunction[9] and that only the temporal sequence of symptoms helps distinguish the two. Specifically, DLB is diagnosed when dementia develops before, or within one year after, parkinsonism onset, while PDD is diagnosed when dementia appears more than one year after the onset of otherwise typical Parkinson's disease. DLB and PDD share the same neuropathology and it is often impossible to differentiate DLB from PDD even upon autopsy[9]. However, there is a frequent coexistence of AD pathology with DLB[10-11] which tends to be less typical in PDD[12]. Additionally, the intersection between DLB and AD is so extensive that "pure" Lewy body disease (without any Alzheimer-type pathology beyond that attributable to normal ageing) is relatively uncommon, accounting for no more than a third of all cases of Lewy body disease and perhaps 10% of all cases of clinical dementia[12]. As cognitive decline and Parkinsonism are insidious, the distinction between PDD and DLB can be difficult to discern and may even be influenced by the sub-speciality interest of the diagnosing neurologist (for example, movement disorder specialist versus behavioural neurologist)[13]. Likewise, data on the relative frequency of DLB and PDD may be similarly affected by sub-speciality referral pattern.

Due to the shared clinicopathology and the diagnostic difficulties referenced above, ideal candidates for clinical trials should consist of those aged 50-85 years with diagnosis of "all cause dementia"[14] specifically due to probable DLB[4] or PDD[15]. The clinical presentation at this stage is difficult to distinguish from delirium, which can be seen in severe Alzheimer's Disease, and this should be seriously considered during the clinical assessment (with testing avoided at that time) particularly when measuring changes in cognitive and behavioural symptoms. The inclusion MMSE range should be fairly wide: 12(10)-24(26) as represented in past studies.

One of the unique features of both PDD and DLB (but not of AD) are cognitive fluctuations, with episodes of confusion, hypersomnolence, incoherent speech, and staring spells. These symptoms are apparent in 15% to 80% of patients with DLB[16] and are also common in patients with PDD[17]. Well-formed and detailed visual hallucinations occur in 60-70% of DLB patients, whereas auditory hallucinations are present in 40-50%

of subjects with DLB. Delusions and misidentifications have been observed in 40-60% of DLB subjects[18] and these can also serve as important inclusion criteria. Enriching on some of these features in a clinical trial setting may be particularly important, despite some loss in generalisability, especially when there is no objective evidence of a history of neuroleptic sensitivity and/or dopaminergic abnormalities in basal ganglia seen upon SPECT/PET.

Endpoint Selection in DLB

DLB studies should ideally be randomised, parallel placebo controlled design with drug exposure for at least 12 but preferably 24 weeks, in order to capture clinically important efficacy and safety signals. As stated earlier, DLB and PDD are very complex diseases and both have nearly identical clinical and neuropathological phenotypes[19-20]. During early stages, DLB and PDD might be differentiated by the predominance of dementia in DLB and of Parkinsonian motor features in PD, but there is no single sign, symptom or biomarker that definitively distinguishes PDD from DLB[20]. Furthermore, targeting one symptom of DLB often leads to complications in other aspects of the disease. Therefore, depending upon the mechanism of action (MoA) of the study drug it is possible that DLB symptoms may be important primarily for either efficacy or for safety reasons.

For example, dopamine replacement for motor symptoms frequently is known to exacerbate neuropsychiatric symptoms; conversely antipsychotic treatment of hallucinations may worsen Parkinsonism and increase the risk of a potentially fatal adverse reaction; while treatment of cognitive symptoms with cholinesterase inhibitors can complicate cardiac and gastrointestinal dysautonomia. Because of this, it may be beneficial to divide the array of DLB symptoms into five symptom target clusters: cognitive, neuropsychiatric, movement, autonomic, and rapid eye movement (REM) sleep behaviour disorder when planning studies. Direct assessments of each of these five symptom clusters can then form the basis of a comprehensive drug research strategy that may ultimately have the best chance for elucidating efficacy and safety signals and ultimately improve patients' overall quality of life.

Just as there is no single sign, symptom or biomarker that definitively distinguishes DLB, there is also no unified scale which can be used as a comprehensive assessment of symptoms or disease progression in DLB, such as those that are ubiquitous in other neurodegenerative disorders (e.g., Unified PD Rating Scale, Unified Multi System Atrophy Rating Scale). Therefore the changes within each of the five symptom clusters noted above need to be assessed with a specific scale tailored to that symptom cluster. For example, the UPDRS-3 can be used to assess motor symptoms, the NPI for neuropsychiatric symptoms and the Scale of the Assessment of Positive Symptoms (SAPS) for assessing hallucination, delusions, and behavioural changes associated with psychosis. Should cognition be selected as the primary efficacy endpoint, the selection of specific assessments matching the prominent visuospatial, executive and attention dysfunction noted in DLB is plentiful and encompasses both traditional pen-and-paper neuropsychological tests as well as computerised cognitive batteries. Importantly, if psychosis or cognition are selected as efficacy endpoints, the assessment of autonomic features, sleep and motor symptoms should be conducted as important safety endpoints. As DLB is a condition characterised by common falls, the potential preventive effect on falls might be ideally investigated as a novel endpoint. Finally, the impact on caregiver burden should be addressed in DLB studies. Of note, greater disability and worse QOL is reported in DLB than in AD regardless of instrument chosen or whether patient or caregiver-reported QoL utilised. The report that almost one in four patients with DLB are in health states considered equal to or worse than death is especially distressing, considering that the corresponding figure for the AD group is six per cent[21].

Conclusions

Despite the fact that DLB is the third the most common form of dementia, the number of therapeutic clinical studies is well below the number that could reasonably be expected and appears to be more in line with the number of studies that might be expected in orphan neurologic disorders. The lack of available interventional studies is not likely due to the lack of drugs whose MoA address important symptoms in DLB, but rather due to the diagnostic uncertainty of DLB and the lack of valid and reliable unified rating scales. The few published

controlled clinical investigations highlight the myriad methodological issues affecting patient selection and assessment, and this review represents an initial attempt to address some of the more salient issues in crafting a clinically feasible, state-of-the-art protocol, which will be able to capture both efficacy and safety signals in this multi-symptom complex neurodegenerative disorder.

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