Living with Lewy body dementia. Treatment, survival & quality of life.

Larsson, Victoria

2018

Document Version:
Publisher's PDF, also known as Version of record

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Treatment, survival & quality of life

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Living with Lewy body dementia

Treatment, survival & quality of life

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UNIVERSITY

DOCTORAL DISSERTATION
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To be defended 14 September 2018 at 9:00 am in Jubileumsaulan,
Medicinskt forskningscenter (MFC), Jan Waldenströms gata 5, Malmö.

Faculty opponent
Dr John-Paul Taylor, Newcastle University

Organization LUND UNIVERSITY Clinical memory research unit Department of clinical sciences, Malmö Faculty of medicine	Document name Doctoral dissertation Date of issue 14th of September 2018
Author(s) Victoria Larsson	Sponsoring organization

Title and subtitle Living with Lewy body dementia – treatment, survival and quality of life

Abstract

Background: Patients with Lewy body dementias (LBD) have a complex clinical picture. With no prevention or cure, management focuses around symptomatic relief, however pharmacological and non-pharmacological options have been inadequately investigated. Moreover, the understanding of survival, prognostic factors and impact of the diagnosis in an already ageing and comorbid population is limited. Even though well-being is the ultimate goal in current management, the constituents of well-being in LBD, as well as the preferences of patients, have not been extensively explored.

Aim: To understand the impact of living with Lewy body dementias, with a focus on pharmacological and non-pharmacological treatments, survival and quality of life.

Study populations: The studies comprise of LBD patients included in an RCT of memantine (Study I-II) and from the Memory Clinic, Malmö, Sweden (Study III-V).

Results: I) Physical activity during sleep decreased in LBD patients treated with memantine compared to placebo over 24 weeks. II) Quality of life in LBD is constructed of physical and socio-environmental domains. Treatment with memantine suggest a possible benefit over placebo for measures of caregiver-rated quality of life over 24 weeks. III) Swallowing dysfunction is common and sometimes asymptomatic in LBD patients. Carbonated thin liquid improves swallowing function compared to thin and thickened liquid. IV) Mortality is over three-times higher in patients with LBD compared to an age- and sex-matched general population. Excess mortality is found primarily in younger patients, females, those with lower MMSE and APOE ε4 carriers. V) It is feasible to conduct in-depth interviews with persons with DLB. Three themes characterise the experience of living with DLB; disease impact, self-perception and coping, and importance of others.

Conclusions: This thesis emphasises the importance of pharmacological and non-pharmacological management in LBD, particularly in view of the poor prognosis compared to the general population. This includes management of non-cognitive symptoms such as swallowing dysfunction, for which carbonated thin liquid might be a therapeutic option. Ultimately, improving well-being is of utmost importance, and for this to be achieved involvement of patients with LBD in research is crucial. A multifaceted approach is recommended, addressing physical, social and psychological needs.

Key words Lewy body disease, dementia with Lewy bodies, Parkinson's disease dementia, memantine, prognosis, survival, mortality, dysphagia, carbonated beverages, swallowing disorders, therapeutics, video recording, quality of life, qualitative research

Classification system and/or index terms (if any)

Supplementary bibliographical information		Language English
ISSN and key title 1652-8220		ISBN 978-91-7619-671-7
Recipient's notes	Number of pages 129	Price
	Security classification	

Signature  Date 2018/08/02

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Cover and portrait photography by Jonathan Silverberg

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ISSN 1652-8220
ISBN 978-91-7619-671-7

Printed in Sweden by Media-Tryck, Lund University
Lund 2018

MADE IN SWEDEN

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Dedicated to my late grandparents

Contents

Abstract

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List of publications

This thesis is based on the following articles, which in the text are referred to by their Roman numerals. Each article is found at the end as appendices.

I. Larsson V, Aarsland D, Ballard C, Minthon L, Londos E. The effect of memantine on sleep behaviour in dementia with Lewy bodies and Parkinson's disease dementia. Int J Geriatr Psychiatry 2010;25(10).

II. Larsson V, Engedal K, Aarsland D, Wattmo C, Minthon L, Londos E. Quality of Life and the Effect of Memantine in Dementia with Lewy Bodies and Parkinson's Disease Dementia. Dement Geriatr Cogn Disord 2011;32(4):227-34.

III. Larsson V, Torisson G, Bulow M, Londos E. Effects of carbonated liquid on swallowing dysfunction in dementia with Lewy bodies and Parkinson's disease dementia. Clin Interv Aging 2017;12:1215-22.

IV. Larsson V, Torisson G, Londos E. Relative survival in dementia with Lewy bodies and Parkinson's disease dementia. PLoS One 2018 Aug. 10;13(8):e0202044

V. Larsson V, Holmbom-Larsen A, Strandberg EL, Torisson G, Londos E. Living with dementia with Lewy bodies: an interpretative phenomenological analysis. *Manuscript submitted.*

Abbreviations

Aβ	β-amyloid
AD	Alzheimer's disease
APOE ε4	apolipoprotein E ε4 allele
BPSD	behavioural and psychological symptoms of dementia
CCI	Charlson comorbidity index
CGIC	clinical global impression of change
ChEI	cholinesterase inhibitor
CSF	cerebrospinal fluid
CT	computed tomography
DAT	dopamine transporter
DaTscan™	dopamine transporter imaging using ioflupane (^{123}I) SPECT
DLB	dementia with Lewy bodies
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	electroencephalography
eHR	excess hazard ratio
ESS	Epworth Sleepiness Scale
FDG	fludeoxyglucose
HR	hazard ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IPA	interpretative phenomenological analysis
LBD	Lewy body dementias
LBs	Lewy bodies
MIBG	^{123}I-metaiodobenzylguanidine

MMSE	mini-mental state examination
MRI	magnetic resonance imaging
MSA	multiple system atrophy
NFTs	neurofibrillary tangles
NMDA	*N*-methyl-D-aspartate
NPI	neuropsychiatric inventory
OH	orthostatic hypotension
PD	Parkinson's disease without recognised cognitive impairment
PDD	Parkinson's disease with dementia
PET	positron-emission tomography
PSG	polysomnography
QOL	quality of life
QOL-AD	Quality of Life in Alzheimer's disease
RBD	REM sleep behaviour disorder
RCT	randomised controlled trial
REM	rapid eye movement
RSWA	REM sleep without atonia
SLT	speech and language therapist
SMR	standardised mortality ratio
SSQ	Stavanger Sleep Questionnaire
SPECT	single-photon-emission computed tomography
TVSS	therapeutic videoradiographic swallowing study

Sammanfattning på svenska

Demens är ett samlingsnamn för flera sjukdomar som drabbar hjärnan och orsakar nedsättning av kognitiva förmågor och påverkar funktionsnivån. År 2015 uppskattades demenssjukdomar drabba 47 miljoner människor över hela världen. Lewy body-demens (LBD) är en av de vanligaste orsakerna till demenssjukdom efter Alzheimers sjukdom. Personer som insjuknar i LBD utvecklar en komplex symtombild med fluktuerande kognitiva besvär, Parkinsonliknande rörelsebesvär med stelhet och förlångsamning, synhallucinationer och störd drömsömn.

Det finns i nuläget inget som förebygger eller botar LBD och behandlingen inriktas därför på symtomlindring. Forskningen kring behandling av sjukdomen, prognostiska markörer och hur diagnosen påverkar återstående livslängd är otillräcklig.

Det finns inte heller några studier avseende hur personer med LBD upplever sin livssituation eller vad som är viktigt för att upprätthålla en god livskvalitet. Denna aspekt saknas också i behandlingsstudier där fokus istället ligger på förbättring av ett specifikt symptom, trots att vi inte besitter kunskap kring huruvida detta leder till ökat välmående för den drabbade.

Målet med denna avhandling är att undersöka olika aspekter av att leva med LBD, med fokus på behandling, överlevnad och livskvalitet. Studierna har främst inkluderat patienter med LBD som följts på Minneskliniken i Malmö, men även patienter som rekryterats i samarbete med forskare i Norge och Storbritannien för att delta i en placebokontrollerad studie av läkemedlet memantin. Läkemedlet är en så kallas NMDA-receptorantagonist som motverkar skadliga nivåer av signalsubstansen glutamat i hjärnan.

I vår första studie visade vi att patienter som fick behandling med memantin hade mindre tecken på störd drömsömn jämfört med patienter som erhöll placebobehandling. I vår andra studie fann vi att anhöriga till patienter som behandlades med memantin skattade deras närståendes livskvalitet högre än anhöriga till de som erhöll placebo. Resultaten stödjer andra studier som visat positiva effekter av behandling med memantin och antyder att memantin bör erbjudas till personer med LBD. Vår andra studie illustrerade också hur en kvantitativ skattningsskala kan användas som utfallsmått vilket även kan användas i framtida behandlingsstudier.

I vår tredje studie inkluderades patienter med LBD som genomgått en terapeutisk sväljningsröntgen. Denna studie visade att sväljningsproblematik som kan leda till

felsväljning är vanligt i denna patientgrupp även om patienten inte har subjektiva besvär. Vid jämförelse av olika vätskekonsistenser visade vi att kolsyrad dryck förbättrade sväljningsförmågan. Detta är således en enkel icke-farmakologisk behandlingsstrategi som kan utprövas i den kliniska vardagen.

I den fjärde studien undersökte vi överlevnadslängden hos personer som diagnosticerats med LBD och prognostiska faktorer för ökad dödlighet. Vi visade att patienter med LBD har en tre gånger ökad dödlighet efter diagnos jämfört med personer i befolkningen med samma ålder och kön. De vars livslängd påverkas mest är framförallt kvinnor, yngre patienter, de med positivt gentest för apolipoprotein ε4 och personer med lägre kognitiv förmåga vid diagnos.

I den sista och femte studien intervjuades personer med LBD för att öka kunskapen kring hur de uppfattar sin livssituation och vilka faktorer som är viktiga för deras välmående. Vi visade att var möjligt att genomföra djupintervjuer med personer med LBD vilket är viktigt att uppmärksamma. Bilden som framkom från intervjuerna var att personer med LBD har flera symtom som leder till fysiska, psykologiska och sociala begränsningar. Livssituationen är också beroende självkänsla, hantering av sjukdom med copingmekanismer och bemötande från omgivningen. Resultaten antyder att god livskvalitet är möjlig trots pågående sjukdom.

Sammanfattningsvis belyser den här avhandlingen att LBD är en allvarlig sjukdom som bidrar till tidig död, men att användning av farmakologiska och icke-farmakologiska behandlingsalternativ kan förbättra både symptom och livskvalitet. För att framtida behandlingar ska vara av värde för personen som lever med LBD måste den drabbades sjukdomsperspektiv och syn på behandling tas in i högre beaktning. Förhoppningsvis så kan detta perspektiv vara till nytta för att kunna förbättra vården för denna patientgrupp.

1. Background

Modern medical advances continue to push the boundaries of survival and life-expectancies, resulting in growing populations which are proportionally older than previous generations, illustrated in Figure 1. Facing the potential challenges that this entails, now and in the future, will be testing to medicine and our wider society.

Aging is associated with a number of serious illnesses, and out of these, dementia is the leading contributor to disability and dependence among older people worldwide.[1] In 2015, the estimated global prevalence of all-cause dementia was 47 million, and predictions believe that the number will double every 20 years, so that by 2050 the number would approximate 132 million.[1]

Dementia affects the individual living with disease, but also relatives and supporters of this person, as well as the wider society in terms of health and social care. This translates to large personal, social and financial burdens, needing to be confronted.

Research conducted in recent decades has expanded our understanding of dementia by great lengths. Importantly, we now know that dementia is not an inevitable consequence of ageing, but that lifestyle factors are likely to influence individual risk of dementia.[2] Furthermore, improved knowledge of underlying pathological mechanisms has enabled attempts at disease-modifying therapies. The hope for these advancements is to delay and reduce dementia incidence.

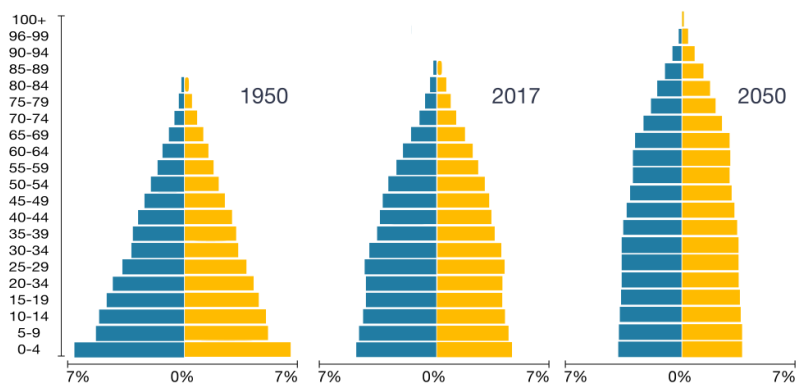

Figure 1. The demographical transformation over time.
Population pyramids illustrating the distributation of population in male (blue) and female (yellow) according to age groups in 1950, 2017 and estimations for 2050 (figure adapted from www.populationspyramid.net).

On the other hand, we do not know if or when absolute prevention or cure might occur. Until then, continued care for people with dementia will be vital. As clinicians, we have an opportunity to manage disease manifestations using pharmacological and non-pharmacological interventions, an aspect of care that this thesis will focus around. Gill Livingston provides a commendable summary of dementia care:

> People live with dementia in our societies, which should encounter, accept, contain, and support them. This entails community design to foster safe, affordable social activity and transportation, in addition to creation of societies in which people with dementia can be integrated. Thus, while we recommend specific interventions to prevent dementia, diagnose it early, manage the cognitive and neuropsychiatric symptoms, support carers, and improve living and dying with dementia, it is important that this health and social care occurs within, rather than separate from, society, so we can become truly dementia friendly.[2]

1.1. Dementia or major neurocognitive disorder?

The term dementia, although widely recognised, has rather negative connotations due to its Latin etymological origins (*de*, out of and *mens*, mind). Perhaps for this reason, the term has been replaced with 'major neurocognitive disorder' in the revised Diagnostic and Statistical Manual of Mental Disorders (DSM-V).[3] Nonetheless, the term dementia is still commonly used by both clinicians and patients and the two terms will be used interchangeably throughout this thesis.

The DSM-V criteria for major neurocognitive disorder include evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (learning and memory, language, executive function, complex attention, perceptual-motor and social cognition), interfering with independence in everyday activities.[3] Cognitive deficits should not occur exclusively in the context of delirium, or be better explained by other mental disorders. Compared to DSM-IV,[4] only one cognitive domain has to be affected, removing memory impairment as an obligatory feature for diagnosing major neurocognitive disorder.

According to these criteria, dementia or major neurocognitive disorder is purely a clinical syndrome, in turn representing a vast number of disorders, with the most common underlying cause being Alzheimer's disease.[1] Changes in diagnostic criteria can therefore alter diagnostic patterns, such as the change in DSM-V allowing a dementia diagnosis in absence of memory deficits. Likewise, novel biomarkers might alter the detection patterns of disease compared to clinical assessment alone. This has been evident in Alzheimer's disease (AD), where additional non-memory subtypes are being investigated using sophisticated neuroimaging methods.[5] Neuropathological verification is often claimed to support a definite dementia diagnosis, but even

neuropathology is not flawless, and its position as the gold standard for diagnosis has been challenged.[6] Further muddling the water is the recognition that many brains contain mixed pathologies – how do these interact, and what should be considered the primary diagnosis?

With this diagnostic complexity in mind, prevalence rates of different types of dementia need to be interpreted with some caution. Current literature suggests that the most common subtypes in order of frequency are Alzheimer's disease, vascular dementia, Lewy body dementias and frontotemporal dementia, illustrated in Figure 2, with rates varying slightly depending on country and study settings.[7]

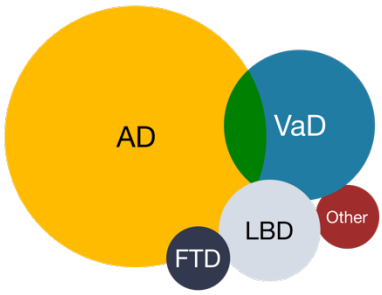

Figure 2. Depiction of dementia subtypes according to prevalence.
AD, Alzheimer's disease; VaD, vascular dementia; LBD, Lewy body dementias; FTD, frontotemporal dementia.

1.2. The history of Lewy body terminology

In 1817, James Parkinson described what we would now refer to as idiopathic Parkinson's disease (PD) in the famous "An Essay of the Shaking Palsy".[8] At this point, he resisted the presence of coexistent cognitive impairment, writing that "…the senses and intellects being uninjured". In the end of the 20th century however, changes in mental abilities were also described, and dementia would eventually be considered part of the disease manifestation of PD,[9] today classified as Parkinson's disease dementia (PDD).

In 1912, Friedrich Lewy described eosinophilic cytoplasmic neuronal inclusions in the subcortical nuclei in brains of persons with PD, named 'Lewy bodies' and subsequently considered the neuropathological hallmark of idiopathic PD.[10] It would take until the 1970s, when researchers in various geographical locations started recognising widespread cortical Lewy bodies on post-mortem examinations in patients with progressive dementia and concomitant parkinsonian features. This resulted in miscellaneous proposed terminology including diffuse Lewy body disease,[11,12] AD with PD changes,[13] Lewy body variant of AD,[14] dementia associated with cortical Lewy

bodies[15] and senile dementia of Lewy body type.[16] An international workshop was held in 1995, from which a consensus report was published, outlining that these patients in deed represented a separate disease entity from both AD and PD, and should be referred to as having 'dementia with Lewy bodies (DLB)'.[17]

Short after the publication of the first DLB guidelines, Maria Spillantini and colleagues published a paper outlining that the main component of Lewy bodies was the protein α-synuclein, revolutionising neuropathological detection and further research in this area.[18] One year later, another disorder was found to stain positively with α-synuclein, namely multiple system atrophy (MSA) with glial cytoplasmic inclusions, revealing a molecular link between the disorders. A number of rare α-synuclein-positive disorders have thereafter been identified. Together, these disorders are referred to as 'synucleinopathies' or disorders with 'Lewy pathology'.[19]

The relationship between DLB and PDD has been a much-debated topic in recent years – are they distinct diseases, different phenotypes on the same spectrum, or in fact the same disease?[20] Since the discovery of shared pathological correlates, this relationship has been eagerly investigated without a definite answer. In 2007, a working group on the topic concluded the diseases to be 'more similar than different',[21] with the main difference being the temporal sequence of cognitive symptoms relative to parkinsonism. The so called '1-year-rule' dictates that if dementia precedes or occurs within one year of the onset of motor features, the diagnosis is DLB. If motor symptoms are present for over one year prior to dementia development this is instead called PDD (a diagnosis which in reality is mostly given in the setting of already established PD).[22]

Recognising clinical and pathological similarities between DLB and PDD have resulted in an umbrella term for the two, 'Lewy body dementias' (LBD).[23] The terminology is further illustrated in Figure 3. The common term LBD will be used throughout this thesis, albeit differences between DLB and PDD will at times also be highlighted.

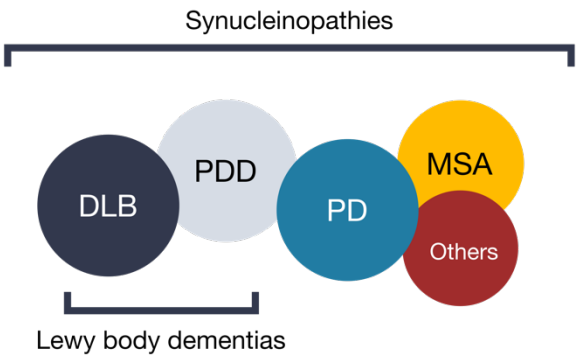

Figure 3. Terminology of synucleinopathies.
DLB, dementia with Lewy bodies; PDD, Parkinson's disease dementia; PD, Parkinson's disease; MSA, multiple system atrophy.

1.3. Diagnosis of Lewy body dementia

In patients with an established diagnosis of PD, cognitive decline is an expected feature. While this can take the form of subjective cognitive decline or mild cognitive impairment, a number of longitudinal studies show that the majority of patients surviving over ten years after PD diagnosis will eventually develop dementia.[24] Diagnosing PDD is therefore relatively straightforward, although exclusion criteria exist (Table 1A).[25] In terms of prevalence, a systematic review found that PDD represented 3.6% of all dementia cases.[26]

Diagnosis of DLB has historically been more complicated with many cases being missed or misdiagnosed as AD. Whereas the consensus criteria in 1996 provided an international standard for diagnosis and improved recognition, sensitivity was still suboptimal.[27] This was addressed in the revised criteria of 2005, aiming to improve sensitivity whilst preserving specificity.[28] Whilst the clinical criteria of 1996 required two out of three core features – fluctuations, visual hallucinations and parkinsonism – for a diagnosis of probable DLB, the 2005 criteria added three suggestive features – rapid eye movement (REM) sleep behaviour disorder, severe neuroleptic sensitivity and low dopamine transporter uptake in basal ganglia – which if present in combination with one core feature would be sufficient for a probable DLB diagnosis. According to one study this improved identification of DLB cases with 25%.[29]

Nevertheless, recent studies suggest persistently low and varying detection rates.[30,31] A systematic review concluded that the prevalence of DLB out of all dementia cases was 4.2% of in community care and 7.5% in secondary care, although ranging widely between 0-24% depending on study.[30] This is in contrast to neuropathological reports, suggesting that up to 25% of dementia cases are attributed to DLB.[32]

In 2017, a fourth consensus report for DLB was published,[22] outlined in Table 1B. The main difference from previous criteria is the clear distinction between clinical features and diagnostic biomarkers, as well as the incorporation of REM sleep behaviour disorder as a core feature.

Table 1. Diagnostic criteria.

A) Criteria for Parkinson's disease dementia[25]
Core features Diagnosis of PD + Dementia diagnosis in established PD
Associated Cognitive profile (impairment in attention, executive, visuo-spatial, memory), behavioural features (apathy, depression, anxiety, visual hallucinations, delusions), excessive daytime sleepiness
Features which make the diagnosis less certain Co-existence of any other abnormality that can cause dementia but not judged to be cause of dementia e.g. vascular disease OR time interval between motor and cognitive symptoms not known
Features which makes it impossible to diagnose PDD Cognitive and behavioural symptoms appearing solely in the context of other conditions such as e.g. systemic disease, intoxication, major depression OR fulfils criteria of probable vascular dementia
Diagnosis
Probable PDD Both core features and impairment in 2 out of 4 cognitive domains and no features making the diagnosis uncertain or impossible (1 or more behavioural symptom supports diagnosis but does not exclude)
Possible PDD Both core features and atypical cognitive impairment with or without behavioural symptoms and presence of 1 or more of features making diagnosis less certain but none making it impossible

B) Criteria for dementia with Lewy bodies[22]
Essential Dementia diagnosis
Core clinical features Fluctuating cognition, recurrent visual hallucinations, REM sleep behaviour disorder, parkinsonism
Supportive clinical features Severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction, e.g. constipation, orthostatic hypotension, urinary incontinence; hypersomnia; hyposmia; hallucinations in other modalities; systematised delusions; apathy, anxiety, and depression
Indicative biomarkers Reduced DAT uptake on SPECT or PET, abnormal MIBG scintigraphy, PSG confirmation of RSWA
Supportive biomarkers Relative preservation of MTL on CT/MRI, generalised low uptake on SPECT/PET perfusion/metabolism scan with reduced occipital activity ± cingulate island sign on FDG-PET imaging, posterior slow-wave activity on EEG with periodic fluctuations in the pre-alpha/theta range
Diagnosis
Probable DLB 2 or more core features with or without indicative biomarkers OR 1 core feature but with 1 or more indicative biomarkers
Possible DLB 1 core feature and no indicative biomarkers OR 1 or more indicative biomarker and no core clinical features
DLB is less likely if Presence of other physical illness explaining the disease, but can indicate mixed pathologies OR if parkinsonian features are the only core feature and appear in severe dementia

Abbreviations: CT, computer tomography, DAT, dopamine transporter; DLB, dementia with Lewy bodies; EEG, electroencephalography; FDG, fludeoxyglucose; MIBG, metaiodobenzylguanidine; MRI, magnetic resonance imaging; MTL, medial temporal lobe; PD, Parkinson's disease; PDD, Parkinson's disease dementia; PET, positron-emission tomography; PSG, polysomnography; REM, rapid eye movement; RSWA, REM sleep without atonia; SPECT, single-photon-emission computed tomography.

1.3.1. Pathological hallmarks of disease

The hallmarks of LBD are aggregated α-synuclein in Lewy bodies (LBs) and Lewy neurites, distributed within the central and peripheral nervous systems.[23] In addition to α-synuclein pathology, significant AD-pathology – β-amyloid (Aβ) plaques, neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau, and cerebral amyloid angiopathy – is frequently present, although not a universal finding.[20]Other neurodegenerative substrates have also been seen such as TAR DNA-binding protein-43 pathology, argyrophilic grain disease, as well as vascular disease.[33] A synergistic relationship between these pathologies is postulated, influencing clinical phenotypes and the diagnostic spectrum.[20,33]

Several neuropathological classification systems exist for the various pathological hallmarks which are beyond the scope of this thesis. In terms of Lewy body pathology however, a staging system has been proposed by Braak and colleagues, suggesting a sequential spread, starting in the medulla oblongata and disseminating rostrally in the brainstem to the limbic system and subsequently to the neocortex (Figure 4).[34] Although accepted as the main theoretical model regarding neuropathological progression in PD, the hypothesis has been questioned since a large proportion of cases with LB-pathology do not adhere to the proposed pattern of progression.[35,36]

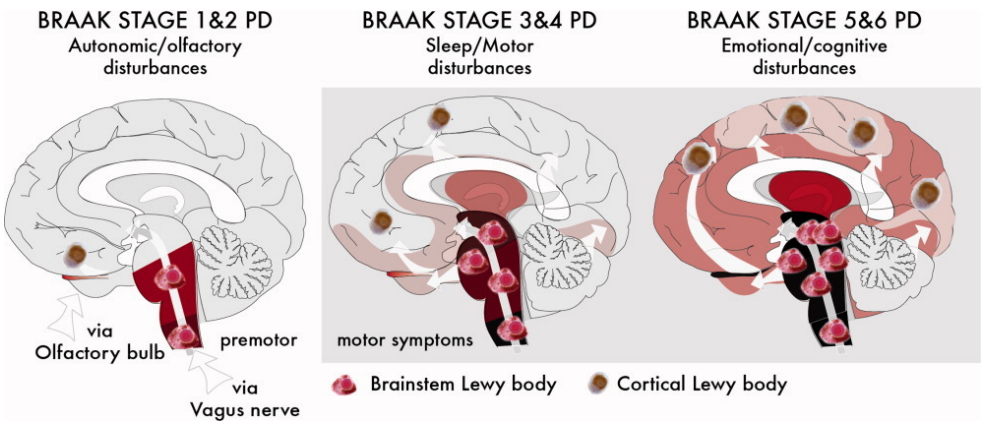

Figure 4. Braak staging for Lewy body pathology in Parkinson's disease.
Demonstrating the initiation sites in medulla oblongata and olfactory bulb with later infiltration in cortex. Permission obtained from John Wiley and Sons © Halliday, G. et al. Mov. Disord. 26, 1015–1021 (2011).

In the initial DLB criteria from 1996, neuropathological verification simply required LBs somewhere in the brain in a patient with a clinical history of dementia. This was a

rather liberal definition, and with increasingly sensitive examination methods it was found that many AD patients would meet pathological criteria for DLB, albeit not demonstrating the typical clinical syndrome. For this reason, revised neuropathological criteria were proposed in the third consensus report of DLB in 2005, taking into account that increasing Alzheimer-related pathology reduce the likelihood of a typical DLB syndrome. These criteria were largely retained only with minor modification in the latest consensus guidelines in 2017, outlined in Table 2. In this staging system, Alzheimer-related pathology is graded based on the National Institute on Aging–Alzheimer's Association criteria incorporating severity of Aβ plaques,[37] neuritic plaques[38] and NFTs.[39-41] Even when the pathological diagnosis is deemed to be LBD over AD, concomitant AD-pathology might be of relevance. Evidence suggest a synergistic relationship whereby AD-pathology contributes to shorter time interval from parkinsonism to dementia,[42,43] and that burden of NFTs predict shorter survival.[44]

Table 2. Neuropathological criteria for dementia with Lewy bodies.
Likelihood of findings being associated with a typical clinical case of dementia with Lewy bodies. Adapted from McKeith et al. (2017).

Lewy-related pathology	Alzheimer-related pathology		
	NIA-AA Not/Low	NIA-AA Intermediate	NIA-AA High
Diffuse neocortical	High	High	Intermediate
Limbic (transitional)	High	Intermediate	Low
Brainstem-predominant	Low	Low	Low
Amygdala-predominant	Low	Low	Low
Olfactory-bulb only	Low	Low	Low

1.3.2. Genetics

Even though both DLB and PDD are primarily sporadic diseases, genetic factors could be relevant in their causation. Defects in genes associated with PD such as *SNCA* gene coding for α-synuclein,[45] leucine-rich repeat kinase 2 (*LRRK2*)[46] or glucocerebrosidase (*GBA*)[47] have in addition to PD been associated with clinical expression of PDD and DLB. Mutations in genes related to AD such as presenilin 1 (*PSEN1*), presenilin 2 (*PSEN2*)[48], apolipoprotein E (*APOE*)[49,50] and microtubule associated protein tau (*MAPT*)[51] have also been associated with DLB. These findings provide further support for a shared underlying pathological mechanism between these disorders.

Out of these identified genetic contributors, the strongest risk factors for DLB were concluded in a recent review to include rare variants in glucocerebrosidase (GBA) and the apolipoprotein E (*APOE*) ε4 allele.[52] Apart from the *APOE* ε4 allele having a strong link with development of AD suggesting increased risk of additional AD-pathology,[53] studies have also shown how *APOE* ε4 increases risk of DLB without AD-pathology, suggesting a separate mechanism of dementia development.[50] Frequency of *APOE* ε4

is approximately 30% in DLB patients, compared to 14% in healthy controls.[52] Poor disease-course and prognosis has been associated with *APOE* ε4 in DLB.[54-56] The role of *APOE* in PDD is less clear.[57]

1.3.3. Clinical manifestations of disease

Cognitive impairment

Dementia, defined as a slowly progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational functions, or impairing daily life, is essential for the diagnosis of LBD.[22,25] Compared to other types of dementia, memory and language functions have been found to be relatively preserved in LBD, with early deficits in attention, executive function and visual perceptual disturbance instead being more typical.[58-61] Patient complaints can include difficulties with multitasking, becoming more passive, not keeping up in conversation, or problems with distance judgement leading to e.g. missing the glass when pouring water. A global screening test such as the mini-mental state examination (MMSE) which predominantly measures memory and language, is therefore not suitable, and a wider range of testing needs to take place.[62] Although some differences have been identified, definite discrimination between cognitive profiles in DLB and PDD has not been established.[63,64]

Fluctuations

Fluctuating cognition is a core clinical feature in DLB, and although similar in quality encountered less frequently in PDD, particularly in the early stages of disease.[65] Fluctuations occur spontaneously, and include sudden episodes of changed behaviour, incomprehensible or confused speech, altered consciousness or alertness.[22] The underlying neurobiological basis is not clear, but might be related to thalamic atrophy and cholinergic deficits.[66,67] Fluctuations have been considered difficult to assess in clinical practice, and specific scales have been developed to reliably distinguish fluctuations in DLB from that of other dementias.[22,68]

Parkinsonism

Parkinsonism in PD is defined as bradykinesia, in combination with either rest tremor, rigidity, or both.[69] Per definition, patients with PDD will have features of parkinsonism prior to diagnosis. Spontaneous parkinsonism is also commonly seen in DLB, eventually occurring in over 85% of patients.[70,71] Resting tremor is less frequent in DLB patients, with postural instability and gait disorder (related to rigidity) being more common.[72-74] This motor type has been suggested to be non-dopaminergic in nature, which could explain the variable levodopa response in DLB compared to PD.[75,76]

Visual hallucinations

Another hallmark of disease is recurrent visual hallucinations, present in up to 80% of patients with LBD.[77] Visual hallucinations are typically complex and detailed, and take the form of animated objects such as people, children or animals, but can also be illusions, feeling of passage or simple visual hallucinations,[78] see Figure 5 for comparison. Patient-response to visual hallucinations differ, but mostly include non-frightening descriptions, although this can change with declining cognition and increasing risk of associated delusions.[79]

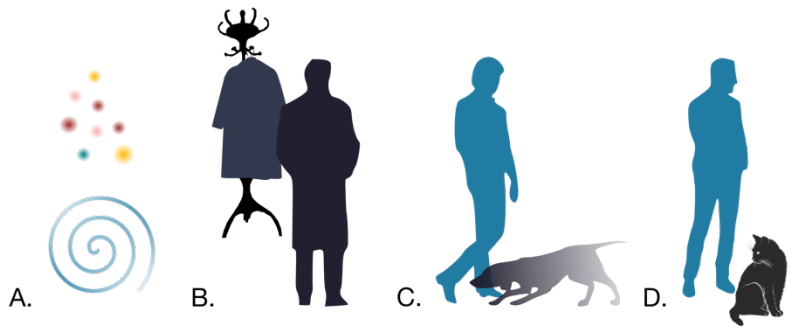

Figure 5. Spectrum of visual phenomenon in Lewy body dementias.
A) Simple visual hallucinations (e.g. lines, dots) B) Illusions (ie incorrect perception of real stimuli eg mistaking coat hanger for a person) C) Feeling of passage (e.g. seeing animal passing by in peripheral field) and D) Complex visual hallucinations (ie seeing detailed animated objects without stimuli).

The structural and functional correlates of visual hallucinations in LBD are not fully understood, with a number of mechanisms proposed.[80,81] For diagnostic purposes, visual hallucinations are useful in patients with mild cognitive impairment or early dementia, as they predict the presence of LB-pathology with high specificity and virtually exclude pure AD-pathology.[60,82,83] In patients with PD, visual hallucinations can precede motor symptoms,[84] and is a predictor for cognitive decline and progression to dementia.[85-87]

REM sleep behaviour disorder

REM sleep behaviour disorder (RBD) is a parasomnia characterised by complex motor behaviours during REM sleep. To fulfil international criteria for RBD, these behaviours should be either suspected based on reports of dream enactment or documented during polysomnography (PSG), together with evidence of REM sleep and loss of muscle atonia on PSG.[88] Dreams are often described to be aggressive in nature, such as being chased or needing to defend oneself from animals or people, resulting in risk of injury to bedpartner or self.[89]

In absence of neurological impairment, patients with RBD are diagnosed with idiopathic RBD. However, cohorts with longitudinal follow-up have demonstrated a strong association with future neurodegenerative disease, specifically the synucleinopathies. The longer the follow-up, the higher the likelihood of conversion to a neurological disorder, with rates up to 90%.[89]

RBD is an early and common symptom in LBD, prevalent in up to 80%, with the ability to improve diagnostic accuracy,[70] endorsing the inclusion of RBD as a core feature in the latest consensus criteria of DLB.[22] The precise pathophysiology of RBD remains unclear, but involvement of brainstem nuclei have been proposed, something which would correspond well with the Braak staging of Lewy body-pathology,[34] considering the temporal sequence of RBD characteristically preceding motor or cognitive symptoms in LBD.[22]

Supportive clinical features

A wide range of other clinical symptoms are seen in LBD, although non-specific in nature and therefore only supportive for diagnosis. These include severe neuroleptic sensitivity, postural instability, repeated falls, syncope, transient episodes of unresponsiveness, severe autonomic dysfunction, hypersomnia, hyposmia, hallucinations in other modalities, systematised delusions, apathy, anxiety and depression.[22]

Dysphagia & swallowing dysfunction

Another non-specific clinical feature, not included in the DLB consensus criteria, is that of swallowing impairment. Swallowing dysfunction is the focus of Study III within this thesis, which is why this is being described in further detail.

Dysphagia is defined as "the perception that there is an impediment to the normal passage of swallowed material".[90] Swallowing dysfunction can in turn be objectively verified using different assessments such as videofluoroscopy, described further in the Methods section. Although not useful for diagnostic purposes, dysphagia is a risk factor for dehydration, malnutrition, aspiration pneumonia, hospitalisation and mortality, which is why it is an important symptom to recognise and treat.[91]

The prevalence of dysphagia, type of swallowing dysfunction and resulting consequences have not been well-characterised DLB. Considerably more research has been conducted in patients with PD, but patients with cognitive impairment have largely been excluded, and findings are variable because of heterogeneity in disease stage and measuring methods.[91] It is generally accepted however that most patients with PD will develop dysphagia at some stage of their disease-course. A meta-analysis showed that the pooled prevalence of subjective dysphagia was 35%, though when measured objectively this increased to over 80%, demonstrating how patients are frequently unaware of this symptom.[92]

In patients with LBD, one study showed that 32% of consecutive patients report subjective dysphagia, of which >90% had an objectively verified swallowing dysfunction when investigated using videofluoroscopy.[93] Another study included patients with LBD irrespective of dysphagia symptoms, and demonstrated that 35% had an objective swallowing dysfunction, which also predicted cumulative pneumonia incidence during follow-up.[94] DLB patients have also shown to have more subjective swallowing symptoms than patients with AD,[95] and shorter survival time from dysphagia onset compared to other synucleinopathies.[96] Additional studies of dysphagia in LBD are currently lacking and further work desirable.

1.3.4. Biomarkers of disease

Several biomarkers have been identified, serving as indirect measures of neuropathology, and aiding differential diagnosis and prognosis in LBD. These range from biochemical biomarkers including analysis of cerebrospinal fluid (CSF), to structural and molecular imaging. For DLB, a number of indicative biomarkers have been included in the most recent revised consensus criteria because of their ability to discriminate DLB from other dementias, primarily AD. Other biomarkers are interesting for research purposes, but further confirmation of their value is needed before they can be considered clinically useful.

Biochemical biomarkers

In AD, decreased levels of 1-42 β-amyloid and increased total and phosphorylated tau protein in CSF are established biomarkers for the pathological disease process. In LBD, the role of these CSF biomarkers are less clear but have been suggested to represent concomitant AD-pathology.[97] They are more commonly found in DLB patients compared to PD, with PDD patients being positioned in between the two,[98] indicating LBD being positioned on a disease spectrum in terms of pathology. There are no clear biochemical biomarkers for LB-pathology, but both CSF and blood α-synuclein are being investigated, with the majority of studies showing a reduction in CSF total α-synuclein in synucleinopathies.[99]

Structural & molecular imaging

Reduced dopamine transport (DAT) uptake in the basal ganglia, measured either with single-photon-emission computed tomography (SPECT) or positron-emission tomography (PET), has been useful in DLB cases where parkinsonian signs have been difficult to assess clinically. This is an indicative biomarker in the revised consensus criteria from 2017, due to its ability to distinguish DLB from AD with a sensitivity of up to 80% and specificity of 92%.[100] Importantly, reduced DAT uptake does not distinguish between DLB and PDD, or other degenerative parkinsonian syndromes

with loss of dopamine neurons including PD, MSA, corticobasal degeneration and progressive supranuclear palsy.[101]

^{123}I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy is a marker of postganglionic cardiac sympathetic innervation, and another indicative biomarker of DLB. It has been useful in discriminating between clinical DLB and AD, with a sensitivity of 69% and specificity of 90%.[102,103] Uptake is also reduced in PD, with no specific studies assessing PDD.[25]

A number of other structural and molecular imaging biomarkers are outlined in Table 1B, less specific for a diagnosis of DLB but potentially supportive in the diagnostic process. Moreover, molecular imaging supporting in vivo visualisation of amyloid and tau pathology in AD patients has flourished in recent years. Patients with LBD have been found to have less uptake compared to AD patients but more than controls, without definite boundaries to aid differential diagnosis.[104] Although not available at present time, molecular visualisation of LB-pathology would be highly desirable to be used in combination with amyloid and tau imaging for better characterisation of the disease spectrum.

Other biomarkers

A definite diagnosis of RBD, one of the core criteria of DLB, requires REM sleep without atonia (RSWA) confirmation on PSG. When present in a person with dementia and history of RBD, this predicts a synucleinopathy in over 90% of cases.[105] In reality, PSG confirmation to aid LBD diagnosis is not possible in many centres where cost and time are the primary barriers. An alternative measurement, although not strictly sufficient for diagnosis, would be validated screening measures.[106]

A number of neurophysiological methods have emerged as potential biomarkers in LBD. Quantitative electroencephalography (EEG) has been found to serve as a good discriminator from AD, which is why it is included as a supportive biomarker in the consensus criteria for DLB.[107,108] Other methods include transcranial magnetic stimulation, magnetoencephalography, and assessments of the blink reflex, although the methodologies and populations have been heterogenous, precluding firm conclusions, with further research needed.[109]

1.4. Treatment for Lewy body dementias

1.4.1. Pharmacological therapies

Pharmacological management for LBD remains a challenging issue. With no prevention or disease-modifying therapies, treatment is symptomatic, aiming to address the complex combination of cognitive, motor, psychiatric and autonomic features encountered. Patients are sensitive to medication changes, and treatment of one symptom can often exacerbate another, creating a difficult balancing act for the treating clinician.

Treatment recommendations in LBD are based on a limited number of pharmacological trials, outlined in Table 3. Further management of the wide range of symptoms, where LBD-specific evidence is missing, is guided by related data from the dementia and PD-field as well as clinical expertise and expert opinion.

Cholinesterase inhibitors

Medications with anticholinergic properties are often prescribed to elderly patients, including those in memory clinics.[110] These medications have been associated with worsening cognition, functional performance, and dementia risk.[111] Prior to prescribing cholinergic medication, the anticholinergic burden should be minimised in those with dementia.

Patients with LBD have early and profound cholinergic depletion, more than that seen in AD.[112-114] In line with this, treatment with cholinesterase inhibitors (ChEIs), which restore cholinergic function by blocking acetylcholine breakdown in the synaptic cleft, is associated with a better response in LBD compared to AD patients.[115,116] Out of all treatments in LBD, the evidence level for ChEIs is the highest, see Table 3, with RCTs demonstrating improvement in global, cognitive, neuropsychiatric and daily function.[117-119] In terms of MMSE, a meta-analysis showed a mean improvement of 1.26 points with 10-24 weeks of treatment.[117] Larger effects were seen with donepezil in DLB, and with rivastigmine in PDD. Visual hallucinations seem to respond particularly well to ChEIs,[120-125] highlighting the potential role of the cholinergic system in generating this symptom.[126] Importantly, no significant motor decline has been shown with ChEI treatment in LBD.[127,128] Common side-effects include gastro-intestinal disturbances, somnolence, dizziness and insomnia. Treatment with cholinesterase inhibitors have also shown relevance in terms of prognosis by delaying nursing home admission[129] and reducing mortality.[118]

Table 3. Pharmacological management in LBD.

Symptom	Treatment options	Highest level of evidence	Comment
Global	Rivastigmine Donepezil	Meta-analyses of RCTs (n=1428)[117-119]	Risk of cholinergic side effects due to underlying autonomic dysfunction.[130] Transdermal patch of rivastigmine if GI side effects.
	Memantine	Meta-analyses of RCTs (n=275)[117,119,131]	Overall high tolerability demonstrated.
Cognitive	Rivastigmine Donepezil	Meta-analyses of RCTs (n=1511)[117-119]	Improvements on MMSE, ADAS-Cog.
	Memantine*	RCTs (n=75)[132,133]	Effects on cognitive speed and attention.
Parkinsonism	Levodopa	Uncontrolled (n=40-51)[75,76,134,135]	Same as in PD but at lower doses and with less benefit.[75] Risk of worsening hallucinations or delusions.[136]
	Zonisamide	RCT (n=158)[137]	Beneficial as adjunct to levodopa without worsening cognitive or psychiatric function.
Visual hallucinations	Rivastigmine*	RCT for DLB (n=120)[120] Open-trial for PDD (n=12)[122]	Review showing reduction of 90% in PDD.[121]
	Donepezil*	RCT for DLB (n=140)[123] Open-trials for PDD (n=6-11)[124,125]	Improvement on NPI scale.[123]
	Memantine*	RCT for DLB (n=199)[138]	Improvement on single-item NPI.
Sleep behaviour	Melatonin	Uncontrolled for DLB (n=7)[139]	Found to decrease RSWA.[140] RCT in PD suggesting subjective improvement.[141]
	Clonazepam	Case serie (n=3)[142]	Reduces phasic activity, but RSWA still present in iRBD.[143]
	Memantine*	RCTs (n=57-75)[138,144]	Improvement on single-item NPI in DLB only;[138] improvement in proxy-rated physical activity at night.[144]
	Rivastigmine Donepezil	Uncontrolled trials (n=6-16)[145,146]	Improvement in PSQI,[145] actigraphy and sleep questionnaire.[146] RCT showing benefit in sleep activity at night in PD.[147]

Abbreviations: ADAS-Cog, Alzheimer's Disease Assessment Scale-cognitive subscale; DLB, dementia with Lewy bodies; ESS, Epworth Sleepiness Scale; iRBD, idiopathic REM sleep behaviour disorder; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory; PDD, PD, Parkinson's disease; Parkinson's disease dementia; PSQI, Pittsburgh Sleep Quality Index; RSWA, REM sleep without atonia. *secondary outcome.

Memantine

Glutamate is the most widely distributed neurotransmitter within the central nervous system, acting on several receptors including the *N*-methyl-D-aspartate (NMDA) receptors. Considerable evidence has suggested that glutamatergic dysregulation can contribute to excitatory neurotoxicity, which is why pharmacological agents counteracting this action have been investigated.[148] One such agent is memantine, a low-to-moderate affinity uncompetitive antagonist at the NMDA-receptor, aimed to suppress activation during pathological conditions, whilst preserving activation during physiological conditions.[148] Because of the recognition of glutamatergic dysfunction in a wide range of neurological and psychiatric diseases, several clinical trials of memantine have been attempted, however with inconclusive results. To date, the only approved use of memantine has been for moderate-to-severe AD, a recommendation based on two placebo-controlled double-blind RCTs, demonstrating improvements in global and functional outcomes.[149,150]

Altered glutamatergic synapses have also been seen in DLB patients at autopsy[151] and parkinsonian animal models,[152,153] suggesting a potential role for memantine in LBD. Initial evidence consisted of case reports in patients with LBD with variable responses, prompting further studies. Three placebo-controlled double-blind RCTs have been conducted in DLB and PDD,[132,138,154] with two studies indicating an improvement in clinical global impression of change (CGIC),[132,138] but no overall convincing evidence in secondary outcomes such as cognitive, psychiatric or motor domains.[117,119,131] Secondary analyses of these studies have been performed, including Study I-II within this thesis investigating effects on sleep measures[144] and quality of life,[155] as well as studies suggesting effect on survival,[156] goal attainment,[157] caregiver burden[157] and attention.[133] Overall, memantine has been well-tolerated in the trials with few reported withdrawals.

Treatment of sleep disturbances

For patients with RBD impacting quality of life or risk of sleep-related injury, pharmacological treatment should be considered. The first step is to assess whether or not the patient is prescribed any medication known to aggravate RBD, predominantly consisting of various classes of antidepressants, and if feasible consider discontinuation or reduction.[158] As outlined in Table 3, suggested pharmacological agents lack a rigorous evidence-base, and no studies have included PSG evidence of improved RBD.

Clonazepam, a long-acting benzodiazepine, has long been considered the first-line option for RBD.[159] Recommendations in LBD are based on expert opinions describing reduction in frequency of RBD, and a case series where two out of three patients with DLB had subjectively improved sleep patterns after clonazepam administration.[142] Clonazepam is however associated with a sedating effect and risk of worsening cognitive function, which is why other agents have been welcomed.[160]

Melatonin is an endogenous hormone secreted by the pineal gland and is involved in circadian rhythm regulation.[159] Melatonin is safe and tolerable and has shown to be beneficial in improving RBD irrespective of the underlying disorder.[158] For LBD specifically, recommendations are based principally on clinical experience, although a small study in a group of neurological patients, which included seven DLB patients, found a clinical improvement with melatonin treatment.[139]

Pathophysiological studies have suggested cholinergic dysfunction as a contributing factor in generating RBD, and ChEIs have therefore been considered as a treatment for sleep disorders.[159] Small uncontrolled trials and a number of case reports of ChEIs in LBD have suggested improvements on various rating scales, with one study using actigraphy to suggest improvements in sleep.[142,145,146,161]

Excessive daytime somnolence, a feature of fluctuations in LBD, has been shown to improve with armodafinil, a wake-promoting agent of unknown mechanism of action, in an uncontrolled trial of a small group of DLB patients.[162] Although good tolerability was reported, case reports have described emerging agitation and psychotic symptoms, suggesting that cautious use might be initially wise.[163] A small uncontrolled trial in six patients also showed improved excessive daytime somnolence with cholinesterase inhibitors.[145]

The lack of controlled studies investigating treatment effects on sleep in LBD provides the rationale for Study I in this thesis.

Treatment of neuropsychiatric symptoms

No controlled trials specifically report on treatment of anxiety and depression in LBD. A range of agents are used in clinical practice, including SSRIs, SNRIs and mirtazapine, with treatment-decisions being largely guided by clinician experience, patient-response and tolerability. Results from two RCTs also show that ChEIs can improve a composite neuropsychiatric score, of which depression is an item, conveying possible benefit.[120,123]

The treatment of psychotic symptoms in LBD is difficult. Overall, patients with dementia are at risk of harm with antipsychotic treatment, with adverse effects such as sedation, extrapyramidal symptoms, increased risk of cerebrovascular events and higher mortality.[164,165] This risk is further increased for LBD patients where severe neuroleptic sensitivity, a potentially fatal condition, occurs in up to half of patients.[166] Antipsychotic medication should therefore only be used when other management strategies, such as treatment of underlying cause and non-pharmacological approaches, have failed to ameliorate symptoms which cause a clear distress or risk of harm to self or others. With this in mind, benefit of antipsychotic treatment is often outweighed by its risk. If treatment is initiated and symptoms do not improve, the medication should be up-titrated, changed or stopped.[2] Even when effective, discontinuation should be considered as RCT evidence shows that withdrawal had little detrimental effects in AD patients with prolonged treatment.[167]

In terms of which antipsychotic agent to use, data shows mixed results. Open-label studies have suggested benefit with quetiapine,[168,169] but no convincing effect was seen in an RCT study in LBD patients,[170] although the medication was well-tolerated. For clozapine, a chart-review study in PDD suggest some benefit,[171] whilst no trials exist in DLB. Despite the scarce evidence regarding efficacy, quetiapine and clozapine are still widely used in LBD, with prevalence reported up to 41%.[172] Newer agents such as pimavanserin, a selective serotonin 5-HT2A inverse agonist, have shown efficacy in PD psychosis, and might be considered for LBD patients in the future,[173] although potential safety concerns have been raised.[174]

Treatment of autonomic dysfunction

No trial evidence exists for treatment of symptoms attributed to autonomic dysfunction in LBD. Treatment recommendations are therefore based on related findings within PD populations or clinical expertise. For neurogenic orthostatic hypotension (OH) in primarily PD patients, a meta-analysis concluded treatment-efficacy with droxidopa, however the effect gradually decreased after two weeks, therefore only supporting short-term use.[175] Midodrine is a frequently used medication, but a meta-analysis concluded that evidence was insufficient and low in quality.[176] Other agents have been suggested but carry limited evidence, including fludrocortisone,[177] domperidone,[177] pyridostigmine[178,179] and sitagliptin.[180]

Urinary incontinence is traditionally treated with medications which have anticholinergic properties and are unsuitable in LBD patients. Alternative medications include mirabegron[181] or botulinum toxin.[182] Improvement in constipation can be positive side-effect from ChEI treatment leading to cholinergic stimulation. In patients with PD, constipation relief has also been achieved with psyllium,[183] macrogols,[184] lubiprostone.[185] Sildenafil can be tried for patients with erectile dysfunction, but use can be limited because of worsening OH.[182] Sialorrhea in PD has been improved with glycopyrrolate,[186] sublingual atropine,[187] ipratropium bromide spray[188] and botulinum toxin.[189,190]

1.4.2. Non-pharmacological therapies

In other types of dementia, non-pharmacological interventions have been demonstrated to be useful in targeting cognitive, psychiatric, physical and social aspects of disease.[2] Because of limited efficacy seen with pharmacological therapies, and the risk of adverse effects, non-pharmacological management options would be of great value for LBD patients. The non-pharmacological interventions that have been under investigation are diverse, see Table 4. High-level evidence for non-pharmacological therapies in LBD patients is however lacking, and there is an overall heterogeneity, with variable outcomes and small sample sizes, leading to difficulties in terms of

management recommendations.[191,192] On the other hand, a number of studies – including three RCTs[193-195] – have already emerged since the publication of the two systematic reviews, which could indicate increasing interest for non-pharmacological approaches. These conducted studies also provide preliminary evidence for non-pharmacological treatments and highlight the importance of considering comprehensive treatment strategies for patients with LBD.

Table 4. Non-pharmacological therapies in LBD.

Interventions	Outcome(s)
Physical and exercise therapy[196-198]	↑ balance, physical function. executive function
Environmental modifications[199,200]	↑ behavioural function, ADL, delusional symptoms
Occupational therapy[201,202]	↑ goal improvement, ADL, QOL, cognition, relationships
Carer education[199]	↑ behavioural function, ADL
Music therapy[203]	↑ NPS, well-being
Simulated presence therapy[204]	↓ distressed behaviour
Goal-oriented cognitive rehabilitation[195]	↑ goal attainment, mood, self-efficacy, QOL, delayed recall
Bright light therapy[205]	↑ sleep disturbances
Auditory cueing[206]	↑ gait
Liquid modification[207,208]	↑ swallowing function
Deep brain stimulation[194,209-212]	Range from no change to motor and cognitive ↑
Electroconvulsive therapy[213-215]	Short-term ↑ in mood and NPS, ↑ depression
Transcranial magnetic stimulation[215]	↑ depression
Transcranial direct current stimulation[193,216]	↑ attention in uncontrolled trial, no change in RCT in PDD

Abbreviations: ADL, activities of daily living; NPS, neuropsychiatric symptoms; QOL, quality of life.

In clinical practice, strategies will also be employed which are rarely investigated in disease-specific interventional trials, but instead based on learnings or clinical experience within the multi-professional team. Management of visual hallucinations for example involves simple measures such as improving lighting, reducing visual triggers and improving visual function by changing glasses or operating cataracts.[217] Similarly, in treating RBD, bedroom safety needs to be addressed e.g. removing dangerous objects from the bedroom and considering locking windows.[159]

Treatment of swallowing dysfunction

Following objective verification of swallowing dysfunction, patients are generally offered conservative functional training by speech and language therapists. This can include exercises to strengthen muscles, improve co-ordination or specific swallowing manoeuvres. Adaptation of food or liquid aiming to redirect boluses away from the airway to decrease risk of aspiration is also a common approach.[91] Although rehabilitation exercises and liquid modification are recognised as clinically useful, evidence is scare, particularly in the LBD population where only one study has been conducted investigating therapeutic swallowing strategies.

In this large-size randomised trial of patients with dementia and PD (including 132 PDD patients), short-term management of aspiration was investigated by comparing three compensatory mechanisms to prevent aspiration; honey-thickened liquid, nectar-thickened liquid and chin-down posturing.[207] Honey-thickened liquid was found to be the most successful in eliminating aspiration, however about half of the patients received no benefit from either of the three interventions, meaning that alternative interventions are needed. Further reinforcing this is the recognition that thickened liquids might not fully support hydration,[207] and that thickened liquids are disliked by many patients.[218]

Chemesthetic receptors cover the mucosa of the pharynx and larynx, with activation leading to protective reflexes preventing aspiration.[219] One way of activating chemesthetic receptors is by administrating carbonated thin liquids.[220] For this reason, carbonation of liquids has been considered as an alternative approach to improve swallowing physiology. Investigations in healthy volunteers have shown improvements in swallowing measures.[221-223] One study used transcranial magnetic stimulation to demonstrate increased excitability in the swallowing pathways, lasting up to 60 minutes after swallowing carbonated thin liquid.[223] Assessments of carbonated thin liquid in clinical populations, including patients with neurological disorders, have also suggested beneficial effects.[224-228] Carbonation has however not been investigated in patients with LBD, providing the rationale for conducting Study III presented within this thesis.

Various other therapies aiming to improve safe swallowing have been explored in PD patients to some extent, including expiratory muscle strength training, video-assisted swallowing therapy, bio-feedback training, and more novel therapies such as deep brain stimulation, transcranial magnetic stimulation or botulinum toxin.[91] High-quality evidence is however rare, precluding generalised recommendations at this point in time,[229] but providing inspiration for future studies in LBD patients.

1.4.3. Future therapies

There are a number of registered trials of pharmacological and non-pharmacological therapies in LBD (www.clinicaltrials.gov). Two neurotransmitter-based therapies have recently been investigated, nelotanserin, an inverse agonist of serotonin receptor subtype 5-HT2A, and intepirdine (RVT-10), a selective 5-HT6 receptor antagonist stimulating the cholinergic system. In a press-release, the pharmaceutical company confirmed that nelotanserin (NCT02640729) met its prespecified primary endpoints regarding safety, and was associated with improved motor function measured by UPDRS, motivating a larger confirmatory trial.[230] Intepirdine did not meet the primary endpoints and no other evidence was found to support further developments (NCT02669433 and NCT02910102).[230] Although not yet recruiting, a phase II study has been registered in DLB for E2027, an oral phosphodiesterase 9 inhibitor aiming to

improve cognitive function, planned to be completed in March 2020 (NCT03467152). Furthermore, disease-modifying approaches are emerging, with one phase II trial of immunotherapy against α-synuclein currently underway in patients with PD (NCT03100149). If found to reduce, or at least slow α-synuclein accumulation, this therapy might be of relevance also to DLB patients. Additionally, a number of non-pharmacological trials are also underway, including music therapy (NCT03011723) and a palliative care intervention (NCT03076671), demonstrating the wider spectrum of potential therapies.

1.5. Survival & prognosis

1.5.1. Survival in LBD

After receiving a diagnosis of LBD, patients and families expect clear and concise information about the prognosis.[231] However, over 40% of caregivers in one study perceived that they received inadequate information about what to expect in the future from their diagnosing physician.[232] Reliable information about survival and prognosis is also important for health and social care planning.

Early studies of survival in LBD might not be entirely representative, due to the nosological debate prior to the consensus criteria in 1996. Furthermore, the majority of these studies are based on retrospective analyses of autopsy series, which are influenced by a referral bias, whereby younger patients with more atypical features and diagnostic uncertainty might be overrepresented. More recent studies of survival have instead included patients with a clinical diagnosis of LBD according to available consensus criteria, only sometimes autopsy-confirmed. A summary of these studies is found in Table 5. Significant variability can be seen in survival time regardless if defined from subjective onset (5.3-11.1 years), first presentation (1.5-7.3 years) or diagnosis (1.9-6.3 years)

Table 5. Summary of studies assessing survival time in LBD.

Study	Diagnosis, n	Starting of survival time	Analysis	Survival, years	Outcomes and prognostic factors
Walker 2000[233]	DLB, 32	Onset (presentation)	Log rank	5.3 (3.2)	No difference AD vs. DLB.
Williams 2006[54]	DLB, 63	Diagnosis	CPH	7.3	HR 1.9 in DLB vs. AD. Increased HR if female, absence of tremor, gait abnormality, *APOE* ε4 allele, comorbidities, loss of ADL.
Jellinger 2007[234]	LBD, 243	Onset	Log rank	5.0	Shorter survival with age, initial dementia, fluctuating cognition, visual hallucinations, male gender.
Koedam 2008[235]	DLB, 52	Presentation	CPH	1.9*	Mean survival time 1.9 years. HR 8.3 in DLB vs. controls.
Boström 2009[236]	DLB, 47	Presentation	RR, CPH	5.6*	RR 8 in DLB vs. controls. Increased mortality with elevated CSF t-tau.
Magierski 2010[237]	DLB, 51	Diagnosis	Survival time	6.3*	
Stubendorff 2011[238]	DLB, 49	Onset (diagnosis)	CPH	8.0 (4.6)	HR 2.0 in DLB vs. AD.
Andersson 2011[239]	DLB, 47 PDD, 17	Presentation	CPH	4.8	No difference DLB vs. AD.
Oesterhus 2014[240]	DLB, 42 PDD, 11	Diagnosis	CPH, SMR	4.4	SMR 2.6. HR 2.1 in LBD vs. AD. No difference DLB vs. PDD.
Garcia-Ptacek 2014[241]	DLB, 461 PDD, 283	Diagnosis	CPH	-	HR 1.6 in DLB cf AD. HR 1.5 in PDD cf AD.
Manabe 2016[242]	DLB, 42	Onset	CPH	8.0	Increased mortality risk with cerebral infarction, muscle weakness, male sex, age.
Connors 2016[243]	DLB, 16	Diagnosis	RR	1.5	RR vs. general population 5.5.
Savica 2017[244]	DLB, 81 PDD, 55	Diagnosis	CPH		In DLB, median survival 4.7 years, HR 3.9 vs. controls. In PDD, median survival 3.8, HR 3.9 vs. controls.
Irwin 2017[44]	DLB, 98 PDD, 115	Onset	CPH	11.1*	Increased mortality with cerebral NFT score.
Price 2017[172]	DLB, 251	Presentation	CPH	3.7	HR 3.0 in DLB vs. AD.

Abbreviations: AD, Alzheimer's disease; CPH; Cox proportional hazards; DLB, dementia with Lewy bodies; HR, hazard ratio; LBD, Lewy body dementias; NFT, neurofibrillary tangle; PDD, Parkinson's disease dementia; RR, relative risk; SMR, standardised mortality ratio.*mean survival time instead of median.

Since survival time is the difference between two dates it will be sensitive to change in either of these dates.[245] Measuring survival from either onset, first presentation or diagnosis will therefore influence survival time, without altering time of death, see Figure 6. Furthermore, all three of onset, first presentation and diagnosis are potentially unreliable time points, which could be influenced by a number of factors, again altering the survival time but similarly not time of death. For example, onset of disease relies on satisfactory recall by patients or relatives, something which is difficult and will be variable since symptoms typically emerge gradually and can be subtle for months or even years. Similarly, measuring survival from time of diagnosis will be influenced by clinical practice and potential diagnostic delay. These factors can probably explain, at least to some extent, the variability in survival times seen in Table 5.

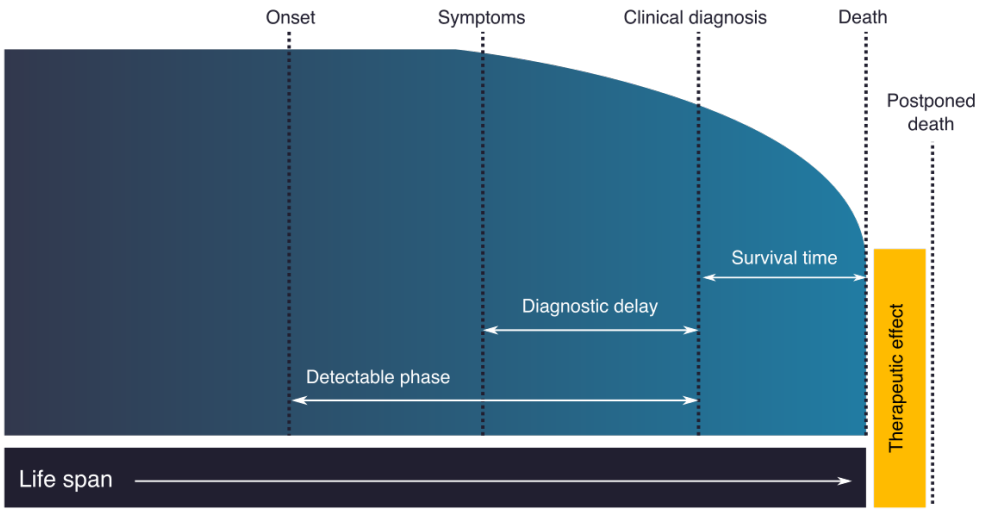

Figure 6. Relevance of detection and diagnosis on survival time.

1.5.2. Relative survival

When studying survival, clinicians are mostly interested in disease-specific mortality. This can however be complicated because of the poor reporting of cause of death, with one study finding that a diagnosis of dementia was missing from the death certificate in over 70% of LBD patients.[246] Moreover, there is a difficulty in separating deaths unrelated from the disease of interest from indirect deaths. For example, should a fatal aspiration pneumonia in a dysphagic LBD patient be classified as related or unrelated to disease?

Instead, the majority of survival studies report on the all-cause mortality, including those in LBD patients, as seen in Table 5. This does not however separate deaths

occurring due to the disease of interest and deaths unrelated to the disease of interest, i.e. competing risks, something which is relevant in an aged and comorbid population.

An alternative measure is relative survival or excess mortality.[247] This is an estimate of disease-specific mortality, obtained by adjusting the all-cause mortality with the expected mortality in the general population, see Figure 7. The expected mortality is estimated based on national life-tables, organised according to age, sex and calendar year. Consequently, excess mortality in the study population can be suggested to be due to disease of interest, irrespective if this is direct or indirect. Relative survival methods have mainly been applied in population-based cancer studies, although are emerging now also in other fields.[248-250] This current situation prompted the investigation of relative survival in an LBD population, presented in Study IV within this thesis.

Figure 7. Relationship between expected, excess disease-related mortality and observed mortality.

1.5.3. Prognostic markers

A number of risk factors in all-cause dementia have been explored in terms of shorter survival, including higher age at diagnosis and male gender. Notably, increasing comorbidity, cognitive impairment measured by MMSE as well as functional impairment have not been convincingly associated with increased mortality.[251]

Specific predictors of survival time in LBD have also been investigated. Clinical characteristics such as gait abnormalities, absence of tremor, fluctuating cognition, hallucinations and orthostatic hypotension have been identified as potential risk factors for shorter survival time.[54,234,238] In patients with DLB, indicators of potential comorbid AD-pathology such as presence of *APOE* ε4 allele,[54,55] decreased hippocampal volume,[252] and a CSF AD profile[236,253] have been associated with shorter survival time. Similarly, both dementia development and AD-pathology are related to shorter survival in patients with PD.[254,255]

LB-pathology itself also seems to influence survival time. One study found that diffuse LB-pathology was associated with shorter survival time compared to transitional pathology, independent of Braak NFT stage or neuritic plaque disease, regardless of whether the clinical phenotype was AD or DLB.[256] A recent study also suggested that extensive thalamic atrophy can predict shortened survival, although underlying reasons for this needs further investigation.[67]

Few studies have associated survival in relation to treatment options. Albeit conducted in a small study sample, an open-label continuation study of an RCT of memantine found that patients had a longer length of survival.[156] Moreover, one systematic review of ChEIs concluded that fewer deaths occurred in the treatment group than the placebo group. In patients with AD, withdrawing antipsychotic treatment has been associated with improved survival,[22,257] a finding which should be relevant for patients with LBD in view of the reported neuroleptic sensitivity in this group.

1.6. Living well & quality of life

Given the absence of definite prevention or cure, a large number of people will live with a dementia diagnosis and its consequences. For most people, little value is placed on living longer if this comes without well-being. Living well is therefore a key priority in dementia treatment and care.

Living well with a chronic illness has been defined as 'the best achievable state of health that encompasses all dimensions of physical, mental and social well-being' so that 'to live well takes on a unique and equally important personal meaning, which is defined by a self-perceived level of comfort, function and contentment with life'.[258] This concept incorporates subjective well-being, life satisfaction as well as quality of life (QOL).[259] There is a growing body of research for QOL in dementia, although certain aspects, e.g. QOL in those with less common forms of dementia such as LBD or QOL as a response-variable to interventions, are rather unexplored.

One challenge is the lack of single definition or theoretical model for QOL in dementia. A generic definition has been provided by the World Health Organization (WHO) stating that QOL is 'a broad ranging concept, affected in a complex way by a person's physical health, psychological state, personal beliefs, social relationships and their relationship to their environment'.[260] Another aspect which has been emphasised, particularly in the dementia-specific framework, has been how adaptation to the perceived consequences of disease is indicative of QOL.[261] Thus, by altering expectations and response to the changing circumstances, good QOL can be maintained despite deteriorating functions. Related to this is the so called 'disability paradox', in which people with serious disabilities report high QOL, suggesting a non-linear relationship between physical health and QOL.[262]

1.6.1. Measuring quality of life

Quality of life can be measured using generic or disease-specific instruments, the latter being preferred and more frequently used in studies of people with dementia. Since no

disease-specific scale exists for LBD, generic or AD-specific scales are instead generally used. A number of these have been developed to encompass the multidimensionality addressed in the QOL definitions. However, many instruments appear to have be developed upon the researcher or caregiver conceptualisation of QOL, rather than those of the patients.[263] It is therefore unclear if assessments of QOL adequately reflects the perspective of people with dementia. The majority of measurements also lack evidence of reliability, validity and utility.[263] Still, because of increased emphasis on the importance of QOL, these measures are increasingly used to evaluate interventions, alongside of physical and cognitive measures.

Whose quality of life is measured?

It is generally agreed that since QOL is a subjective concept, the appraisal of QOL should ideally be made by the person living with disease.[263] This notion has however been somewhat overlooked in people with dementia, with some researchers suggesting that people with dementia cannot reliably report on their subjective state and life situation due to cognitive or affective fallacies.[264] Some instead believe that observable behaviours are needed as proxy-markers of QOL, leading to the development of external measurements of QOL and caregiver-rated QOL-instruments.[265]

Even if this approach is taken with the intention to improve QOL for people with dementia, it is not unproblematic. A proxy measure is not able to take into account values, needs and adaptations to life circumstances relevant to QOL that are only truly available to the person in question.[266] Informants are also found to impose their own subjective negative perceptions of diminishing health when judging QOL, and in doing so disregard how the illness-experience itself can lead to new meanings and values in life.[261] Judgements have also been recognised to be coloured by informant well-being, mood, relationship to the patient and burden of care, which might not necessarily be related the person living with disease.[266] Inevitably, studies measuring proxy QOL do not actually measure patient QOL, demonstrated by studies persistently finding a discrepancy between patient- and proxy-ratings of QOL, with proxy-ratings being consistently lower.[267,268]

Qualitative explorations of quality of life

Another way of assessing QOL in dementia, and to understand the subjective lived experience, is by exploratory qualitative studies involving persons with dementia. In-depth interviews have the advantage of being able to comprehensively investigate the complexities of feelings, opinions and perceptions, giving voice to those living with disease, whilst distilling concepts of relevance.[269] Findings can subsequently be used to develop measurement instruments or alongside quantitative methods. Two meta-analyses have been conducted of qualitative studies investigating factors influencing quality of life or well-being in dementia. The following factors were identified: connectedness, relationships, agency in life today, wellness perspective, sense of place,

happiness, engaging with life in ageing, engaging with dementia, identity and growth.[270,271] Notably, like in a recent quantitative meta-analysis, there is an absence of physical or cognitive functions as major influencing factors, and instead the focus is on social, personal and care factors.[272]

1.6.2. Quality of life in LBD

The majority of research in LBD has been concerned with biomedical aspects of disease. However, a few studies are starting to address also socio-psychological implications and quality of life.[231] Focus has primarily been on caregiver distress and disease burden, largely overlooking the perspective of persons with LBD.[232,273,274] One study did however show that people with DLB have lower QOL compared to people with AD, with nearly a quarter of people with DLB falling below acceptable thresholds.[275] At current date, there are no published studies involving specifically LBD patients which are qualitative in nature or investigate the lived experience in LBD. The limited work in this area of LBD research provides the rationale for carrying out Study II and V in this thesis.

2. Aims of thesis

This thesis presents a broad range of studies, both in terms of methodology and outcomes, however with the shared aim to understand the impact of living with Lewy body dementias, with a focus on treatment, survival and quality of life.

The specific aims of the separate studies are:

I. To investigate the effect of memantine treatment on sleep behaviours in patients with LBD over 24 weeks.

II. To describe quality of life in patients with LBD, and how this is affected by memantine treatment over 24 weeks.

III. To investigate swallowing difficulties in patients with LBD and the effect of carbonated thin liquid on swallowing response.

IV. To estimate the relative survival after being diagnosed with LBD compared to an age- and sex-matched population, and factors contributing to excess mortality.

V. To explore the subjective experience of living with LBD, and factors influencing well-being.

3. Methods

Table 6. Summary of methods.

Study	N	Setting	Study design	Outcomes	Analytical approach
I	57	MEM-DLBPDD	Randomised double-blinded placebo-controlled	Sleep; SSQ, ESS	Mann-Whitney *U* test, Wilcoxon signed-rank test, logistic regression
II	75	MEM-DLBPDD	Randomised double-blinded placebo-controlled	Quality of life; QOL-AD	Factor analysis, Mann-Whitney *U* test, Wilcoxon signed-rank test, and within thesis Cronbach's α, ICC
III	48	Memory clinic	Observational	Swallowing function; descriptive, PTT, PRS, PS	Friedman test, Wilcoxon signed-rank test, Mann-Whitney *U* test
IV	177	Memory clinic	Observational	Survival time, excess mortality	SMR, Cox regression, relative survival regression
V	5	Memory clinic	Qualitative analysis of in-depth interviews	Illness-experience, well-being	Interpretative phenomenological analysis

Abbreviations: ICC, intraclass correlation; ESS, Epworth Sleepiness Scale; PRS, pharyngeal retention scale; PS, penetration scale; PTT, pharyngeal transit time; QOL, quality of life; QOL-AD, Quality of Life in Alzheimer's Disease; SMR, standardised mortality ratio; SSQ, Stavanger Sleep Questionnaire.

3.1. Study settings

3.1.1. Memory Clinic, Malmö, Sweden

The majority of patients included in the studies in this thesis have been clinical patients the Memory Clinic, Skåne University Hospital, Malmö, Sweden. The clinic specialises in cognitive disorders, and patients are usually referred from their general practitioner or other secondary care physicians. A clinical assessment includes a structured medical history, physical, psychiatric and neurological examination, cognitive testing, blood samples and CT or MRI of the brain. Further investigations, such as *APOE* genotyping, CSF analysis, EEG or molecular imaging, are conducted when judged appropriate by the responsible clinician. A small number of patients are referred for post-mortem examination.

3.1.2. Study of memantine (MEM-DLBPDD)

Between 2005-2008, patients with LBD were recruited from neurological and psychiatric outpatient clinics in Sweden (Malmö), Norway (Stavanger) and the United Kingdom (London and Essex), for a multi-centre, randomised double-blinded placebo-controlled trial of memantine. Participants included in the study underwent systematic assessments including a full medical history, physical, neurological and psychiatric examination, laboratory tests, ECG and CT or MRI. Some were also investigated with EEG, DaTscan™ and CSF analysis. The primary outcome of the MEM-DLBPDD study was clinical global impression of change (CGIC) and the results were published in 2009.[132] Additional assessments were conducted as part of the study protocol which have been used for the secondary analyses presented in Study I and II of this thesis.

3.2. Study designs, populations & interventions

3.2.1. Study I & II

These studies were secondary analyses of the MEM-DLBPDD trial described above. For inclusion, patients had to meet the 2005 consensus criteria for DLB,[28] or in cases of PDD fulfil the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for Parkinson's disease[276] and develop dementia according to DSM-IV[4] at least 1 year after the onset of motor symptoms. Patients with MMSE ≤ 12, other brain diseases, recent major changes in health status, major depression, moderate-to-severe renal impairment, heart disease, pulmonary disease, hepatic impairment or known allergy to memantine were excluded. Patients were randomised to treatment with the active substance memantine or placebo, based on centre, MMSE and use of ChEIs. Treatment was given for 24 weeks, with memantine increased incrementally from the initial 5 mg to 20 mg by week 4. Compliance was assessed by counting the unused tablets.

For Study I, patients from the UK were excluded as the studied outcome consisting of sleep assessments were not collected at these centres. For Study II, two patients were excluded in the published paper due to having missing data at baseline (see Appendix II). For the purpose of transparency within this thesis all randomised patients (n=75) have been considered included and instead indicated to be lost to follow-up.

3.2.2. Study III

This was a study of all LBD patients who had been referred to the Diagnostic Centre of Imaging and Functional Medicine, Malmö, Skåne University Hospital from the

Memory Clinic, Malmö, for a therapeutic videoradiographic swallowing study (TVSS) as part of clinical practice between 2006-2016. Patients were identified by reviewing all patients referred for a TVSS from the Memory Clinic and excluding patients not fulfilling the criteria of DLB[28] or PDD[25]. If patients had multiple examinations, only the first was used. There were no other exclusion criteria. All data used for the study was collected as part of the clinical process and retrieved from hospital electronic medical records. Videoradiographic material from the TVSS was accessed through a hospital-based electronic archiving system (PharyDoc®) and used for quantitative analysis.

3.2.3. Study IV

This was an observational study of survival in all outpatients diagnosed with DLB or PDD at the Memory Clinic, Malmö, between 1997-2014. The only exclusion criterion was if patients did not fulfil diagnostic criteria,[25,28] verified by reviewing hospital electronic medical records. All data used was collected as part of clinical process and retrieved from hospital electronic medical records. Survival time was defined as the time from diagnosis to death or until end of study. Survival status was determined from the Swedish Population Registry.

3.2.4. Study V

The study consisted of in-depth interviews with patients with DLB. Purposive sampling was used, with a senior clinician identifying possible participants for the study. To be included in the study, participants had to have a diagnosis of DLB,[28] and be Swedish-speaking, community-dwelling as well as be able to consent to the study.

3.3. Procedures & outcomes

3.3.1. Clinical measures

Mini-mental state examination (Study I-V)

The MMSE was developed by Folstein et al. in 1975 as a short screening tool of cognitive function.[277] Since then, it has become the most widely used cognitive instrument in both clinical and research settings.[278] Scores are influenced by age, educational level, language and cultural barriers.[62]

Although the MMSE is often referred to as an overall measure of cognitive impairment, it is heavily based on memory and language functions, and has less sensitivity for frontal, executive and visuospatial functions.[62] This is relevant in the setting of LBD as attentional, visuospatial and executive dysfunctions predominate in both prodromal and established disease.[279,280] For example, visuospatial function represents only one point on MMSE, but can have profound impact on daily function. This suggests that LBD patients could perform relatively well on the MMSE, yet be adversely affected by their disease in ways not measured. Nevertheless, MMSE is frequently used in this patient group, and a large multi-centre study concluded that MMSE can be used to follow decline in DLB patients, which is more rapid than in AD patients.[281]

MMSE has been used to indicate overall level of cognitive impairment throughout the thesis, and as a predicting variable for survival Study IV.

Charlson comorbidity index (Study IV)

In 1987, Charlson et al.[282] developed an index of combined comorbidity for the purpose of predicting risk of mortality in longitudinal studies. It has since been widely used, and is one of the most extensively studied comorbidity measures in terms of validity and reliability for research studies.[283] The original CCI includes 19 different conditions with varying weights, whereby dementia is included and has a weight of 1.

The CCI was calculated for patients in Study IV and used as a measure for comorbidity and predicting variable for survival.

3.3.2. Patient & caregiver rating scales

Epworth Sleepiness Scale (Study I)

The Epworth Sleepiness Scale (ESS) was initially developed to assess daytime sleepiness in a heterogeneous group of patients in sleep medicine.[284] In this self-administered questionnaire, respondents are asked to rate the chance of dozing off while engaging in different activities on a scale from 0 (would never doze) to 3 (high chance of dozing). The total score ranges between 0 and 24, with abnormal values suggested to be above 10.[285] Although not formally validated for patients with dementia, the ESS is one of the most frequently used scales for rating daytime sleepiness.[286] Hypersomnolence is a recognised feature in LBD, and studies have demonstrated higher ESS compared to healthy controls and AD patients.[287,288] The measurement has also been found to be responsive to change in LBD over 12 weeks' time in a small treatment study.[162]

In Study I, the ESS was administered at baseline, 12 weeks and 24 weeks to measure daytime somnolence in response to treatment.

Stavanger Sleepiness Questionnaire (Study I)

The Stavanger Sleepiness Questionnaire (SSQ) was developed as a clinical evaluation tool for sleep behaviour in patients with PD.[289,290] The SSQ is designed to obtain information about sleep during day and night, and consists of 14 items rated by either the patient or caregiver. One question addresses RBD (Table 7), with scores of 2 or higher indicating probable RBD.[290]

Table 7. Probable REM sleep behaviour disorder assessed by Stavangeer Sleep Questionnaire.

Is the patient physically active during night sleep?	
0	No
1	Twist and turns, sometimes talks
2	Very active, can wake up spouse, shouts during sleep
3	Severely active, both physically and verbally. Fights during sleep and hurt bedpartner or self.

Although not formally validated, the SSQ has been used in a number of studies assessing sleep in PD.[291-294] The question in Table 7 also have similarities to the well-validated diagnostic tool Mayo Sleep Questionnaire (MSQ), used to screen older patients with cognitive impairment and used in larger LBD populations.[89] The MSQ consists of one main question to the bedpartner; *Have you ever seen the patient appear to "act out his/her dreams" while sleeping? (punched or flailed arms in the air, shouted or screamed)",* where the answer is yes or no. In one study, this question was found to have a sensitivity of 98% and specificity of 74% for detecting polysomnography-confirmed RBD in patients with LBD, AD and healthy volunteers.[106] False positives can occur in those with obstructive sleep apnoea (OSA), where dream enactment behaviour can also occur, and polysomnography is needed for accurate distinction.[295]

In Study I, the SSQ was administered to the caregivers at baseline, 12 weeks and 24 weeks, with the question in Table 7 used as a marker of probable RBD in response to treatment.

Quality of Life in Alzheimer's Dementia (Study II, V)

Logsdon et al. developed the assessment scale Quality of Life in Alzheimer's Dementia (QOL-AD) in view of an increased recognition of improved quality of life and not just symptom amelioration as a treatment goal.[296] The scale consists of 13 items; 'Physical health', 'Energy', 'Mood', 'Living situation', 'Memory', 'Family', 'Marriage', 'Friends', 'Self as a whole', 'Ability to do chores', 'Ability to do things for fun', 'Money' and 'Life as a whole'. Each item is rated on a 4-point scale; 1 (poor), 2 (fair), 3 (good) and 4 (excellent), with total scores ranging from 13-52. QOL-AD is designed to be administered to both patients and caregivers.

To date, there is no disease-specific scale assessing QOL in LBD. The QOL-AD is a multidimensional and feasible scale, and although developed specifically for AD it has been used in number of other settings and populations. Throughout, the scale has had

good to excellent internal consistency and modest intra-class correlations between patients and caregivers.[297] For these reasons the QOL-AD was chosen as a quantitative measure of QOL also in LBD.

In Study II, QOL-AD was administered at baseline, 12 weeks and 24 weeks to investigate baseline QOL in LBD and to measure QOL in response to treatment. In Study V, QOL-AD was used as a cross-sectional measure of subjective QOL.

3.3.3. Assessment of swallowing function

Therapeutic videofluoroscopic swallowing study (Study III)

Videofluoroscopy is a radiological investigation, recording moving images whilst the patient is swallowing a radiopaque bolus, allowing visualisation of bolus passage through the oral cavity, pharynx and oesophagus, see Figure 8. It is one of the instrumental gold standards for investigating dysphagia, together with fiberoptic endoscopic evaluation of swallowing.[91] A therapeutic videofluoroscopic swallowing study (TVSS) involves administering differently modified solids and liquids mixed with barium, and possible therapeutic strategies to immediately assess the effect on swallowing physiology.

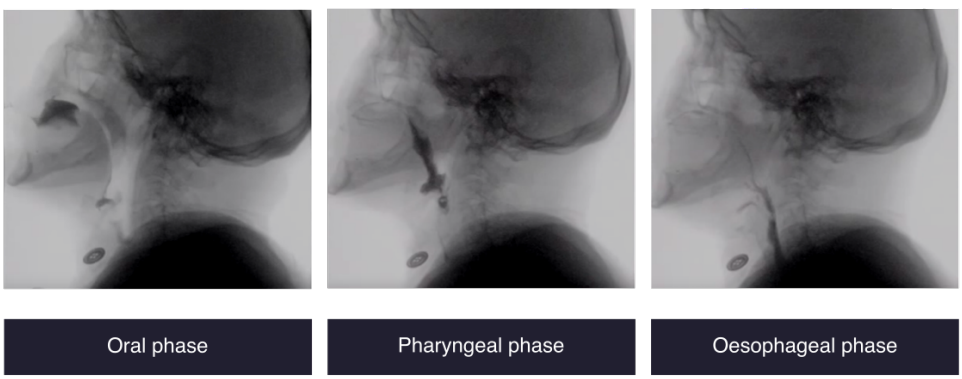

Figure 8. Videofluoscopic swallow study.
Demonstration of the three major swallowing phases in a patient with retention and aspiration. Pictures are stills from videoappendix to study III published with patient consent.

In Study III, the TVSS procedure was conducted as part of clinical practice, carried out at the radiology department by a radiologist and a speech and language therapist (SLT) according to a set protocol, described in detail in the publication (Appendix III). In brief, the materials are mixed with barium sulfate and generally tested in the order of smooth fruit pudding, smooth puree, thick pâté, chopped normal food, thickened liquids, carbonated thin liquids and thin liquids. The liquids are given in doses of 3

and 5 mL, and the patients are also encouraged to drink freely if possible. The swallowing response is analysed by the SLT and the analysis is summarised to a descriptive assessment immediately after the examination, commenting on the full examination (every swallow and every consistency), including what type of swallowing dysfunction is present and what modifications improve swallowing function (example shown in Table 8). These assessments were reviewed for the analysis in Study III.

Table 8. Example of descriptive swallowing assessment provided by speech and language therapist.

Assessment of oral and pharyngeal swallowing	
Patient is assessed	Sitting, drinking independently and fed by spoon.
Consistencies tested	Smooth fruit pudding, smooth puree, thick pate, normal food, thin liquid, thick liquid and carbonated liquid.
Assessment	Mild-to-moderate retention in valleculae. Subepiglottic penetration of thickened fluid. Carbonated liquid leads to a more effective swallow.
Recommendations	Retention in valleculae with supepiglottic penetration of thickened liquid. We recommend modified intake with soft food and carbonated liquid with meals. Patient is given a leaflet with swallowing recommendations.

Quantitative videoradiographic assessment

Videofluoroscopic studies also allow temporal and spatial quantitative measurements of swallowing function. Although quantitative measures are increasingly recognised, there are currently no standard protocols of which measurements to use, and studies are heterogenous.[91]

In Study III, archived videographic material was analysed to compare swallowing response specifically to thin, thickened and carbonated thin liquid. The quantitative assessments were performed by one experienced SLT and one clinician, unblinded to the consistencies, with air bubbles being clearly visualised with carbonated thin liquid. The first swallow of each consistency was examined. Three quantitative measures were chosen, based on a previous study; pharyngeal transit time (PTT), pharyngeal retention and penetration.[224]

PTT was defined as the time from when the apex of the bolus crossed the level of the faucial isthmus, to when the peristaltic wave left the cricopharyngeal muscle.[298] Pharyngeal residue was defined as retention of material in the valleculae or pyriform sinuses and scored using a set based on residue severity, see Table 9A.[299] Penetration was defined as the entrance of bolus material into the airway and graded using a departmental protocol similar to the Penetration– Aspiration Scale,[300] see Table 9B.

Table 9. Grading for pharyngeal residue scale and penetration scale.

A)	Pharyngeal residue scale
1	No residue
2	Mild residue
3	Moderate
4	Severe

B)	Penetration scale
1	No penetration
2	Subepiglottic penetration (just below the epiglottis)
3	Supraglottic penetration (above the true vocal cords)
4	Tracheal penetration (below the true vocal cords)

3.3.4. In-depth interviews

A number of different methods can be used to collect data in qualitative studies, with interviews being the most common.[301] For Study V, in-depth interviews were deemed to be the most suitable method to explore the research question.

All interviews were conducted in the participants' homes by VL. Participants were encouraged to be alone to allow speaking openly and without restrictions.[302] Each interview started with an open question "Could you start by telling me a little bit about yourself?". The interviews took form of a conversation using open-ended questions to facilitate a flexible discussion and rich material. There was no strict interview guide, but prompts and questions were used to explore the illness-experience as well as barriers and facilitators of well-being. Examples of questions asked in the interview are shown in Box 1 (following page).

Box 1. Example of interview questions.

Can you tell me about yourself?
Is today a good day? Why is that so?
Can you tell me about the symptoms of your illness?
Is there anything you have started or stopped doing because of your illness?
What do you spend your days doing?
Is there anything that would make your life better the way it is now?
What would you change about your current situation if you could?
What makes you happy or makes life worth living?
How do you consider your quality of life?

No repeat interviews were conducted. Interviews were audio-recorded and transcribed verbatim. Accuracy was assessed by VL re-listening to the interviews. Transcripts were not returned to participants and they did not comment on findings. Field notes were made after the interview and used to reflect around potential challenges in the interview situation.

3.4. Analytical approach

3.4.1. Statistical analysis

The SPSS software was used to carry out most statistical analyses, using two-tailed p-values with a significance level of $p<0.05$ unless otherwise specified. Non-parametric methods were used where data was found to be non-normally distributed. In Study III, estimates of effect size were calculated using the formula $r=Z/\sqrt{N}$.[303]

3.4.2. Survival analysis

Modelling for overall and relative survival in Study IV was carried out in R.[304] Detailed methods and the R script are found as supplements to the publication (Appendix IV). Impact of diagnosis was estimated using the standardised mortality ratio (SMR).[305] Cox proportional hazards modelling was used to determine effect of covariates on survival. The assumption of proportional hazards was tested using Schoenfeld residuals. Expected survival rate was calculated using the recommended Hakulinen method[306,307] and life-tables from the Swedish population, obtained from and the Human Mortality Database (www.mortality.org) and split by sex, age and calendar year. Relative survival curves were calculated using the Pohar-Perme method and relative regression modelling was performed using transformed survival times.[308] Excess hazard ratios (eHR) were yielded, allowing estimation of covariate effect on excess mortality. As with Cox regression analysis, relative survival allows for multivariate modelling and adjusting for several cofactors. The proportional hazards assumption for relative survival models was tested forming a Brownian Bridge.[309]

3.4.3. Interpretative phenomenological analysis

Interview data in Study V was analysed using guidelines for interpretative phenomenological analysis (IPA).[310] Although similar to other thematic approaches, this method comes with theoretical commitments based on phenomenology, hermeneutics and ideography.[311] This means that although IPA gives experience primacy (phenomenology) and aspires to understand this in great detail in a particular context (ideography), it also recognises that this must involve an interactive and interpretative interplay between participant and researcher (hermeneutics).[312] This method of analysis has been considered particularly relevant for response to illness.[310] The steps of the analytical process are illustrated in Figure 9.

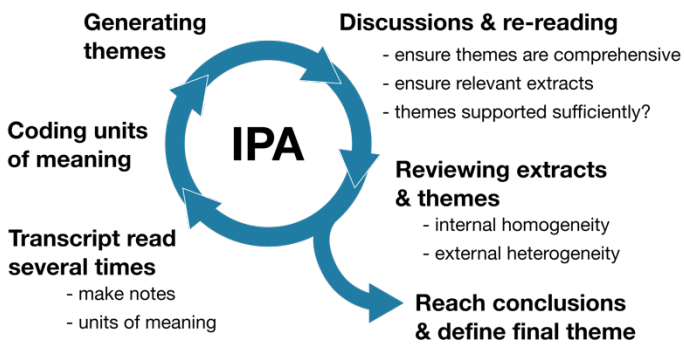

Figure 9. Illustrating the analytical process according to interpretative phenomenological analysis (IPA).

The first phase of analysis consisted of three researchers (VL, EL and AHL). All data was coded manually, rather than using a software program. Themes were identified as those aspects of the data that captured something important in relation to the research question. A fourth researcher (ELS) was involved at the stage of re-reading the transcripts to provide a validity check of analysis and interpretation. ELS has an expertise in qualitative research and supported the remaining analytical process including the definition of the final themes. This last review process was iterative, processing back and forth between themes and raw data in order to reach a collective agreement around the important patterns, and to confirm the internal homogeneity and external heterogeneity of the themes.[313] Consequently several versions were constructed before reaching an agreement on the final thematic structure.

All data analysis was conducted in the Swedish language using the original transcripts. Extracts were translated only in the write-up phase by VL who is native to the local region and has lived many years in the UK. The translation from Swedish was kept as literal as possible, except where minor modifications were necessary to preserve conversational style, idioms, colloquialisms or level of affect. In the presented extracts […] indicates that some text without substantial importance has been removed, whilst … without brackets indicates silence within a sentence.

3.5. Ethics

All studies were approved by the institutional review board in Lund, Sweden. For the MEM-DLBPDD study, ethical approval was also sought at each participating centre (#791/2005 in Lund, Sweden).

An amendment for a previous ethical approval was sought and accepted for Study III (#2016/209) and Study IV (#2014/451). Separate ethical approval was sought and approved for Study V (#2015/895).

All patients gave written informed consent for Study I, II and V. Study III and IV were retrospective studies of clinical data where the majority of patients were deceased at the time of the study, or no longer patients, at the clinic meaning that they could not be contacted according to Swedish legislation. Therefore, an opt-out strategy was recommended by the institutional review board, consisting of an advertisement in a local newspaper instead of written consent.

4. Main results

Table 10. Baseline characteristics for studies I-V.

	I (n=57)	II (n=75)	III (n=48)	IV (n=177)	V (n=5)
Age	76.4 (5.7)	76.8 (6.0)	76.0 (6.8)	75.7 (5.8)	80.0 (4.0)
Male:Female	40:17	57:18	30:18	114:63	5:0
DLB:PDD	27:30	33:42	38:10	131:46	5:0
Disease duration, years	7.0 (3.0-9.0)†	7.0 (4.0-10.0)†	1.9 (0.3-3.3)§	-	3.5 (2.3-6.8)§
MMSE score	19.8 (4.1)	20.0 (4.2)	19.3 (5.9)	22.1 (4.9)	25.2 (4.2)
ChEI	29 (51%)	41 (54%)	42 (88%)	152 (86%)	5 (100%)
***APOE* ε4 carrier**	-	-	-	67/141*	-

Abbreviations: *APOE*, apolipoprotein E; ChEI, cholinesterase inhibitor; DLB, dementia with Lewy bodies; MMSE, mini-mental state examination; PDD, Parkinson's disease dementia. Data are mean (SD), median (IQR), number (%). *missing in 36 patients. †from symptom onset to study inclusion; §from diagnosis to study inclusion.

4.1. Results Study I

This study investigated the effect of memantine on sleep in patients with LBD in an RCT setting over 24 weeks. The outcomes studied were an item on Stavanger Sleep Questionnaire (SSQ), measuring physical activity during sleep, and the Epworth Sleepiness Scale (ESS), measuring daytime somnolence.

4.1.1. Baseline results

This was a secondary analysis of the trial MEM-DLBPDD where patients from the UK were excluded due to that these centres did not collect the outcomes of interest for this study. An updated trial profile is shown in Figure 10 instead of Figure 2 in the publication (Appendix I).

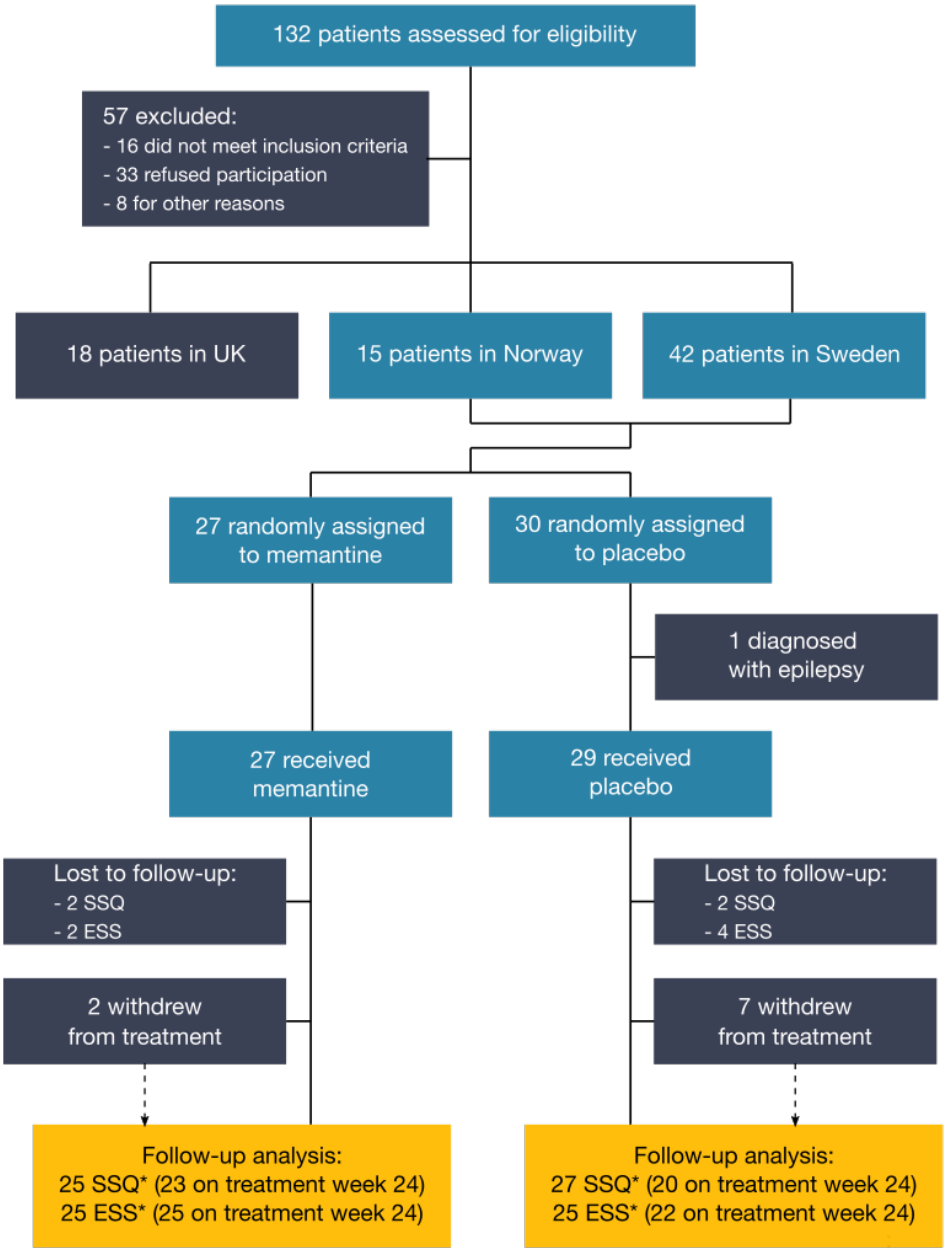

Figure 10. Updated trial profile. ESS, Epworth Sleepiness Scale; SSQ, Stavanger Sleep Questionnaire; *Last observation carried forward used to impute value from week 12 in case of missing value at week 24.

As noted in Figure 10, a number of cases had missing SSQ or ESS. Using the method of last observation carried forward (LOCF), the value from week 12 was imputed in case of missing value at week 24, as shown in Table 11.

Table 11. Missing outcome data.
Outlining the number of cases with present or missing values and the action for handling missing values at each time point (excluded or imputed).

Time, outcome	Memantine group (n=27)			Placebo group (n=29)		
	Present	Missing	Action	Present	Missing	Action
Baseline						
SSQ	25	2	excl.	27	2	excl.
ESS	27	0	excl.	28	1	excl.
12 weeks						
SSQ	25	2	excl.	27	2	excl.
ESS	25	2	excl.	25	4	excl.
24 weeks						
SSQ	22	5	3 imp.	20	9	7 imp.
ESS	25	2	0 imp.	22	7	3 imp.

Abbreviations: ESS, Epworth Sleepiness Scale; SSQ, Stavanger Sleep Questionnaire.

No significant differences were observed in the baseline variables between the memantine group and the placebo group (see Table 1 in publication, Appendix I). Abnormal scores for ESS indicating excess daytime somnolence was found in 30/55 at baseline, with a mean ESS of 11.6 (SD±5.9). Baseline SSQ scores for physical activity during sleep are found in Table 12. No statistically significant differences were found in SSQ and ESS at baseline between patients in the memantine and placebo group, or between DLB and PDD patients. Even so the distribution of SSQ is variable between patients in the memantine and the placebo group, as can be seen in Table 12.

Table 12. Baseline distribution of physical activity during sleep using Stavanger Sleep Questionnaire.

Is the patient physically active during night sleep?		Memantine (n=25)	Placebo (n=27)	Total (%)
0	No	10	14	24 (46)
1	Twist and turns, sometimes talks	4	6	10 (19)
2	Very active, can wake up spouse, shouts during sleep	11	4	15 (29)
3	Severely active, both physically and verbally. Fights during sleep and hurt bedpartner or self.	0	3	3 (6)

4.1.2. Treatment effect on sleep behaviours

The difference in physical activity during sleep between baseline and 24 weeks in both the memantine and the placebo group is illustrated in Figure 11, as an alternative to Table 2 and Figure 3 in the published article (Appendix I). In the memantine group, 11/25 patients had an improved score (within-group difference using Wilcoxon signed-rank test, p=0.005). In the placebo group, 3/27 patients had an improved score which was not statistically significant. The between-group difference at week 24 was 0.5 points (95% CI 0.05-0.90, p=0.006 using Mann-Whitney *U* test). No significant differences were found in ESS scores over time.

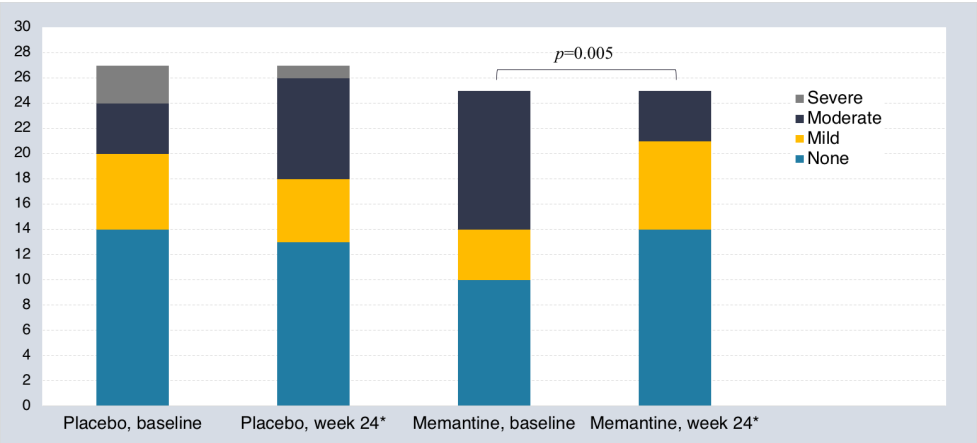

Figure 11. Scores of physical activity at baseline and 24 week follow-up in placebo group and treatment group. *Last observation carried forward was used impute values from week 12 in case of missing values at week 24. P-value indicates change within memantine group from baseline to follow-up using Wilocoxon signed ranks test. Between-group difference was significant using Mann-Whitney *U* test (p=0.006).

4.1.3. Further elaborations

Alternatives in handling missing values

In Study I, 14/56 patients who received treatment had missing SSQ at the 24-week follow-up (Table 11). No significant differences were found in the baseline variables between those with complete and missing outcomes (data not shown). The method LOCF was used to impute values from week 12 in case of missing values at week 24.

Performing instead complete case analysis gave similar results. Out of 22 complete cases in the memantine group; 11 improved, 1 worsened and 10 remained unchanged. In the placebo group, out the 20 complete cases; 3 improved, 3 worsened and 14 remained unchanged. This was associated with improvement within the memantine group

(p=0.005) but not within the placebo group, resulting in a significant between-group difference (p=0.022).

Regression modelling

A logistic regression model including 11 covariates was included in Study I. Considering the insufficient ratio between case numbers and the number of covariates this model has not been pursued further in this thesis because of risk of overfitting as well as multicollinearity.[314]

4.1.4. Comments

What are the limitations in interpreting these results?

The primary MEM-DLBPDD study was powered to detect a 0.6-point change on the primary outcome CGIC,[132] and not for these secondary analyses of sleep. Furthermore, the sample size was small and there was substantial missing follow-up data. This is common in RCTs and methods of handling missing outcomes are important as they can influence study results.[315] Methods vary from omitting all participants without an outcome (complete case analysis) to imputing their missing outcome data. The LOCF method used in this study has been heavily criticised since no statistical publication has been able to demonstrate its validity and its high risk of introducing bias.[316] Still, the method is continuously used even within the top journals.,[315] and was utilised in the primary MEM-DLBPDD study and the study on memantine by Emre and colleagues, both published in Lancet Neurology.[132,138]

An alternative method is to use complete case analysis, which in this study showed similar results. Nevertheless, it also carries disadvantages, including reduced sample size and power. Unless data is missing completely at random it also introduces a bias because of underlying factors contributing to drop-out, which could influence results.[317] A better method would possibly be that of multiple imputation.[317]

In our sample, missing outcomes were related to withdrawals which were primarily due to worsening in disease, without other overt differences. The majority of withdrawals were in the placebo group rather than the treatment group, a pattern less commonly seen in clinical trials. Since the LOCF method serves as an artificially stabilising effect in the group with the majority of drop-outs, particularly in a population expected to decline over time, this would in theory give the placebo group an advantage. Because the positive change was seen in the memantine group, this might explain why the results are similar between the analysis using LOCF and the complete case analysis.

Does this study show that memantine improves REM sleep behaviour disorder?

The only way to confidently determine improvement in RBD would be by polysomnographic verification, which was not used in this study. Instead, physical activity during night measured by SSQ served as a proxy-marker for RBD. Although the SSQ is not a polysomnography-validated scale, the similarities with the well-validated MSQ can probably suggest a capacity to detect and screen for RBD.[106] Whether or not this also represents an ability to detect change over time has not been assessed, limiting the interpretation of the results. Moreover, there is a lack of consensus around what actually represents a clinically meaningful change in probable RBD and the clinical interpretation of these results is therefore not straightforward.

Could another regression model have been applied?

Fitting a logistic regression model using less covariates could perhaps be possible, for example to assess the interaction between treatment and diagnosis on the odds of improving on the SSQ. Attempting this analysis demonstrated very wide confidence intervals (data not shown), suggesting lack of stability in the model, perhaps dues to sparsity of data.[318] Another alternative would be an ordinal regression analysis, accounting for the ordinal nature of the dependent variable i.e. not assuming equal spacing between levels of the response variable.[314] However, using this method revealed difficulties in fulfilling the assumption of proportionality (data not shown), and pursuing this method of analysis would require complex compensatory actions which are not suitable considering the small data set.

4.1.5. Summary

Physical activity during sleep, serving as a proxy-marker of probable RBD, decreased in patients treated with memantine compared to placebo. No effect was found on daytime sleepiness.

Novelty of study

This is the first study to specifically assess the effect of memantine on probable RBD and daytime somnolence in this patient population.

4.2. Results Study II

This study investigated QOL in LBD using the instrument Quality of Life-Alzheimer disease (QOL-AD), and the effect of memantine on QOL-AD in an RCT setting over 24 weeks.

4.2.1. Baseline results

The first part of this study investigated QOL at baseline using patient- and caregiver-rated QOL-AD. There were four patient-rated QOL-AD and three caregiver-rated QOL-AD missing at baseline. Two participants were missing both QOL-AD assessments at baseline and were excluded in the published article resulting in total n=73 (see Appendix II). To improve reporting transparency, all randomised patients have been included within this thesis, as demonstrated in the updated trial profile in Figure 13 (replacing Figure 2 in the published article, see Appendix II). Change in QOL was measured using follow-up data of QOL-AD at 24 weeks. Complete case analysis was employed with listwise deletion of those with missing follow-up.

4.2.2. Quality of life at baseline in Lewy body dementias

Quality of life was explored using the theoretical framework of health outlined by the World Health Organization (WHO) International Classification of Functioning, Disability and Health (ICF) model.[319] Each item of QOL-AD was organised into domains according the parts of health described by WHO ICF; 'Body function', 'Body structure', 'Activity and participation', 'Environmental factors', with 'Life as a whole' and 'Self as a whole' kept separately, see Figure 12.

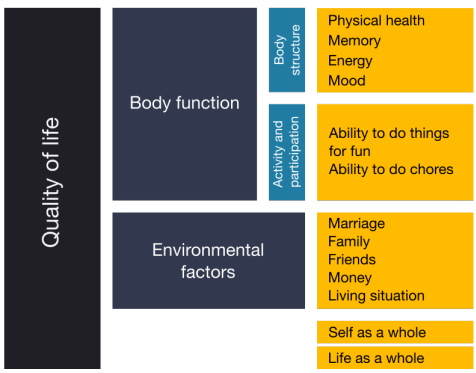

Figure 12. Quality of life. Items of rating scale Quality of Life in Alzheimer's Disease (QOL-AD) (yellow) according to domains in World Health Organization International Classficiation of Health (grey and blue).

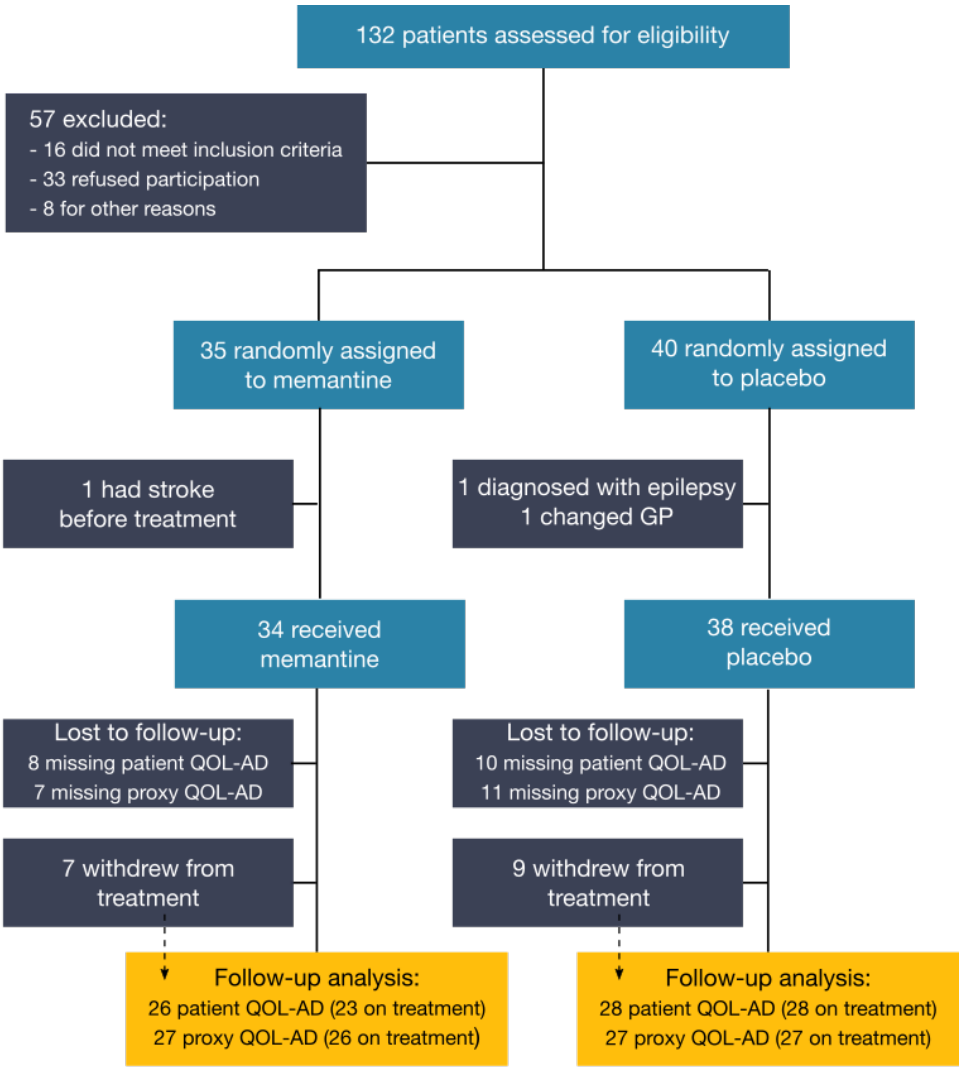

Figure 13. Updated trial profile.QOL-AD, Quality of life-Alzheimer's disease.

Patient- and caregiver-rated QOL-AD are shown in Figure 14-15. Both patients and caregivers rated items included in the domain 'Body function' lower than those included in the domain 'Environmental factors'.

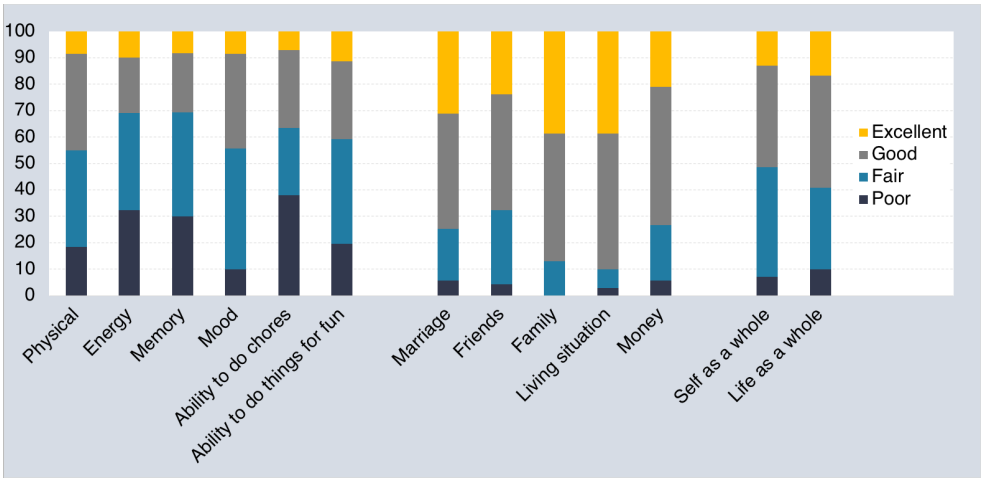

Figure 14. Patient-rated quality of life according to items in QOL-AD (n=71).

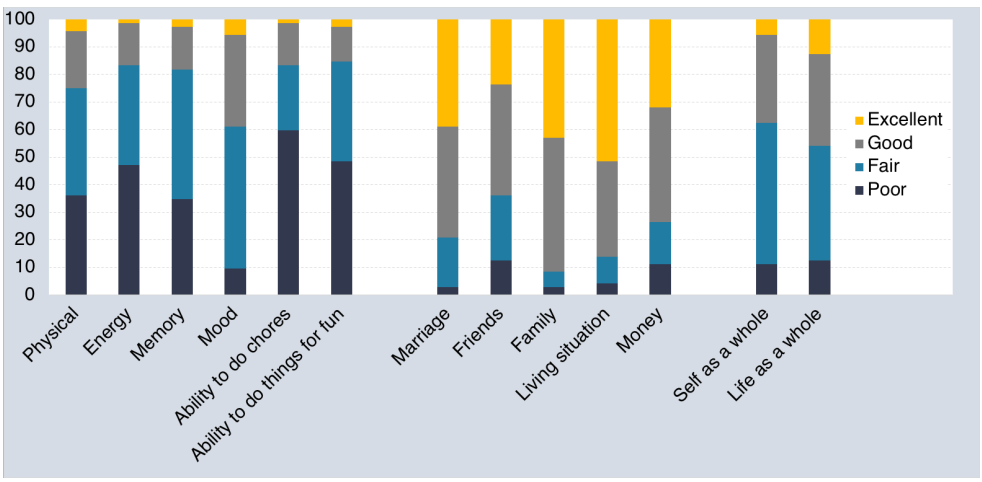

Figure 15. Caregiver-rated quality of life according to items in QOL-AD (n=72).

The QOL-AD instrument was further explored by i) performing a principal components analysis to assess whether the WHO ICF model for QOL-AD had statistical support within our data and ii) comparing the categorisation of items compared to findings in an exploratory factor analysis of QOL-AD in a non-demented population.[320]

Factor analysis was only performed on the caregiver-rated QOL-AD, excluding the items 'Life as a whole' and 'Self as a whole'. This revealed a four-factor structure labelled 'Activity', 'Social', 'Financial' and 'Memory', see Table 13.

Table 13. Factor analysis of caregiver rated Quality of Life-Alzheimer's disease (QOL-AD). The rotated factor solution of the principal components analysis is displayed. Factor loading values below 0.5 were not included.

	Activity	Social	Financial	Memory
Physical	0.742			
Energy	0.772			
Mood	0.544			
Living situation		0.575		
Memory				0.972
Family		0.869		
Marriage		0.515	0.528	
Friends		0.714		
Ability to do chores	0.778			
Ability to do things for fun	0.797			
Money			0.903	
% variance	36.3	14.6	9.8	9.3

The items included within these factors were plausible and overlapped with the two models of comparison, see Figure 16, suggesting an underlying construct of QOL-AD, separating items associated with physical function and socio-environmental function.

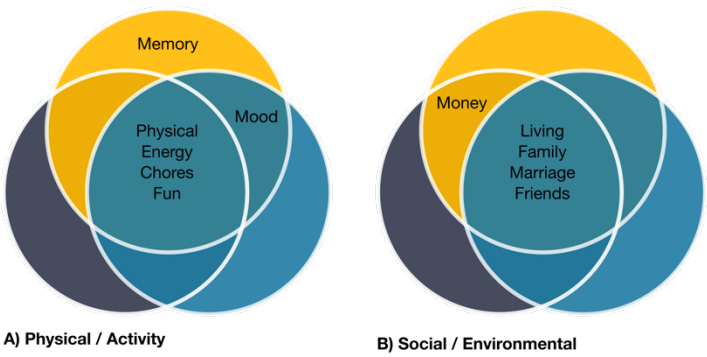

Figure 16. Models of comparison. Overlap between three different categorisations of Quality of Life Alzheimer's Disease (QOL-AD) items; World Health Organization model (yellow), factor analysis in our population of Lewy body dementia patients (blue) and factor analysis in a non-demented population (grey).

4.2.3. Treatment effect on quality of life

Total QOL-AD

No significant difference was found in total QOL-AD between the memantine or placebo group for either patient- or caregiver-rated scores. A within-group difference was seen for caregiver-rated QOL-AD in the memantine group, with an increased mean change score of 1.96 (95% CI 0.18-3.75, Wilcoxon signed rank-test, p=0.04).

Domain-specific QOL-AD

Separate analyses were conducted comparing patient- and caregiver-rated QOL-AD between baseline and 24 weeks in the memantine and placebo group for each domain ('Body function', 'Body structure', 'Activity and participation', 'Environmental factors', 'Life as a whole' and 'Self as a whole').

In caregiver-rated QOL-AD, 11/27 patients in the memantine group improved in the item 'Life as a whole', compared to 4/27 in the placebo group over 24 weeks, as demonstrated in Figure 17. This represented a significant between-group difference, with a mean change improvement of 0.38 points (95% CI 0.15-0.61, Mann-Whitney *U* test, p=0.010) in the memantine group. No other between-group differences were found.

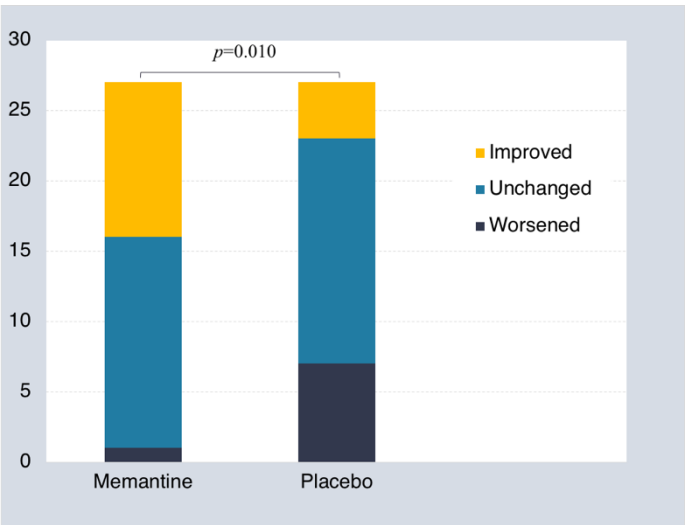

Figure 17. Between-group differences of caregiver-rated QOL-AD item 'Life as a whole'. Difference from baseline to 24 week follow-up in memantine and placebo group. P-value indicates between-group difference using Mann-Whitney *U* test.

Within-group differences from baseline to 24 weeks were investigated using Wilcoxon signed-rank test, demonstrating statistical improvements in the memantine group for 'Life as a whole' (p=0.004), 'Body function' (p=0.016), 'Body structure' (p=0.047). No improvement was seen in 'Activity', 'Environment' and 'Self as a whole'. No improvements over time was seen in the placebo-group. No between- or within-group differences were found in the patient-rated QOL-AD.

Factor-specific QOL-AD

Based on the exploratory factor analysis, factor scores generated from the factor coefficient matrix were compared. Investigating improvements over time in the generated factors demonstrated no differences between the placebo or memantine group in caregiver-rated QOL-AD.

4.2.4. Elaborations of baseline results

The QOL-AD instrument has been used to compare quality of life in AD and DLB patients,[275] however total scores have not previously been reported, and the reliability and validity has not been assessed. Elaborations of this kind were outside of the scope of Study II but have been included here for completion.

Reliability & validity

Caregivers rated total QOL-AD lower than patients (mean 34.0 v. 31.4, pairwise t-test, p <0.012), as well as all individual items other than 'Living situation', 'Family' and 'Money'. Intra-class correlation between patients and caregivers was 0.36 for total QOL-AD, with ICC for separate items ranging from 0.17 ('Living situation') to 0.44 ('Marriage'), see Table 14.

Reliability was assessed by internal consistency using Cronbach's alpha which was 0.85 for both self and proxy ratings. The item-total correlations ranged from 0.40 ('Memory') to 0.73 ('Ability to do chores') in the patient-ratings, and in caregiver-ratings from 0.40 ('Memory') to 0.72 ('Physical' and 'Life as a whole'), see Table 14.

Table 14. Mean scores, standard deviations, item-total correlation and intra-class correlations for patient- and caregiver-reported QOL-AD.

	Patient		Caregiver		ICC
	Mean (SD)	ITC	Mean (SD)	ITC	
Physical	2.35 (0.88)	0.67	1.93 (0.86)	0.72	0.28
Energy	2.08 (0.97)	0.59	1.71 (0.78)	0.61	0.31
Mood	2.43 (0.79)	0.64	2.35 (0.74)	0.69	0.38
Living situation	3.26 (0.72)	0.50	3.33 (0.82)	0.56	0.17
Memory	2.10 (0.93)	0.40	1.86 (0.78)	0.40	0.34
Family	3.25 (0.68)	0.47	3.32 (0.71)	0.56	0.27
Marriage	3.01 (0.84)	0.67	2.78 (0.96)	0.69	0.44
Friends	2.87 (0.83)	0.43	2.76 (0.96)	0.69	0.30
Self	2.57 (0.81)	0.65	2.32 (0.75)	0.62	0.20
Chores	2.06 (0.98)	0.73	1.58 (0.80)	0.65	0.33
Fun	2.32 (0.92)	0.58	1.69 (0.80)	0.62	0.28
Money	2.89 (0.80)	0.53	2.94 (0.96)	0.45	0.25
Life as a whole	2.66 (0.88)	0.72	2.46 (0.87)	0.72	0.23
Total score	34.00 (6.00)	1.00	31.40 (6.40)	1.00	0.36
Cronbach's alpha		0.850			0.848

Abbreviations: ICC, intraclass correlation coefficient; SD, standard deviation.

Weak correlations were found between total QOL-AD and other clinical assessments in the study, see Table 15. All correlations were in the expected direction. The strongest association was found between caregiver-rated QOL-AD and the Neuropsychiatric Inventory (NPI).

Table 15. Clinical correlations between QOL-AD and other baseline measurements

	Patient-rated	Caregiver-rated	Expected direction
Age	-0.14	-0.07	-
Female sex	-0.29	-0.01	-
PDD diagnosis	-0.05	0.12	?
MMSE	0.29	0.09	+
NPI total	-0.24	-0.40	-
DAD	0.38	0.26	+
AQT colour	-0.26	-0.07	-
AQT form	-0.06	-0.08	-
AQT colour-form	-0.14	0.01	-

Abbreviations: AQT, a quick test for cognitive speed; DAD, disability assessment for dementia; MMSE, mini-mental state examination; NPI, neuropsychiatric inventory.

4.2.5. Missing data analysis

There was a considerable loss of follow-up in QOL-AD over 24 weeks. Listwise deletion was employed, meaning that nearly 30% of data was missing at follow-up. The majority of patients without complete QOL-AD data had dropped out prior to medication or withdrawn from the study due to worsening of disease or adverse events. These patients were older, had a lower MMSE score at baseline, and a fewer percentage were on concomitant treatment with ChEIs, see Table 16.

Table 16. Missing data analysis. Comparison between patients with complete and incomplete data for both patient- and caregiver-rated QOL-AD over 24 week follow-up.

	Complete QOL-AD (n=48)	Incomplete QOL-AD data (n=27)
Memantine	23 (48)	12 (44)
Withdrawn	1 (2)	18 (67)
Male:Female	36:12	21:6
DLB:PDD	22:26	11:16
Age	75.3 (5.5)	79.4 (6.1)
MMSE	20.6 (4.2)	18.9 (3.9)
ChEI	31 (65)	10 (37)
L-dopa	40 (83)	23 (85)

Abbreviations: ChEI, cholinesterase inhibitor; DLB, dementia with Lewy bodies; MMSE, mini-mental state examination; PDD, Parkinson's disease dementia; QOL-AD, Quality of Life Alzheimer's Disease; L-dopa, levodopa. Data are numbers (%) or mean (SD).

4.2.6. Comments

Is QOL-AD reliable and valid in an LBD population?

Caregivers rated QOL-AD lower compared to patients, with ICC between patients and caregivers being similar to other studies.[297] High internal consistency was found in both patient- and caregiver-ratings, suggesting good reliability. Weak associations were found with other clinical measures. The inverse relationship with NPI is a plausible finding suggesting validity of the scale. Overall, these findings suggest that QOL-AD could be both reliable and valid in an LBD population, something which however needs to be confirmed in a larger material.

Are there underlying constructs of QOL-AD in LBD?

The principal components analysis demonstrated a separation between items relating to physical functioning and socio-environmental aspects of disease. This corresponds well to the categorisation using the WHO ICF model, as well as factor analyses of QOL-AD in other study populations including medical inpatients, suggesting a general underlying construct of QOL-AD.[297,320]

Interestingly, the item 'Memory' had a low item-total correlation in both patients and caregivers and loaded on to its own factor in the principal components analysis. There

was also only a weak-to-absent association of QOL-AD and the cognitive tests (MMSE and AQT) in both patients and caregivers. Taken together, this could further indicate that cognition is not a strong determinant of QOL in LBD. Since this relationship was similar in caregivers, it cannot be attributed to poor memory leading to inaccurate QOL-AD ratings.

What are the limitations in the factor analysis?

There are a number of comments regarding the methodological choices for factor analysis. To start, the method of principal components analysis is by some critics not considered a true method of factor analysis, but rather a summation of variance into smaller components.[321] Principal axis factoring is an alternative method commonly used in similar studies which could instead have been used.[320-322] Furthermore, in the interpretation of the factor solution, factors were retained based on if their eigenvalues were over 1 or not. This is a selection method which tends to over-extract variables,[321] and could explain why one factor contained only two items, and another one item in our four-factor structure. A better representation could perhaps have been achieved by using different methods of extractions and attempting both two- and three-factor solutions. Moreover, items 'Self as a whole' and 'Life as a whole' were excluded on a theoretical rather than statistical basis, and patient-rated QOL-AD was not investigated. More importantly however is the small sample size. Although recommendations vary,[321] a rule of thumb is that a sample of 200 is considered fair, with 500 being very good and over 1000 excellent.[323] In view of our small sample, a confirmatory study would therefore be required in order to confidently confirm underlying constructs of QOL-AD in LBD.

How does QOL in LBD compare to other populations?

Total patient-rated QOL-AD was 34.0 (±6.0) points and caregiver-rated 31.4 (±6.4) points. In other studies of patients with mild to severe AD, the range of total QOL-AD is wide, spanning between 26.2-40.6 in patients and 23.4-36.0 in caregivers.[297,324-327] No direct comparison, suggesting better or worse QOL, can therefore be made from this study alone. Other studies have described QOL-AD to be associated with cognitive function,[297] a finding not replicated in our study as discussed above.

Are treatment effects significant?

Similar to Study I, this too was a secondary analysis and although QOL-AD was included in the main protocol, the study was not powered for these analyses. Treatment effects were modest, and if accounting for multiple comparisons would not be significant. The loss in follow-up and listwise deletion might further bias the results.

Furthermore, treatment effects were only found in caregiver-rated QOL. There are two possible explanations for this: i) a true difference exists, but caregiver-rated QOL-AD is more sensitive to change or more reliable than patient-rated QOL-AD ii) no true

difference is experienced by patients, and caregiver-rated QOL-AD is an unreliable measure of patient QOL in LBD.

Considering these issues, treatment effects in patients with LBD are suggestive rather than definite.

4.2.7. Summary

The QOL-AD scale was found to have good reliability and validity in an LBD population. Caregivers rated total QOL-AD lower than patients, similar to findings in other studies. In both patients and caregivers, QOL-AD seems to represent two main underlying constructs, whereby physical functioning is rated lower than socio-environmental factors. Treatment effects with memantine suggest a possible benefit in caregiver-rated QOL-AD.

Novelty of study

The QOL-AD scale has not previously been evaluated in patients with LBD. The effect of treatment with memantine on QOL has not previously been assessed.

4.3. Results Study III

This was a preliminary investigation of the effect of carbonated thin liquid on swallowing difficulties in LBD assessed by videofluoroscopy.

Figure 18 illustrates patient selection and analyses. Due to absence of videographic material, 23/48 patients were not included in the quantitative analysis. No differences in baseline variables were found between those with or without videographic material (data not shown).

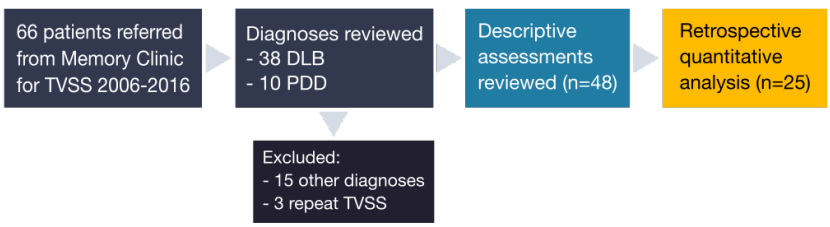

Figure 18. Flow chart illustrating patient selection and analyses.

4.3.1. Descriptive assessment

Out of the 48 patients referred with a suspected swallowing problem, 40 had a confirmed swallowing dysfunction when assessed with TVSS, see Table 17. Out of these 40, a total of 14 patients did not have any subjective swallowing problems and were referred for another reason. Pharyngeal swallowing dysfunction, present in 24 patients, was the most common finding, followed by combined oropharyngeal dysfunction and oral dysfunction only. Half of the patients were visualised to have pharyngeal retention, and just over a quarter evidence of tracheal penetration. When testing the swallowing response with carbonated thin liquid, improvement was seen in 87%.

Table 17. Summary of descriptive statements from TVSS.

	All (n=48)	DLB (n=38)	PDD (n=10)
Reason for referral:			
Subjective swallowing difficulties	32 (67%)	23 (61%)	9 (90%)
Cough only	9 (19%)	9 (24%)	0 (0%)
Unable to straighten neck	1 (2%)	1 (3%)	0 (0%)
Excess saliva	1 (2%)	1 (3%)	0 (0%)
Clearing throat	1 (2%)	1 (3%)	0 (0%)
History of pneumonia	2 (4%)	1 (3%)	1 (10%)
No symptoms but other clinical suspicion	2 (4%)	2 (5%)	0 (0%)
Swallowing dysfunction confirmed on TVSS:	40 (83%)	31 (82%)	9 (90%)
Type of swallowing dysfunction observed:			
Oral dysfunction only	4 (8%)	4 (11%)	0 (0%)
Pharyngeal dysfunction only	24 (50%)	19 (50%)	5 (50%)
Combined oropharyngeal dysfunction	10 (21%)	7 (18%)	3 (30%)
Pharyngeal retention	24 (50%)	19 (50%)	5 (50%)
Tracheal penetration	13 (27%)	9 (24%)	4 (40%)
Improved swallowing with carbonated liquid:	34 (87%)*	27 (87%)	7 (88%)

*One patient with confirmed swallowing dysfunction not tried on carbonated liquid (n=39).

4.3.2. Quantitative swallowing measures

Pharyngeal transit time

A difference in pharyngeal transit time (PTT) was seen between thin, thickened and carbonated thin liquid (Friedman test, x^2 =12.65, p=0.002). Carbonated thin liquid had a faster PTT (median 633 ms, IQR 516–786) compared to thin (760 ms, IQR 613–940, Wilcoxon-signed rank test, p=0.014, r=-0.36), and thickened liquid (880 ms, IQR 600–1500 ms, Wilcoxon-signed rank test, p <0.001, r=-0.51) No significant difference was found between thin and thickened liquids. No differences were found depending on diagnoses or sex, and no association was found with levodopa dose (data not shown).

Table 18. Comparison of grading on penetration and residue scales.
Comparison between different liquid consistencies in each patient with abnormal findings in quantitative analysis.

#	Pharyngeal retention scale						Penetration scale					
	thin	thick	CTL	Δ thin-thick	Δ thin-CTL	Δ thick-CTL	thin	thick	CTL	Δ thin-thick	Δ thin-CTL	Δ thick-CTL
5	3	3	1	0	**-2**	**-2**	2	1	1	**-1**	**-1**	0
7	1	1	1	0	0	0	2	1	1	**-1**	**-1**	0
8	1	2	1	+1	0	**-1**	1	1	1	0	0	0
15	1	1	1	0	0	0	1	2	1	+1	0	**-1**
17	4	3	2	**-1**	**-2**	**-1**	1	1	1	0	0	0
18	2	2	1	0	**-1**	**-1**	1	1	1	0	0	0
20	1	2	-	+1	-	-	1	1	-	0	-	-
21	1	2	1	+1	0	**-1**	1	1	1	0	0	0
22	2	3	3	+1	+1	0	1	1	1	0	0	0
23	2	2	2	0	0	0	1	1	1	0	0	0
25	2	2	1	0	**-1**	**-1**	1	1	1	0	0	0

Abbreviations: CTL, carbonated thin liquid; thin, thin liquid; thick, thick liquid. Bold numbers represent abnormal values and positive change scores.

Retention & penetration

Out of the 25 patients, 11 subjects had an abnormality in at least one of the three swallows studied on either residue or penetration, see Table 18. Thickened liquid worsened the degree of residue in four patients compared to thin liquid. Carbonated thin liquid improved the severity of pharyngeal retention in six out of nine patients compared to thin or thickened liquid. The depth of penetration was improved with carbonated thin liquid in the three patients with observed penetration on thin or thick liquid.

A difference was seen in retention scores between thin, thickened and carbonated thin liquid (Friedman test, x^2 =6.64, p=0.036). Carbonated thin liquid had lower scores of retention than thickened liquid (Wilcoxon-signed rank test, p=0.020). No significant differences in retention were found between thin and thick, or thin and carbonated thin liquid, or in penetration scores.

4.3.3. Comments

What makes this study relevant?

Albeit small and retrospective in nature, this study highlights that swallowing dysfunction is of relevance in patients with LBD, and not always associated with symptoms, which is why a formal examination needs to be carried out as part of clinical routine. Although not evaluated in LBD, speech and language therapists can offer patients with swallowing dysfunction specific posturing manoeuvres, training programs or suggest liquid modifications. Earlier intervention is believed to be better, specifically in view of predicted cognitive deterioration.[91]

Carbonated thin liquid is a cheap and easily administered intervention, which is already utilised in clinical practice for other neurological disorders to a varying degree. Descriptive assessments suggested improvement with carbonated thin liquid also in LBD, and the quantitative analysis confirmed improved speed of transit through the pharynx (PTT). Improved PTT cannot alone indicate a safe swallow but can possibly serve as a proxy marker, since it has shown to be associated with misdirected swallows[224,328] and also found to be prolonged in patients with parkinsonism and a history of pneumonia.[328,329] This was supported by the number of individuals whereby retention and depth of penetration was improved with carbonated thin liquid (Table 18), though non-significant with Bonferroni adjustment. This is in line with clinical observations, where pharyngeal residues after e.g. swallowing thickened liquid are seen to clear by the administration of carbonated thin liquid, reducing the risk of delayed aspiration.

Importantly, positive immediate effects from carbonated thin liquid do not necessarily indicate long-term usefulness. Longitudinal follow-up would therefore be needed to determine changes in health status including pneumonia and survival, parameters which would be clinically relevant.

What methodological aspects would be important for future studies?

Study rigour could be improved by producing specific liquids to ensure entirely similar consistencies, measuring centipoise values i.e. viscosity for comparison,[207] randomisation in order of presentation of different liquids, and analysing additional swallows in the examination to get a better pick-up rate or retention and aspiration.

For the analysis, both the descriptive and quantitative analyses are biased. Ideally, another evaluator should be included, enabling reliability testing to validate swallowing measures. Improved technical equipment allowing a higher frame rate would also make the quantitative measurements more precise. Patient experience of swallowing symptoms could be assessed with subjective rating scales e.g. Sydney Swallow Questionnaire,[330] and whether patients preferred the sensation of carbonated liquid.

Furthermore, this study also does not answer whether or not carbonated thin liquid is better in LBD compared to in other neurological or cognitive disorders, something which could be addressed by including other groups of comparison.

Clearly, well-designed randomised controlled studies in larger cohorts would be important to better understand the role of carbonated thin liquid in LBD swallowing dysfunction. Importantly, methodological standardisation regarding what technique equipment to use, liquid preparation and administration, as well as which quantitative measures to use would be key.

4.3.4. Summary

Swallowing dysfunction is common and can be asymptomatic in LBD patients. Compared to thin and thickened liquid, carbonated thin liquid improves swallowing when assessed by descriptive and quantitative measures.

Novelty of study

This is the first study to assess liquid-modification in order to improve swallowing function specifically in DLB patients, and the first to assess the effect of carbonated thin liquid in patients with DLB and PDD.

4.4. Results Study IV

This study investigated relative survival in patients with LBD compared to the general population, and factors contributing to excess mortality.

Patient selection is shown in Figure 19. Other than the demographics outlined in Table 10, CCI scores were calculated for the population with 66.7% of patients having no other significant comorbidities than dementia.

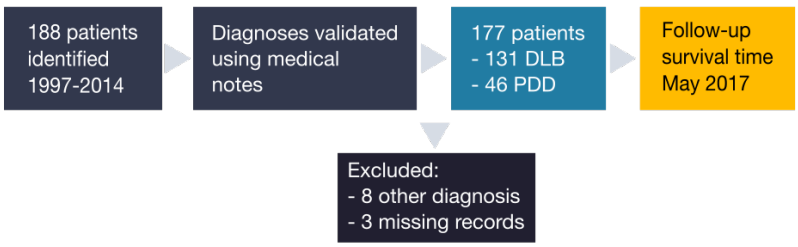

Figure 19. Patient flow chart.

4.4.1. Survival analysis

A total of 143 patients (80.7%) were deceased at follow-up. The median survival time was 4.1 years (IQR 2.6-6.0) from diagnosis for the overall group. The 10-year standardised mortality rate (SMR), estimating the likelihood of death in patients with an LBD diagnosis compared to the general population, was 3.44 (95% CI 2.92-4.04).

The observed, expected and relative survival curves for the patient group is illustrated in Figure 20 (following page).

The observed 5-year and 10-year survival was 40.5% and 5.6% respectively, compared to the expected survival rates of 78% at 5 years and 62% at 10 years. Adjusting the overall mortality with expected mortality results in a 5-year and 10-year relative survival rate of 52.5% and 9.1% respectively.

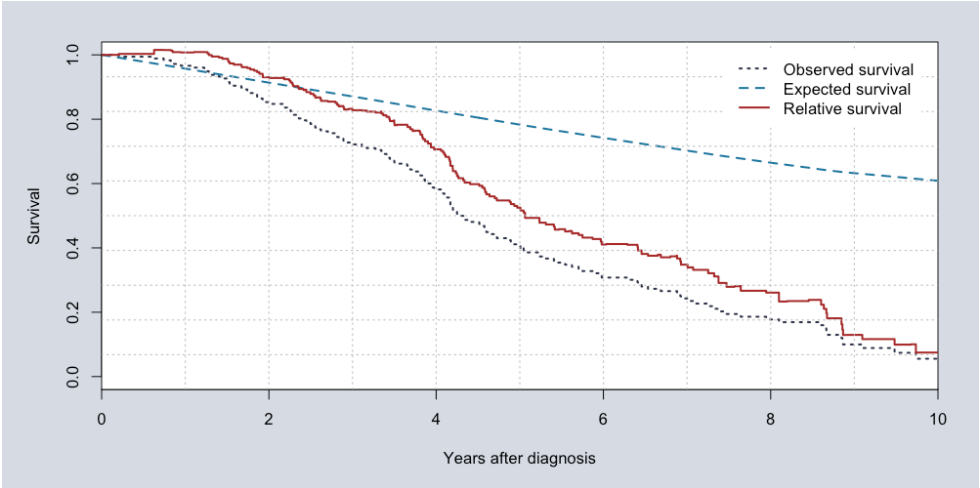

Figure 20. Survival curves in all patients.
Comparison of observed, expected and relative survival times after diagnosis.

Because relative survival is dependent on the expected mortality within the group studied, it will be influenced by age, as illustrated in Figure 21. Even though older patients have a worse overall survival than younger patients, some of this difference is attributed to increased background mortality and not due to worsened mortality due to the LBD diagnosis. There is consequently a larger discrepancy between observed and relative survival in the older age group.

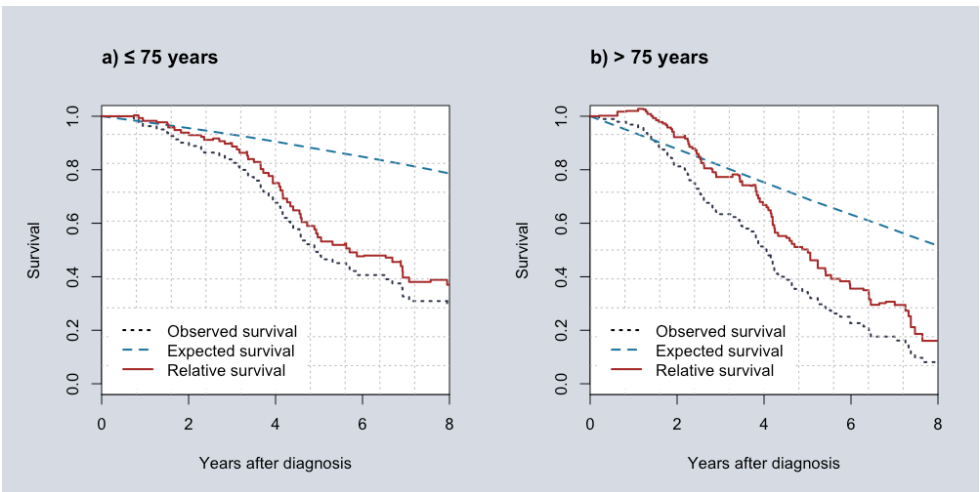

Figure 21. Observed, expected and relative survival in patients younger than 75 years and patients older than 75 years.

Factors influencing overall survival were assessed using a Cox proportional hazards model including the baseline variables, showing that older age and lower MMSE predicted mortality, see Table 19.

Table 19. Multivariable Cox proportional hazards model. Predictors of overall survival by hazard ratios for baseline variables.

Variable	β	HR	95% CI		SE	z	p value
Age at diagnosis, years	0.07	**1.07**	1.04	1.11	0.02	4.28	**<0.001**
Year at diagnosis	-0.01	0.99	0.94	1.04	0.03	-0.45	0.66
Presentation to diagnosis, months	0.00	1.00	0.99	1.02	0.01	0.68	0.50
Sex, 0=male, 1=female	-0.18	0.84	0.58	1.20	0.18	-0.97	0.33
Diagnosis, DLB = 0, PDD = 1	-0.05	0.95	0.64	1.41	0.20	-0.26	0.80
Nursing home residency, 0=no, 1=yes	0.20	1.22	0.67	2.20	0.30	0.66	0.51
CCI score, 0 = 1, 1= 2/more	-0.01	0.99	0.68	1.43	0.19	-0.06	0.95
MMSE at diagnosis, score	-0.07	**0.93**	0.90	0.96	0.02	-4.30	**<0.001**

Abbreviations: *β,* regression coefficient; CCI, Charlson comorbidity index; CI, confidence interval; DLB, dementia with Lewy bodies; HR, hazard ratio; MMSE, mini-mental state examination; PDD, Parkinson's disease dementia; SE, standard error.

Similarly, excess mortality in patients with LBD is illustrated in Table 20 using excess hazard ratios (eHR). In comparison to Cox regression, age is negatively associated with excess mortality (eHR 0.91), which can be attributed to higher expected survival in younger patients. Conversely, excess mortality was significantly increased in females (eHR 1.45), attributable to the increased expected survival in this group. Lower MMSE was again associated with increased mortality (eHR 0.93).

Table 20. Multivariable relative survival model. Predictors of relative survival expressed by excess hazard ratios for baseline variables.

Variable	β	HR	95% CI		SE	z	p value
Age at diagnosis, years	-0.09	**0.91**	0.88	0.94	0.02	-5.34	**<0.0001**
Year at diagnosis	0.02	1.02	0.97	1.08	0.03	0.84	0.40
Presentation to diagnosis, months	0.00	1.00	0.99	1.02	0.01	0.50	0.62
Sex, 0=male, 1=female	0.37	**1.45**	1.01	2.09	0.19	1.99	**<0.05**
Diagnosis, DLB = 0, PDD = 1	-0.08	0.92	0.62	1.37	0.20	-0.42	0.68
Nursing home residency, 0=no, 1=yes	0.35	1.42	0.77	2.65	0.32	1.12	0.26
CCI score, 0 = 1, 1= 2/more	-0.04	0.96	0.67	1.39	0.19	-0.21	0.84
MMSE at diagnosis, score	-0.07	**0.93**	0.90	0.96	0.02	-4.35	**<0.0001**

Abbreviations: *β,* regression coefficient; CCI, Charlson comorbidity index; CI, confidence interval; DLB, dementia with Lewy bodies; eHR, excess hazard ratio; MMSE, mini-mental state examination; PDD, Parkinson's disease dementia; SE, standard error.

4.4.2. Subgroup analysis with *APOE* ε4

Nearly half (47.5%) of those with *APOE* genotyping carried one or two *APOE* ε4 alleles. No significant differences were found in baseline demographics between carriers and non-carriers (data not shown).

Both overall and relative survival was influenced by *APOE* ε4 status (HR of 1.45, 95% CI 1.03-2.16, and eHR 1.77, 95% CI 1.22-2.57). A significant interaction was found with diagnosis, whereby both overall and excess mortality was increased in *APOE* ε4 carriers with DLB but not in PDD (Table 21). However, 11/46 patients with PDD did not have *APOE* genotyping which could cause bias.

Table 21. Interaction between *APOE* ε4 and diagnosis. Age- and sex-adjusted Cox proportional hazards model and relative survival regression model.

Variable	HR (95% CI)	eHR (95% CI)
Diagnosis**APOE* ε4		
0 = non-carriers	ref	ref
1 = PDD**APOE* ε4 carriers	1.40 (0.73-2.65)	1.04 (0.49-2.24).
2 = DLB**APOE* ε4 carriers	1.85 (1.25-2.74)	2.00 (1.35-2.97)

Abbreviations: *APOE,* apolipoprotein E; *β*, regression coefficient; CI, confidence interval; DLB, dementia with Lewy bodies; eHR, excess hazard ratio; HR, hazard ratio; PDD, Parkinson's disease dementia.

4.4.3. Comments

What is the difference of relative survival rate and standardised mortality ratio?

These measure different epidemiological concepts. Relative survival quantifies the lethality of a disease at different time points taking into account expected mortality, as can be seen in Figure 20. Applied in our setting it answers whether deaths occurring in the LBD population are simply because of age and other comorbidities, or if they can be attributed to diagnosis. As can be seen in Figure 20, there is a clear discrepancy between expected and observed survival, indicating poor survival with diagnosis.

The standardised mortality ratio (SMR) describes the impact of the diagnosis, by estimating the likelihood of death in patients with the diagnosis of interest compared to the general population.[305] In comparison to relative survival methods, SMR does not provide any information on survival time or background mortality.[331] An older population will generally have a lower SMR, because of the high rates of mortality within that population, meaning that even if the relative survival is low, the impact of disease is less.

Why do females have an increased excess mortality?

Male sex has been considered a key risk factor for earlier mortality in dementia, although evidence in LBD patients has been varied. In this study, years of survival after diagnosis was nearly identical in males and females. However, because females are expected to live longer they will 'lose more', which is associated with a higher excess mortality. In a way, one could say that the LBD disease ameliorates the natural longevity in women compared to men. Since relative regression methods of survival have not been performed in other similar populations, it is difficult to say if the same phenomenon would also be present in for example AD.

How does survival in LBD compare to AD?

Even though this was not the focus of our study, reasonable comparison can be made with findings in the existing literature. Other studies have reported an SMR of 1.50 for AD[240] and 1.49 for all-cause dementia (of which 37% were AD and 25% mixed AD-VaD).[241] This is less than half of that seen in our study and others,[240] thus indicating increased mortality in LBD compared with AD, supporting the findings in other comparative studies (see Table 5 in Background).

Why do patients with LBD have a poor prognosis?

Lewy body disease is a disseminated neurodegenerative process including both the central and peripheral nervous system, leading to widespread disease manifestations including swallowing dysfunction with subsequent risk of aspiration pneumonia and cardiac sympathetic denervation predisposing to cardiac dysfunction.[332] In line with this, respiratory and cardiovascular causes have been found to be the two main causes of death after the neurodegenerative disease itself in studies investigating causes of death in LBD using death certificate reports.[244,333]

On the other hand, poor survival could be attributed to poor care. Hospitalisations are frequent due to infections or falls, and result in longer stays compared to AD patients.[334] Episodes of hospitalisations are notoriously precarious for patients with dementia, being associated with inadequate assessment, treatments and investigations.[335] Discrimination of persons with dementia and lack of knowledge from hospital staff are recognised contributors to this situation. Given the complex neuropsychiatric symptoms in LBD, the risk of antipsychotic use might also be increased. If receiving insufficient or inaccurate treatment for otherwise treatable conditions, this is likely to influence survival rates in LBD.

4.4.4. Summary

The mortality is over three-times higher in patients diagnosed with LBD compared to an age- and sex-matched population. Excess mortality is found primarily in younger patients, females, those with lower MMSE and carriers of *APOE* ε4.

Novelty of study

This was the first study to utilise relative regression models in LBD patients, and by doing so identifying those at a higher risk of excess mortality.

4.5. Results Study V

This study investigated the subjective experience of living with LBD using in-depth interviews and interpretative phenomenological analysis (IPA).

4.5.1. Patient population

Participants were all white males between the ages of 78-88 years with disease duration between 1.5-7 years. No females meeting inclusion criteria were identified at the time of the study. All participants but one lived with their spouse. The last performed MMSE, done as part of clinical routine, was retrieved from hospital electronic medical records, with scores ranging between 18-29 points. Participants also completed QOL-AD with scores ranging between 21-42 points. Included participants consequently had varying cognitive impairment and levels of subjective quality of life.

4.5.2. Findings

Demonstrated in Table 22, is the process of identifying a data extract, initial coding and final theme. Three overarching themes were identified, characterising the experience of living with DLB: 1) Disease impact, describing symptom experience and resulting consequence 2) Self-perception and coping and 3) Importance of others. Each theme is described in subsequent sections.

Table 22. Example of data extracts and coding with themes.

Data extract	Coding	Theme
The thing which is limiting my life the most is simply that I so frequently have to pass water […] It can sound very prosaic, but it is an actual problem […] It makes me not be able to… to… transfer myself… travel… it is very restricting […] Yes it is… it different in different environments… partly that you have to monopolise the toilet for quite some time [5]	Symptom restricting participation	Disease impact
Yes, it is called Lewy body dementia but I think that's so rotten… if you tell colleagues then they change so that you have Lewy body dementia so they… then… then they will put a mark in your forehead… dementia that's no point… no point in telling him…that's too complicated… he will never get it. Or a joke or something funny… there's not point… he won't get it anyway. And… it's not true… because you will… I think but maybe the surroundings don't… but they… in your own eyes… you have to protect yourself… in your soul… against this… dementia… mark [3]	Experience of stigmatisation	Self-perception and coping
It has been so bad that for a year I couldn't… or the head office is in another city… where we have our board meetings… instead the board has come down here and we have been sitting in the dining room and suddenly someone would say "hey, should you not go and have a little nap?" [laughs] Fully open, fully open! [2]	Trusting those around	Importance of others

Disease impact

Experience of symptoms, and how these affected the person's everyday life, had an impact on disease-experience in LBD. A range of symptoms would be accounted for including cognitive, motor, psychiatric and autonomic symptoms. Cognitive symptoms would extend beyond the memory and language problems previously described in the literature,[336] and include fluctuations, reduced processing speed, visuospatial difficulties and passivity, in line with the cognitive profile recognised in persons with LBD.[279,280] One participant described:

> I know the last times I was… visiting… someone that we know… and I got more tired and tired… all of a sudden I'm sitting there nodding… I had to go and sit a little bit off and sleep… and then I wake up… and then I'm awake… so that is what is not normal right, of course not [1]

The subjective experience of excessive somnolence, REM sleep behaviour disorder and visual hallucinations were also reported, something which has previously been relatively absent from literature. Notably, the most concerning symptom would be that which interfered most with everyday life. The greater variety in symptoms, compared to other dementia types contributed to different barriers. For example, previous studies have attributed loss of confidence in moving outside due to fear of getting lost,[337] whilst the participants of this study identified fear of falling and risk of being dependent on others as the major concern. The barriers could thus be cognitive, physical or psychological in nature, as exemplified by the first extract Table 22. If the barriers were unsurmountable

this would naturally lead to reduced activity, independence, participation and socialisation, with resulting negative feelings such as exclusion and loneliness.

Self-perception & coping

A sense of self was identified in all participants throughout the interviews, regardless of cognitive dysfunction, suggesting that this does not necessarily weaken because of LBD. Disease-related changes, both cognitive and physical, were found to threaten self-perception, and participants expressed that these influenced identity, skills, traits and role-position. Psychological aspects, such as the belief concerning how others viewed them, could also affect sense of self, see for example the second extract in Table 22.

Threatened self-perception would require adopting strategies and coping mechanisms, including active fighting strategies and attitudes serving to protect the self. Some strategies would be related to early personality traits, such as valuing yourself and having a positive outlook in life:

> I have probably always, as I mentioned initially when you came… tried to keep… me… or let me… let me contained the thought of the disease on the whole, and instead tried to live a life as natural as possible like I've always lived… and not let the illness… dominate me [5]

Others would concentrate on accepting the changes experienced and adjusting expectations in order to avoid disappointment. This challenges a view often portrayed by the public, whereby persons with dementia are simply submissive sufferers. Overall, coping strategies had the ability to alter the perception of disease-related changes and losses, influencing well-being.

Importance of others

Symptoms of disease and self-perception can be thought of as internal processes influencing experience of LBD. However, it was also recognised that external processes, represented by actions of others, would be important in how LBD disease was experienced and the resultant well-being. This would include persons in the health care system, family, friends and acquaintances. Participant narratives demonstrated how positive actions from others could be helpful in maintaining sense of self and well-being throughout the disease-course, see for example last extract in Table 22, whilst negative encounters would have the opposite effect. Lack of understanding or respect would create a poor relationship and lead to secondary behaviours such as withdrawal, lack of trust and inflamed self-perception.

One participant described the resulting social isolation:

> People don't reach out to me anymore… it's not that they avoid me, they just don't recognise me… I was thinking just that when we met, it was a person I had worked with a lot who… who came walking in the stairways over there… where the elevator is… so I waved and screamed "hello" and he looked like a question mark… we have travelled together, all over the world […] Yes, it feels sad. I am excluded, really excluded, very good word actually, I am excluded, I am unbelonging. And it… it of course has an impact… [3]

Accepting help from others was viewed as an inevitable consequence due to the progressive nature of the LBD disease. However, there was a wish for a balance whereby support was given respectfully, yet allowed independence, dignity and sense of self to be maintained.

4.5.3. Overall model

Although the themes described represent distinct entities, the conceptual view is that they are dynamically interrelated. This is illustrated in Figure 22, where one can see how the disease process generates symptoms, leading to change in function and behaviour (Theme 1), which in turn threatens self-perception leading to the need for coping strategies (Theme 2). In this model, persons surrounding the person with disease (Theme 3) are viewed as external processes feeding into the sequence, also having an effect on lived experience.

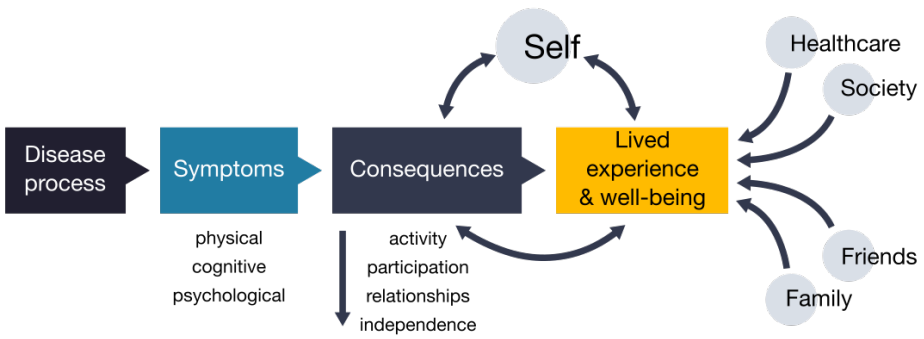

Figure 22. Experience of living with DLB. The ongoing disease process is generating symptoms influencing function and behaviours. This leads to secondary consequences relating to sense of self and well-being, a relationship which is bidirectional. External processes can feed in to this model, in turn influencing lived experience and sense of self.

4.5.4. Comments

What are the methodological challenges in this study versus qualitative research?

Qualitative research has a tendency to generate some scepticism within the wider medical community.[338] Even so, the substantial increase seen in qualitative research suggests that it contributes to clinical understandings which cannot be answered by quantitative approaches.[339] Because qualitative and quantitative research questions are inherently different, so are the methodologies, and the knowledge gap for clinicians in understanding this type of research might be an underlying factor explaining some of the apprehension.[340]

For the researcher primarily familiar with quantitative methods, qualitative methodologies can feel subjective or unscientific. This position has not been aided by the sometimes inconsistent and poorly reported qualitative research, complicating straightforward understanding of the methods and findings. In an attempt to improve this, the COREQ (Consolidated criteria for reporting qualitative research) checklist was developed.[341] For the novice qualitative researcher or appraiser these guidelines also provide a structural framework for conducting or interpreting qualitative research.

Assessment of rigour in qualitative studies, concerned with complex phenomena occurring in their natural context, is naturally not supported by statistical methods. The COREQ checklist emphasises however that appraisal of validity and credibility are still essential, sometimes termed trustworthiness. One major aspect includes reflexivity i.e. a systematic evaluation of the researchers' own background and position, and how this influences the research process in terms of what to investigate, how to go about this and the framing of conclusions.[340,341] This study was e.g. influenced by, as outlined in the discussion (see Appendix V), the pre-existing understanding of LBD within the research team, and one of the researcher's prior relationship to the participants. This was addressed by introducing a researcher with expertise in qualitative research but not in LBD in the analytical process, hoping to minimise the risk of bias.

Rigour is also dependent on transferability, describing the extent to which the findings can be applied in other settings or groups, something which requires adequate sampling and contextual descriptions.[340] In this study, the purposive sample was affected by excluding non-Swedish speakers and by including male participants only, due to not finding suitable females for the study. In addition, all participants were home-dwelling and four out of five lived with a spouse, which might limit transferability.

In terms of sample size, five participants can feel unsatisfactory in quantitative research studies (although not unprecedented, and sometimes forming the highest level of evidence with regards to treatment in LBD, see Table 3 in Background). However, rather than power calculations, study size is determined in parallel with the analytical process, and a single individual can be sufficient for qualitative research depending on the topic and scope.[312,340] The aim is data saturation, a point whereby additional data

do not generate any new concepts, implying satisfactory sampling,[342] something which was achieved in this study.

The analytical and interpretative procedure in qualitative research is often centred around categorisation of data into patterns, from which concepts are generated. Credibility is enhanced if data is analysed by more than one researcher, known as researcher triangulation, coming to similar agreements in analysis and interpretation.[343] This is why several researchers were involved in the analytical and interpretative process of this study. Another type of triangulation involves member checking by participants or utilising other data material, something which was not employed. Credibility is also improved by providing thick descriptions and quotations, demonstrating that the themes have in fact been derived from the data and not from the preconceptions of the research theme, explaining the numerous data extracts in the manuscript.[340]

4.5.5. Summary

Three main themes were identified, characterising the experience of living with LBD; 1) Disease impact; 2) Self-perception and coping and 3) Importance of others. The diversity in factors offers opportunities for improving well-being without necessarily modifying disease-process.

Novelty of study

This study demonstrates for the first time the feasibility in conducting in-depth interviews with persons with LBD, and outlines areas of importance for the disease-experience.

5. Reflections

5.1. Results in context

The impact of LBD can be examined in a number of possible ways. One perspective includes epidemiological measures and societal or economic consequences, however this focus has not been taken within this thesis. Instead emphasis has been on the impact on those persons living with disease. In the LBD research field, this has often taken the form of measuring symptoms of disease, and either comparing these to other dementia types or assessing their response to various interventions. Overall there has been an emphasis on ascertaining statistical differences in cognitive, psychiatric or motoric measures, which to some degree has overshadowed the concept of actually living well with disease. Few studies have considered patient preferences or their quality of life. In this thesis, studies with varying methodology and outcomes are presented, attempting to address both symptom relief and well-being in LBD.

REM sleep behaviour disorder is one of the core clinical features in the updated criteria of DLB. Current treatment options are based on few studies in patients with mixed underlying diagnosis and RBD. Study I within this thesis is the first study to focus on treatment effects of sleep behaviours in LBD patients specifically. Patients treated with memantine improved with regards to physical activity during night, serving as proxy-marker for probable RBD, supporting the global improvement recognised in meta-analyses.[117,119,131]

Another clinical symptom, rarely emphasised in LBD care, is swallowing dysfunction. Therapeutic strategies for swallowing problems have been assessed only in one study including only PDD patients and no DLB patients, investigating the effect of thickened liqiud.[207] Carbonated thin liquids, found to be useful in other neurological disorders, have not been tested in LBD.[224-228] For this reason, Study III examined swallowing function in patients with LBD, demonstrating that carbonated thin liquid improves swallowing function compared to thin and thickened liquid. This subsequently provides preliminary evidence for a previously unestablished potential therapy for swallowing dysfunction in LBD.

Well-being in LBD was examined using two different approaches within this thesis. Quantitative assessment of QOL in LBD was conducted by administered the instrument QOL-AD to both patients and caregivers. Whilst the properties of the

QOL-AD scale have not previously been assessed in LBD, the findings in Study II suggest good reliability and validity in both patients and their caregivers. Caregivers rate total QOL-AD higher than LBD patients, not previously demonstrated in LBD, but similar findings in other patient groups.[297] Study II also examined the treatment response in terms of QOL, suggesting that memantine could improve caregiver-rated QOL-AD. To date, this study and one study of armodafinil,[162] are the only two pharmacological trials in LBD whereby QOL measures have been evaluated, despite the clear importance in terms of outcome.

Another way to understand well-being and the first-hand reports of what it is like to live with a disease is to use qualitative methodology and to conduct in-depth interviews. This has the advantage that it can explore the complexities of illness-experience in greater detail. To date, there are no published studies involving specifically persons with LBD in qualitative work. In comparison, lived experience has been reasonably investigated in people with other dementias.[336,344,345] This was addressed in Study V, demonstrating for the first time the feasibility in involving persons with LBD in this type of research. The findings highlight aspects of disease-experience specific to persons with LBD, which could not be related from work in other dementias.

The final aspect of impact considered within this thesis extends to survival and prognosis. Previous survival studies have shown significant variability in survival times and prognostic markers. In Study IV, the use of relative regression methods was used for the first time in this patient population. This enabled a different perspective on mortality, and results demonstrates increased mortality risk in patients with LBD compared to the general population, in line with previous findings. However, whilst male sex has traditionally been considered a key risk factor for earlier mortality in dementia, Study IV demonstrates that the highest excess mortality is seen in females who have a longer life-expectancy compared to males.

5.2. Methodological considerations

Comments have been added after each results section to address methodological challenges and questions in response to the studies. There are however additional general areas of reflection relevant to the overall work, presented below.

5.2.1. Representativity

When conducting a study, it is rarely possible to examine every person within the target population. Instead a sample will be used which should ideally be representative of the population of interest, in order to make inferences based on the study results, see Figure

23. Whilst RCTs are considered superior evidence, the study populations are often highly selected, with lower risk profiles than the target population and exclusion of elderly patients with multiple comorbidities.[346,347] This can compromise external validity, as it means that the study findings are not transferable to the target population.

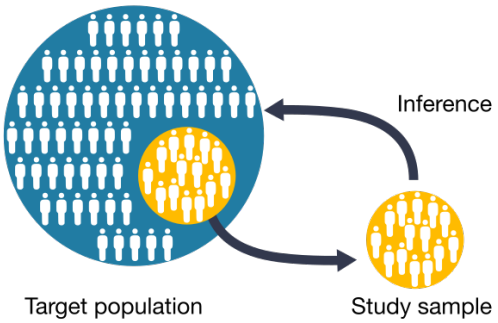

Figure 23. Importance of representativity in study sample. A representative sample is needed in order to make inferences about target population.

Patients from Study III-IV were relatively unselected with few exclusion criteria applied, suggesting a fairly representative sample for the LBD population treated as outpatients at the Memory Clinic, Malmö, Sweden. Assessment of representativity in the samples from the RCT setting (Study I-II) can therefore be made by comparing baseline data with the other studies, see Table 10 in Results. This shows that age at baseline were similar in Study I-IV, although disease duration was shorter prior to inclusion in Study III, suggesting older population at diagnosis. Cognitive impairment, measured with MMSE had similar means across Study I-IV, proposing that patients in Study I-II were not superior in terms of prior cognitive level. A difference was seen in number of patients on ChEI treatment, with a lower percentage found in Study I-II, perhaps owing to changes in clinical practice over time. On the whole, participants in Study I-II appeared similar to those in Study III-IV, and thus representative of target population. This is further implied by the very few patients not meeting exclusion criteria (Figure 10 in Results) and the allowance of concomitant ChEIs, in line with conventional clinical practice.

The patients included in Study V were older, had a shorter disease duration and a higher MMSE, indicating perhaps that they were clinically superior and maybe not entirely representative of the ordinary LBD patient. Importantly, this thesis also does not represent persons with LBD cared for elsewhere e.g. primary care or those who remain undiagnosed. In terms of PDD patients, these are initially managed as PD patients ay the neurology clinic and only sometimes referred the memory services, contributing to a referral bias and explaining the discrepancy in numbers between DLB and PDD patients in the samples. Moreover, participants in Study I-II had to have a spouse or responsible caregiver, and similarly four out of five in Study V lived with a

spouse. This of course could affect representativity, particularly with regards to QOL. Finally, the sample is inherently affected by the population attending the Memory Clinic in Malmö, consisting mostly of white Swedish-speaking people.

5.2.2. Statistical challenges

Sample size

An ideal sample size should have a high probability, i.e. power, in detecting a clinically significant difference if this difference exists.[317] Sufficient sample size can be determined for hypothesis testing a priori by taking into account the clinical difference to be detected, the level of type I (α) error i.e. finding a difference when it does not exist, and type II (β) error i.e. not detecting a difference when it does exist. A larger sample is generally preferred as it increases power and reduces both errors.

In this thesis, Study I-II were both secondary analyses of an RCT study for which the sample size was determined in order to detect a clinically significant difference on the CGIC scale, in other words not measures of sleep behaviour or QOL. There was also a considerable loss of follow-up in both studies, as well as exclusion of participants from one centre in Study I, leading to further reduction in sample size. In Study III, no power calculation was performed as this was a retrospective analysis of all available cases at that point in time.

Small sample sizes carry risk of low statistical power. This is common in research trials, meaning that small but clinically meaningful effects are missed.[317] Low power also reduces the positive predictive value i.e. the probability that a detected effect represents a true difference.[348] There is also a risk that when an underpowered study does discover a difference, the estimate of the magnitude of this effect will be exaggerated. This is because only large effects can be detected in small and low-powered studies, meaning that the true effect can be overestimated. This is relevant for future studies as these will not be able to reach the same effect.[348]

Furthermore, studies with smaller sample sizes are more vulnerable because any parameter variation has a higher risk of altering the final results. This means that e.g. misclassification and loss of follow-up will have a larger effect in a smaller study than in a large one, creating further uncertainty.[348] The results in Study I-III therefore need to be considered in view of these potential limitations.

Multiple comparisons

Statistical inference is often based on testing hypotheses. The probability of false-positive results varies depending on the chosen α level, but commonly this set at 0.05 meaning that the null-hypothesis would be wrongly rejected less than once out of every twenty times that the same test is performed. However, if more than one test is

performed, the risk of making at least one type I error increases.[349] In Study I-II a number of hypotheses are tested, for which adjustments were not made. Furthermore, these studies are secondary analyses which per se are repeated investigations using the same data, even though the studies ask separate questions and have different end-points. While these exploratory comparisons are important in establishing new hypotheses, they cannot be used to draw firm conclusions until confirmatory analyses are performed.

Multiple comparisons can be addressed using a number of methods. The Bonferroni adjustment, used in Study III, is the most commonly used approach, wishing to control the type I error by dividing the significance level by the number of hypotheses tested.[350] This method is however rather conservative and reduces statistical power,[351] which is why more sophisticated methods have been developed.[350] Moreover, the problem can be reduced by considering multiplicity already in the planning stages of the studies with a predefined statistical analysis plan consisting of less intended comparisons.[317] If followed by an adequate description of what was done and why,[351] the reader should be able to judge the relevance of the conclusions, regardless of statements of 'significance' or 'non-significance'.

P-values

'Statistically significant effects' based on small p-values are often misunderstood and misused, the most common misinterpretation being that the p-value represents the probability that the hypothesis is true.[352] The p-value is simply the probability, under a specific statistical model, that a statistical summary of the data would be equal to or more extreme than its observed value.[352] It cannot work backwards and make statements about the underlying reality. The p-value also does not measure the size of the effect meaning that smaller p-values do not imply larger effects, and scientific significance does not equal to clinical significance or meaningfulness. One example is a study of over 19,000 people indicating that spouses who met online are less likely to divorce than others ($p<0.002$).[353] However, the divorce rates were 5.96% and 7.67% respectively. This demonstrates the increased likelihood of finding a small p-value with a larger sample size. The authors then focus on the significant p-value, and ignore the more important question – how large is the actual effect and is it relevant?[354]

Effect size

Measures of effect size provide information about the magnitude and the direction of an observed change. These are commonly standardised, to allowed comparisons between studies. Ideally, confidence intervals should also be presented, indicating the precision or uncertainty of the estimate. In Study I-II, effect sizes were not emphasised. In Study I, effect size could have been described by comparing the percentage of persons improving in SSQ in each group, being 44% and 11% in the memantine and placebo group respectively i.e. a percentage difference of 33%. For non-parametric tests,

standardised effect size can also be estimated by adjusting the Z value with the number of observations obtaining an r value ($r=Z/\sqrt{N}$). Using this method, the magnitude is considered small if ≥0.1, medium if ≥0.3 and large if ≥0.5.[355] In Study I, the r value was 0.38, indicating a medium effect size in reducing physical activity during sleep in the treatment group. In Study II, an improvement in the item 'Life as a whole' was present in 41% and 15% of patients in the memantine and placebo group respectively, with a percentage difference of 26%, or a standardised effect size of r=0.35. Similar effect size was found in Study III, with an r=0.36 for the effect of carbonated thin liquid compared to thin liquid in swallowing times. In studies of survival, hazard ratios (HR) can be used as an estimate of effect size, with suggestions of HR as 1.22, 1.86 and 3.00 taken as small, medium and large effect sizes respectively.[356] Although not described for excess hazard ratios, this might be applied similarly, in the case of Study IV indicating mainly small effect sizes. The overall estimated effect sizes in this thesis are therefore small to medium.

Research & publication issues due to statistical fallacies

A problem with the misunderstood p-value is that it influences which results get reported and which studies get published.[357] This means that there is a publication bias, whereby more positive results are published in favour of negative studies, and non-publication i.e. whereby 'non-significant' results are voluntarily or involuntarily not published.[358] In one study examining the non-publication rates in interventional clinical trials in MCI and AD, it was found that 73% of completed trials were not published, meaning that over 60,000 patients experienced the risks of study participation without this leading scientific contributions.[359] It also represents collected information which is never incorporated in science, leading to a bias in the field. Notably, the majority of non-published trials were industry-sponsored rather than funded by academia.[359]

A healthy amount of scepticism is probably useful when considering trials sponsored by pharmaceutical companies where 'positive results' are associated with profit. A recent Cochrane review summarised that industry-sponsored drug studies, compared to non-industry sponsored studies, more often had favourable efficacy results and conclusions.[360] Out of the eleven RCTs published on ChEIs and memantine in LBD,[120,123,128,132,138,154,361-365] only two were published without industry sponsorship. Two studies, published in high-impact journals, even highlighted that the sponsoring pharmaceutical company were involved in data analysis and in writing the initial draft.[361,365] With such a situation, transparent reporting is clearly pertinent.

Reporting in medical research has however been described to be overall poor, either reflecting lack of knowledge or inappropriate incentives for publishing research, extending beyond improving medical science and clinical practice.[366,367] This is enhanced by the ever-growing number of medical journals struggling to keep up with high-quality peer review. One way to improve this is to make reporting guidelines such

as CONSORT mandatory for publication.[317] Other ways include replication of research, raw data sharing, sharing statistical scripts, a priori registration of trials with pre-defined outcomes and analyses, as well as improving the peer review process and collaborations with medical statisticians. Ultimately, it comes down to improving the statistical understanding of those partaking in research, and encouraging research done for the right reasons, since poor medical research is both wasteful and potentially dangerous.[366]

5.3. Implications

5.3.1. Clinical & societal implications

Treatment

Effective management in LBD starts with early diagnosis and recognition of troublesome symptoms. Treatment then focuses around symptom relief and meeting care needs. High-level evidence is rare for both pharmacological and non-pharmacological interventions in LBD, see Table 3 in Background. The strongest pharmacological evidence comes from meta-analyses of ChEIs describing global improvements, as well as cognitive and psychiatric symptom improvement.[117-119] It is therefore reasonable to recommend all LBD patients to be tried on ChEIs, and if tolerable receive continued treatment, specifically with studies in AD indicating that continuous treatment despite severe disease is beneficial and cost-effective.[368]

Meta-analyses of memantine have showed high tolerability and improvement in global measures.[117,119,131] Findings in Study I-II demonstrate additional potential benefits with regards to probable RBD and QOL. Clinically, some patients display an excellent response to memantine. The reasons for why this is not replicated in the RCT setting can be numerous; difficulties in determining adequate outcome measures, presence of fluctuations, unaccounted differences between treatment groups, loss of follow-up, lack of power and small sample sizes.[369] However, since few participants experience side-effects, treatment with memantine could be attempted since even mild to moderate responses might be of relevance to the individual patient with otherwise limited treatment options. Evidence is uncertain for the remaining potential therapies in LBD, and muddled by varying methodological qualities, lack of controlled designs, small samples or poorly defined study populations. Practically, treatment is guided by clinical expertise and consensus.

Swallowing dysfunction, highlighted in Study III, is a neglected symptom in LBD which can result in aspiration leading to fatal pneumonias, therefore being of high clinical relevance.[370] Patients are not always symptomatic, which is why clinicians and

other health care professionals need to be vigilant in suspecting a dysfunction e.g. with recurrent pneumonias or unintentional weight loss. Using a checklist for screening non-cognitive symptoms in LBD could perhaps be helpful, alternatively offering a swallowing assessment as part of routine clinical practice. Identifying swallowing dysfunction allows potential non-pharmacological interventions, such as carbonated thin liquid preliminary investigated in Study III, as well as other therapies to be tested.

Survival & prognosis

Managing LBD extends beyond symptomatic relief. It also means managing questions about what to expect in terms of prognosis. Studies have shown that that many caregivers receive inadequate information,[231,232] perhaps reflecting clinician uncertainty around this subject. Improving the understanding of the naturalistic disease-trajectory and survival is therefore important, as well as identification of prognostic markers, addressed in Study IV. The poor prognosis, compared to an age- and sex-matched population, also emphasises the importance of correct and timely diagnosis, as well as the need for adequate symptomatic treatment and future disease-modifying therapies. Further identifying those at risk of excess mortality is important to be able to provide support and direct resources specifically towards these patients.

Quality of life

With no prevention or cure, the ultimate goal of treatment should be improvement in well-being for patients and caregivers. Although only small effects in QOL-AD were found with memantine treatment, this study demonstrates that well-being in LBD consists of both physical and social aspects. Similar findings have been found in other research and in Study V, whereby well-being is recognised to be a multifaceted concept, and something which can be preserved in spite of progressive neurodegeneration. This is also somewhat positive in view of the current absence of a disease-modifying treatment in LBD, as factors other than symptoms of the disease can be addressed in order to improve well-being in LBD. For example, demonstrating that persons with LBD use coping strategies to manage well-being might also suggest that they could benefit from extended services such as counselling, psychological support or goal-oriented rehabilitation.[195]

Study V also found that persons with LBD experience an overall ignorance within the healthcare system for their diagnosis, which could contribute to delayed or incorrect diagnosis, and subsequently inadequate treatment, similar to findings in a survey-based study.[232] This indicates that further educational resources and clinical support are still needed in settings where LBD persons are encountered. It also emphasises the importance of good clinical care, both in terms of healthcare personnel's experience in the complex management issues, but also in interpersonal skills.

Persons with LBD also communicate an experience of stigma and being misunderstood with regards to what their disease entails, reflecting an unawareness within the wider society for the many expressions of dementia. The dementia term was identified as being inherently problematic, and one initial step to increase public awareness could be to transition to the use of neurocognitive disorder as suggested by the DSM-V.[4]

5.3.2. Research implications & future directions

Treatment

There is an urgent need to develop and investigate pharmacological and non-pharmacological trials, including disease-modifying treatments, for LBD patients. Rather than conducting many small studies of questionable quality, the LBD research community should strive towards larger collaborations and high methodological rigour to ensure valuable research which can influence clinical practice. Certain symptoms appear to be addressed less frequently in interventional trials, e.g. sleep behaviours or swallowing difficulties. These might however be of relevance to patients and should be considered as future treatment targets. Overall, non-pharmacological approaches have received less attention than pharmacological trials. This might be because of lack of funding due to a relative disinterest from the industry for interventions less likely to generate profit, but also owing to challenges in methodology with trials being difficult to control, standardise and blind.[371] Considering the medication sensitivity of LBD patients, non-pharmacological therapies could be highly relevant, and actions should be taken to overcome these barriers.

Importantly, RCTs are only as useful as the measuring instruments used. Many RCTs, including Study I-II, use unvalidated scales. This might explain the lack of success of some clinical trials. Moreover, most trials still chose to use cognitive, psychiatric or motor primary outcomes, and base their recommendations on statistical rather than clinical significance. Despite increasing emphasis on user-involvement most trials fail to take into account patient-related outcomes or the views of either patients or caregivers, displaying a clear disconnect between research and clinical practice.[117] When trialling a therapy not aimed at modifying disease, what is more relevant – improvement of the MMSE with 1.26 points over 24 weeks,[117] or improvement in patient satisfaction with life?

In terms of future clinical trials, disease-modifying therapies including vaccination studies are desirable. However, if we wish to halt the underlying pathology, better characterisation of population samples is needed. Rather than clinical criteria, patients could be included based on sophisticated biomarkers measuring pathology in vivo. One example of this is the A/T/N system, categorising patients based on amyloid- and tau pathology, as well as neurodegeneration, rather than clinical diagnosis.[372] Ideally, this would be complemented by a yet undiscovered in vivo biomarker for alpha-synuclein

pathology. Describing both AD and LBD patients in terms of biomarkers status representing underlying pathology would be particularly relevant considering the overlaps in genetics, pathophysiology and clinical syndromes. Another aspect could be to further investigate and target patients with idiopathic RBD, as they can represent a pre-stage for the synucleinopathies. Theoretically, this group offers a window of opportunity of disease-modifying interventions, prior to the development of overt neurodegenerative disease.

Survival & prognosis

Survival studies in LBD have mostly utilised overall mortality, disregarding the background mortality expected in an elderly and comorbid population. Relative survival methods, presented in Study IV, are useful as they account for expected mortality due to age and gender, identifying those at risk of excess mortality. Extending this to larger materials could further evaluate factors which can be relevant to clinical practice in terms of directing resources and better understand LBD disease. Prognostic features could also be utilised for targeted treatment studies.

Quality of life

As outlined, current management involves improving well-being for the persons and caregivers living with disease. With this in mind, it is surprising that the constituents of well-being in LBD, as well as the preferences of patients and their caregivers, have not been extensively investigated. Findings in Study V demonstrate that persons with LBD are willing and able to engage with qualitative research such as in-depth interviews. This is encouraging and means that persons with LBD should not be excluded from research, a stigmatising action in its own right, which should influence both qualitative and quantitative research in the future. Quality of life further needs to be used as an outcome variable in interventional trials.

6. Conclusions

This thesis has provided an overview of the complexities of living with Lewy body dementias, and various aspects of care which can and need to be addressed. A number of topics have been explored, and the individual studies reflect various designs, methodologies and outcomes, exemplifying the diversity in research which can be relevant to this patient population.

The specific conclusions of this thesis are:

- Pharmacological treatment with memantine has the potential to improve aspects of sleep behaviour and quality of life in LBD patients. Meta-analyses of memantine in LBD have concluded that effects are small, but treatment is safe and without significant side-effects. Considering that a dramatic response is sometimes reported clinically, treatment with memantine could be attempted and individual response assessed. Future research could investigate factors predicting a positive response to treatment.
- Swallowing dysfunction is a neglected non-cognitive symptom in LBD patients which can be asymptomatic. Liquid modification with carbonated thin liquid can improve swallowing in LBD patients, with the eventual hope of improving risk of aspiration and subsequently shortened life-expectancy.
- Even when accounting for the expected mortality in an age- and sex-matched comorbid general population, life expectancy is significantly reduced in LBD patients. Patients who are female, younger, and carriers of *APOE* ε4 are affected to a higher degree.
- Quality of life is a multifaceted concept in LBD comprising physical, social and psychological factors. The quantitative instrument QOL-AD has good reliability and validity in the LBD population. Caregivers rate QOL lower than patients. Qualitative exploration of well-being in LBD is possible through in-depth interviews. Persons with LBD report diverse symptoms and resulting consequences. Internal and external processes can influence the disease-experience and well-being.

7. Acknowledgements

My deep of appreciation goes to my main supervisor **Elisabet Londos**, whom without my life would not be the same. I will forever be grateful for your tactful guidance throughout all these years, professionally and personally. You have enthusiastically taught me about clinical research, whilst trusting, respecting and cheering me on, through the highs and lows. The compassion and determination you show towards your patients has had a profound impact on me. Thank you for everything!

Lennart Minthon, my co-supervisor, who together with Elisabet took me on in the early days. Thank you for providing the right support at the right time. You make those around feel like anything is possible, and your sympathetic leadership is an inspiration. What you have done for the dementia care and research is extraordinary.

Gustav Torisson, my co-supervisor. Even years before you agreed to become my co-supervisor you motivated me to do better. Your strong belief in always doing the right thing for the right reason is much-needed to improve current healthcare and research. As a supervisor you offer a questioning and critical perspective, which has helped me develop and improve beyond what I thought possible. I hope I can pay it forward.

Margareta Troein, who as a mentor during these last years has taught me assertiveness, the concept of good enough and how and when to ask for help. Thank you for your care and reading recommendations, they were at times very needed.

My co-authors **Dag Årsland, Clive Ballard, Knut Engedal, Carina Wattmo**. You are all experts in your field and I have been honoured to work with you. Thank you for your contributions to the manuscripts and for your inspiring work.

Many thanks to **Margareta Bülow**, for the hands-on collaboration in conducting the swallowing study, and for educating me on swallowing physiology. My dysphagia adventures have also been facilitated by **Lucie Forester**, who patiently has answered clinical and research questions, day or night. I admire you both for your tireless engagement in improving care for your patients.

Thanks to **Eva Lena Strandberg**, who co-authored the final manuscript and assisted my tentative attempts at qualitative research, and to **Ingrid Fioretos**, **Eva Granvik** and **Andreas Jönsson** for valuable input on this work.

All of my fellow researchers associated with the **Clinical Research Memory Unit**, thank you for interesting discussions and companionship over the years. I specifically want to thank: **Anna-Märta Gustavsson** for engaging in numerous conversations around statistics and medical sciences and for input on articles and this thesis. **Axel Holmbom-Larsen**, for co-authoring the qualitative study and the never-ending discussions about life and medicine. **Alexander Frizell Santillo,** for many great ponderings and for the input on this thesis. **Kajsa Stubendorff**, for the earlier research collaborations and good times away on conferences. Also specific thanks to **Erik Stomrud, Katarina Nägga, Sebastian Palmqvist, Iris Zahirovic, Anna Svenningsson, Erik Nilsson, Nina Schultz, Elin Byman, Niklas Mattsson, Oskar Hansson, Ruben Smith, Sara Hall** and **Nils Fälth** for inspiring and entertaining me, and to **Joanna Grzegorska** and **Agneta Nilsson** for continuous administrative and emotional support throughout this time.

To everyone working at the Memory Clinic in Malmö, thank you for the welcoming atmosphere and for teaching me about cognitive disorders during my clinical work. Specific thanks to **Sibylle Mayer** and the team on the second floor from whom I learnt so much in the summer of 2016. **To all of my colleagues at the Neurology Department in Lund,** thank you for making me feel like part of the team from day one, and clinical and scientific support, I look forward to the years to come! Special thanks to **Daniel Jaraj** for the input on this thesis and for keeping me sane.

My wonderful friends, you are many and are to be found across the world; **Veronica, Sofie, Emma, Isabella, IL2L+PG+NG, Alice, my London crew, Unsdagsmiddagen, my Malmö women**. You are all my self-selected family! Thank you for always being there, making me feel loved and happy. In terms of this thesis, special thanks go out to: **Jonathan**, whose brilliance produced the cover of this thesis! **Oliver**, for providing continuous support in the scientific world including input on this thesis. **Anna**, for knowing what it's all about and for constantly useful advice along the way. **Jasmin, Ava & Ines**, for providing an abundance of cuddles and love. Finally, **Michael**, my rock, for making me see things differently and for always being by my side.

My loving family, consisting of aunties, uncles, cousins, first cousins once and more, both in Sweden and Bulgaria, make me feel fortunate for the endless support provided for all my undertakings. **Christian**, I am so glad to have a brother like you, who constantly challenges my views and teaches me determination by example. With **Kamilla** you have hit the jackpot. **Pappa**, you have never said no and you always find solutions no matter what. **Mamma**, you keep doing your own thing and continuously impress me. As parents you have both given me everything and more for which I will be eternally grateful.

Lastly, I would like to express my gratefulness to the patients and their families who have made this research possible, I hope I have honoured your commitment.

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Victoria Larsson graduated from UCL medical school in 2013 and then completed her two-year foundation training in London. She is currently undertaking specialist training in neurology at Skåne University Hospital.

In this thesis, various aspects of living with Lewy body dementia are being investigated; personal illness-experience, the impact on survival as well as how treatment can influence symptoms and well-being.

Printed by Media-Tryck, Lund 2018 NORDIC SWAN ECOLABEL 3041 0903

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FACULTY OF MEDICINE

Department of Clinical Sciences Malmö

Lund University, Faculty of Medicine
Doctoral Dissertation Series 2018:103
ISBN 978-91-7619-671-7
ISSN 1652-8220