Title: Short-term efficacy of rivastigmine transdermal patch in patients with mild cognitive impairment with Lewy bodies (MCI-LB) and REM sleep behaviour disorder: a single-arm open-label pilot study

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Background:
Acetylcholineesterase inhibitors (AChEIs) is a class of cognitive enhancer that is proven to help improve cognitive functions in dementia of Alzheimer's type and dementia of Lewy bodies(1)(2). Yet, AChEIs' efficacy in patients with mild cognitive impairment, a pre-dementia stage, has not been proven by clinical studies(3). However, the result of these studies may not be generalisable to patients suffering from mild cognitive impairment with Lewy bodies (MCI-LB) since the subjects of these studies mainly were suffering from Alzheimer's disease MCI (MCI-AD). Lewy bodies disease is suggested to have a more significant cholinergic deficit than Alzheimer's disease, which can explain the superior efficacy of AChEIs in improving cognitive symptoms in patients with DLB over AD. This is reasonable to hypothesise that patients with MCI-LB might respond to AChEI better than patients with MCI-AD. One of the key obstacles in studying MCI-LB has been its diagnostic ambiguity. Research in the past two decades has established the specificity of REM sleep behaviour disorder in predicting Lewy bodies disease. In recognising this, the recent research definition of MCI-LB stated that patients with MCI and RBD can be diagnosed as having MCI-LB(4).In other words, the diagnosis of RBD is a key feature that allows us to identify MCI-LB patients for clinical trials with high specificity. Rivastigmine transdermal patch is approved by the FDA to treat mild-to-moderate dementia of Alzheimer's type and mild to moderate dementia associated with Parkinson's disease. The drug is safe and generally well tolerated. Compared to oral preparation, Rivastigmine transdermal patch has a better side effect profile. In this study, we aim to conduct a pilot open label study to test rivastigmine transdermal patch's efficacy in improving the cognitive function, mood and anxiety symptoms and quality of life in patients with MCI-LB with RBD in 6 months.

Methodology:

This is a single-arm, open-label clinical trial.

Subject recruitment: Subjects will be recruited through the Sleep Clinic, Prince of Wales Hospital, and the Sleep Assessment Unit, Shatin Hospital.

Inclusion criteria:
1. Aged 60 to 80 years old;
2. Video-polysomnography confirmed diagnosis of RBD;
3. Presence of probable LB-MCI as diagnosed by a specialist psychiatrist or neurologist according to the Research criteria for the diagnosis of prodromal dementia with Lewy bodies by the prodromal DLB Diagnostic Study Group (4).
4. Capable of giving written informed consent

Exclusion criteria:
1. Presence of Parkinson's disease, multi-system atrophy, or other neurodegenerative disorders

2. Condition that is contraindicated against rivastigmine patch: Presence of heart block, history of allergic reaction to rivastigmine, or drugs that have cross-hypersensitivity with rivastigmine.
3. Conditions that render adverse events more likely: sick sinus syndrome, conduction defects (sino-atrial block, atrioventricular block), gastroduodenal ulcerative conditions (including those predisposed to such situations by concomitant medications), asthma or chronic obstructive pulmonary disease, urinary obstruction, and seizures.
4. Body weight <50kg.
5. history of being treated with AChEI or other cognitive enhancers.
6. Undergoing other structural, non-pharmacological cognitive-enhancing therapy.
7. Other suspected causes of primary causes of cognitive impairment as suggested by clinical examination, blood tests and imaging investigations.

Target sample size: 10 subjects

Sample size justification: Studies showed that AChEI improves the MMSE scores of patients with DLB by about 2 points in 6 months. Assuming an expected improvement of a more modest 1.5 points in MoCA, in a group with a standard deviation of MoCA score of 1 point (majority of the eligible subjects should have MoCA score between 18 to 22), we will need seven subjects to achieve alpha of 0.05 and power of 90%. A previous study on rivastigmine transdermal patch reported a <10% dropout. Assuming that we have 20% drop-outs, we will need ten subjects to gain the same statistical power.

Primary hypothesis:

Use of rivastigmine transdermal patch improves the global cognitive function of patients with MCI-LB with RBD in 6 months.

Secondary hypotheses:

1. Use of rivastigmine transdermal patch improves the global cognitive function of patients with MCI-LB with RBD in 3 months.

2. Use of rivastigmine transdermal patch reduces depressive and anxiety symptoms of patients with MCI-LB with RBD in 6 months.

3. Use of rivastigmine transdermal patch improves the quality of life of patients with MCI-LB with RBD in 6 months.

Intervention: Exelon transdermal patch will be started at a standard starting dose of 4.6mg/24 hours. If the subject tolerates the treatment, the dosage will be increased to 9.5mg/24 hours after four weeks, and we will continue this dosage til the end of the trial. If the patient reported intolerable side effects with the dosage of 9.5mg/24hours, the dosage would be reduced back to 4.6mg/24hours after clinical assessment. If the patient cannot tolerate 4.6mg/24 hours, the drug will be discontinued. Research nurse or clinician will demonstrate the proper use of the patch before the beginning of the trial.

Compliance monitoring: We will provide the patient with a logsheet that allows them to collect the used patch according to the administration date. Using this method, the subject's compliance can be monitored. We will also call subjects twice weekly to remind them of the proper medication use in the first two weeks and once every two weeks after that.

Assessment:

1. Clinical history enquiry: The subject's eligibility will be ascertained by history taking and reviewing of assessment and treatment records.
2. Global cognitive function will be measured by Hong Kong Montreal Cognitive Assessment (MoCA-HK). We will use alternative version in T0, T0.5 and T1 to prevent learning effect.
3. Mood and anxiety symptoms will be measured by the self-reported PHQ-9 and GAD-7 respectively.
4. Quality of life will be measured by the self-reported WHOQOL-BREF questionnaire (excluding the Environment domain).

Adverse event monitoring: Rivastigmine transdermal patch is safe and well-tolerated within the approved dosage. The side effects listed as having a frequency of >=2 % at our target dose (9.5mg/24 hours) will be monitored(5). They are 1. Significant weight loss, 2. nausea and vomiting, 3. diarrhoea, 4. Abdominal pain, 5. Depression and anxiety, 6. Application site skin reaction, 7. Headache, 8. Dizziness, 9. Fatigue, 10. Fall, 11. Urinary tract infection, 11. Agitation. Adverse effects that are theoretically plausible but not shown to have increased in clinical trials will also be monitored. That includes: 1. Bradycardia, 2. Gastric ulcer, 3. Gastrointestinal bleeding, 4. Urinary obstruction, 5. Increase in parkinsonism. Local skin reaction to the patch will also be monitored.

See Appendix 1 for the full follow-up schedule and Appendix 2 for the Adverse Events Monitoring Checklist.

Primary outcome measures: Difference in MoCA-HK score between T1 (6 months post-treatment) and T0 (baseline assessment).

Secondary outcome measures:
1. Difference in MoCA-HK score between T0.5 (3 months post-treatment) and T0 (baseline assessment).
2. Difference in PHQ-9 score between T1 and T0.
3. Difference in GAD-7 score between T1 and T0.
4. Difference in WHOQOL-BREF score (excluding the Environment domain) between T1 and T0.

Statistical analysis:
We will use repeated-measure ANOVA to assess change in outcome measures.

Ethics consideration:
Informed consent will be obtained from all subjects. The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki and ICH-GCP. The research would be conducted in compliance with

infection control guidelines of the Hospital Authority, Shatin Hospital, Prince of Wales Hospital and the Department of Psychiatry. Subjects will not be required to pay for the study or the medication being studied. Subjects' follow-up fees will be reimbursed, but they will not receive extra compensation or payment. The study team will be responsible for managing clinically significant adverse events or making proper referrals for unified management.

Appendix: Full follow-up schedule

Time	Activities
Before consent	Clinical enquiries and ECG to establish eligibility
Baseline assessment after consent	MoCA-HK (form A or B), GAD-7, PHQ-9, WHOQOL-BREF
T0 (the day that treatment starts, no later than 1 week after baseline assessment)	Start Rivastigmine 4.6mg/24hours, Education to be provided to subjects on proper patch administration
Between T0 and first follow-up	Telephone reminder on compliance and patch administration technique twice weekly
2 weeks post T0	Medical follow-up on adverse effect, proper patch administration technique and compliance.ECG. Body weight monitoring
4 weeks post T0	Medical follow-up on adverse effects, proper patch administration technique and compliance. If subject tolerate the medication, the dosage will be stepped up to 9.5mg/24hours. Body weight and heart rate monitoring
2 weeks post dosage increase	Medical follow-up on adverse effects, proper patch administration technique and compliance. ECG. Body weight monitoring
From 4 weeks post T0 to T1	Weekly phone reminder and compliance check
T 0.5 (3 months post T0)	Medical follow-up on adverse effects, proper patch administration technique and compliance. ECG .Body weight monitoring. MoCA.
T1 (6 months post T0)	Endpoint assessment. Medical follow-up on adverse effects. MoCA-HK, GAD-7, PHQ-9, WHOQOL-BREF. Body weight monitoring and heart rate.

Follow-up schedule may change in case of an adverse event.

Appendix 2

Adverse Events Monitoring Checklist:
Date of assessment: Assessor:

Adverse events	Date of onset	mild	moderate	severe	Life-threatening
Nausea					
Vomiting					
Diarrhea					
Abdominal pain					
Poor appetite					
Weight loss >5% from baseline					
Fatigue					
Headache					
Dizziness					
Increase in depressive mood					
Increase in anxiety					
Bradycardia					
Heart conduction problem					
Increase in Parkinsonism					
Urinary tract infection					
Urinary obstruction					
Local skin reaction to patch					
Systemic allergic reaction					
Others					

Definitions:
Mild: adverse reaction that is present but does not cause significant distress and does not require treatment. Trial can continue; **Moderate**: adverse reaction that cause tolerable distress and may require treatment. Trial can continue if patient agrees. **Severe**: adverse reaction that cause significant distress, resulting in Accident and Emergency Department attendance or hospitalisation. Trial must terminate for the subject. **Life-threatening:** adverse reaction that requires intensive medical care, resuscitation or resulting in death.

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