Review article:

The efficacy of Rivastigmine in the management of the behavioral and psychological symptoms of lewy body dementia- a review of literature

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Abstract

Dementia with Lewy bodies (DLB) is seen in 20% of the cases of dementia. Behavioral and psychological symptoms of dementia (BPSD) are commonly seen in patients with DLB. BPSD are however difficult to control especially in DLB and this is one of the main reasons leading to the institutionalization of DLB patients. An electronic search was done on PubMed using the key words ‘Rivastigmine’ AND ‘Lewy Body Dementia’ AND ‘Behavioral and psychological symptoms of dementia’. Only studies relating to the use of Rivastigmine for the management of BPSD in DLB were selected. The data of 6 studies were extracted under the following headings – author, year of publication, study design, sample size, tools for the assessment of the severity of dementia / BPSD and rivastigmine usage (dose, frequency, duration, side-effects and efficacy).

6 studies reported about the efficacy of Rivastigmine for BPSD in DLB according to consensus criteria. All studies were foreign studies published from the year 2000-2010. Two studies received grants. Most were case reports but there was also a randomized-double blind-placebo control trial, an open-label trial and a case series study. Most used the MMSE, for the assessment of the severity of dementia, NPI for the assessment of the control BPSD and the UPDRS for the assessment of Parkinson symptoms.

The maximum rivastigmine dosage was 12mg/day given in two divided doses. Gastro-intestinal side effects were the most common side effects. There were no serious life-threatening adverse effects. Rivastigmine was efficacious for the management of BPSD in DLB. The maximum efficacy was for the control of hallucinations. A good response was also seen for the control of agitation, apathy and delusions. Another prominent feature reported was a partial or complete resolution of the sleep/wake cycle and the relief of confusion symptoms. Only one study recorded a dosage-dependent reversible worsening of the Parkinson symptoms and one a prominent improvement in Parkinson symptoms. There exists evidence for the efficacy of Rivastigmine in the management of BPSD in DLB. These have important implications for patient care, training of mental health professionals and further research.

Keywords: Rivastigmine, Lewy body dementia, BPSD

Introduction

Dementia with Lewy bodies (DLB) is seen in 20% of patients with dementia. The clinical features are cognitive decline, inattention to routine activities, visual hallucinations, Parkinsonism and other neuropsychiatric symptoms. The diagnosis of Lewy body dementia on a clinical level is made by the consensus criteria established by the report of the consortium on the DLB international workshop[1]. Many cases of DLB present with behavioral and psychological symptoms of dementia (BPSD). BPSD is a mixed group of symptoms of agitation, depression and apathy. They are difficult to control and lead to a major source of caregiver burden and hence early institutionalization of DLB patients[2,3].

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Various pharmacotherapies have been used for the control of BPSD in DLB. Neuroleptic medication is known to have adverse side effects like exacerbations of extrapyramidal symptoms and increase mortality[4,5,6,7]. Benzodiazepines although useful in treating anxiety and agitation have been known to lead to falls, injuries and delirium[8]. SSRIs have also been tried however definitive evidence is still lacking[9]. Cholinergic drugs are primarily used for the treatment of cognitive decline in dementia. However there are some reports regarding the use of them for the control of BPSD in patients with DLB[10]. Various cholinergic drugs have been tried but amongst them rivastigmine, a carbamate type of cholinesterase inhibitor, has shown good efficacy. Rivastigmine inhibits both acetylcholinesterase and butyrylcholinesterase enzymes and has predominantly a central action with less peripheral side effects[14]. At present there are no previous reviews regarding the efficacy of Rivastigmine in the management of BPSD in DLB. This review will examine the evidence regarding the efficacy of Rivastigmine in the management of BPSD in DLB. This has important implications for clinical management, training and future research in patients of DLB with BPSD.

Methods
We did an electronic search in the database ‘PubMed’, using a combination of the following search items:
Rivastigmine, Lewy body dementia and Behavioral & psychological symptoms of dementia. Only articles from the year 2000 to 2014, related to the use of Rivastigmine, for the management of BPSD in Lewy body dementia (DLB) were selected. Animal studies, postmortem studies and theory based studies were excluded. Studies in languages other than English were also excluded due to the unavailability of translations. Data from the selected articles were extracted under the following headings: authors, year of publication, study design, sample size, tools for the assessment of dementia/severity of BPSD and Rivastigmine usage (dose, duration, frequency, side-effects & efficacy). The results obtained were tabulated.

Results
6 studies related to the efficacy of Rivastigmine in management of BPSD in DLB were studied.

Year of publication
All 6 studies were published during the period 2000 to 2010. Two were in the year 2000, one in 2001, one in 2005, one in 2007 and one in 2010. The earliest was in 2000 the latest study was in the year 2010.

Location of the study
All 6 studies were foreign studies. There were no Indian studies.

Funding
Out of the 6 studies, 2 received grants[12,15], 2 did not receive[14,16] and two did not mention whether grants were received[11,13].

Study design
Out of the 6 studies, one was a randomized-double –blind-placebo controlled trial[11], one an open- label- trial[12], one a case series[13] and 3 were case reports[14,15,16].

Sample size
There were 120 patients reported in the randomized -double –blind- placebo controlled trial[11] and 11 patients in the open label trial[12]. The case series mentioned 8 cases of which case 7 was excluded as it was atypical and treated with haloperidol[13]. There were 3 case reports[14,15,16].

Type of dementia studied
All 6 studies evaluated only cases of DLB, using the consensus criteria for clinical diagnosis[11,12,13,14,15,16].

Scales used
Various scales were used to measure the severity of dementia, BPSD and the symptoms of Parkinson’s disease.

The MMSE (Mini-mental status examination) was used to assess the level of cognitive function and the severity of dementia in 5 out of the 6 studies[11,12,13,14,16].

NPI (Neuropsychiatric inventory) was used to assess the severity of BPSD in 4 out of the 6 studies[11,12,13,15].

NPI-4 was used in 2 out of the 6 studies[11,12]. It is a
subscale (modification) of the NPI and is more specific in to assessment BPSD than the conventional NPI. Only one study employed video polysomnography as a method to document BPSD symptom of a patient[16].

UPDRS (Unified Parkinson disease rating scale) was used for the assessment of concomitant Parkinson’s disease in 3 of the 6 studies[11,12,15].

**Rivastigmine**

Used in the dose range of 6mg/day to 12mg/day [11,12,13,14,15,16]. The drug was administered in all the studies as a twice daily dosing regimen. The response to treatment (control of BPSD) at follow up was assessed using the NPI scale and/or the NPI-4 subscale.

**Side effect profile**

Most studies reported gastrointestinal side effects like nausea, vomiting and diarrhea [11,12,13]. There were no serious adverse effects reported. Only one study recorded a dosage-dependent reversible worsening of the Parkinson symptoms [15]. The case series study mentions about the waning off of gastrointestinal side effects due to the development of tolerance [13].

**Efficacy of Rivastigmine**

All the six studies concluded that Rivastigmine was efficacious in the management of BPSD in DLB. The maximal efficacy of Rivastigmine was seen in the amelioration of hallucinations[11,12,13,14,15]. A good response was also seen for agitation[11,12,15], apathy[11,12] and delusions[11,12,13,15]. Another prominent feature affected in most studies was a partial or complete resolution of the sleep/wake cycle disturbance[13,16] and the relief of confusion symptoms[13,16]. Only one study recorded a dosage-dependent reversible worsening of the Parkinson symptoms[15] and one an improvement in Parkinson’s symptoms[12]. This shows that there is evidence for the efficacy of Rivastigmine for the control of BPSD in DLB. It is safe without serious adverse effects, elevated mortality and no increase in Parkinson symptoms.

**Limitations**

Studies on Rivastigmine in BPSD in DLB were rare and difficult to locate. There were no recent studies after 2010. These all studies were foreign studies and no Indian studies. There could have been some bias in the selection of some studies as there was marked heterogeneity in the studies. Most studies were of lower in the hierarchy of evidence namely case reports.

**Strength of the study**

6 studies were carefully evaluated for the efficacy of Rivastigmine in the treatment of BPSD in Lewy body dementia. A clearer picture emerges regarding the efficacy of rivastigmine for the management of BPSD in DLB.
<table>
<thead>
<tr>
<th>Sr no</th>
<th>Author</th>
<th>Year of pub.</th>
<th>Study design</th>
<th>Sample size</th>
<th>Tool for grading dementia</th>
<th>Tool for grading BPSD</th>
<th>Dose of Rivastigmine employed</th>
<th>Duration of treatment</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Mckeith et al</td>
<td>2000</td>
<td>RDBPCM trial</td>
<td>120</td>
<td>MMSE, CGC-PLUS</td>
<td>NPI, NPI-4</td>
<td>6mg BD</td>
<td>23 weeks</td>
<td>Nausea, vomiting, diarrhoea.</td>
</tr>
<tr>
<td>2</td>
<td>Mckeith et al</td>
<td>2000</td>
<td>Open label trial</td>
<td>11</td>
<td>MMSE</td>
<td>NPI, NPI-4</td>
<td>Mean dose 9.6mg/day (4.8mg BD)</td>
<td>35 weeks</td>
<td>Nausea, diarrhoea</td>
</tr>
<tr>
<td>3</td>
<td>Maclean et al</td>
<td>2001</td>
<td>Case series</td>
<td>8</td>
<td>MMSE</td>
<td>NPI</td>
<td>Mean dose employed is 10mg/day (5mg BD)</td>
<td>Not mentioned</td>
<td>4/8 cases reported GIT side effects</td>
</tr>
<tr>
<td>4</td>
<td>Alwahhabi et al</td>
<td>2005</td>
<td>Case report</td>
<td>1</td>
<td>MMSE</td>
<td>Not mentioned</td>
<td>4.5mg BD</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>5</td>
<td>Clerici et al</td>
<td>2007</td>
<td>Case report</td>
<td>1</td>
<td>Not reported</td>
<td>NPI</td>
<td>6mg/day</td>
<td>9 months</td>
<td>Parkinsonian worsening</td>
</tr>
<tr>
<td>6</td>
<td>Terzaghi et al</td>
<td>2010</td>
<td>Case report</td>
<td>1</td>
<td>MMSE, MRI, SPECT</td>
<td>Video-PSG</td>
<td>3mg BD</td>
<td>Not mentioned</td>
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### Table: Part II

<table>
<thead>
<tr>
<th>BPSD</th>
<th>Apathy relief</th>
<th>Agitation</th>
<th>Hallucination</th>
<th>Delusion</th>
<th>Sleep/wake cycle</th>
<th>Confusional symptoms</th>
<th>Anxiety</th>
<th>Other</th>
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</thead>
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<tr>
<td>Good control</td>
<td>Partial control</td>
<td>Partial control</td>
<td>Partial control</td>
<td>No effect</td>
<td>No effect</td>
<td>Partial control</td>
<td>No effect</td>
<td>Nil</td>
</tr>
<tr>
<td>Good control</td>
<td>Partial control</td>
<td>Partial control</td>
<td>Good control</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Parkinsonian symptoms improved</td>
</tr>
<tr>
<td>C1</td>
<td>No effect</td>
<td>No effect</td>
<td>Good control</td>
<td>No effect</td>
<td>Partial control</td>
<td>Good control</td>
<td>No effect</td>
<td>Nil</td>
</tr>
<tr>
<td>C2</td>
<td>No effect</td>
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<td>Partial control</td>
<td>No effect</td>
<td>Good control</td>
<td>No effect</td>
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<td>Nil</td>
</tr>
<tr>
<td>C3</td>
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<td>Good control</td>
<td>No effect</td>
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<td>Nil</td>
</tr>
<tr>
<td>C4</td>
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<td>Good control</td>
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<td>No effect</td>
<td>Nil</td>
</tr>
<tr>
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<td>No effect</td>
<td>Good control</td>
<td>Good control</td>
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<td>Partial control</td>
<td>No effect</td>
<td>Nil</td>
</tr>
<tr>
<td>C6</td>
<td>No effect</td>
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<td>Partial control</td>
<td>No effect</td>
<td>Partial control</td>
<td>Partial control</td>
<td>No effect</td>
<td>Nil</td>
</tr>
<tr>
<td>C7</td>
<td>This case has been excluded from the review as it is an atypical case.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>C8</td>
<td>No effect</td>
<td>No effect</td>
<td>Good control</td>
<td>Good control</td>
<td>Good control</td>
<td>Good control</td>
<td>No effect</td>
<td>No effect</td>
</tr>
<tr>
<td></td>
<td>No effect</td>
<td>No effect</td>
<td>Good control</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Nil</td>
</tr>
<tr>
<td></td>
<td>No effect</td>
<td>Partial control</td>
<td>Partial control</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>No effect</td>
<td>Depression partially controlled</td>
</tr>
<tr>
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<td>No effect</td>
<td>No effect</td>
<td>Partial control</td>
<td>Partial control</td>
<td>No effect</td>
<td>No effect</td>
<td>Nil</td>
</tr>
</tbody>
</table>

[Video- PSG= video polysomnography; Year of Pub.= Year of publication; GIT= Gastrointestinal tract; CNS= Central nervous system; C(1-8)= Cases; RDBPCMT= Randomized double blind placebo controlled multicentric trial]
Conclusions

6 studies reported about the efficacy of Rivastigmine for BPSD in DLB. All studied reported only about cases of DLB according to consensus criteria. Most studies were from the year 2000-2010. All were foreign studies. Two studies received grants[12,15]. Most were case reports[14,15,16] but there was also a randomized-double bind-placebo control trial[11], an open-label trial[12] and a case series study[13]. Most used the MMSE, for the assessment of the severity of dementia[11,12,13,14,16], NPI for the assessment of the control BPSD[11,12,13,15] and the UPDRS for the assessment of Parkinson symptoms[11,12,15].

The maximum rivastigmine dosage was 12mg/day given in two divided doses[11]. Gastro-intestinal side effects were the most common side effects. There were no serious life-threatening adverse effects. Rivastigmine was efficacious for the management of BPSD in DLB. The maximum efficacy was for the control of hallucinations [11,12,13,14,15]. A good response was also seen for the control of agitation, apathy and delusions. Another prominent feature reported in most studies was a partial or complete resolution of the sleep/wake cycle and the relief of confusion symptoms[13,16]. There was a reversible dose dependent worsening of Parkinson’s symptoms in one study[15] and in one there was improvement in Parkinson’s symptoms[12].

Implications

We studied the efficacy of rivastigmine in the management of BPSD in DLB. This has implications for patient care, training of mental health professional and further research. Rivastigmine is a safe and efficacious treatment for the control of BPSD in DLB. Mental health professionals need to be made aware of the management of BPSD in DLB in a safe manner with rivastigmine. Better quality studies are further required to establish stronger evidence for the efficacy of Rivastigmine for BPSD in DLB.

References:


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