World Journal of Psychiatry

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5498/wjp.v3.i3.62

World J Psychiatr 2013 September 22; 3(3): 62-64
ISSN 2220-3206 (online)

MINIREVIEWS

Acetylcholinesterase inhibitors in cognitive impairment in Huntington's disease: A brief review

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Received: June 29, 2013 Revised: August 24, 2013
Accepted: September 3, 2013
Published online: September 22, 2013

Abstract

Huntington's disease (HD) is a neurodegenerative disease associated with cognitive deficits. Cognitive dysfunction may be present in the early stages of the disease, even before the onset of motor symptoms. The cognitive dysfunction includes executive dysfunction, psychomotor symptoms, visuospatial deficits, perceptual deficits, memory loss and difficulty learning new skills. Acetylcholinesterase inhibitors have shown good effect in the treatment of other types of dementia and it is postulated that it might delay cognitive decline in HD. We reviewed the evidence for Acetylcholinesterase inhibitors in the treatment of cognitive decline and dementia associated with Huntington's disease. We identified 6 articles that investigated the role of Acetylcholinesterase inhibitors for treatment of cognitive deficits in Huntington's disease. Following the review, the authors concluded that there is limited evidence for the use of Acetylcholinesterase inhibitors for cognitive impairment in HD.

Key words: Huntington's disease; Huntington's dementia; Cognitive deficits; Acetylcholinesterase inhibitors; Donepezil; Rivastigmine; Galantamine

Core tip: The evidence for Acetylcholinesterase inhibitors in the treatment of cognitive decline and dementia associated with Huntington's disease is reviewed in this article. Six articles were identified that investigated the role of Acetylcholinesterase inhibitors for treatment of cognitive deficits in Huntington's disease (HD). We concluded that there is limited evidence for the use of Acetylcholinesterase inhibitors for cognitive impairment in HD.

Vattakatuchery JJ, Kurien R. Acetylcholinesterase inhibitors in cognitive impairment in Huntington's disease: A brief review. *World J Psychiatr* 2013; 3(3): 62-64 Available from: URL: http://www.wjgnet.com/2220-3206/full/v3/i3/62.htm DOI: http://dx.doi.org/10.5498/wjp.v3.i3.62

INTRODUCTION

The clinical description of Huntington's disease (HD) was reported by George Huntington in 1872 and led to increased recognition of the condition[1]. The prevalence of the illness is about 5.70 per 100000 births[2]. HD is characterised by movement disorder, cognitive deficits and psychiatric symptoms. HD is a progressive neurodegenerative autosomal dominant disorder caused by a single defective gene on chromosome 4. In HD, mutation of *HTT* gene leads to abnormal CAG trinucleotide repeat[3]. A larger number of repeat is associated with earlier onset of the illness[4].

The clinical features of HD frequently include cognitive dysfunction[5]. Cognitive dysfunction may be present in the early stages of the disease, even before the onset of motor symptoms[6]. Cognitive dysfunction includes executive dysfunction, psychomotor symptoms, visuospatial deficits, perceptual deficits, memory loss and difficulty learning new skills. Cognitive dysfunction lead to frontal and subcortical dementia[7]. There are structural and

Table 1 Trials and reports of Acetyl cholinesterase use in Huntington's disease

Ref.	Design	Medication used	Outcome measures	Result
Fernandes *et al*[11]	Open labelled study	Donepezil	UHDRS, MMSE, Wechsler memory scale-Ⅲ, Symbol Digit, Odd Man Out test, Hopkins Verbal Learning test	No statistical significance between mean scores at baseline and 6 wk on all neuropsychological tests.
Rot *et al*[12]	Longitudinal study	Rivastigmine	UHDRS, MMSE, Trail making test	Improvement on cognitive tests and behavioural part of UHDRS
Petrikis *et al*[13]	Case report	Galantamine	PANSS ESRS MMSE	Improvement on PANSS and ESRS but no improvement on MMSE
de Tommaso *et al*[14]	Prospective, open labelled randomized controlled trial	Rivastigmine	MMSE, Marsden and Quinn Chorea Severity Scale, Total Functional Capacity score, Abnormal Involuntary Movement scale	Improvement on MMSE compared to baseline
Cubo *et al*[15]	Randomized controlled trial	Donepezil	UHDRS, Alzheimers Disease Assessment Scale, Sickness Impact Profile	No significant improvement except for improvement on UHRDS-FAS (Verbal Fluency test)
de Tommaso *et al*[16]	Randomized, blinded, controlled, open labelled prospective	Rivastigmine	MMSE, Marsden and Quinn Chorea Severity scale, Total Functional Capacity score, Abnormal Involuntary Movement scale	Slight increase in MMSE but not statistically significant

UHDRS: Unified Huntington's Disease Rating Scale; MMSE: Mini Mental State Examination; PANSS: Positive and negative syndrome scale; ESRS: Extrapyramidal symptom rating scale.

functional brain changes in HD that correlate to cognitive deficits[8]. Decreased Acetyl Choline levels have been noted in HD patients[9,10].

REVIEW OF LITERATURE

Search strategy

We used Medline, EMBASE and PsychINFO databases and used key terms such as Acetylcholinesterase inhibitors, HD, Huntington's dementia, Donepezil, Galantamine and Rivastigmine. The bibliographies of all identified articles and previously published reviews were scanned for additional studies.

Description of identified studies

Six studies were identified that investigated the effect of Acetylcholinesterase inhibitors inhibitors in HD.

Fernandez *et al*[11] conducted an open label trial of 8 patients with HD and prescribed Donepezil. Two patients had slight improvement in memory and concentration at 5 mg/d. There was no statistically significant improvement at 6 wk from baseline scores on all neuropsychological tests. Due to 4 patients dropping out, analysis at 12 wk was not done due to lack of statistical power.

Rot *et al*[12] investigated the effect of Rivastigmine on four symptomatic HD patients (3 females, 1 male). Unified Huntington's Disease Rating Scale (UHDRS), Mini Mental State Examination (MMSE) and Trail making test were used to assess change in cognitive function. They were evaluated at baseline and 26 wk of therapy. The results showed an improvement in cognitive and behavioral parts of UHDRS, MMSE and Trail making test. There was no improvement in motor and functional subscales of UHDRS. As the study had only four subjects (only 3 completed the trial) and did not have a control group, it is difficult to make any worthwhile conclusions about the efficacy of Acetylcholinesterase inhibitors from this study.

Petrikis *et al*[13] report a case of a 35-year-old male patient with HD who presented with symptoms of an acute psychotic episode. He was evaluated using Positive and Negative Syndrome Scale, Extrapyramidal Symptom Rating Scale and MMSE. He was initially treated with Haloperidol Decanoate and after a month this was changed to Galantamine. The authors report good improvement of psychotic symptoms and chorea on Galantamine but there was no improvement in his cognitive functioning (Table 1).

de Tommaso *et al*[14] conducted a single centre; short term randomised open labelled controlled study in twenty one patients affected by HD. Patients received Rivastigmine as an add-on therapy for 8 mo. Fourteen patients were allocated to Rivastigmine group and 7 to control group. Patients were evaluated using MMSE, Marsden and Quinn Chorea Severity Scale and Abnormal Involuntary Movements Scale. Patients on Rivastigmine approached statistically significant improvement ($P = 0.06$) in MMSE score compared to their basal score. Statistical significance was not achieved when intervention group was compared to control group during repeated measures of other clinical features in the 8 mo of the study. Rivastigmine did not appear to reduce hyperkinesia in the intervention group. This study has several drawbacks. The study had only 21 patients and the lack of statistically significant results may be due to the lack of power. Secondly, MMSE was used to assess cognitive function. This may not be an appropriate tool because MMSE fails to capture frontal lobe dysfunction, which is typically impaired in HD.

Cubo *et al*[15] investigated the effect of Donepezil on motor and cognitive function in HD. Thirty patients were randomly allocated to active or placebo groups. Drug and placebo were administered for 6 wk (Donepezil 5 mg) and donepezil was increased to 10 mg at 6 wk for further 6 wk. Patients were evaluated at baseline, 6 and 12 wk.

Unified Huntington's Disease Rating Scale (UHRDS) was used to evaluate motor performance. Cognitive function was assessed using cognitive section of Alzheimer's Disease Assessment Scale and UHDRS. Chorea change was used as primary outcome measure and cognitive function change was used as a secondary outcome measure. There was no significant improvement in chorea measure between the two groups. There was no significant improvement in any measure of cognition except of a trend towards improvement on UHRDS-FAS (Verbal Fluency test). The study was not designed to evaluate change in cognitive function on donepezil as chorea change was used as primary outcome measure. One of the exclusion criteria was dementia with HD.

de Thommaso *et al*[16] reported the results of two-year follow up of HD patients on Rivastigmine therapy previously evaluated in a short-term study. This was a long term, open-label, blinded, controlled study. The evaluation was carried out in a final group of 11 treated patients and 6 non-treated patients. The results showed a slight increase in MMSE scores in patients Rivastigmine compared to non-treated group who exhibited a mild decline in MMSE scores. However, these differences were not statistically significant. This study has similar drawbacks as those raised about their original study.

CONCLUSION

Cognitive deficits due to Huntington's disease are common and cause significant morbidity. Cubo *et al*[15] postulates that the role of cholinergic system in cognitive deficits may be less relevant than previously thought and cholinergic stimulation may not be beneficial. There are no adequately powered well-designed trials to support the use of Acetylcholinesterase inhibitors in treating cognitive impairment in HD[17]. Review of existing studies suggests that there is limited evidence for the use of Acetylcholinesterase inhibitors in the treatment of cognitive deficits associated with HD. Large randomised controlled trials with adequate follow up are needed to investigate the efficacy of Acetylcholinesterase inhibitors in HD.

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P- Reviewer: Orlacchio A **S- Editor:** Song XX **L- Editor:** A
E- Editor: Wang CH

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