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Efficacy, Safety and tolerability of the once-daily 10 cm² rivastigmine patch formulation in the patients with dementia (with probable Alzheimer's disease)

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Abstract

Back ground: *Treatment compliance in patients with Alzheimer's disease is particularly important as patients receiving regular treatment have a greater chance of slowing or delaying disease progression. Transdermal delivery has the potential for providing continuous drug delivery and steady plasma levels. Current study aimed to evaluate safety and tolerability of rivastigmine patch, to assess patient compliance and to assess the efficacy of treatment in patients with dementia (with probable Alzheimer's disease).* ***Methods:*** *A total of 112 dementia patients (with a diagnosis of probable Alzheimer's disease) from 12 centers were enrolled who were residing with someone in the communities throughout the study. After eligibility, and baseline assessments, patients were entered a 24-week open label treatment phase. All patients were started with application of one 5 cm² patch, followed by an up-titration to the target dose of 10 cm² patch size. Efficacy assessments were performed at weeks 12 and 24 in terms of MMSE and GDS score. Safety was monitored at all assessment points based mainly on the frequency of adverse events.* ***Results:*** *Analysis of baseline and available data until the drop out revealed no significant differentials. Around 95% of the study participants could receive 10 cm² patch size, showing a very high tolerability of the patch. Concurrent medication use also showed significant reduction to 16.3% patient in the end from 25% at baseline. The average MMSE score increased to 19.3 (±3.1) at 12th week and to 20.6(±3.4) at 24th week from 16.8 (±3.2) at baseline. GDS score reduced to 3.7 (±1.4) at 12th week and to 3.2 (±1.3) at 24th week from 4.3 (±1.5) at baseline. Only eight occasions of adverse event was reported (8.2%); no serious adverse event (SAE) were reported. Lost to follow up in the study was 14 (12.5%). Analysis of baseline data shows no significant difference. Their withdrawal seems to be unrelated to the adverse events and treatment outcome. Among the lost to follow up only one 1 (7.1%) had some side effect.* ***Conclusion:*** *Our study supports the pharmacokinetic rationale for the rivastigmine patch, indicating that smooth and continuous delivery of rivastigmine translates into an improved tolerability profile versus conventional oral administration, while maintaining clinical effectiveness.*

Key words: *Dementia, Alzheimer's disease, rivastigmine patch, tolerability, safety, MMSES, GDS*

Background:

Alzheimer's disease (AD) is the most common form of dementia. There is no cure for the disease, which worsens as it progresses[1]. Most often, AD is diagnosed in people over 65 years of age,[2] although the less-prevalent early-onset Alzheimer's

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can occur much earlier. In 2006, there were 26.6 million sufferers worldwide. Alzheimer's is predicted to affect 1 in 85 people globally by 2050[3]. As life expectancy increases, Alzheimer becomes an important health problem for societies and causes significant impacts on family and community.

As the disease advances, symptoms can include confusion, irritability and aggression, mood swings, trouble with language, and long-term memory loss[4]. Gradually, bodily functions are lost, ultimately leading to death. Since the disease is different for each individual, predicting how it will affect the person is difficult. AD develops for an unknown and variable amount of time before becoming fully apparent, and it can progress undiagnosed for years. On average, the life expectancy following diagnosis is approximately seven years[1]. Fewer than three percent of individuals live more than fourteen years after diagnosis[6].

The cause and progression of Alzheimer's disease are not well understood. Research indicates that the disease is associated with plaques and tangles in the brain[7]. Current treatments only help with the symptoms of the disease. There are no available treatments that stop or reverse the progression of the disease. Clinical trials have been or are being conducted to find ways to treat the disease, but it is unknown if any of the tested treatments will work. Mental stimulation, exercise, and a balanced diet have been suggested as possible ways to delay symptoms in healthy older individuals, but they have not been proven as effective. Because AD cannot be cured and is degenerative, the sufferer relies on others for assistance. The role of the main caregiver is often taken by the spouse or a close relative. Alzheimer's disease is known for placing a great burden on caregivers; the pressures can be wide-ranging, involving social, psychological, physical, and economic elements of the caregiver's life[8].

Cholinesterase (ChE) inhibitors have been major treatment of Alzheimer's disease. Rivastigmine a member of Cholinesterase (ChE) inhibitors family have been shown to be effective in improving cognitive and global functioning in AD patients[9,10,11]. Rivastigmine is a selective, reversible acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) inhibitor. It could also be classified as a pseudo-irreversible cholinesterase inhibitor, as the duration of cholinesterase inhibition is longer than its elimination half-life[12].

The European Federation of Neurological Societies guidelines recommend considering the use of cholinesterase inhibitors in patients with severe disease, based on evidence of treatment benefit in these patients[13]. Current treatment guidelines recommend that the choice of therapy for patients with Alzheimer's disease be based on the tolerability profile and ease of use[14]. One of the primary objectives for AD treatment with cholinesterase inhibitors is to improve tolerability. Cholinesterase inhibitors enhance central cholinergic function, thereby increasing the availability of Achytylecholine (ACh) to stimulate nicotinic and muscarinic receptors within the brain[15].

Although cognitive symptoms of Alzheimer's disease can be managed with these pharmacological agents, treatment may be complicated by several factors, including the patient's age and concomitant conditions[16]. Cholinesterase inhibitors that are administered orally can sometimes lead to gastrointestinal AEs, particularly nausea and vomiting, which may prevent patients from achieving and maintaining optimal therapeutic doses in clinical practice. Patients with Alzheimer's disease are usually older individuals who are likely to receive concomitant medication for other conditions, which increases the risk of drug interactions and adverse events[17]. Treatment compliance in patients with Alzheimer's disease is particularly important as patients receiving regular treatment have a greater chance of slowing or delaying disease progression. As most patients with Alzheimer's disease require caregiver support for daily aspects of life, including managing and taking their medication, which results in caregiver stress and increased workload. Simplifying treatment regimens (once daily) and providing more patient and caregiver-friendly modes of administration would go a long way in improving adherence/ compliance[17].

One such mode of drug administration is transdermal delivery, which has the potential for providing continuous drug delivery and steady plasma levels, with minimal fluctuation between peak and trough plasma levels, thereby reducing adverse events and potentially minimizing voluntary noncompliance[18]. Moreover, by avoiding the gastrointestinal tract and the first-pass effect observed with oral administration, transdermal patches are likely to provide more predictable and reliable delivery of the drug[17]. In addition, patches may serve as visual reminders for patients or caregivers, offer visual reassurance that the medication is being taken and reduce the likelihood of accidental overdose[17]. The overall clinical benefit of transdermal patches is dependent on the balance between drug delivery, skin adhesion and skin tolerability[19,20].

Rivastigmine is well suited for transdermal delivery because of its low molecular weight and amphipathic properties, which allow it to pass easily through the skin to the bloodstream[21]. Although its precise mechanism of action is unclear, rivastigmine is believed to facilitate cholinergic neurotransmission by increasing the concentration of acetylcholine through reversible inhibition of its hydrolysis in functionally intact cholinergic neurons. Absorption of rivastigmine from the transdermal patch is slow, with rivastigmine being detected in the plasma after a lag time of 0.5–1 hour after the first dose[22]. Approximately 50% of the drug load is released from a patch during the 24-hour application period[23]. Peak plasma concentrations are reached in 10–16 hours after a single dose, with a slow decrease in concentration over the remainder of the 24-hour period[24].

Pharmacokinetic studies conducted with patch have shown that transdermal administration of rivastigmine prolongs tmax, lowers Cmax and reduces fluctuation in plasma concentration. The 10cm^2 rivastigmine patch provides equivalent exposure to the highest capsule dose, delivering optimal rivastigmine exposure to provide a therapeutic effect. The patch formulation has been evaluated by studies with rivastigmine patch, 10cm^2 and showed similar efficacy to the highest doses of rivastigmine capsules with three times fewer reports of nausea and vomiting. Caregivers also showed to prefer patch to the capsule. The patch was significantly preferred to the capsule with respect to ease of following the schedule and ease of use.

Current study aimed to evaluate efficacy, safety and tolerability data of rivastigmine patch, to assess patient compliance, to assess the change in cognitive and global outcome of treatment in patients with dementia (with probable Alzheimer's disease).

Methods:

Study subjects: A total of 112 dementia patients (with a diagnosis of probable Alzheimer's disease) from 12 centers were enrolled who were residing with someone in the communities throughout the study. Inclusion criteria for patients are a. Males and females not of child-bearing potential, b. Mini-Mental State Examination (MMSE) score of 10-26, c. Residing with someone in the communities throughout the study or living alone, in contact with the responsible caregiver every day, primary caregiver was willing to accept responsibility for supervising the treatment and condition of the patient throughout the study and providing input of efficacy assessment in accordance with all protocol requirements. Patients were excluded from the study if a. diagnosis of an active skin lesion that would prevent accurate assessment of the adhesion and potential skin irritation of the patch, b. history of allergy to topical products containing any of the constitution of the patches, c. evidence of severe or unstable physical illness (i.e., acute and severe asthmatic conditions, history of seizure, severe or unstable cardiovascular disorders, active peptic ulcer disease, clinically significant laboratory abnormalities or any patient with a medical condition which would prohibit them from completing the clinical trial), d. patient have bradycardia or sick sinus syndrome or conduction defects (sino-atrial block, second degree A-V blocks), e. body weight less than 40 kg and f. hypersensitivity to cholinesterase inhibitors.

Treatment exposure: After eligibility and baseline assessments, patients were entered a 24-week open label treatment phase. Baseline assessments include

vital signs, physical examination, inclusion/exclusion criteria, and concomitant medications history and drug indication. All patients were started with application of one 5 cm² patch, followed by an up-titration to the target dose of 10 cm² patch size. Starting on the day following the baseline visit, all eligible patients were given with one 5 cm^2 patch in the morning, for 24 hours. Patches were applied by the caregiver to the upper arm or the back area, on clean and dry skin with no cuts, rashes, or other skin problems. Placements were alternated from the right to the left side daily. After week 4 assessment, dosages were increased to the target patch size of 10 cm² with adjustments as necessary for safety and tolerability. The subjects were then maintained at their highest well-tolerated patch size for an additional 20 weeks. Compliance was assessed at each visit using information provided by the caregiver. Data regarding psychotropic medications was captured; any other concomitant medications and/or significant non-drug therapies applied to the patient throughout the trial were recorded.

Outcome assessment: Efficacy assessments were performed at weeks 12 and 24, and safety was monitored at all assessment points. There were provisions of the unscheduled visit if necessary. The primary endpoint is the proportion of patients treated by 10 cm² patch sizes for at least 8 weeks at week 24. Safety evaluations include vital signs, adverse events, concomitant medications and physical examination. Efficacy evaluations include the MMSE score, and the Global Deterioration Scale (GDS) score. The MMSE test consists of five sections and results in a total possible score of 30, with higher scores indicating better function. GDS is broken down into 7 different stages. Within the GDS, each stage is numbered (1-7), given a short title (No cognitive decline, very mild cognitive decline, Mild cognitive decline, Moderate cognitive decline, moderately severe cognitive decline, severe cognitive decline and Very severe cognitive decline).

Safety assessments were done based mainly on the frequency of adverse events. The adverse events were decided to be summarized by the number and percentage of patients in each primary system organ class and preferred term. Appearance or worsening of any undesirable sign, symptom, or medical condition occurring was considered as an adverse effect even if the event is not considered to be related to study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, with potential for study drug discontinuation or require therapy. An SAE was defined as an event which was fatal or life-threatening, might result in persistent or significant disability/incapacity constitutes a congenital anomaly/birth defect requires inpatient hospitalization or prolongation of existing hospitalization. Multiple occurrences of the same AE or SAE in the same patient were counted only once, using the worst severity and drug relationship.

The safety and efficacy variables were descriptively analyzed using summary statistics. The study was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki. Eligible patients were included in the study after providing written informed consent.

Results:

Baseline characteristics

A total of 112 patients were enrolled from twelve centers. Of them 98 (87.5%) completed study. Final analysis included 98 subjects. Analysis of baseline and available data until the drop out revealed no significant differentials. At enrollment average age of the patients was 68.9 (±8.7) years and 66.3% were male. 23.5% were of an age between 50 – 64 years, around 75% were of age between 65 - 85 years and 2% were aged over 85 years. Average weight of the patients was 61.8 (±7.7) kg. (Table 1)

Table-I

Patient characteristics

Age group	Frequency (%)
50 - 64 years	23 (23.5)
65 - 85 years	73 (74.5)
> 85 years	2 (2.0)
Sex Frequency (%)	
Male	65 (66.3)
Female	33 (33.7)
Age (n=98)	
Mean (SD)	68.9 (8.7)
Median (IQR)	68 (65 -75)
Weight	(n=98)
Mean (SD)	61.8 (7.7)
Median (IQR)	61 (56.2 - 61)

Treatment profile

All patients started treatment with the application of one 5 cm² patch, followed by an up-titration to the target dose of 10 cm² patch size. Rivastigmine 5 cm^2 patch size were loaded with 9 mg and providing 4.6 mg per 24 hour and 10 cm^2 patch size were loaded with 18 mg and providing 9.5 mg per 24 hour. At first visit 43.9% received 10 cm^2 patch, with upward titration 79.6% at 2ndvisit, 91.8% at third visit and 94.9% could receive 10 cm^2 patches. Concurrent medication was received by 25.5% patient at baseline, by 20.4% patient at 2ndvisit, by 17.3% patient at 3rdvisit and 16.3% patient at 4thvisit. Concurrent medication had to be changed in 17.3% patients at 2ndvisit, in 16.3% in 3rdvisit and 13.3% at 4thvisit (Table 2).

Efficacy assessment

Efficacy assessment was done in term of MMSE and GDS at 12thand 24thweek. Average MMES at base line was 16.8 (±3.2) units. At 12th week the average score increased to 19.3 (±3.1) unit and at 24th week it rose to 20.6(±3.4) (Table 3). Over the two assessments the average scores showed steady improvement from baseline (figure 1). Average GDS score at baseline was 4.3 (±1.5), the score reduced to 3.7 (±1.4) at 12thweek and to 3.2 (±1.3) at 24thweek. Average GDS score showed a decreasing trend from baseline towards the end of the study. GDS score is broken down into 7 different stages from 'no cognitive decline' to 'very severe cognitive decline'. Towards the end of the study the proportion of subjects with 'severe cognitive decline' or 'very severe cognitive decline' reduced to zero (Table 3).

Safety assessment

Appearance or worsening of any undesirable sign, symptom, or medical condition occurring was considered as an adverse event even if the event

Table-II

Treatment Profile

	Visit 1	Visit 2	Visit 3	Visit 4
Patch size				
5 cm	55 (56.1)	20 (20.4)	8 (8.2)	5 (5.1)
10 cm	43 (43.9)	78 (79.6)	90 (91.8)	93 (94.9)
Concurrent Medication				
Yes	25 (25.5)	20 (20.4)	17 (17.3)	16 (16.3)
No	73 (74.5)	78 (79.6)	81 (82.7)	82 (83.7)
Change in medication				
Yes		17 (17.3)	16 (16.3)	13 (13.3)
No		81 (82.7)	82 (83.7)	85 (86.7)

Results are presented in n (%)

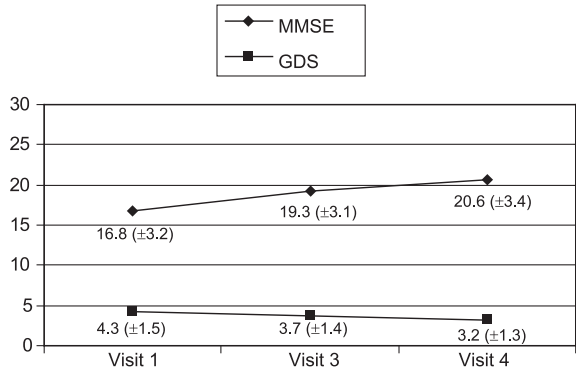

Fig.-1: *Efficacy assessment in terms of MMSE and GDS at 12thand 24thweek*

Table-III

Efficacy assessment in terms of GDS category

GDS	Baseline	week 12	week 24
No cognitive decline	12(12.2)	17 (17.3)	19 (19.4)
Very mild cognitive decline	1 (1.0)	0 (0)	6 (6.1)
Mild cognitive decline	3 (3.1)	7 (7.1)	15 (15.3)
Moderate cognitive decline	28 (28.6)	49 (50)	48 (49)
Moderately severe cognitive decline	37 (37.8)	22 (22.4)	10 (10.2)
Severe cognitive decline	14 (14.3)	3 (3.1)	0 (0)
Very severe cognitive decline	3 (3.1)	0 (0)	0 (0)

Results are presented in n (%)

is not considered to be related to study drug. Over all 8 (8.2% 95% CI 3.8, 19.9) person developed adverse event during the study period (AE) and none developed serious adverse event (SAE). At 2nd assessment (8thweek) none reported any adverse event. At 12th week follow up 6 (6.1% 95% CI 2.5-12.3) and at 24thweek follow up 2 (2.0% 95% CI 0.3 – 6.6) reported adverse events (Table 4). Systolic BP, diastolic BP and heart rate were assessed at all the four assessment points. No significant fluctuation in BP and heart rate was seen across the assessment points over the study period (table 5).

Table-IV

Adverse event

Adverse event	Visit 2	Visit 3	Visit 4	All visits
Yes	0 (0)	6 (6.1)	2 (2.0)	8 (8.2)
No	98 (100)	92 (93.9)	96 (98.0)	90 (91.8)

Results are presented in n (%)

Table-V

Systolic and diastolic BP and heart rate

	Visit 1	Visit 2	Visit 3	Visit 4
SBP	130.9 (13.2)	129.6 (11.6)	128.4 (10.2)	128.7 (9.6)
DBP	82.6 (6.4)	82.4 (4.9)	81.5 (4.9)	81.7 (3.9)
HR	75.4 (5.9)	74.8 (5.7)	74.5 (5.7)	74.7 (6.3)

Results are presented in mean (sd)

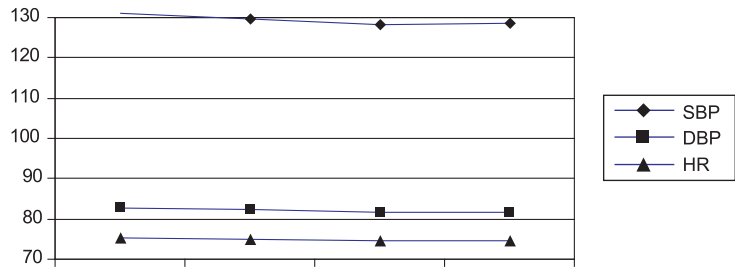

Fig.-2: *Trend in systolic and diastolic BP and heart rate*

Discussion:

One of the primary objectives of the study was to evaluate in a clinical practice setting the proportion of patients who can reach the target patch size of 10 cm^2 and our result shows that around 95% could receive 10 cm^2 patch size, showing a very high tolerability of the patch. In our study concurrent medication use also showed significant reduction to 16.3% patient in the end from 25% at baseline.

Rivastigmine is the first agent of its class to be developed as a transdermal patch and is indicated for the treatment of mild to moderate Alzheimer's disease in several countries worldwide. It is a low-molecular weight amphipathic molecule well suited for transdermal delivery. Prior experience with oral rivasigmine suggested that transdermal delivery of the agent had the potential for better tolerability, as strategies for reducing Cmax, delaying the time to Cmax and reducing the fluctuation index of oral rivastigmine were associated with reduced frequency and severity of gastrointestinal adverse events[12].

MMSE is a practical screening test for cognitive dysfunction[25]. The test consists of five sections namely orientation, registration, attention-calculation, recall, and language and results in a total possible score of 30, with higher scores indicating better function. In our present study efficacy of treatment in term of Mini-Mental State Examination (MMSE) at 12^{th} and 24^{th}week showed significant improvement. The Global Deterioration Scale (GDS) provides caregivers an overview of the stages of cognitive function for those suffering from a primary degenerative dementia such as Alzheimer's disease[26]. It is broken down into 7 different stages. Stages 1-3 are the pre-dementia stages. Stages 4-7 are the dementia stages. Beginning in stage 5, an individual can no longer survive without assistance. With the GDS, caregivers can get a rough idea of where an individual is at in the disease process by observing that individual's behavioral characteristics and comparing them to the GDS. Average GDS score showed a significant decreasing trend from baseline towards the end of the study. Studies have shown that the transdermal rivastigmine patch provides continuous drug delivery over 24 hours, with less fluctuation in plasma rivastigmine concentrations than oral rivastigmine administration and was associated with a generally better tolerability profile than that of oral rivastigmine. The efficacy of rivastigmine transdermal patch in patients with mild to moderate dementia of the Alzheimer's type was demonstrated in the large, 24-week IDEAL trial[27]. Patients receiving 24 weeks of treatment with rivastigmine transdermal patch in this study, experienced significant improvement in global and cognitive function, with the improvement in cognitive function being non-inferior to that observed with rivastigmine capsules. Moreover, most caregivers preferred the patch over the capsules, mainly because of the ease of following the schedule and the ease of use.

As the route of entry of the drug is skin, dermatological tolerability is a relevant issue to address. Rivastigmine patch had good skin adhesion, including in patients living in countries with hot and humid climates, and did not appear to interfere with normal daily activities[28]. The skin tolerability of rivastigmine patch was also favorable during the 24-week IDEAL trial and its 28-week open label extension, with <9% of patients/ evaluations experiencing severe application-site reactions during this period. Moreover, patients receiving rivastigmine patch appeared to be more likely to reach target dosages relative to patients receiving rivastigmine capsules, suggesting an advantage of the transdermal route of administration[29].

According the study finding only eight occasions of adverse event was reported (8.2%) no serious adverse event (SAE) were reported. Appearance or worsening of any undesirable sign, symptom, or medical condition occurring was considered as an adverse effect even if the event is not considered to be related to study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, with potential for study drug discontinuation or require therapy. Most adverse events were gastrointestinal and of mild to moderate intensity. Mostly nausea and few vomiting episodes were reported. None of the study discontinuation was reported due to adverse effect. No fluctuation in BP and heart rate

was seen either across the assessment points over the study period.

Adverse events associated with orally administered cholinesterase inhibitors are likely during the titration phase, which are believed to be caused by the rapid increase in ACh levels in the CNS[18]. Transdermal rivastigmine patch provide continuous delivery of the drug, thereby reduce fluctuations in plasma levels and potentially reduce the incidence of adverse events[12]. There have been reports of deterioration of fine motor behavior in patients with Alzheimer's disease during treatment with cholinesterase inhibitors[30]. However, rivastigmine transdermal patch applied once daily was not associated with impairment of complex movement performance in patients with Alzheimer's disease in a 42-day study[31]. Comparison of the pharmacokinetics of rivastigmine transdermal patch with those of oral rivastigmine revealed the patch being favorable for human condition[32]. Absorption of rivastigmine from the transdermal patch is slow, with rivastigmine being detected in the plasma after a lag time of 0.5–1 hour after the first dose[26].

One important limitation of the series is that the lost to follow up was 14 (12.5%). We analyzed the baseline data of those of the lost to follow up cases and also their available data before they left. Their withdrawal seems to be unrelated to the adverse events and treatment outcome. Among the lost to follow up only one 1 (7.1%) had some side effect.

In summary, the patch was generally well tolerated in trial setting regardless of concomitant treatment, with most treatment-emergent adverse events being mild to moderate in severity. Moreover, according to this analysis, patients receiving rivastigmine patch appeared to be more likely to reach target dosages. Our study supports the pharmacokinetic rationale for the rivastigmine patch, indicating that smooth and continuous delivery of rivastigmine translates into an improved tolerability profile versus conventional oral administration, while maintaining clinical effectiveness. This may allow patients easier access to optimal therapeutic doses, potentially improving the effectiveness of treatment. A transdermal patch may be the optimal way of delivering rivastigmine in the pharmacological treatment of AD. Well designed additional studies, including direct head-to-head comparisons, would help to confirm these results in line with the published clinical data.

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References:

1. Berchtold NC, Cotman CW. Evolution in the conceptualization of dementia and Alzheimer's disease: Greco-Roman period to the 1960s. *Neurobiol.Aging*. 1998;19(3): 173–89
2. Brookmeyer R., Gray S., KawasC.. Projections of Alzheimer's disease in the United States and the public health impact of delaying disease onset. American Journal of Public Health. 1998;88(9):1337–42.
3. Brookmeyer R, Johnson E, Ziegler-Graham K, MH Arrighi. Forecasting the global burden of Alzheimer's disease.Alzheimer's and Dementia. 2007 [cited 2008-06-18];3(3): 186–91.
4. Waldemar G. Recommendations for the diagnosis and management of Alzheimer's disease and other disorders associated with dementia: EFNS guideline. Eur J Neurol. 2007;14(1):e1–26.
5. Mölsä PK, Marttila RJ, Rinne UK. Survival and cause of death in Alzheimer's disease and multi-infarct dementia.ActaNeurol Scand. 1986;74(2):103–7.
6. Mölsä PK, Marttila RJ, Rinne UK. Long-term survival and predictors of mortality in Alzheimer's disease and multi-infarct dementia.ActaNeurol Scand. 1995;91(3):159–64.
7. Tiraboschi P, Hansen LA, Thal LJ, Corey-Bloom J. The importance of neuritic plaques

and tangles to the development and evolution of AD.Neurology. 2004;62(11):1984–9.

8. Thompson CA, Spilsbury K, Hall J, Birks Y, Barnes C, Adamson J. Systematic review of information and support interventions for caregivers of people with dementia.BMC Geriatr. 2007;7:18
9. Corey-Bloom J, Anand R, Veach J. (1998) A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Geriatr Psychopharm;1:55–65.
10. Rösler M, Anand R, Cicin-Sain A, et al. (1999) on behalf of the B303 Exelon Study Group. Efficacy and safety of rivastigmine in patients with Alzheimer's disease: International randomized controlled trial. BMJ;318:633–638.
11. Raskind MA, Peskind ER, Wessel T, et al. (2000) Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. Neurology;54:2261–2268.
12. Guay DR. Rivastigmine transdermal patch: role in the managementof Alzheimer's disease. Consult Pharm 2008 Aug;23 (8): 598-609
13. Hort J, O'Brien JT, Gainotti G, et al. EFNS guidelines forthe diagnosis and management of Alzheimer's disease. EurJ Neurol 2010 Oct; 17 (10): 1236-48
14. Qaseem A, Snow V, Cross JTJ, et al. Current pharmacologictreatment of dementia: aclinical practice guideline fromthe American College of Physicians and the AmericanAcademy of Family Physicians.AnnInternMed 2008Mar 4;148 (5): 370-8
15. Grossberg GT. Cholinesterase inhibitors for the treatmentof Alzheimer's disease: getting on and staying on. CurrentTherapeutic Research 2003 Apr; 64 (4): 216-35
16. Bassil N, Grossberg GT. Novel regimens and delivery systemsin the pharmacological treatment of Alzheimer's disease.CNS Drugs 2009; 23 (4): 293-307
17. Small G, Dubois B. A review of compliance to treatment inAlzheimer's disease: potential benefits of a transdermalpatch. Curr Med Res Opin 2007 Nov; 23 (11): 2705-13
18. Oertel W, Ross JS, Eggert K, et al. Rationale for transdermaldrug administration in Alzheimer disease. Neurology2007 Jul 24; 69 (4 Suppl. 1): S4-9
19. Cummings JL, Farlow MR, Meng X, et al. Rivastigminetransdermal patch skin tolerability: results of a 1-yearclinical trial in patients with mild-to-moderate Alzheimer'sdisease. Clin Drug Invest 2010; 30 (1): 41-9
20. Peterson TA. Transdermal drug formulation and processdevelopment [online].Available from URL: http://pharmtech.findpharma.com/pharmtech/dat/articlestandard//pharmtech/232003/59304/article.pdf [Accessed 2012 Jan 24]
21. Grossberg GT, Sadowsky C, Olin JT. Rivastigmine transdermalsystem for the treatment of mild to moderate Alzheimer'sdisease. Int J Clin Pract 2010; 64 (5): 651-60
22. Lefe'vre G, Sedek G, Huang HLA, et al. Pharmacokinetics ofa rivastigmine transdermal patch formulation in healthyvolunteers: relative effects of body site application. J Clin Pharmacol 2007 Apr; 47 (4): 471-8
23. Lefe'vre G, Bu¨ che M, Sedek G, et al. Similar rivastigminepharmacokinetics and pharmacodynamics in Japanese andwhite healthy participants following the application of novel rivastigmine patch. J ClinPharmacol 2009; 49 (4):430-43
24. Lefe'vre G, Pommier F, Sedek G, et al. Pharmacokineticsand bioavailability of the novel rivastigmine transdermalpatch versus rivastigmine oral solution in healthy elderlysubjects. J Clin Pharmacol 2008; 48 (2): 246-52
25. Folstein MR, Folstein SE, McHugh PR. (1975) "Mini-mental state": A practical method for

grading the cognitive state of patients for the clinician. J Psychiatr Res; 12:189–198

26. Reisberg B, Ferris SH, de Leon MJ, et al. (1982) The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry; 139(9):1136–1139.

27. Winblad B, Cummings J, Andreasen N, et al. A six-monthdouble-blind, randomized, placebo-controlled study of atransdermal patch in Alzheimer's disease-rivastigminepatch versus capsule.Int J Geriatr Psychiatry 2007 May;22 (5): 456-67

28. Winblad B, Grossberg G, Fro¨ lich L, et al. IDEAL: a6-month, double-blind, placebo-controlled study of thefirst skin patch for Alzheimer disease. Neurology 2007 Jul24; 69 (4 Suppl. 1): S14-22

29. Lee JH, Sevigny J. Effects of Body Weight on Tolerability ofRivastigmine Transdermal Patch: a Post-hoc Analysis of aDouble-blind Trial in Patients With Alzheimer Disease.Alzheimer Dis AssocDisord 2011 Jan 31; 25 (1): 58-62

30. Muller T. Rivastigmine in the treatment of patients withAlzheimer's disease. Neuropsychiatr Dis Treat 2007; 3 (2):211-8

31. Muhlack S, Przuntek H, Mu¨ ller T. Transdermal rivastigminetreatment does not worsen impaired performanceof complex motions in patients with Alzheimer's disease.Pharmaco psychiatry 2006 Jan; 39 (1): 16-9

32. Lefe'vre G, Sedek G, Jhee SS, et al. Pharmacokinetics andpharmacodynamics of the novel daily rivastigmine transdermalpatch compared with twice-daily capsules in Alzheimer'sdisease patients. Clin Pharmacol Ther 2008 Jan;83 (1): 106-14.