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RIVASTIGMINA *PATCH* NA DOENÇA DE ALZHEIMER: IMPACTO SOBRE A QUALIDADE DE VIDA E ADESÃO AO TRATAMENTO

TESE DE DOUTORADO

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Tese apresentada ao Colegiado do Programa de Pós-graduação em Medicina e Saúde, da Faculdade de Medicina da Universidade Federal da Bahia, como pré-requisito obrigatório para a obtenção do grau de Doutor em Medicina, da área de concentração em Medicina e Saúde.

Orientador: Prof. Dr. Ailton de Souza Melo

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À minha mãe Idalina
Que transformou minha vida no passado, no presente e no futuro;
Aos meus avos que sempre me deram o carinho e o incentivo para alcançar novos desafios;
Ao meu querido marido Juraci que esteve ao meu lado em todos os momentos, apoiando e sendo uma grande inspiração na minha vida.

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RESUMO

Os quadros de demência, em especial a doença de Alzheimer, interferem na qualidade de vida dos pacientes e seus cuidadores. Para tanto, um dos tratamentos medicamentosos estabelecidos é o uso de anticolinesterásico. Atualmente, encontram-se disponíveis pelo Ministério da Saúde e Secretaria de Saúde as medicações rivastigmina (na forma oral e transdérmica), galantamina e donepezila por via oral. **Objetivos:** Com a primeira pesquisa objetivou-se descrever as reações adversas da rivastigmina patch em comparação com as dosagens de 4,6 e 9,6mg; Na segunda pesquisa objetivou-se avaliar a segurança e a tolerabilidade dos pacientes à medicação transdérmica. Conjuntamente aos estudos anteriores, foi avaliada a ação da atividade física na qualidade de vida dos pacientes em uso de rivastigmina *patch* em comparação com os pacientes apenas em tratamento medicamentoso, **Método:** Para a primeira pesquisa foi realizada uma revisão sistemática com metanálise, sendo feita uma pesquisa nas bases de dados científicas sobre as reações adversas da rivastigmina patch comparando as dosagens de 4,6 e 9,6mg. Resultado: Esta evidenciou que o aumento dos efeitos adversos podem estar relacionados com a dosagem plasmática da medicação, pois eram mais expressivos na dosagem de 9,6mg. Em seguida foi realizado um ensaio clinico com os pacientes com doença de Alzheimer em uso de rivastigmina *patch* no período de janeiro a março de 2011 para avaliar a segurança e a tolerabilidade destes pacientes a medicação transdérmica. Resultado: Neste estudo observou-se a ocorrência de 31% dos 91 pacientes estudados com dermatite de contato e 1% com úlcera gástrica e esofagite. Estes resultados foram mais expressivos, do que os verificados na literatura, o que mostra mais veemência na necessidade de estudos em países com diferenças climáticas e distintas condições socioeconômicas e culturais. Conjuntamente aos estudos anteriores, foi avaliada a ação da atividade física na qualidade de vida destes pacientes em uso de rivastigmina *patch* em comparação com os pacientes apenas em tratamento medicamentoso, sendo realizado um ensaio clinico controlado, verificou-se a melhora neste parâmetro na análise da qualidade de vida e no desenvolvimento das atividades de vida diária no grupo que realizou o uso da medicação transdérmica, associado à atividade física ao uso da medicação. **Conclusão:** o estudo de revisão sistemática com metanálise verificou o aumento dos efeitos colaterais nas maiores dosagens plasmáticas da rivastigmina patch. Através dos ensaios clínicos realizados, foi possível verificar que as ações das medicações na qualidade de vida podem estar relacionadas a fatores externos e as alterações nas diferentes condições onde são empregadas, tanto ambientais como socioculturais e econômicas. No outro ensaio clinico observou-se a melhor resposta dos pacientes com a associação de atividade física e do tratamento medicamentoso, mostrando a resposta medicamentosa pode ser intensificada com as atividades fisioterápicas. Os estudos mostraram a necessidade de mais pesquisas sobre o assunto na população brasileira, pois os estudos verificaram mudanças na eficácia das medicações em diferentes ambientes e características populacionais.

Palavras-chave: Doença de Alzheimer/Terapia; Rivastigmina patch; Rivastigmina oral; Qualidade de vida; Adesão à medicação.

FERES. Ana Cristina. **Rivastigmine *Patch* in Alzheimer's disease: impact on quality of life and accession to treatment.** 58 f. 2015. Thesis (Ph.D.) - Federal University of Bahia. Faculty of Medicine.

ABSTRACT

The In the dementia disease of dementia, in particular Alzheimer's disease, affect the quality of life of patients and their caregivers. Therefore, one of the established drug treatments is the use of anticholinesterase. Currently, rivastigmine medications (in oral and transdermal form), galantamine and donepezil for oral use are available by the Ministry of Health and the Health Department. **Objectives:** In the first research it was aimed to describe the adverse reactions of rivastigmine patch compared to the dosages of 4.6 and 9.6 mg; The second study aimed to evaluate the safety and tolerability of patients with transdermal medication. In conjunction with previous studies, the action of physical activity on quality of life was evaluated of patients taking rivastigmine patch, compared to patients only in drug treatment. **Method:** For the first survey a systematic review was conducted with meta-analysis, a search being made in scientific databases on the adverse effects of rivastigmine patch comparing dosages of 4.6 and 9,6mg. This showed that the increase in adverse events may be related to plasma dosage of medication because they were more expressive in dosage 9.6 mg. Then a clinical trial was conducted with patients with Alzheimer's disease in use of rivastigmine patch, from January to March 2011 to evaluate the safety and tolerability of these patients to transdermal medication. **Result:** In this study the incidence of 31% was observed for 91 patients studied with contact dermatitis and 1% with gastric ulcers and esophagitis. These results were more significant than those found in the literature, which shows more strongly the need for studies in countries with climatic differences and different socioeconomic and cultural conditions. Together with previous studies, the effect of physical activity on quality of life of these patients in use of rivastigmine patch was evaluated compared to patients only in drug treatment being carried out a controlled clinical trial, there was found improvement in this parameter in the analysis of quality of life and development of activities of daily living in the group that made use of transdermal medication, associating the use of medication with physical activity. **Conclusion:** The study of systematic review and meta-analysis found an increase in side effects in higher plasma doses of rivastigmine patch. Through clinical trials, the actions of drugs on quality of life was found that may be related to external factors and changes in different conditions where they are employed, both environmental and socio-cultural and economic. In the other clinical trial there was the best response of patients with the combination of physical activity and drug therapy, showing that drug response can be enhanced with physical therapy activities. Studies have shown the need for more research on the subject in Brazilian population, as studies have found changes in the efficacy of drugs in different environments and population characteristics.

Descriptors: Alzheimer disease/Therapy; Rivastigmine patch; Oral Rivastigmine; Quality of life; Adherence to medication.

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ARTIGO 3: Tolerability and compliance of rivastigmine transdermal patch in subjects with Alzheimer`s disease.

LISTA DE ABREVIATURAS E SIGLAS

CNPq	Conselho Nacional de Desenvolvimento Científico e Tecnológico
DA	Doença de Alzheimer
DINEP	Divisão de Neurologia e Epidemiologia
HUPES	Hospital Universitário Professor Edgar Santos
UFBA	Universidade Federal da Bahia

SUMÁRIO

1 INTRODUÇÃO

Com o aumento da expectativa de vida devido às mudanças na qualidade de vida e com os desenvolvimentos na área da saúde, os números de enfermidades que acometem à população idosa estão crescendo vertiginosamente. Estudos demonstram que entre 50 a 70% das pessoas com demência apresentam a doença de Alzheimer (OLIVEIRA *et al*., 2005).

Este mesmo autor reporta que a demência é uma degradação progressiva da capacidade mental, onde a memória, a reflexão, concentração, capacidade de aprendizado e senso crítico são afetados. Na fase inicial da patologia, pode ser confundida pelos familiares, com algumas alterações que ocorrem no processo do envelhecimento, sendo que a demência não afeta as funções normais e não piora com o tempo.

Na demência, uma das principais queixas dos pacientes e familiares é a dificuldade de memória. Esses déficits causam alguns prejuízos na realização das atividades diárias e de vida prática dos pacientes, podendo comprometer sua qualidade de vida (AVILLA e MIOTTO, 2002).

As alterações cognitivas estão relacionadas ao déficit de neurotransmissores cerebrais, como acetilcolina, noradrenalina e serotonina. Dessa forma, o tratamento sintomático consiste em restaurar a função colinérgica. Assim, acredita-se que com a elevação dos níveis de acetilcolina poderá haver melhora do quadro de déficit de aprendizagem. Atualmente, utilizam-se alguns fármacos que estão liberados pela *Food and Drug Adminstration* (FDA) como rivastigmina (oral ou transdérmico), donepezil e galantamina, mas ainda não há evidências da eficácia desses tratamentos nas fases de moderada para grave (ROWLAND, 2007).

Segundo esse autor a rivastigmina é um anticolinesterásico que diminui a hidrólise da acetilcolina liberada pelo neurônio pré-sináptico na fenda sináptica pela inibição da acetilcolinesterase, levando à estimulação do receptor colinesterásico. Uma das vantagens desse fármaco é o não metabolismo pelo sistema microssomal hepático, como ocorre em grande parte dos medicamentos utilizados pelos idosos, sendo menos uma medicação para a sobrecarga hepática. Além disso, em estudo multicêntrico evidenciou melhora na cognição e nas atividades de vida diária com seu uso (BOTTINO *et al*., 2002).

Rowland (2007) ainda reporta que a rivastigmina apresenta melhora moderada da função cognitiva e nas atividades de vida diária dos pacientes, quando utilizada em altas doses.

A medicação rivastigmina *patch* foi liberada pelo FDA em 2007, existindo assim alguns questionamentos sobre esta droga. O questionamento inicial foi quanto aos efeitos colaterais. A revisão sistemática realizada por Small e Dubois (2007) de 1987 a 2007 reporta que os pacientes apresentavam melhor tolerabilidade à forma *patch* em relação à oral com a diminuição dos efeitos colaterais e melhor forma de administração da droga pela via transdérmica. Como demonstra o estudo realizado por Cumming e colaboradores (2010), 3,7% de 1195 pacientes em tratamento com rivastigmina *patch* tiveram que descontinuá-lo devido às afecções de pele apresentadas após o uso da medicação.

Por outro lado, alguns autores reportam os benefícios da associação das atividades físicas com o uso de anticolinesterásicos, onde em pesquisa utilizando rivastigmina *patch* associada a exercício físico observou-se melhora na qualidade de vida desses pacientes (HUANG *et al*., 2009). Já a metanálise realizada por Forbes e colaboradores (2008) demonstra a insuficiência de dados que relatem os benefícios dos exercícios nos pacientes com demência.

Desta forma a autora resolveu ingressar nas pesquisas sobre o tema de segurança da medicação rivastigmina *patch* e, considerando sua experiência profissional como reabilitadora, resolveu analisar também os efeitos deste medicamento associado com a atividade física.

2 OBJETIVO

Determinar o impacto dos exercícios físicos na qualidade de vida e frequência de eventos adversos e avaliação da adesão ao uso de rivastigmina patch em pacientes com doença de Alzheimer.

3 REVISÃO DE LITERATURA - ARTIGO DE REVISÃO SISTEMATICA

3.1 ARTIGO 01: SAFETY AND COMPLIANCE OF RIVASTIGMINE TRANSDERMAL PATCH IN ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Safety and compliance of rivastigmine transdermal patch in Alzheimer's disease: a systematic review and meta-analysis.

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Safety and compliance of rivastigmine transdermal patch in Alzheimer's disease: a systematic review and meta-analysis.

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Abstract

Introduction: Frequency and severity of adverse events (AE) are considerable determinants of treatment compliance and may compromise efficacy. Oral rivastigmine, a cholinesterase inhibitor (ChI), is generally associated with mild to moderate gastrointestinal events(GI). However, in the patch presentation, skin site-application reactions are more frequently observed. The aim of this study was to assess safety and compliance of rivastigmine transdermal patch (RTP) in different daily doses for Alzheimer's disease (AD) treatment.

Methods: We performed a comprehensive literature this systematic review search with Meta-analysis from March 2007 to November 2014 using the following descriptors: *"Alzheimer's disease", "Alzheimer's dementia", "Adverse events", "Safety", "Tolerability", "Acetylcholinesterase inhibitors", "Cholinesterase inhibitors", "Anticholinesterase agents", "Rivastigmine" and "Rivastigmine transdermal patch"*. All randomized, double-blinded trials that met eligibility criteria and assessed safety or tolerability of RTP in AD were included in the review. Effect-sizes were presented as odds ratio (OR) and the pooled analysis was performed with a fixed-effects model. Outcomes considered for meta-analysis were the following: presence of any AE, gastrointestinal (GI) AE, skin-site application effects and compliance. Degree of heterogeneity between studies was measured with the I^2 test and significance level was established at 5%.

Results: An initial search retrieved 42 references. After applying eligible criteria, three randomized trials with 2.478 AD patients were included in the meta-analysis. The pooled analysis showed that the frequency of any AE (OR 1.43; CI 95% 1.17-1.74) or GI events (OR 2.88; CI 95% 2.28-3.64) were significantly lower in the low dose RTP group. However, when analyzing skin-site application effects (OR 1.11; CI 95% 0.71-1.72) and compliance (OR 1.12; CI 95% 0.84-1.50), there was no significant difference between groups. Most frequently AE reported were related to drug mechanisms of action and increase in daily dose was not correlated with marked increase in AE frequency or new AE.

Conclusions: According to the results of this systematic review and meta-analysis, higher doses of RTP are associated with more frequent GI events, also observed in AD subjects

treated with the oral formulation. However, skin-site application effects like pruritus and erythema, frequently observed in the patch presentation, were not significantly different between low and high doses of RTP. Also, compliance was not affected by AE in any of the studied doses. Several studies highlight that mild to moderate skin site-application reactions are frequently observed in subjects treated with RTP and might be responsible for treatment discontinuation. A pooled analysis of randomized trials showed that even in higher doses, RTP was not responsible for lower compliance. Further trials assessing safety profile and tolerability are necessary to define which one is the better way of drug administration with major compliance and lower adverse events.

Keywords: Alzheimer’s disease; Rivastigmine; Safety Management; Transdermal Patch.

Segurança e conformidade de remendo rivastigmina transdérmica na doença de Alzheimer: uma revisão sistemática e meta-análise.

Resumo

Introdução: A freqüência e gravidade dos eventos adversos (EA) são determinantes consideráveis de adesão ao tratamento e pode comprometer a eficácia. Rivastigmina oral, um inibidor de colinesterase (CHI), é geralmente associado com ligeira a moderada eventos gastrintestinais (GI). No entanto, na apresentação patch, reacções cutâneas no local de aplicação são observados mais frequentemente. O objetivo deste estudo foi avaliar a segurança e conformidade de remendo rivastigmina transdérmica (RTP) em diferentes doses diárias para a doença de Alzheimer (DA) de tratamento.

Métodos: Foi realizada uma literatura abrangente esta pesquisa revisão sistemática com meta-análise a partir de março de 2007 a novembro 2014 utilizando os seguintes descritores: "a doença de Alzheimer", "demência de Alzheimer", "eventos adversos", "Segurança", "Tolerância", " Os inibidores da acetilcolinesterase "," Os inibidores da colinesterase "," anticolinesterásicos "," Rivastigmina "e" Rivastigmina sistema transdérmico ". Todos os ensaios duplo-cegos randomizados que preencheram os critérios de elegibilidade e avaliados segurança e tolerabilidade da RTP em AD foram incluídos na revisão. Efeito de tamanhos foram apresentados como odds ratio (OR) e a análise conjunta foi realizada com um modelo de efeitos fixos. Resultados considerados para meta-análise foram os seguintes: presença de qualquer AE, gastrointestinal (GI) AE, efeitos de aplicação da pele do local e compliance. Grau de heterogeneidade entre os estudos foi medida com o nível de teste e significado I2 foi estabelecido em 5%.

Resultados: Uma busca inicial recuperadas 42 referências. Depois de aplicar critérios elegíveis, três estudos randomizados com 2.478 pacientes com DA foram incluídos na meta-análise. A análise conjunta mostrou que a freqüência de qualquer AE (OR 1,43; IC 95% 1,17-1,74) ou eventos gastrointestinais (OR 2,88; IC 95% 2,28-3,64) foram significativamente menores no grupo de baixa RTP dose. Entretanto, ao analisar os efeitos de aplicação de pele local (OR 1,11; IC 95% 0,71-1,72) e conformidade (OR 1,12; IC 95% 0,84-1,50), não houve diferença significativa entre os grupos. Na maioria das vezes AE relatados foram relacionados a mecanismos de drogas de ação e aumento da dose diária não foi correlacionada com aumento acentuado na frequência AE ou nova AE.

Conclusões: De acordo com os resultados desta revisão sistemática e meta-análise, doses mais elevadas de RTP estão associados a eventos gastrointestinais mais freqüentes, também observadas em indivíduos AD tratados com a formulação oral. No entanto, os efeitos da aplicação da pele do local, como prurido e eritema, frequentemente observadas na

apresentação patch, não foram significativamente diferentes entre baixas e altas doses de RTP. Além disso, a adesão não foi afectada por AE em qualquer das doses estudadas. Vários estudos destacam que leve a reacções no local de aplicação moderada da pele são freqüentemente observadas em pacientes tratados com a RTP e pode ser responsável pela interrupção do tratamento. A análise dos resultados dos ensaios clínicos randomizados mostrou que, mesmo em doses mais elevadas, a RTP não foi responsável pelo menor adesão. Mais estudos avaliando perfil de segurança e tolerabilidade são necessários para definir qual é a melhor forma de administração da droga com grande respeito e eventos adversos mais baixos.

Palavras-chave: doença de Alzheimer; Rivastigmina; Gestão da Segurança; Sistema transdérmico.

Introduction

Increased life expectancy due to improvement in quality of life and health assistance play a major role in the rising prevalence of aging related diseases, specially Alzheimer's dementia (AD), accounting for approximately one third of all dementia cases([1]). AD is chronic and neurodegenerative leading to progressive deterioration of cognition (memory, attention, executive and visuospatial abilities, praxis) impacting progressively in activities of daily living (ADL) and quality of life (QOL).

The pathological mechanisms of neuronal deterioration in AD are not fully understood. However, the accumulation of abnormal proteins in the aging brain leading to inflammatory processes, oxidative stress and neuronal apoptosis are the main findings responsible for the gradually impaired cholinergic transmission([2]). Reduction of acetylcholine (Ach) levels in the central nervous system (CNS) and decreased cholinergic transmission are believed to be the major responsible for the progressive decline in cognitive functions associated with AD. In this way, the main treatment goal is to enhance cholinergic transmission pathways by increasing Ach levels in synaptic gaps through inhibition of Ach hydrolysis with efficacy and minimal adverse events (AE)([2]).

Cholinesterase inhibitors are indicated for the treatment of AD and results from randomized clinical trials (RCT) show that these drugs may stabilize or slow cognition decline([2]). Rivastigmine in its oral presentation is a cholinesterase inhibitor generally associated with gastrointestinal (GI) AE such as nausea, vomiting and diarrhea, probably due to a fast increase in CNS Ach levels, particularly in the titration phase([3]). These events may interfere with patient compliance and treatment efficacy. In order to reduce GI AE and enhance patient compliance the patch presentation was developed RTP until 2007. By delivering continuously and slower the drug directly through the skin into the bloodstreamand, GI effects would be diminished and compliance increased, enhancing treatment efficacy([1]). However, several trials have shown that skin-site application effects like pruritus and erythema even in a mild way may be responsible for patient discontinuation and efficacy reduction([3]). Until now, the frequency of most common AE and its relation to RTP drug concentration leading to diminished compliance and drug discontinuation was not assessed.

The aim of this systematic review was to assess safety and compliance of RTP in low and high doses in AD patients.

Methods

Literature search

A literature search with meta-analysis search in MEDLINE, EMBASE, SCORPS, LILACS, Web of Science and the Cochrane library for controlled trials was performed from March 2007 to April 2014. All randomized and double-blind trials published in English, Portuguese, French, Spanish and German that assessed tolerability and safety of RTP in subjects with AD were considered for inclusion in the review. The descriptors used were *"Alzheimer's disease", "Alzheimer's dementia", "Adverse events", "Safety", "Tolerability", "Acetylcholinesterase inhibitors", "Cholinesterase inhibitors", "Anticholinesterase agents", "Rivastigmine" and "Rivastigmine transdermal patch"* with the Boolean operators AND, OR

and NOT (MEDLINE search procedures). The website "http://www.clinicaltrials.gov" was also consulted in order to identify ongoing trials.

Study selection and quality assessment

After the initial search, all trials retrieved that fulfilled the eligible criteria were considered and evaluated (titles and abstracts) by two independent reviewers. Inclusion criteria were randomized, double-blinded trials that assessed tolerability and safety of RTP in subjects with AD. We excluded all studies that did not describe clearly the concealment procedure. The Jadad scale was used and scores were compared between two raters. Scores in the Jadad scale up to 2 were considered as low quality, and over 3, as high quality trials([4]). Duplicated publications were also excluded from the review. All disagreements concerning whether or not to include a study were resolved by a third reviewer opinion.

Data extraction

Data were extracted and placed in a standardized form elaborated by the reviewers. All trials that met eligibility criteria were included in the review and the following variables were extracted from the original articles by two independent reviewers: first author, publication year, location, population, type of intervention, duration of study, frequency of adverse events, tolerability and trial quality. If there were missing data, an attempt to contact the authors was performed. Inconsistent results among reviewers were resolved by consensus.

Statistical analysis

Data were considered for analysis using the software Comprehensive Meta-analysis version 2.2 (Biostat Inc. Englewood, New Jersey). Low RTP dose was defined as a patch concentration $\leq$ 9.6mg/day. The *Odds ratio* their 95% confidence interval (CI) were calculated for each trial and to estimate the summary *effect-size*. The fixed-effects model was used to assess the results in the meta-analysis, and the degree of heterogeneity was calculated by the

I^2 test. A degree of heterogeneity above 50% was considered as substantial. Subgroup analysis and metaregression were hampered by the small numbers of studies included in the analysis.

Results

Forty-two references were retrieved after a comprehensive literature search from electronic databases and other sources (figure 1). Twenty-eigth studies were excluded after title and abstract evaluation, and reasons for exclusion are described in table 1. Fourteen randomized trials were fully evaluated and eleven were excluded because they not fulfilled the eligibility criteria. A total of three references were included in the review. The characteristics of the included studies are summarized in table 2.

Figure 1: Flowchart for inclusion/exclusion of studies and reasons for exclusion

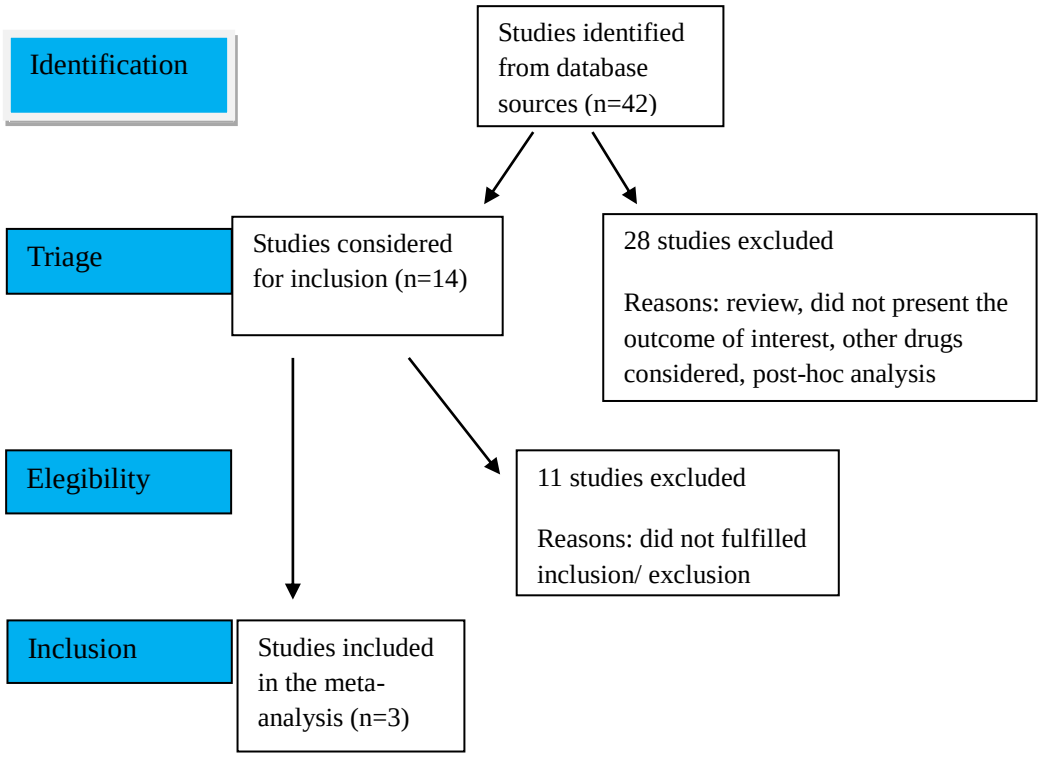


Table 1. References fully analyzed for reasons of criteria exclusion in the review

Study ID	Rivastigmine transdermal patch	Reason for exclusion
2013, Grossberg et al.([5])	Yes	Activities of daily living
2011, Choi et al.([6])	Yes	Memantina add-on; open-label
2011, Blesa et al.([7])	Yes	Review
2010, Wouters et al.([8])	Yes	Comparison with galatanmine
2010, Grossberg et al.([9])	Yes	Review
2010, Sadowsky et al. **([10])**	Yes	Switch from donepezil
2010, Sadowsky et al. **([3])**	Yes	Switching from oral to patch
2010, Darreh-Shoriet al.([11])	Yes	Parkinson`s disease dementia and AD
2009, Grossberg et al.([12])	Yes	Open-label
2009, Birks et al.([13])	Yes	Review
2009, Sadowsky et al.([14])	Yes	Switch from donepezil

Table 2. References included in the review and outcomes of interest

Author	Year	Study design	Population	Duration Interventions	Outcomes	Jadad score
Winblad([15])	2007	Randomized double-blinded, placebo-controlled trial	1195 subjects from 21 different countries	24 weeks Placebo RTP 10 cm^2, RTP 20 cm^2 Oral capsule rivastigmine	Any adverse event GI events Skin effects Compliance	5
Cummings([16])	2012	Randomized double-blinded, clinical trial	567 subjects from 147 centers in North America and Europe	48 weeks RTP 13.3mg/day *versus* RTP 9.5mg/day	Any adverse event GI events Skin effects Compliance	5
Farlow([17])	2013	Randomized controlled trial	716 subjects from 82 centers in USA	24 weeks RTP 13.2mg/day *versus* RTP 4.6mg/day	Any adverse event GI events Skin effects Compliance	5

Legend: RTP- Rivastigmine Transermal Patch,
GI - Gastrointestinal

The results of this systematic review and meta-analysis suggested that in addition to besides the development of a new delivery system of the drug avoiding fluctuations of plasma drug concentration GI AE are still frequent, specially on high drug concentrations. When comparing low versus high RTP doses as defined previously, a pooled analysis of three RCT showed that the frequency of any AE (OR 1.43; CI 95% 1.17-1.74) (figure 2) or GI events (OR 2.88; CI 95% 2.28-3.64) (figure 3) were significantly lower in the low dose RTP group. However, when analyzing skin-site application effects (OR 1.11; CI 95% 0.71-1.72) (figure 4) and compliance (OR 1.12; CI 95% 0.84-1.50) (figure 5), there was no significant difference between groups. Most frequently AE reported were related to drug mechanisms of action and increase in daily dose was not correlated with marked increase in AE frequency or new AE.

Figure 2. Frequency of any adverse event when comparing high and low RTP dose

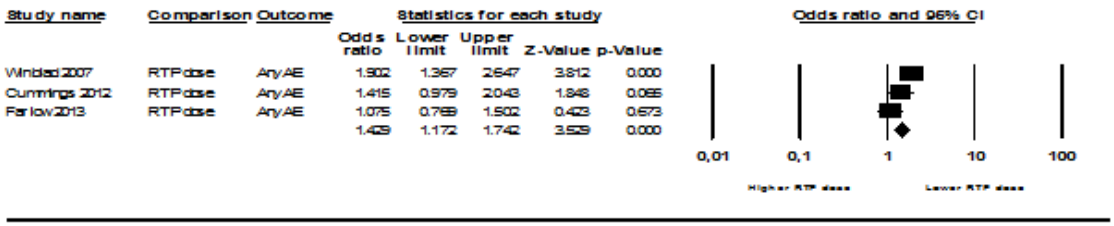


Figure 3. Frequency of gastrointestinal adverse events when comparing high and low RTP dose

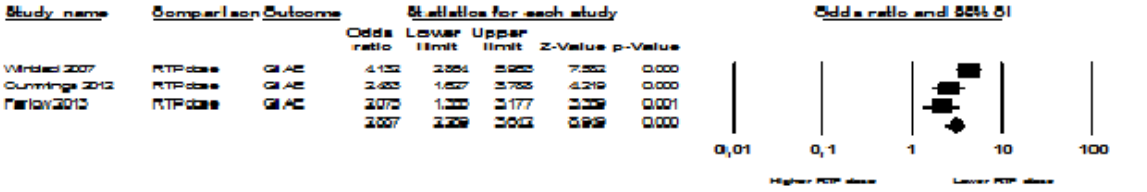


Figure 4. Frequency of skin pruritus in application site when comparing high and low RTP dose

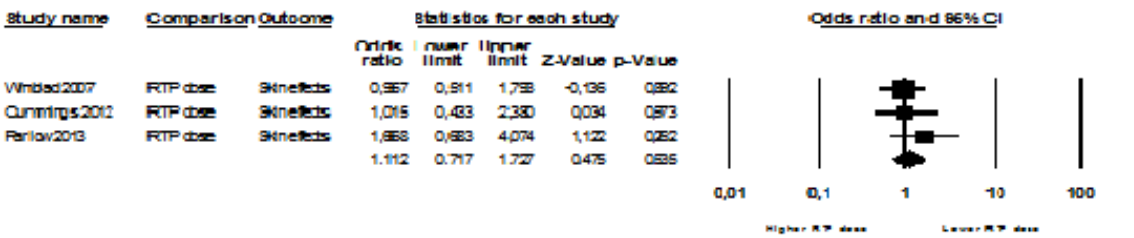
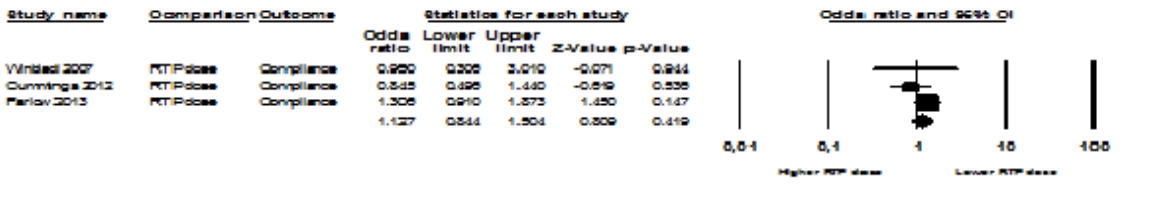


Figure 6. Frequency of treatment discontinuation due to adverse events when comparing high and low RTP dose



Discussion

Skin-site application effects, a new AE related to the patch presentation, besides frequent in both doses, was not associated significantly with higher doses. Compliance was not affected by RTP dose.

RTP has been recently developed for the treatment of AD and efficacy on cognition and quality of life of patients and caregivers was extensively studied in several trials. The main goal for RTP development was based on drug pharmacokinetics. Besides avoiding the first-pass effect, a continuous and smooth bloodstream drug delivery enabled by patch presentation reducing fluctuations and plasma peaks should reduce AE, specially those related to GI tract([18]). Compliance also would be enhanced by easier administration and fewer AE when compared to oral presentations.

In the double-blinded trials included in this systematic review with RTP (IDEAL; OPTIMA; ACTION), GI events such as nausea and vomiting remained the most frequently AE observed and frequency was associated with increasing in daily doses. However, patients in oral presentation present three times more GI AE than patients in patch presentation, limiting higher treatment doses and increasing discontinuation([19]). In addition, most AE observed in RTP were considered mild to moderate and did not interfere with compliance and tolerability significantly. A Cochrane review of rivastigmine concluded that both doses of RTP is associated with fewer AE and greater tolerability, with higher doses presenting with more AE maintaining the efficacy, compatible with our results([13]). Open label trials showed similar profile of AE, specially skin-site application reactions, suggesting that severity of skin effects is not associated with prolonged patch treatment([18]).

Some aspects related to skin condition in patients with AD should be take into consideration and may interfere with severity of lesions due to patch application. One are some characteristics of the population selected for trials that may confound results and interfere with severity of local skin AE. Lee et al. performed a *post-hoc* analysis to determine if body weight could affect the frequency of AE or drug tolerability in patients with AD taking RTP (12mg/day) rivastigmine capsules (12mg/day) or placebo([20]). Besides the balanced number of discontinuations due to AE in the three groups, patients with extreme low-weight

and RTP presented with higher discontinuation due to AE (one with application skin-site erythema). Schmidt et al. reported a frequency of local skin reactions of 23% mostly mild in severity, however, 6.8% discontinued treatment with RTP. The earliest skin effect was observed after 3 months of treatment([21]). These data support the idea that special attention should be taken with nutritional status and hygiene conditions in populations treated with RTP. Another key point highlighted by Lockart et al. is that in RCT enrolled subjects are submitted to very restrictive inclusion/exclusion criteria, sometimes limiting extrapolation of results for the "day-to-day" clinical practice([22]).

Further clinical trials to reassure the local effects of patch presentations in different doses and long-term assessments to evaluate patient tolerability and quality of life may optimize the results and allows a better evaluation of local AE of cholinesterase inhibitors in AD.

Acknowledgments

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Rivastigmine Transdermal Patch and Physical Exercises for Alzheimer's Disease: A Randomized Clinical Trial

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Rivastigmine Transdermal Patch and Physical Exercises for Alzheimer's Disease: A Randomized Clinical Trial

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Abstract: Objective: To determine the effects of rivastigmine patch associated with physical exercise *versus* rivastigmine patch alone in quality of life (QOL), cognition, activities of daily living (ADL) and functional mobility in Alzheimer's disease (AD)subjects. Methods: A randomized, controlled, single-blinded trial was conducted in 40 patients with mild to moderate stages of AD. All patients were daily treated with rivastigmine transdermal patch at a stable dose of 4.6 mg and randomized into two groups: physical exercises or control. The exercise program consisted of aerobic, flexibility, strength and balance movements, twice a week for 6 months. Main outcomes were Quality of Life in Alzheimer's disease scale (QOL), Activities of Daily Living Questionnaire (ADL), Mini-Mental State Examination (MMSE) and "Time Up and Go Test". Results: Thirty-four patients completed the study. After 6 months, there was a significant improvement in QOL of patients randomized to physical exercise group ($P< 0.05$). In both groups, there was an improvement on caregivers QOL ($P>0.05$). When considering cognitive functions, there was no difference between groups. The ability to perform ADL worsened in the group enrolled to RTP alone. There was an improvement in functional mobility in the group treated with RTP. Conclusion: Our results suggest that the association between physical exercises and RTP improves QOL in patients with AD. Cognition remained unchanged in both groups. Regarding the effect of physical exercises in ADL, further trials are necessary to confirm these results.

Keywords: Activities of daily living, Alzheimer's disease, dementia, exercise, quality of life, rivastigmine.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia and is considered as a public health problem due to its high prevalence and burden for patients and caregivers [1-3].

The most widely used clinical criteria for AD diagnosis are impaired memory associated with at least another cognitive deficit, such as decreased concentration, difficulty in apprehension of new information, apraxia, agnosia and aphasia [4]. Such decline in cognitive functions interferes with activities of daily living (ADL), thereby causing significant deficit in social and occupational performance [5]. Moreover, AD impacts quality of life (QOL) in patients and caregivers [6].

It has been demonstrated the efficacy of rivastigmine, a cholinesterase inhibitor, in cognition, ADL and severity of dementia for patients in mild to moderate stages of AD with both lower (4mg daily) and higher doses (6 to 12mg daily). Mild adverse events have been reported, mostly nausea and vomiting. However, the patch presentation is associated with fewer gastrointestinal effects than oral presentation [7].

A randomized controlled study with 16 AD patients demonstrated that a combined training program (resistance, joint mobility and coordination exercises) significantly improved the ability to perform ADL after a 12-week period [8]. In a 12-week follow up pilot study, QOL and cognitive/behavioral symptoms of 14 AD subjects submitted to cognitive stimulation, physical activity (balance, coordination and muscle trophism exercises) and socialization showed no significant changes in cognition. However, there was a significant improvement in QOL in the intervention group [9].

The benefits of non-pharmacological approaches for patients with AD have been previously reported, but randomized controlled trials on the topic are rare [10]. In a systematic review followed by meta-analysis, Forbes *et al.* suggest that there was insufficient evidence to determine whether physical activity programs were beneficial for individuals with dementia [11].

The aim of this study was to investigate, in a prospective, randomized, single-blinded way, the effects of RTP combined with physical exercises *versus* RTP alone in QOL, ADL and functional mobility on AD subjects.

METHODS

Study Design

Randomized, controlled, single-blinded trial.

Participants

Patients were referred by a neurologist/geriatrician for RTP treatment. The following inclusion criteria were applied: a) age ≥55 years; b) diagnosis of AD; c) the same caregiver for at least three months, d) no previous use of

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cholinesterase inhibitors for AD; e) stable systemic blood pressure.

The following exclusion criteria were applied: a) Mini-Mental State Examination (MMSE) score superior to 12; b) inability to follow simple commands; c) having undergone physiotherapy, occupational therapy and/or systematized physical activity in the previous two months; d) psychiatric illness; e) orthopedic, neurological limitations, behavioral or other conditions that could prevent the practice of exercise; f) severe visual or auditory deficits that could preclude the application of the program.

Study Settings and Ethical Acknowledgements

The study was performed at the Cognitive Functions Outpatient Clinic in the Federal University of Bahia, Northeastern, Brazil. This protocol was approved by the local Ethics Committee, and all participants signed an informed consent form before starting study procedures.

Randomization

After screening evaluations, patients were randomly assigned into two groups using a computer program: RTP alone (Group 1) or physical exercise associated with RTP (Group 2). Patients and their respective caregivers who were randomized to exercise group were referred to a follow-up appointment with a physical therapist, and received instructions and information regarding the exercise program. Group allocation was kept in an opaque envelope and sealed until the study was completed.

Blinding

An investigator who did not participate in any of the assessments performed the randomization. The investigator who assessed outcomes was also blinded.

Interventions

Initially, selected patients were treated with daily RTP at doses of 4.6 mg. After approximately two months, the dose was increased up to 9.5 mg/daily until it reached stable doses with minimal side effects.

Each patient was followed for 6 months. Exercises were conducted by a certified physical therapist at the Cognitive Functions Outpatient Clinic Patients for each patient individually. The intervention was consistent with 40 programmed training interventions performed twice a week, 40 minutes per section. The training program consisted of aerobic activity, flexibility, strength and balance exercises. This protocol and frequency of the exercise was based on previously published studies [10,12,13]. The program included flexibility exercises for all sections and was conducted interchangeably between sessions A (aerobic activity) and B (resistance exercise and balance training) (Table **1**).

Outcomes

Visits were performed every month for 6 months to reassess cognition, QOL, ADL and functional mobility. Cognitive evaluation was performed using the Mini-Mental State Examination (MMSE) [14]. QOL of patients and caregivers were assessed using the Scale of Quality of Life in Alzheimer's Disease (QOL-AD) [15]. The QOL-AD assessment tool consists of 13 items, each of which can be rated from 1 (poor) to 4 (excellent). The total scores ranged from 13 to 52 and considers the patient and caregiver QOL perception. ADL were assessed through the Activities of Daily Living Questionnaire (ADLQ), that consists of six subscale scores that address different activity areas, and each subscale has three to six items. Each of these items is rated from 0 (no problem) to 3 (no longer capable of performing the activity). For each item, there is also a rating of 9 ("Never did this activity" or "Do not know"). The final score represented the severity level of the ADL impairment and was rated as "none to mild" (0–33), "moderate" (34–66), or "severe" (66-100). [16]. Both QOL-AD and ADLQ have been translated, adapted and validated into Portuguese by Novelli *et al.* [5] and Medeiros e Guerra [17], respectively.

Functional mobility was tested through the "Time Up an Go" test (TUG) [18]. The TUG test is widely employed in the examination of elders as a basic test for functional mobil-

Table 1. Exercise program.

Exercise	Description	Time or Progression
Stretching	Passive stretching: Lower limbs: gluteus maximus, hamstrings, triceps surae; adductors, quadriceps femoris. Upper limbs: pectoralis major, biceps brachii, triceps brachii, flexors for wrist and fingers.	Five minutes of warm-up and a five minute cool-down period
Aerobicactivity	Walking (hallway and external environment) and stair-climbing training (step)	Initially 20 minutes, progressing to 30 minutes
Resistance training	Sit and stand up Lower limbs Quadriceps Femoris, Hamstrings, Middle gluteal and adductor. Upper limbs: deltoids, Rotator Cuff and Biceps brachii.	Initially no load, progressing to 1.5 kg or light manual resistance, depending on the patient's tolerance.
Dynamic balance training	Circuit gait with obstacles	Increased speed and change of direction

ity. The TUG score measures gait speed and measure time to rise from the chair, walk 3 meters, turn, walk back and sit down.

Statistical Methods

Mean and standard deviation (SD) of continue variables were calculated, and normality of the sample was tested using the Kolmogorov-Smirnov test. Fisher's exact test was used to compare frequency ratios and proportions between the categorical variables, and Student's t-test was used for comparing the averages, the medians and SD of continuous variables.

Statistical significance was set at 5%. The data were analyzed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Patients were enrolled between July 2010 and November 2011. Forty patients were randomized, and six did not complete the study (Fig. **1**). Four patients discontinued due to adverse skin reactions (two erythema and two itching reactions), and two patients no longer wished to participate. Seventeen patients remained in each group until the end of the study. All patients initiated therapy with RTP at doses of 4.6 mg/daily, and finished the study with a dose of 9.5 mg/daily.

Baseline characteristics of the studied population are described in Table **2**. During trial assessments, RTP group was questioned about possible physical activity during follow-up period. However, no systemized exercise activity was reported during the study period.

There was a significant improvement in QOL of patients receiving combined therapy (RTP and physical exercises). Considering QOL in caregivers, there was no difference between baseline and end of study assessments (Table **3**). Cognitive scores as assessed by MMSE remained stable in both groups ($p>0.05$). Surprisingly, functional mobility improved in patients treated with RTP alone, and showed no difference in the combined therapy group. There was a worsening of ADL in the RTP group (Table **3**).

DISCUSSION

Our results suggest that the association of RTP with physical exercises is superior to RTP alone to improve QOL in patients with AD. However, caregivers QOL remained unchanged between groups.

Although the efficacy and safety of RTP versus oral rivastigmine have been exhaustively investigated, fewer trials focused on the effects of RTP in QOL[19-22].

Despite the worsening in ADL observed in the RTP group, there is prior evidence that subjects with AD may

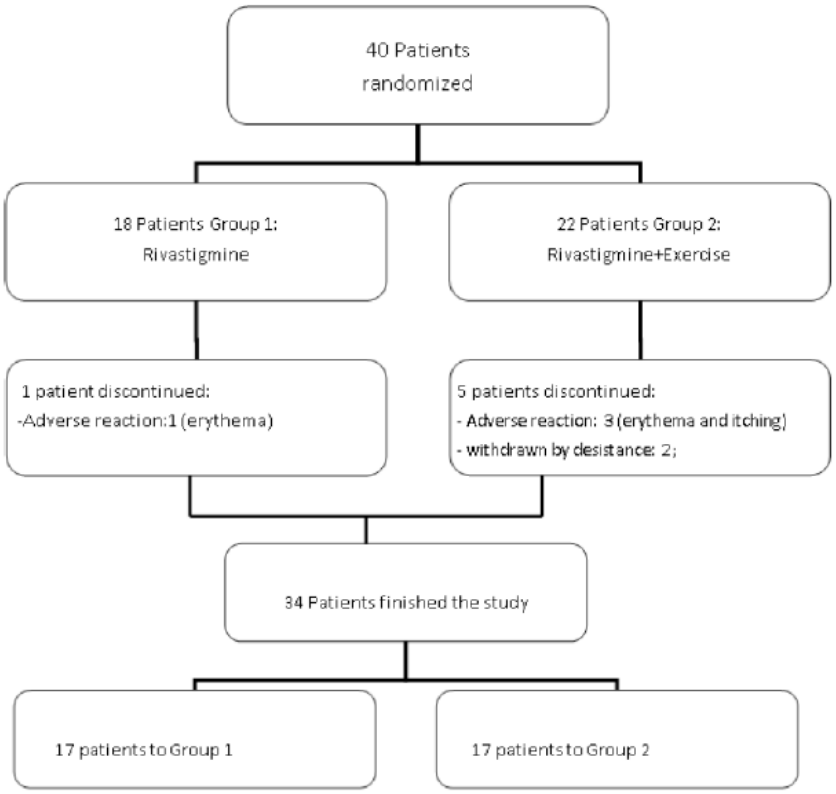

Fig. (1). Trial flowchart.

Table 2. Baseline characteristics of the patients.

	Group 1 (n = 17)	Group 2 (n = 17)	*P value*
Age	74.7 ± 7.4	78.6 ± 8.4	0.157*
Years of education	5.5 ± 4.3	7.2 ± 4.7	0.295*
Disease duration (months)	19.0 ± 12.7	24.9 ± 17.9	0.273*
Sex, n(%)			
Male	5 (29.4)	4 (23.5)	1.000#
Female	12 (70.6)	13 (76.5)	
Comorbidities			
Yes	4 (23.5)	5 (29.4)	1.000#
No	13 (76.5)	12 (70.6)	

* Student's t-test, # Fisher's exact test

Table 3. Outcome assessments for patients and caregivers after interventions.

Variable	Group 1	Group 2	*P* value*	Combined
	m ± dp	m ± dp		
Quality of Life of patients				
Before	33.7 ± 5,3	32.1 ± 4.1	0.339	32.9 ± 4.7
After	33.8 ± 3.2	34.6 ± 4.1		34.2 ± 3.6
P value	0.774	**0.049**		0.090
Difference	0.06 ± 3.80	2.47 ± 4.45	0.140	
Quality of Life of the caregiver				
Before	39.4 ± 5.3	38.9 ± 5.9	0.973	39.1 ± 5.6
After	44.8 ± 4.9	45.8 ± 4.3		45.3 ± 4.5
P value	**<0.001**	**<0.001**		**<0.001**
Difference	5.35 ± 4.00	6.94 ± 5.54	0.375	
Mini-Mental State Examination				
Before	20.8 ± 4.0	20.1 ± 4.5	0.454	20.4 ± 4.2
After	21.1 ± 4.6	21.0 ± 4.7		21.1 ± 4.6
P value	0.587	0.179		0.196
Difference	0.35 ± 3.32	0.94 ± 2.93	0.563	
Activities of Daily Living				
Before	24.6 ± 16.0	39.2 ± 14.7	**0.013**	31.9 ± 16.8
After	32.9 ± 15.5	38.8 ± 20.4		35.9 ± 18.1
P value	**0.009**	0.981		0,063
Difference	8,35 ± 11,84	-0,47 ± 15,27	0,062	
TUG				
Before	14.5 ± 4.9	15.0 ± 5.2	1.000	14.7 ± 5.0
After	12.9 ± 4.2	15.0 ± 5.6		13.9 ± 5.0
P value	**0.016**	0.831		0.076
Difference	-1.59 ± 2.35	0.00 ± 1.73	0.062	

* Student's t-test, TUG: Time Up and Go test

benefit from physical exercises in order to improve ADL [23]. The reduced number of patients in each intervention arm might have limited the results and was not sufficient to show differences between groups. Nevertheless, this remains a matter of discussion and further trials in this way would help to solve this issue. Cognition, as measured by MMSE remained stable and similar in both groups. These results are similar to those reported in a systematic review [23] and whether physical exercise can improve cognitive functions in AD patients remains unclear.

We demonstrated that the level of dependence in ADL is unrelated to cognitive scores in these patients. The decline in ADL observed in the RTP group may point out that despite the absence of cognitive improvement, physical exercises may improve physical capacity and interferes positively in daily abilities of these patients [8].

Increases in QOL of AD patients who underwent physical exercise associated with RTP are not consistent with recent systematic reviews that reported no benefit of physical exercise on QOL in patients with dementia [11, 24]. It should be noted that many of the studies included in the review did not describe properly the type of dementia or the drugs prescribed. Furthermore, the majority of participants in these previous studies consisted of institutionalized elderly subjects who were not assisted closely by a caregiver. In this study, patients were in early stages of AD, well established in a pharmacological treatment protocol, lived in their community and had responsible caregivers. These aspects may have interfered positively, thereby diminishing possible factors that could limit interpretation of results.

As improvement in QOL was not associated with cognitive or ADL changes, other factors may have influenced this result, such as changes in mood and behavior. In a randomized clinical trial, Stella *et al.* observed that an aerobic exercise program that involved flexibility, strength and functional balance components decreased the neuropsychiatric symptoms of patients with mild to moderate AD and reduced their caregiver burden [25].

The improvement in QOL for caregivers in both groups may be related to an indirect impact of the regular use of RTP in these patients. During the study, monitoring and attention that was given to these caregivers by the rehabilitation staff (doctors, nurses, and physical therapists) may also have influenced the QOL of these individuals.

There is no prior evidence that RTP is associated with improvement in functional mobility. Further studies are necessary to confirm these results.

This study has limitations that impair extrapolation of results. The small sample size may have influenced the magnitude of the difference and resulted in a lower statistical power. The tool used to assess cognition (MMSE) is extremely sensitive as a screening test for dementia. However, it is not the ideal instrument to assess cognition in clinical trials, as there are other specific and refined tests for dementia. In conclusion, the association between physical exercises and RTP improves QOL in patients with AD and there is a possible positive effect of physical exercises in ADL in this group of patients. However further trials are necessary to confirm these results.

This trial is registered at ClinicalTrials.gov under the number NCT01183806.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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Declared none.

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Artigo N^{0}3

Tolerability and compliance of rivastigmine transdermal patch in subjects with Alzheimer`s disease

Artigo submetido à revista: Arquivos de Neuro-psiquiatria

Tolerability and compliance of rivastigmine transdermal patch in subjects with Alzheimer`s disease

Rivastigmine transdermal in AD

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Introduction: Rivastigmine transdermal patch (RTP) was developed to reduce frequent adverse events (AE) related to cholinesterase inhibitors mechanisms of action, mainly gastrointestinal (GI) such as nausea and vomiting, which may interfere with compliance and efficacy. However, skin-site application effects such as erythema and pruritus are frequent in patch presentation and severity of lesions may suffer influence from subjects characteristics and caregivers attention.

Objective: The aim of this study was to determine the frequency and severity of skin-site application events due to RTP treatment in subjects with AD and poor nutritional status and skin hygiene

Methods: Patients with mild to moderate diagnosis of AD and indication of treatment with cholinesterase inhibitors were enrolled in this open-label trial. Naïve patients who initiated treatment with RTP or switched from oral presentation to RTP were included and evaluated for AE and drug compliance for 12 weeks. Study assessments were performed every 4 weeks. Significance level was established at 5%.

Results: Ninety-one patients were evaluated for AE and we observed a high frequency of skin site-application lesions, specially itching and severe dermatitis (31%). Frequency of GI effects, such as nausea and vomiting were low, however, one patient in the path presentation developed esophagitis and gastric ulcer that was considered related to RTP use. This patient was naïve for cholinesterase inhibitors use and did not have gastritis or another risk factor for gastric ulcer. One percent of our population presented with poor nutritional status and skin hygiene conditions were inappropriate in 64%.

Conclusions: Our results suggest that specific characteristics of some populations may interfere in patient's tolerability and compliance, due to higher frequency of AE not demonstrated in previous trials. Nutritional status and skin conditions in AD patients treated with RTP should be take into consideration, as compliance and efficacy may be compromised in these patients. Further studies are necessary to reassure these results.

Keywords: Alzheimer's disease; Rivastigmine; Transdermal patch; Skin/adverse effect; Safety Management.

Resumo

O objetivo deste estudo foi determinar a frequência e gravidade dos eventos adversos (EA) na aplicação Rivastigmina transdérmica (RTP) em pacientes com doença de Alzheimer (DA). Pacientes com diagnóstico de DA leve e indicação de tratamento com inibidores da colinesterase foram incluídos neste ensaio clinico. Noventa e um pacientes foram avaliados quanto aos EA, sendo observada uma alta freqüência de lesões cutâneas no local da aplicação, prurido e dermatite severa (31%). Um paciente apresentou ulcera gástrica mesmo sem história pregressa de gastrite, ulcera gástrica ou uso de anticolinesterásicos. Nossos resultados sugerem que as características específicas de algumas populações podem interferir na tolerabilidade do paciente e adesão, devido à maior freqüência de EA não demonstrados em estudos anteriores. Condições da pele em pacientes com DA tratados com RTP devem ser levadas em consideração, como a adesão e eficácia. Mais estudos são necessários para confirmar esses resultados.

Palavras-chave: doença de Alzheimer; Rivastigmina; Gerenciamento de Segurança; Adesivo Transdérmico/efeito adverso.

Introduction

Alzheimer's dementia (AD) is characterized by progressive deterioration of multiple cognitive domains, where memory, attention, behavior and activities of daily living are progressively affected[1]. In early phases, symptoms may be interpreted as a natural aging process by family members or caregivers, leading to delayed diagnosis and restricting pharmacological and rehabilitation interventions[2].

The main theory associated with the progressive cognitive decline observed in AD is the cholinergic hypothesis, where a deficiency in the biosynthesis of acetylcholine (Ach) could be responsible for progressive deterioration in several cognitive domains[2]. In this way, the development of drugs that restores cholinergic pathways through inhibition of Ach degrading enzyme remains the major target in order to improve cognitive performance in subjects with AD[3].

Cholinesterase inhibitors (ChI) are associated with adverse events (AE) that may interfere with compliance, treatment efficacy and indirectly, increase caregiver's burden[3]. Several drugs with theses mechanisms of action were developed to treat mild to moderate AD[4]. However, oral administration is generally associated with gastrointestinal (GI) AE such as nausea and vomiting, due to rapid increase in drug blood levels[4]. Transdermal administration was developed to minimize GI adverse events and

rapid increase in blood peaks, leading to continuous and smooth drug delivery, diminishing AE linked to drug fluctuations in the blood[4]. The most frequent AE associated with rivastigmine transdermal patch (RTP) besides GI events are skin site-application lesions, specially pruritus and erythema[4].

Several trials demonstrated the efficacy and safety of RTP in AD treatment[4]. They also highlight skin-site application effects but they are frequently mild to moderate and do not interfere with compliance and patient tolerability when compared to placebo or rivastigmine oral presentation[4].

In this way, the aim of this study was to determine the tolerability and compliance of rivastigmine transdermal patch in subjects with Alzheimer`s disease.

Methods

Study design and participants

An open label trial was developed from February to April 2011 in a reference center for dementia diagnosis and treatment in Northeastern, Brazil. Inclusion criteria were i) subjects with mild to moderate AD diagnosed by a certificated neurologist; ii) age superior to 55 years; iii) indication of CI treatment. Exclusion criteria were i)other neurologic or psychiatric diseases associated; ii) previous RTP treatment; iii)chronic diseases that could affect subject adhesion to treatment; iv) Mini Mental State Exam (MMSE) score less than 12, that could interfere with study procedures.

Study procedures and outcomes

Subjects who met eligibility criteria and their respective caregivers (established as the first accompanying person in the baseline visit, or someone else indicated by a family member) were included in the study. Patients who initiated treatment with RTP or with previous indication to switch from oral to patch presentation were included in the study. In each study visit the following scales were applied for patients and caregivers: MMSE, quality of life scale (QOL) and a standardized drug compliance questionnaire.

Study assessments were performed every 4 weeks for 12 weeks after intervention. This study was approved by the local Ethical Committee, and all procedures were performed after signing a consent form.

Statistical analysis

Mean and standard deviation (SD) of continue variables were calculated, and normality of the sample was tested using the Kolmogorov-Smirnov test. Fisher's exact test was used to compare frequency ratios and proportions between the categorical variables, and Student's t-test was used for comparing the averages, the medians and SD of continuous variables.

Statistical significance was set at 5%. The data were analyzed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Baseline characteristics of 91 study participants included are presented in table 1. There was a female predominance, and a family member caregiver assisted the majority of patients.

When considering adverse events, we observed a high frequency of skin site-application lesions, specially itching and severe dermatitis (31%) (Table 2). Figures 1 and 2 show the most common presentation of skin lesions observed in our population. Frequency of GI effects, such as nausea and vomiting were low, however, 1 patient in the path presentation developed esophagitis and gastric ulcer during the study. This patient was naïve for CI use and did not have gastritis or another risk factor for gastric ulcer (figure 3)

Table 1 - Characteristics of patients in rivastigmine transdermal patch treatment with Alzheimer's disease and caregivers.

Patients	n (%)
Gender	
Male	25 (27.5)
Female	66 (75.5)
Marital status	
Single	38 (41.7)
Married	24 (27.5)
Widow	29 (30.8)
Origin	
Salvador	78 (85.7)
Bahia	10 (11)
Other state	3 (3.3)
Occupation	
Retired	86(94.5)
Unemployed	1 (1)
Actual work	3 (3.3)
Inactive	1 (1)
Family composition	
Home alone	37 (41.7)
Live with Family	48 (51,6)
Paid caregivers	3 (3.3)
Caregiver availability to bring patients to medical consults	
Available	85 (93.4)
Not available	6 (6.6)
Other pathology	
Hypertension	60 (67)
Diabetes	12 (13.2)
Respiratory allergies	3 (3.3)
GI disease *	0 (0)
Respiratory disease	0 (0)
Caregiver	**n (%)**
Relationship to patient	
Spouse	17 (18.7)
Offspring	56 (62.6)
Familiar	4 (4.4)
Caregiver	4 (4.4)
Have caregiver	
Yes	82 (90)
No	9 (10)
Gender	
Male	27 (34.2)
Female	55 (65.8)
School years	
0-9 years	12 (14.3)
10-13 years	20 (22)
Superior	4 (4.4)

GI-gastrointestinal

Table 2 - Adverse events according to rivastigmine transdermal patch dose.

Adverse reaction	4,6mg	9,6mg	Total	%
Skin lesions (*)	**20**	**08**	**28**	**(31%)**
Skin-site application pruritus	**20**	**08**	**28**	**(31%)**
Orthostatic hypotension	00	01	01	1,1%
Nausea	06	01	07	7,7%
Vomiting	03	00	03	3,3%
Diarrhea	02	00	02	2,2%
Hallucination	01	00	01	1,1%
Disorientation	02	00	02	2,2%
Humor changes	01	00	01	1,1%
Anorexia	00	00	00	
Decreased appetite	01	00	01	1,1%
Dyspepsia	02	00	02	2,2%
Abdominal pain	00	00	00	
Headache	01	00	01	1,1%
Liver dysfunction	00	00	00	
Insomnia	01	00	01	1,1%
Dizziness	00	00	00	
Arrhythmia	01	00	01	1,1%
Cramps	00	00	00	
Diaphoresis	00	00	00	
Syncope	00	00	00	
Low heart rate	00	00	00	
Gastric ulcer (**)	**01**	00	**01**	**1,1%**
Esophagitis (**)	**01**	00	**01**	**1,1%**

(*) Redness in skin-site application associated or not to bruises and local edema

(**) Adverse events presented until 15 days of rivastigmine transdermal patch application. No gastric complaints before medication use

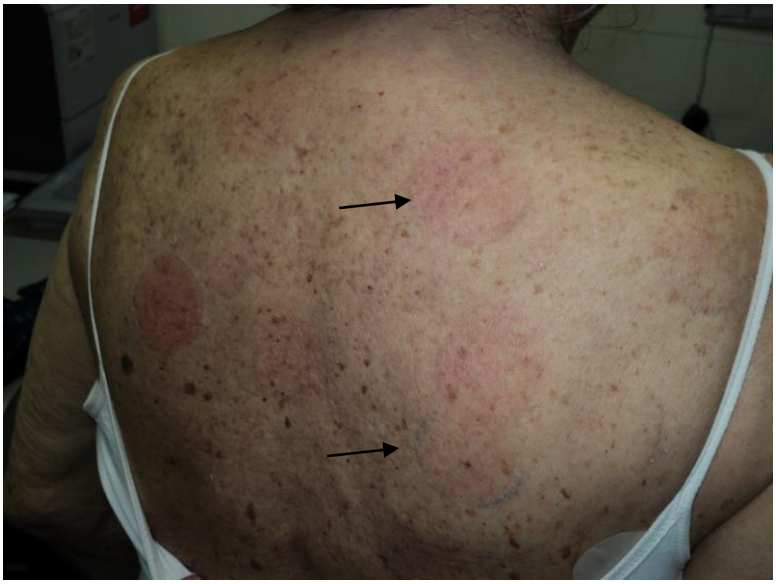

Figure 1: Skin lesions in a patient treated with rivastigmine transdermal patch for 2 months.

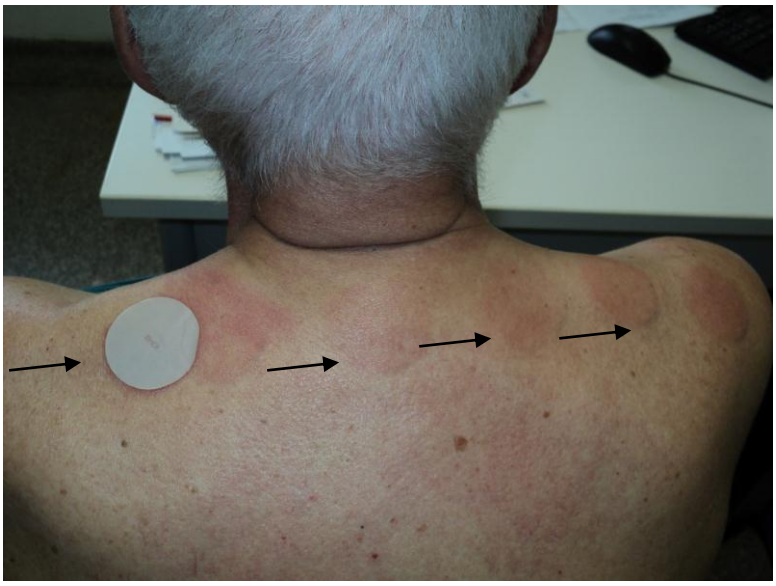

Figure 2: Skin lesions a patient treated with rivastigmine transdermal patch for 1 month.

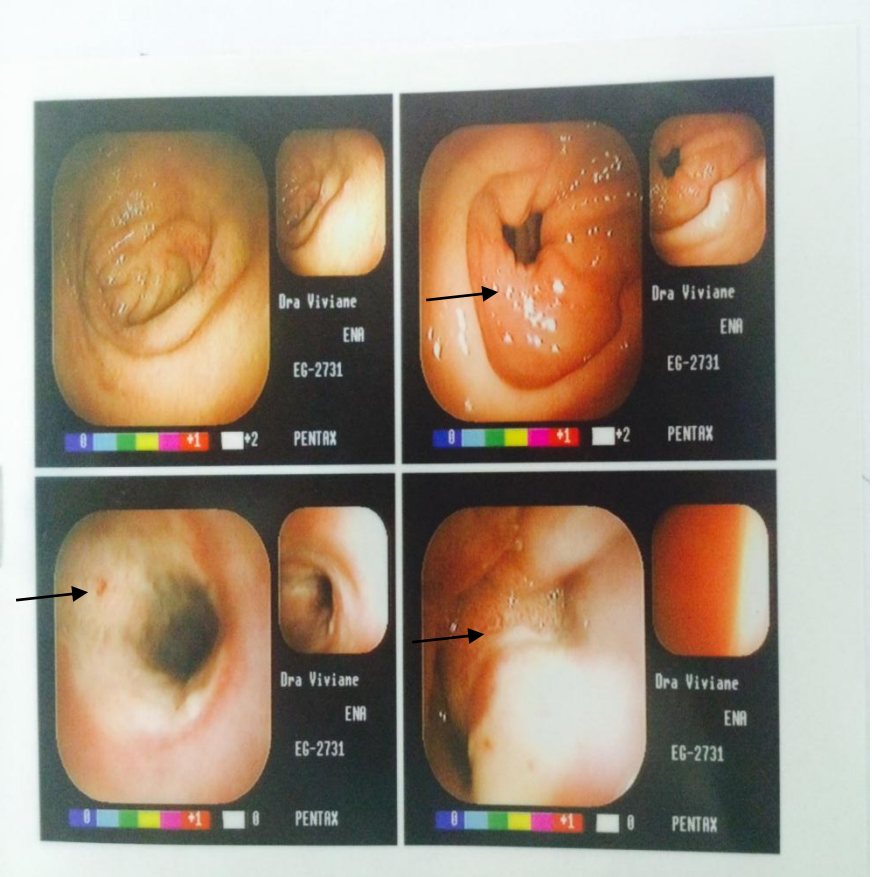

Figure 3: Endoscopy showing gastric ulcer and esophagitis in a patient treated with rivastigmine transdermal patch previously naïve for Alzheimer's disease treatment.

Caregivers were responsible for RTP administration in 96% of patients; however three patients were temporarily withdrawn from intervention due to caregivers relapse. When questioning about disease burden, only 15% were aware of disease characteristics and progression. Only 1 patient discontinued intervention through the study (patient with gastric ulcer) for safety reasons. Even with moderate to severe skin reactions, patients did not discontinued medication, mainly because of caregivers and family member's incentive.

Discussion

Our results showed a high frequency of moderate and severe AE in AD patients using RTP, especially application skin-site dermatitis (31%) and gastric ulcer (01 patient).

Several trials in Europe and US addressed the frequency of AE associated with RTD in several doses[5]. In a trial with 1.195 AD patients treated for 24 weeks with RTP 10 cm^2, 20 cm^2, oral

rivastigmine and placebo[5], they described that subjects treated with presented with lower GI effects than oral rivastigmine or placebo, however there were skin-site application lesions considered mild to moderate in 10% of the patch population, and discontinuation due to skin AE were 2% in both doses of RTP[5]. Schmit et al. in an open-label study with 103 patients from Austria observed mild skin lesions in 23% of the population[6]. González et al. in Spain observed 16.7% of skin lesions in 142 patients analyzed[7]. Lee et al. in a post-hoc analysis of 1.195 patients from IDEAL study described that those subjects with extreme low body weight had the highest percentages of discontinuation in the RTP 9.5mg treatment arm due to skin lesions[8]. He also emphasize that the majority are mild and can be minimized with simple skin care.

Our results showed some divergent results, specially a high frequency of moderate to severe skin-site application reactions, such as dermatitis, intense pruritus and erythema. Also, gastric ulcer considered related to RTP use was observed, and after discontinuation of treatment, the patient became cured.

The results showed in this study suggest that special characteristics of some populations may interfere with treatment efficacy due to severe AE not observed in previous trials that did not control for these variables. Nurse's orientations to patients and caregivers, may enhance tolerability and increase compliance in AD patients treated with RTP.

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CONFIRMAÇÃO DA SUBMISSÃO A REVISTA ARQUIVOS DE NEURO-PSIQUIATRIA

Arquivos de Neuro-Psiquiatria

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5 CONCLUSÕES

- A associação das atividades físicas ao uso da medicação anticolinesterásica melhorou a qualidade de vida destes pacientes, verificando-se assim que a melhora da resposta da medicação pode ser intensificada pela associação com a fisioterapia.
- Elevada frequência de eventos adversos dermatológicos, principalmente eritema, edema e prurido no local de aplicação da medicação transdérmica associada ao baixo índice nutricional e as precárias condições de higiene podem ter interferido no tratamento e no aparecimento dos eventos dérmicos.
- A participação ativa dos cuidadores e familiares são de extrema significância para o tratamento dos pacientes, sendo uma parte fundamental no tratamento, estando associada à adesão ao tratamento.
- Apesar da gravidade das reações adversas, não foi evidenciada interferência destes eventos na adesão ao tratamento.

6 CONSIDERAÇÕES FINAIS

Este estudo tem relevância quanto à observação das reações adversas relatadas na literatura e as observadas nos pacientes residentes na cidade de Salvador. Foi possível verificar que estão acima dos padrões estabelecidos pelas pesquisas realizadas nos países europeus, americano, canadense e australiano. Assim, podemos inferir que as condições climáticas, metabólicas e o nível de dependência agem diretamente nas reações adversas de medicações transdérmicas, já que as condições ambientais são distintas das reportadas pelos estudos.

A hidratação da pele e nutrição podem ter influenciado na absorção da medicação e no aparecimento dos efeitos adversos, como reportado no artigo 2 da pesquisa, que podem estar associados as condições climáticas da cidade.

A presença dos efeitos adversos não influenciou diretamente na adesão dos pacientes, sendo a adesão dos familiares ao tratamento um dos maiores ícones para a verificação do uso da medicação.

O fator que também influenciou foi o fornecimento da medicação pelos órgãos públicos e falta de regularidade na dispensação da medicação.

Os fatores sociais estão diretamente relacionados com o uso das medicações transdérmicas, onde a disponibilidade dos cuidadores e familiares podem impactar diretamente na presença de reações dérmicas nestes pacientes.

Assim, medidas voltadas para a educação dos cuidadores e adesão da família devem ser valorizadas e incentivadas e o comprometimento dos órgãos fornecedores deve ser intensificado.

7 PERSPECTIVAS DE ESTUDOS:

O presente trabalho mostrou a presença de coeficientes mais expressivos de efeitos adversos que os desenvolvidos em outros países, verificando a necessidade de estudos sobre a área na nossa localidade, já que os fatores econômicos, culturais, climáticos e demográficos são distintos dos observados nos demais estados.

Diante disto, verificou-se a necessidade de estudo destes pacientes, já que a qualidade de vida pode ser afetada diretamente com alterações significativas para este grupamento.

São necessários outros estudos relacionados com este tema para verificarmos as características dos pacientes brasileiros em relação ao uso de anticolinesterásicos.

Diante a diversidade da nossa população, que apresenta diferentes níveis nutricionais e de hidratação, o grupo de pesquisa em demência de Alzheimer pretende desenvolver um ensaio clínico abordando pacientes com IMC baixo, normal, sobrepeso, com peles pouco hidratadas e hidratadas.

8 REFERÊNCIAS DA INTRODUÇÃO

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ANEXOS

ANEXO 1 - PARECER DO COMITÊ DE ÉTICA (scaneado)

COMITÊ DE ÉTICA EM PESQUISA – CEP/MCO/UFBA
MATERNIDADE CLIMÉRIO DE OLIVEIRA
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IORG0003460. IRB00004123 June 30, 2012 – January 31, 2014
Assurance FWA00002471, May 31, 2011 – February 08, 2014

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PARECER/RESOLUÇÃO N.º 007/2011

Registro CEP. 002/11. (Este número, bem como o do Parecer acima, devem ser citados nas correspondências referentes a este projeto).

Título do Projeto: "Impacto da rivastigmina patch na qualidade de vida dos pacientes com doença de Alzheimer e seus cuidadores".

Patrocínio/Financiamento: A ser subsidiado pelo CITECS – Ciências, Inovação e Tecnologia em Saúde.

Pesquisadora Responsável: Ana Cristina Feres, Pesquisadora da Divisão de Neurologia e Epidemiologia da Universidade Federal da Bahia, Mestre orientada por Ailton de Souza Melo, Doutor, Livre Docente da UFBA. Equipe relacionada no Projeto. "Curricula Vitae" apensos.

Instituição: Associação Bahiana de Parkinson e Alzheimer - ABAPAZ

Área do Conhecimento: 4.00, Ciências da Saúde; 4.01, Medicina; Nível: Terapêutico; Grupo: III

Objetivos: Avaliar o impacto da rivastigmina patch na qualidade de vida dos pacientes com doença de Alzheimer e dos seus cuidadores. Avaliar a adesão dos pacientes e acompanhantes ao regime terapêutico. Verificar os eventos adversos apresentados com o uso diário desta droga.

Sumário: Com o aumento da expectativa de vida pelas mudanças na qualidade de vida e com desenvolvimento na área da saúde, o número de enfermidades que acometem a população idosa está crescendo vertiginosamente. Estudos têm sido realizados quanto à doença de Alzheimer a nível mundial, sendo abordado tratamento medicamentoso para esta patologia. Cinqüenta (50%) a 70% das pessoas com demência têm a doença de Alzheimer. As alterações cognitivas estão relacionadas a déficit de neurotransmissores cerebrais, como acetilcolina, noradrenalina e serotonina. Atualmente dispõe-se de tratamentos farmacológicos como rivastigmina oral, donepezila, galantamina e mais recentemente a rivastigmina patch. A medicação rivastigmina patch foi liberada para uso, existindo, no entanto alguns questionamentos quanto aos efeitos colaterais freqüentes (por volta de 4%) em relação à mesma droga via oral. Em análise dos potenciais benefícios da rivastigmina patch em relação à mesma droga administrada via oral, observa-se em revisão realizada de 1987 a 2007 que os pacientes apresentavam melhor tolerabilidade a forma patch e os cuidadores apontaram os benefícios desta apresentação devido a diminuição dos efeitos colaterais em relação a forma oral e melhor forma de administração da droga. Cem (100) pacientes terão a qualidade de vida (Minimental, Escala de qualidade de vida para doença de Alzheimer – pacientes e acompanhantes), os efeitos colaterais contabilizados (fotografados) avaliados no tempo zero (antes da troca), 1, 2,3 e 6 meses após a troca ou introdução da medicação.

COMITÊ DE ÉTICA EM PESQUISA – CEP/MCO/UFBA
MATERNIDADE CLIMÉRIO DE OLIVEIRA
UNIVERSIDADE FEDERAL DA BAHIA
IORG0003460. IRB00004123 June 30, 2012 – January 31, 2014
Assurance FWA00002471, May 31, 2011 – February 08, 2014
Rua do Limoeiro, nº 137 – Nazaré Cep: 40.005-150 – Salvador-Bahia
Telefax.: (71) 3283-9210/9211 e-mail: cepmco@ufba.br/cepmco@gmail.com

Critérios de inclusão: Pacientes com doença de Alzheimer de leve a moderado, acima de 55 (cinqüenta e cinco) anos, tiverem mudado para a rivastigmina patch por eventos adversos da droga anticolinesterásica em uso (donepezila, rivastigmina ou galantamina) ou iniciarem a terapêutica com rivastigmina patch, de acordo com o protocolo do Ministério da Saúde e não ter feito uso de anticolinesterásicos orais há menos de quinze dias. **Critérios de exclusão:** Apresentem outras doenças neurológicas ou psiquiátricas associadas, doenças crônicas, que possam afetar a qualidade de vida ou a adesão terapêutica e os pacientes que apresentarem mini-mental inferior a 12 (excluídos pelos parâmetros estabelecidos pelo Ministério da Saúde, para a inclusão do paciente no programa de medicação excepcional de Alzheimer).
Análise de riscos: Risco mínimo de coleta de dados.
Retorno de benefícios para o sujeito e/ou para a comunidade: A comunidade pode se beneficiar pelo conhecimento adquirido do novo tratamento dos pacientes e provavelmente uma perspectiva de manejo melhor a partir das conclusões do estudo. Os sujeitos de pesquisa podem se beneficiar com um melhor manejo futuro de suas manifestações.
Existem dois **Termos de Consentimento Livre e Esclarecido** (TCLE): um para o cuidador e outro para o sujeito.
Os TCLEs utilizam termos simples para tal população. Contém justificativa, descreve os objetivos, procedimentos, riscos, benefícios, a participação voluntária, a retirada de dúvidas e a compensação de danos. A gratuidade da intervenção, bem como a confidencialidade das informações colhidas e privacidade dos dados, durante e após o protocolo estão asseguradas. O endereço e telefone ou forma de contatar os investigadores, bem como o Comitê de Ética em Pesquisa estão citados adequadamente.

Comentários: O protocolo está bem argumentado, seus fins são éticos e o conhecimento advindo pode trazer benefícios aos pacientes e a comunidade. **Protocolo aprovado.**

Salvador, 24 de fevereiro de 2011

Professor, Doutor Eduardo Martins Netto
Coordenador – CEP/MCO/UFBA

Observações importantes. Toda a documentação anexa ao Protocolo proposto e rubricada pelo (a) Pesquisador (a), arquivada neste CEP, e também a outra devolvida com a rubrica da Secretária deste (a) ao (à) mesmo (a), faz parte intrínseca deste Parecer/Resolução e nas "Recomendações Adicionais" apensas, **bem como a impostergável entrega de relatórios parciais e final como consta nesta liberação,** (Modelo de Redação para Relatório de Pesquisa, anexo).

ANEXO 2 - TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Paciente

TÍTULO DO PROJETO: Impacto da rivastigmina *patch* na qualidade de vida dos pacientes com doença de Alzheimer e seus cuidadores.

INSTITUIÇÕES: Divisão de Neurologia e Epidemiologia (DINEP/UFBA) e Associação Bahiana de Parkinson e Alzheimer – ABAPAZ

Pesquisador responsável: Ana Cristina Feres

Orientador: Ailton Melo

O presente termo de consentimento refere-se a um convite a participação do (a) Sr (a) _____, ou sob a responsabilidade do seu presente legal Sr (a) _____ a participar como sujeito da pesquisa intitulada **"Impacto da rivastigmina patch na qualidade de vida dos pacientes com a doença de Alzheimer e seus cuidadores".** A pesquisa tem como objetivo avaliar o impacto da rivastigmina patch (adesivo) na qualidade de vida dos pacientes com doença de Alzheimer e seus cuidadores. Será realizada uma avaliação no início do uso da rivastigmina patch, 01 mês e 02 meses de uso desta droga. Nestas avaliações os participantes responderão um questionário que avalia qualidade de vida, o mini-exame do estado mental do pacientes e o formulário de avaliação da adesão ao tratamento. Estes questionários não trarão nenhum dano à saúde e nem prejuízo ao paciente, tendo apenas o objetivo proposto acima. Não será realizado nenhum procedimento invasivo nos pacientes ou nos cuidadores. Este termo será lido e esclarecido verbalmente antes da sua entrega e analise pelos indivíduos envolvidos.

Durante estas avaliações será realizado o registro fotográfico no caso de observações de lesão de pele ou outra reação adversa registrada através de filme. Caso ocorra presença de reação adversa ou não adesão do paciente e / ou acompanhante o caso será repassados a equipe medica para estabelecimento de conduta apropriada.

Sua identidade será preservada e não haverá nenhuma forma de pagamento pela sua participação no estudo e caso o (a) Sr (a) se recuse a participar, sua vontade será respeitada. Esta pesquisa trará maior conhecimento sobre o tema abordado.

Se houver dúvidas sobre os seus direitos como participante desta pesquisa entre em contato com o comitê de ética da Maternidade Climério de Oliveira na rua do Limoeiro, 137 – Nazaré ou pelo telefone 3283-9274.

Assim, se o (a) Sr (a) aceitar participar desta pesquisa, preencher os espaços abaixo:

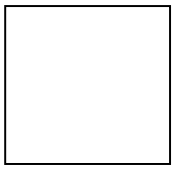
Eu, _____RG_____

Fui devidamente esclarecido (a) quanto ao Projeto de Pesquisa supracitado e aceito o convite para participar.

_____,_____de_____ de 2011

_____

Assinatura do Paciente ou responsável



Impressão digital

_____

Assinatura do pesquisador: Ana Cristina Feres

Telefone: 8756-6076

Este Termo será preenchido em duas vias: uma será mantida com o pesquisador responsável e a outra será entregue ao paciente.

ANEXO 3 - TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO – CUIDADOR

TÍTULO DO PROJETO: Impacto da rivastigmina *patch* na qualidade de vida dos pacientes com doença de Alzheimer e seus cuidadores.

INSTITUIÇÕES: Divisão de Neurologia e Epidemiologia (DINEP/UFBA) e Associação Bahiana de Parkinson e Alzheimer – ABAPAZ

Pesquisador responsável: Ana Cristina Feres

Orientador: Ailton Melo

O presente termo de consentimento refere-se a um convite a participação do (a) Sr (a) _____, ou sob a responsabilidade do seu presente legal Sr (a) _____ a participar como sujeito da pesquisa intitulada **"Impacto da rivastigmina patch na qualidade de vida dos pacientes com a doença de Alzheimer e seus cuidadores".** A pesquisa tem como objetivo avaliar o impacto da rivastigmina patch (adesivo) na qualidade de vida dos pacientes com doença de Alzheimer e seus cuidadores. Será realizada uma avaliação no início do uso da rivastigmina patch, 01 mês e 02 meses de uso desta droga. Nestas avaliações os participantes responderão um questionário que avalia qualidade de vida, o mini-exame do estado mental do pacientes e o formulário para avaliação da adesão ao tratamento. Estes questionários não trarão nenhum dano à saúde e nem prejuízo ao paciente, tendo apenas o objetivo proposto acima. Não será realizado nenhum procedimento invasivo nos pacientes ou nos cuidadores. Este termo será lido e esclarecido verbalmente antes da sua entrega e analise pelos indivíduos envolvidos.

Durante estas avaliações será realizado o registro fotográfico no caso de observações de lesão de pele ou outra reação adversa registrada através de filme. Caso ocorra presença de reação adversa ou não adesão do paciente e / ou acompanhante o caso será repassados a equipe medica para estabelecimento de conduta apropriada.

Sua identidade será preservada e não haverá nenhuma forma de pagamento pela sua participação no estudo e caso o (a) Sr (a) se recuse a participar, sua vontade será respeitada. Esta pesquisa trará maior conhecimento sobre o tema abordado.

Se houver dúvidas sobre os seus direitos como participante desta pesquisa entre em contato com o comitê de ética da Maternidade Climério de Oliveira na rua do Limoeiro, 137 – Nazaré ou pelo telefone 3283-9274.

Assim, se o (a) Sr (a) aceitar participar desta pesquisa, preencher os espaços abaixo:

Eu, _____RG_____

Fui devidamente esclarecido (a) quanto ao Projeto de Pesquisa supracitado e aceito o convite para participar.

_____,_____de_____ de 2011

_____

Assinatura do Paciente ou responsável

Impressão digital

_____

Assinatura do pesquisador: Ana Cristina Feres

Telefone: 8756-6076

Este Termo será preenchido em duas vias: uma será mantida com o pesquisador responsável e a outra será entregue ao paciente.