Patient Preference and Adherence

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ORIGINAL RESEARCH

Clinicians' Perspectives of Twice-Weekly Rivastigmine Patches for Alzheimer's Disease Treatment in Spain: The VIITAL 2S Study

Gerard Piñol-Ripoll[1,2], Mario Salas Carrillo[3,4] On behalf of the VIITAL 2S study group

[1]Cognitive Disorders Unit, Hospital Universitari Santa Maria - IRBLleida, Lleida, Spain; [2]Alzheimer's Disease and other Cognitive Disorders Group - Service of Neurology, Hospital Clínic de Barcelona - Fundació Recerca Clínic Barcelona - IDIBAPS, Barcelona, Spain; [3]Cognitive Impairment Unit, Health Research Institute San Carlos (IdISSC), Madrid, Spain; [4]Geriatrics Department, Hospital Clínico San Carlos, Madrid, Spain

Correspondence: Gerard Piñol-Ripoll, Cognitive Disorders Unit, Hospital Universitari Santa Maria, Rovira Roure street, 44, Lleida, 25198, Spain, Tel +34-937-727222, Ext. 173, Email gerard_437302@hotmail.com

Purpose: Administration routes and dosage significantly impact Alzheimer's disease (AD) treatment effectiveness, as compliance in older patients depends on interactions between concomitant treatments, complex dosages, adverse effects, or medication tolerance. This study aims to describe patient and caregiver preferences concerning treatment with rivastigmine twice-weekly transdermal patches from the neurologists' and geriatricians' perspectives.

Methods: VIITAL-2S was an ecological study based on aggregated data. A total of 250 Spanish neurologists and geriatricians answered a survey on the use, adherence, patient and caregiver satisfaction, and safety (skin tolerability) of twice-weekly rivastigmine patches.

Results: Most participating physicians reported having over 11 years of experience in their specialty. According to their responses, patients with AD attending Neurology and Geriatrics were usually in mild-moderate condition, and a mean of 61.4% received rivastigmine. Around 60% of patients lived with a family member, and over 80% had a caregiver, mainly their partner/spouse or other relative. Of note, more than half of patients attending Neurology and nearly 75% of patients in Geriatrics received 4–10 medications daily. Both specialists recommended the transdermal formulation to patients receiving rivastigmine. In 33.8% and 41.0% of patients receiving daily patches, neurologists and geriatricians, respectively, recommended switching to twice-weekly patches, considering higher administration comfort and caregiver preferences. Physicians reported high/very high satisfaction with twice-weekly patches in nearly 80% of patients. Comparing twice-weekly to daily patches, they observed higher comfort, more caregiver satisfaction, and enhanced adherence. Both specialists manifested preferring twice-weekly rivastigmine patches over daily ones, especially to increase caregivers' comfort, for patients without full-week caregiver support, and in cases of poor compliance with previous treatments.

Conclusion: Neurologists and geriatricians consider the twice-weekly rivastigmine patch formulation beneficial for AD treatment in terms of treatment compliance, skin tolerability, satisfaction and comfort for patients and caregivers.

Keywords: Alzheimer's disease, Spain, rivastigmine, transdermal patch, twice-weekly posology, compliance

Introduction

Alzheimer's disease (AD), the most common form of dementia, is a progressive neurodegenerative disease often associated with memory deficits and cognitive decline.[1,2] Given its increasing global tendency and its impact on society and patients who suffer from it, AD is recognized by the World Health Organization as a public health priority.[3] Recent data estimate that 50 million people are currently affected by this disease.[4] Statistical projections suggest that these numbers will triple in 2050 since the main risk factor for AD is age and the population over 65 is growing at an unprecedented rate.[5]

AD pathogenesis is highly complex and still subject to controversy; even though two neuropathological events characterize it: the accumulation of senile plaques, mainly of insoluble beta-amyloid protein, around neurons and glia, and the formation of intracellular neurofibrillary tangles.[6,7]

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The current treatment available for most patients with AD worldwide consists of reducing disease symptoms (symptomatic treatment) with acetylcholinesterase inhibitors (AChEi) and memantine. AChEi increase the availability of acetylcholine at synapses and have been proven very useful in clinical practice, delaying the cognitive impairment of AD, and improving cognitive and behavioral symptoms.[8] The benefits of these inhibitors have been demonstrated in mild to severe AD, with greater evidence in mild to moderate stages. Although they may cause cholinergic side effects, such as cramps in the extremities and gastrointestinal discomfort, they are usually well tolerated, especially if dosing is finely monitored.[9] While some anti-amyloid drugs have recently shown promising results in slowing the progression of AD, there remain many limitations in treating the disease.[10–12] Since AChEi will continue to be indicated for patients receiving anti-amyloid drugs, tools that support adherence and reduce caregiver burden will become increasingly important as AD treatment becomes more complex.

Rivastigmine, a reversible AChEi, is recommended for the treatment of mild to moderately severe AD.[13,14] Since its approval by the European Medicines Agency (EMA) in 1998, different formulations have been developed. Compared to capsules, rivastigmine transdermal patches showed equal efficacy and reduced gastrointestinal adverse events, providing a continuous and easier drug administration method in the treatment of long-term AD.[15] By avoiding gastrointestinal absorption and hepatic first-pass metabolism, transdermal drug delivery reduces the adverse effects related to maximum plasma drug concentrations and promotes patient compliance.[16] This is especially relevant in patients with AD, as most are elderly and frequently polymedicated and/or may have difficulty swallowing.[17]

AD not only affects the patients but also impacts their environment, especially their caregivers. Indeed, dementia is one of the leading causes of dependency among older adults, resulting in substantial medical and care costs that are typically borne by family members.[18–20] Therefore, patient and caregiver perceptions of AD burden and treatment effectiveness are key to improving therapeutic adherence but, despite this, barely investigated. The novel rivastigmine multi-day patch is designed to deliver the drug constantly over a period of up to four days, allowing twice-weekly transdermal posology, and with demonstrated bioequivalence compared to the patch for daily use.[21,22] This may result in better drug adherence (less frequent dose), less patient-caregiver planning, and reduced caregiver burden.[21]

The VIITAL 2S study aims to provide a perspective on patient and caregiver preferences in the use of rivastigmine administered as a twice-weekly transdermal patch, compared to the patch for daily use. Moreover, the management of patients with AD, drug adherence to this posology, and skin tolerability of this method of administration were also evaluated.

Methods

Study Design and Population

VIITAL 2S was an ecological observational study based on aggregated data. The data source was the knowledge and expertise of neurologists and geriatricians with experience treating patients with AD in Spain, collected through a survey. Neurologists and geriatricians from different regions (Autonomous Communities) of the country were invited to participate to obtain a representative sample at the regional and national levels. No data were extracted from clinical records, and all treatments were prescribed under routine clinical practice. Given the retrospective nature of the study, treatments were not altered by the participation of the physicians in the study.

This study was conducted in the Neurology and Geriatrics units of Spanish hospitals, in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and in compliance with European and national regulations. The Ethics Committee of the Hospital Clínico San Carlos (Madrid, Spain) approved the study.

Data Collection and Survey

Data were collected through an online 40-question survey, available in Supplementary Figure 1, and designed to gather information on the management of patients with AD seen in Neurology and Geriatrics units, regarding the use of rivastigmine administered by transdermal patches. In particular, the questionnaire evaluated the adherence and satisfaction of patients and caregivers with the twice-weekly transdermal patch, as perceived by neurologists and geriatricians, as well as the safety (in terms of skin tolerability) of this administration method.

Between February and April 2023, a total of 200 neurologists and 50 geriatricians participated in the study and completed the survey. The geographical distribution of the centers in which they conduct routine clinical practice is listed in Supplementary Table 1.

Statistical Analysis

The sample size calculation was based on the precision of 3.1% (95% confidence interval, CI) considering that a sample size of 1000 random patients (ie four patients per participating physician) would be sufficient to estimate the percentage of patients in each category of the questions and a missing data rate of ≤5%, resulting in an estimated sample of 250 participants.

A descriptive statistical analysis of the responses to the survey was performed, including the calculation of frequencies and valid percentages for qualitative variables referring to the experience of the participating physicians; and measures of central tendency and dispersion (mean and standard deviation [SD], median and interquartile range [IQR]) for quantitative variables in the case of questions referring to the frequency of patients. Those data related to the number of patients who met a certain question were transformed into percentages, and average percentages (and SD) are shown. All statistical analyses were conducted using the SAS system, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Participating Physicians

As shown in Table 1, 32.0% of the neurologists and geriatricians participating in the study had between 11 and 20 years of experience in their specialty, and 43.2% reported having more than 20 years of experience. Most (81.6%) of the participating physicians reported seeing more than 20 patients with AD per month, conducting their follow-up every 3–6 months in more than half of the cases (56.4%). Almost all surveyed physicians (98.4%) carry out their follow-ups through face-to-face visits with patients with AD, although 61.6% of them use occasional telematic support (via e-mail, phone, video call, etc).

Table 1 Characteristics of the Participating Physicians

Study Parameter	Neurologists, n (%) N=200	Geriatricians, n (%) N=50	Total, n (%) N=250
Years of experience			
1–5 years	27 (13.5)	3 (6.0)	30 (12.0)
6–10 years	26 (13.0)	6 (12.0)	32 (12.8)
11–20 years	69 (34.5)	11 (22.0)	80 (32.0)
>20 years	78 (39.0)	30 (60.0)	108 (43.2)
Number of patients with AD seen in the last month			
Less than 10	4 (2.0)	0 (0.0)	4 (1.6)
10–20 patients	36 (18.0)	6 (12.0)	42 (16.8)
More than 20	160 (80.0)	44 (88.0)	204 (81.6)
Frequency of follow-up of patients with AD			
Every less than 3 months	2 (1.0)	2 (4.0)	4 (1.6)
Between 3 and 6 months	101 (50.5)	40 (80.0)	141 (56.4)
Between 7 and 12 months	96 (48.0)	8 (16.0)	104 (41.6)
Every more than 12 months	1 (0.5)	0 (0.0)	1 (0.4)
Follow-up mode			
In-person visits	79 (39.5)	13 (26.0)	92 (36.8)
Normally in person, with occasional telematic support	119 (59.5)	35 (70.0)	154 (61.6)
Normally by remote visits, with some in-person	2 (1.0)	2 (4.0)	4 (1.6)
Remote visits	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: AD, Alzheimer's disease; n, number of physicians choosing this option; N, total of participating physicians.

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Treatment of Patients with AD

According to the responses provided by the neurologists and geriatricians, a mean (SD) of 94.3% (14.5) of patients received specific pharmacologic treatment for AD. In almost half of the patients (47.2%), this treatment started during the first three months from the diagnosis of AD. Rivastigmine was the drug of choice in a mean (SD) of 61.4% (22.5) of patients with AD, followed by donepezil (23.9% [18.2]), memantine in combination with an AChEi other than rivastigmine (8.8% [16.5]), memantine alone (3.8% [9.8]), and galantamine (2.1% [7.0]) (Figure 1A).

Overall, the participating specialists reported that they recommended treatment with rivastigmine to a median (IQR) of 100.0 (50.0–150.0) patients with AD during the last year. Most of them recommended this treatment considering their clinical experience with the medication (88.4%), the effectiveness of rivastigmine for cognitive and behavioral symptoms (85.2% and 78.4%, respectively), and rivastigmine's safety profile (75.2%), among other relevant aspects (Figure 1B).

Profile of Patients with AD Seen at Neurology and Geriatrics Services and Treated with Rivastigmine, and Profile of Their Caregivers

When asked about the disease and symptoms, the neurologists reported that around 80.0% of patients with AD under treatment with rivastigmine were in mild to moderate condition, and 53.4% suffered a combination of cognitive and neuropsychiatric symptoms. From the point of view of the geriatricians, nearly 80.0% of their patients with AD treated with rivastigmine presented mild to moderate stage, while a higher percentage (61.5%) of them suffered a combination of cognitive and neuropsychiatric symptoms. A mean of 51.6% (28.0) of patients seen at Neurology units received 4–10 medications daily, and 3.5% (9.4) received more than 10 medications. Compared to them, the percentage of patients seen in Geriatrics with polypharmacy diagnosis was sharply higher: a mean of 74.5% (21.7) of patients received 4–10 medications daily, and 5.0% (10.1) received more than 10 medications (Table 2).

Moreover, according to both neurologists' and geriatricians' responses, around 60% of patients reside in the home of a family member (62.6% [30.2] as reported by neurologists and 60.5% [31.2] by geriatricians). While 27.3% (30.8) of patients seen at Neurology lived alone at their home, this was reported in less than 20% (19.0% [22.9]) of patients in Geriatrics (Table 2).

As shown in Table 3, more than 80% of patients seen at Neurology and Geriatrics consultations had a caregiver. In most cases, the caregiver of the patient with AD was their partner/spouse (53.6% [20.7] as indicated by neurologists vs 38.5% [26.4] by geriatricians) or another family member. However, geriatricians also reported that 25.5% (23.4) of patients had a professional caregiver. Neurologists reported that around a third (32.5%) of patients lived with their caregiver less than five days a week; of those patients who did not live with their caregiver, around 75% were assisted by

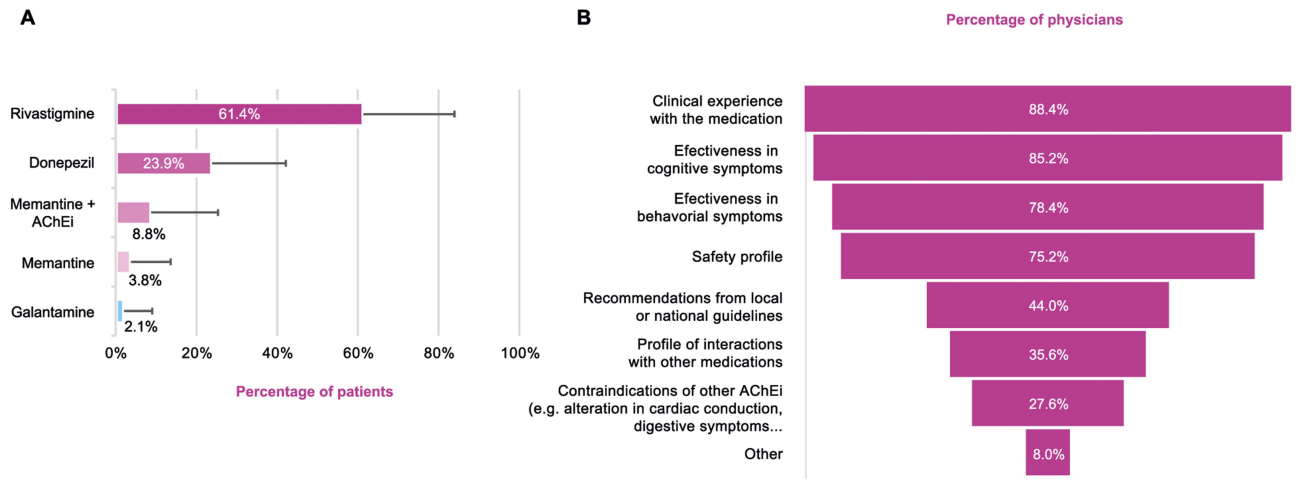

Figure 1 Treatments most frequently recommended to patients with AD and reasons to recommend rivastigmine. (**A**) Percentage of patients receiving the indicated symptomatic treatments for AD. AChEi, acetylcholinesterase inhibitor. (**B**) Percentage of physicians choosing the indicated statements to recommend rivastigmine (multiple-choice question).

Table 2 Profile of Patients With AD Seen at Neurology and Geriatrics Consultations

Patient Characteristics	Patients at Neurology	Patients at Geriatrics
Age, mean (SD) %		
≤65 years	9.5 (14.1)	2.0 (8.9)
65–80 years	64.0 (20.9)	34.0 (28.9)
>80 years	26.5 (20.6)	64.0 (31.2)
Sex, mean (SD) %		
Women	63.8 (17.0)	71.0 (14.6)
Men	36.3 (17.0)	29.0 (14.6)
Stage of AD, mean (SD) %		
Mild	40.8 (20.6)	34.5 (20.1)
Moderate	41.5 (18.3)	44.0 (18.6)
Severe	17.8 (13.9)	21.5 (17.5)
Symptoms of AD, mean (SD) %		
Both cognitive and neuropsychiatric	53.4 (26.8)	61.5 (29.5)
Cognitive	40.1 (24.7)	30.5 (25.9)
Neuropsychiatric	5.9 (12.0)	7.0 (12.4)
Other	0.6 (3.9)	1.0 (5.0)
Concomitant medications, mean (SD) %		
1–3 medications daily	41.5 (28.0)	20.0 (20.8)
4–10 medications daily	51.6 (28.0)	74.5 (21.7)
>10 medications daily	3.5 (9.4)	5.0 (10.1)
Without concomitant treatment	3.4 (10.2)	0.5 (3.5)
Place of residence, mean (SD) %		
Family member's home	62.6 (30.2)	60.5 (21.2)
Alone at their home	27.3 (30.9)	19.0 (22.9)
Residence	10.1 (15.3)	20.5 (24.6)

Abbreviations: AD, Alzheimer's disease; SD, standard deviation.

Table 3 Profile of Caregivers of Patients With AD Seen at Neurology and Geriatrics Consultations

Caregiver Characteristics	Patients at Neurology	Patients at Geriatrics
Profile, mean (SD) %		
Partner/spouse	53.6 (20.7)	38.5 (26.4)
First-degree relative	29.6 (17.6)	32.5 (23.3)
Other family member	1.9 (6.6)	1.5 (6.0)
Professional caregiver	14.5 (16.5)	25.5 (23.4)
Other	0.4 (3.1)	2.0 (6.9)
Days living with the patient, n (%)		
>5 days/week	135 (67.5)	36 (72.0)
3–5 days/week	51 (25.5)	14 (28.0)
1–2 days/week	9 (4.5)	0 (0.0)
Any day	5 (2.5)	0 (0.0)
Time dedicated to assistance*, n (%)		
1–2 hours/day	50 (25.0)	15 (30.0)
3–6 hours/day	77 (38.5)	20 (40.0)
7–15 hours/day	42 (21.0)	10 (20.0)
>15 hours/day	31 (15.5)	5 (10.0)

Note: *In those caregivers who do not live with the patient.
Abbreviations: n, number of physicians choosing this option regarding their patients; SD, standard deviation.

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this figure for at least three hours a day. On the other hand, geriatricians manifested that nearly two-thirds (72.0%) of patients seen at Geriatrics lived with their caregiver more than five days a week.

Rivastigmine Administration and Posology: Physician Preferences

The treatment with rivastigmine was recommended in transdermal patches to a mean of 95.5% (12.2) and 96.5% (10.1) of patients by the neurologists and geriatricians, respectively (Figure 2A and B). Compared to the oral administration of rivastigmine, both specialists valued the comfort of this route of administration (96.0% of geriatricians, 89.0% of neurologists), their experience with the medication (80.0% of geriatricians, 79.0% of neurologists), and the safety profile (78.0% of geriatricians, 69.5% of neurologists) of transdermal patches (Figure 2C).

When asked about the available formulations of rivastigmine transdermal patches, the neurologists recommended the twice-weekly option to a mean of 62.8% (27.6) of their patients (Figure 3A), and they reported recommending the switch from the daily to the twice-weekly patch to a mean of 33.8% (27.4) of patients. Most of the neurologists took into consideration the higher comfort of administration (83.5%), caregiver preferences (70.5%), and potential improvements in drug adherence (47.0%), in those patients to whom they recommended the switch to the twice-weekly patch (Figure 3C).

Geriatricians recommended the twice-weekly posology to a mean of 55.5% (30.8) of their patients (Figure 3B), and they recommended the switch from the daily to the twice-weekly patch to a mean of 41.0% (31.9) of patients. In those cases to whom the switch to the twice-weekly patch was recommended, the participating geriatricians mainly considered its higher comfort of administration (84.0%), caregiver preferences (50.0%), and potential improvements in drug adherence (48.0%) (Figure 3C).

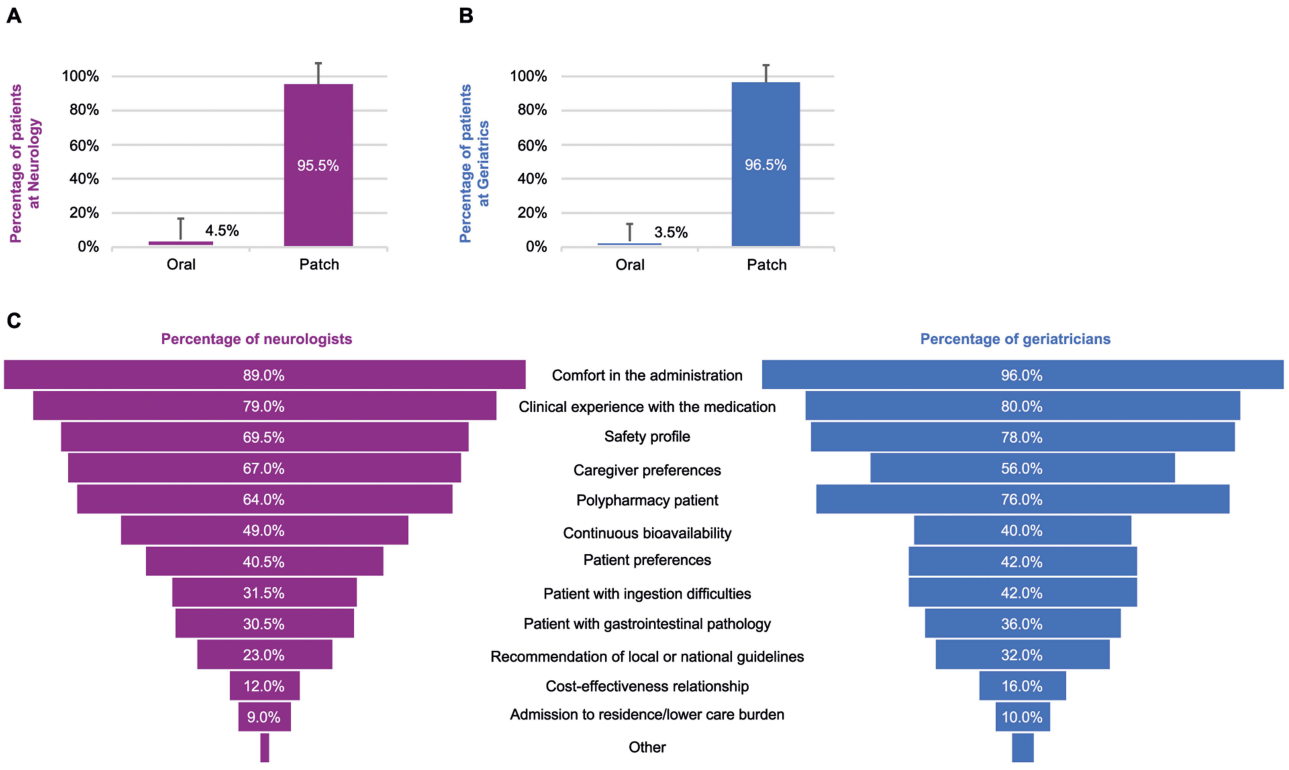

Figure 2 Method of administration of rivastigmine most frequently recommended to patients with AD and reasons to recommend the transdermal patch. (**A**) Percentage of patients with AD to whom neurologists recommended oral administration vs transdermal patches of rivastigmine. (**B**) Percentage of patients with AD to whom geriatricians recommended oral administration vs transdermal patches of rivastigmine. (**C**) Percentage of physicians (neurologists in purple, geriatricians in blue) choosing the indicated statements regarding rivastigmine patch recommendations (multiple-choice question).

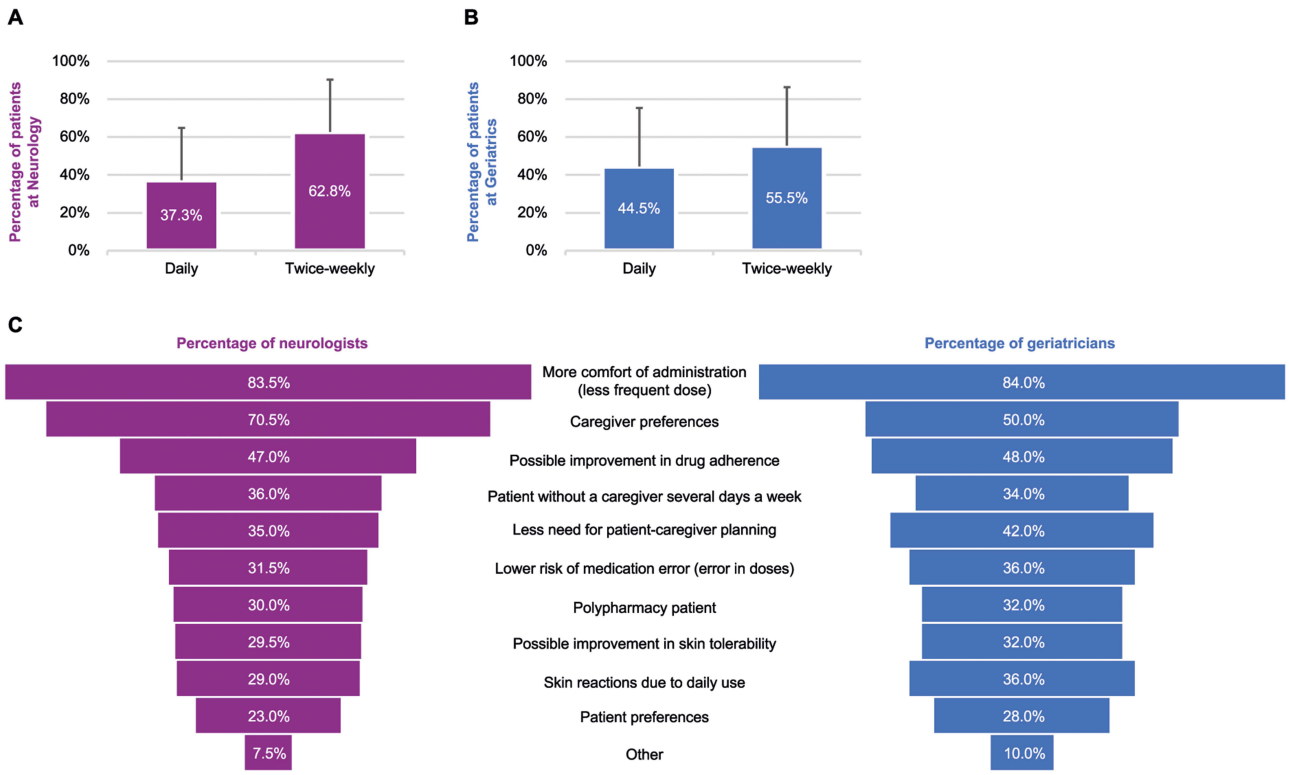

Figure 3 Formulations of rivastigmine transdermal patches most recommended for the treatment of mild to moderate AD and reasons considered by the specialists when recommending the switch from the daily to the twice-weekly patch. (**A**) Percentage of patients with AD to whom neurologists recommended daily vs twice-weekly transdermal patches of rivastigmine. (**B**) Percentage of patients with AD to whom geriatricians recommended daily vs twice-weekly transdermal patches of rivastigmine. (**C**) Percentage of physicians (neurologists in purple, geriatricians in blue) choosing the indicated statements regarding the reasons considered when recommending the switch from daily to twice-weekly rivastigmine patches (multiple-choice question).

Satisfaction, Adherence, and Safety of Twice-Weekly Transdermal Patches

When comparing the twice-weekly rivastigmine patch with the one for daily use, the neurologists observed higher comfort of administration in a mean of 74.3% (31.0) of patients, more satisfaction of caregivers in 70.6% (31.8), more satisfactory drug adherence in 63.5% (33.3), and better skin tolerability in 53.4% (35.9), with the twice-weekly patch (Figure 4A). For those patients who preferred the daily patch, this choice was often because of difficulty following the regimen (44.4% [35.1]; not shown). Neurologists also reported a high or very high degree of satisfaction in nearly 80% of their patients with the twice-weekly rivastigmine patch (Figure 4B). They considered that these high rates of patient satisfaction were due to a greater comfort of caregivers in a mean of 33.9% (31.0) of cases, and easy administration in 28.9% (32.1), among other reasons (Figure 4C).

According to the geriatricians, the twice-weekly rivastigmine patch showed a more satisfactory drug adherence in a mean of 69.5% (31.7) of their patients, more satisfaction of caregivers in 68.5% (29.8), higher comfort of administration in 67.0% (33.3), and better skin tolerability in 59.5% (35.7), compared with the patch for daily use (Figure 5A). For geriatric patients who preferred the daily patch, the primary reason for this choice was the tendency to forget to use the twice-weekly patch after several days (36.0% [30.8]; not shown). Similar to neurologists, geriatricians reported that nearly 80% of patients showed a high or very high degree of satisfaction with the twice-weekly patch (Figure 5B). According to their perceptions, these high rates of patient satisfaction were due to a greater comfort of caregivers in a mean of 37.0% (33.2) of cases, and easy administration in 28.5% (30.3), among other reasons (Figure 5C).

The surveyed neurologists reported considering the use of the twice-weekly patch over the one for daily use mainly in those patients who do not have a caregiver during the whole week (89.5%), to increase the caregivers' comfort (88.3%), and in case of poor compliance with previous treatments (87.6%), among other situations. Overall, they would consider

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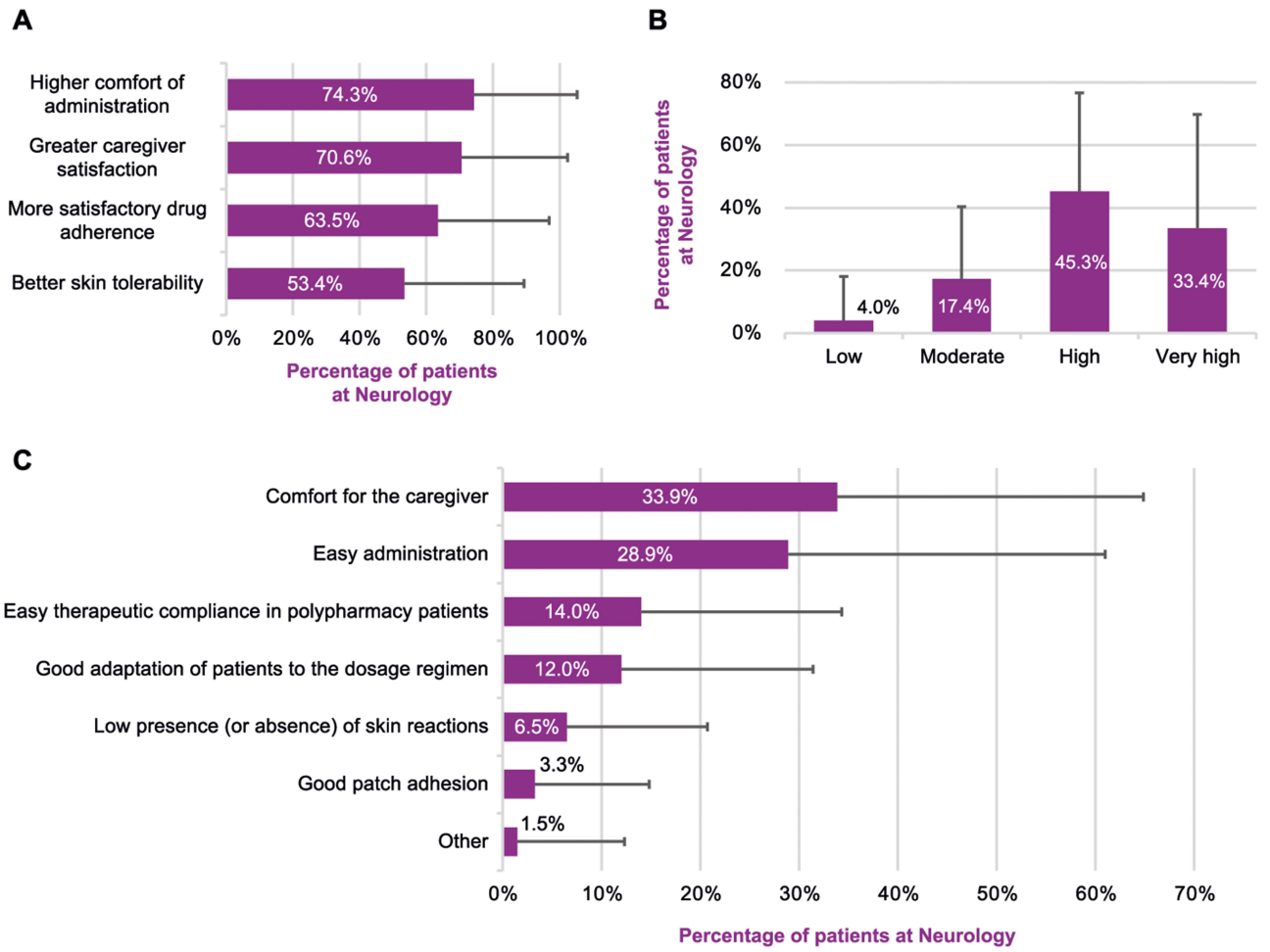

Figure 4 Satisfaction, adherence, and tolerability of twice-weekly rivastigmine patches in patients with AD as perceived by the neurologists. (**A**) Percentage of patients with AD in whom neurologists perceived higher administration comfort, greater satisfaction and drug adherence, and better skin tolerability, with the twice-weekly rivastigmine patch compared to the one for daily use. (**B**) Degree of satisfaction perceived by the participating neurologists in patients with AD treated with the twice-weekly rivastigmine patch. (**C**) Neurologists' perceptions to explain the high degree of patient satisfaction with the twice-weekly rivastigmine patch.

preferential the use of the twice-weekly rivastigmine patch in a mean of 81.1% (26.8) of patients, taking into account the bioequivalence of both patch formulations (Figure 6A).

As displayed in Figure 6B, the geriatricians reported considering the use of the twice-weekly rivastigmine patch preferential over its daily posology mainly to increase the caregivers' comfort (87.0%), in those patients who do not have a caregiver during the whole week (85.5%), and in case of poor compliance with previous treatments (84.5%), among other situations. Overall, the participating geriatricians would consider the twice-weekly patch over the daily patch in a mean of 86.0% (25.3) of patients, taking into account their bioequivalence.

Discussion

The causes of the Alzheimer's degenerative process have not yet been definitively determined. However, the course and symptoms of AD require continuous support and treatment to improve patients' comfort, dignity, and independence for a longer period, which may also reduce the burden of their caregivers.[23] Rivastigmine is prescribed for mild to moderate AD symptoms and has been demonstrated as a successful therapeutic strategy to address the progression of the disease.[24] Even though its mild gastrointestinal-associated adverse events and a profile of improbable interactions with other medications,[25,26] treatment compliance remains a major obstacle in elderly patient management. The VIITAL 2S study presents an overview of patient and caregiver preferences in the treatment of AD with rivastigmine administered as a twice-weekly transdermal patch, from the perspective of the surveyed neurologists and geriatricians. This study shows that the twice-weekly posology resulted

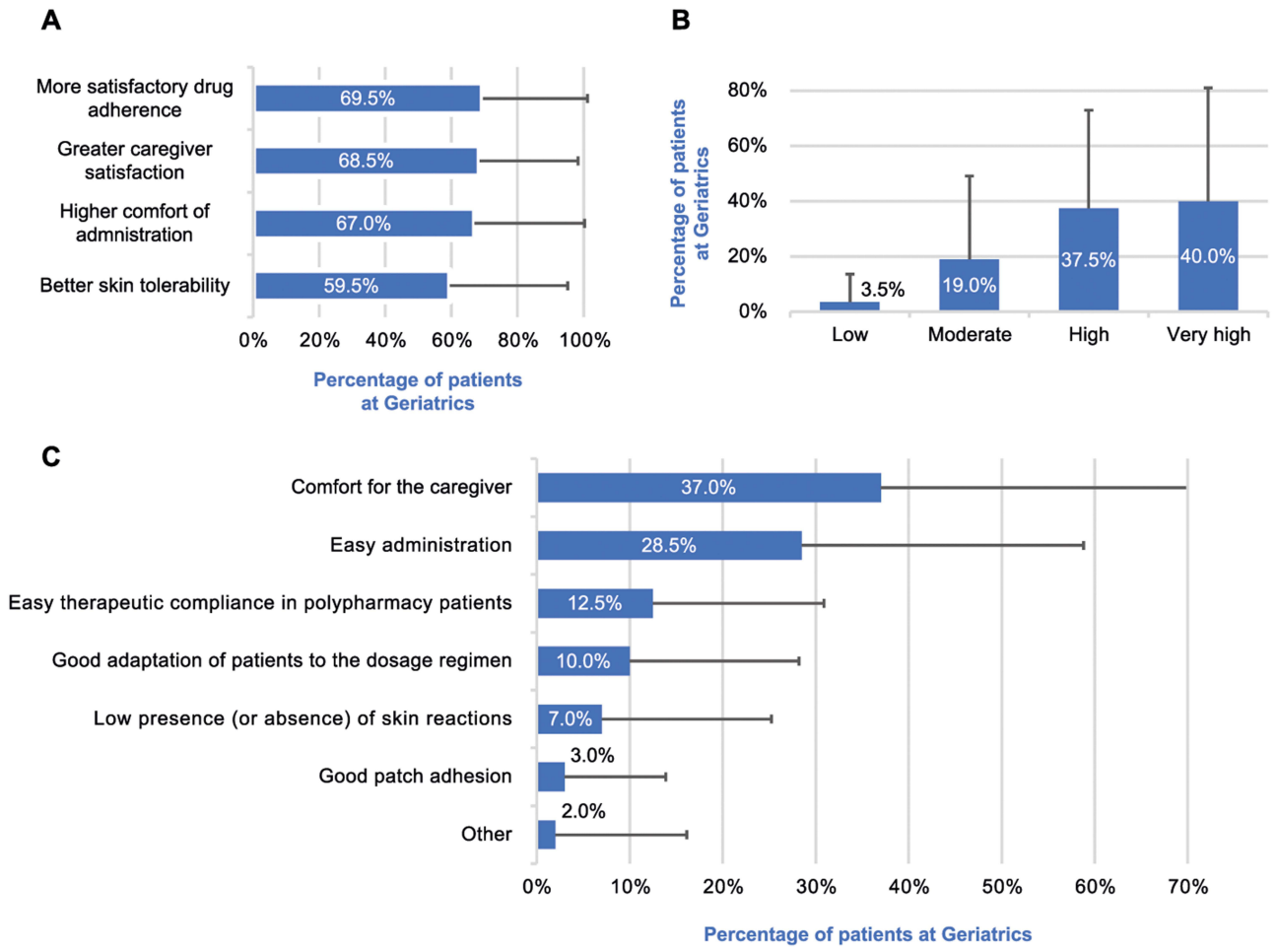

Figure 5 Satisfaction, adherence, and tolerability of twice-weekly rivastigmine patches in patients with AD as perceived by the geriatricians. (**A**) Percentage of patients with AD in whom geriatricians perceived higher administration comfort, greater satisfaction and drug adherence, and better skin tolerability, with the twice-weekly rivastigmine patch compared to the one for daily use. (**B**) Degree of satisfaction perceived by the participating geriatricians in patients with AD treated with the twice-weekly rivastigmine patch. (**C**) Geriatricians' perceptions to explain the high degree of patient satisfaction with the twice-weekly rivastigmine patch.

in higher comfort of administration, better skin tolerability, and more satisfaction of caregivers than the patch for daily use, which may be translated into improvements in patient satisfaction and drug adherence.

Treatments for AD can be substantially impacted on their efficacy by varying their routes of administration and posology, especially when considering factors that affect treatment compliance and satisfaction, such as adverse events, low tolerability of the medication, complex posologies, and interaction with concomitant medications.[27–29] In July 2007, the rivastigmine patch was the first patch approved to treat AD and encompassed several advantages, including continuous release with constant levels in plasma, and independent absorption of ingestion and gastrointestinal interaction, which reduced gastrointestinal adverse events.[15,16] Easy application of the patches increased patient compliance.[30,31] Furthermore, Blesa-González et al reported higher patient satisfaction with the rivastigmine patches compared with capsules, and Windblad B. et al showed caregiver preference for this method of administration.[32–34] In accordance, we observed that neurologists and geriatricians recommended rivastigmine patches to almost all patients with AD (95.5% in Neurology vs 96.5% in Geriatrics), while oral administration was scarcely recommended. The comfort of administration, caregiver preferences, and potential improvements in drug adherence were the most valued attributes of transdermal patches by the participating physicians. Of note, 76% of geriatricians also highlighted the use of patches in the case of polypharmacy patients, likely because, compared with neurologists, they managed older patients (64% vs 26.5% >80 years old), who receive concomitant medication more frequently (74.5% vs 51.6% received 4–10 medications daily, and 5% vs 3.5% received >10).

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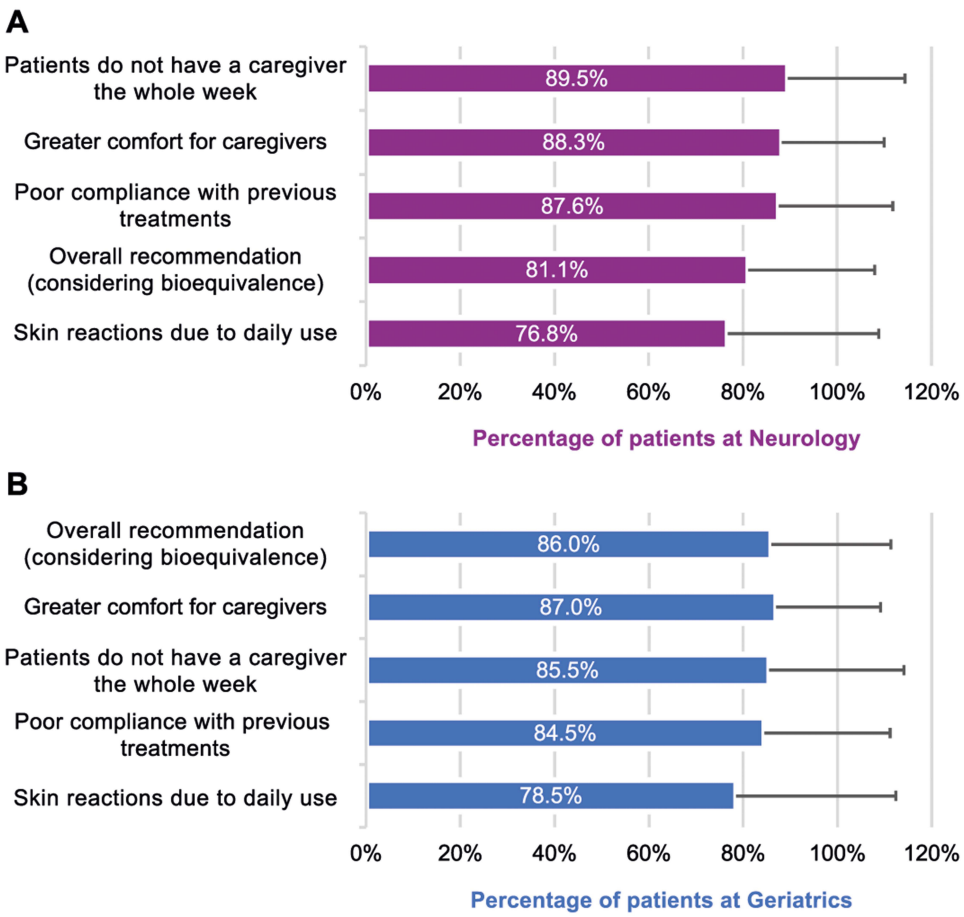

Figure 6 Reasons to recommend the twice-weekly preferentially to the daily rivastigmine patch considered by the participating physicians (neurologists in purple, geriatricians in blue). (**A**) Percentage of patients with AD to whom neurologists would recommend the twice-weekly rivastigmine patch preferably than the daily use one considering the indicated circumstances. (**B**) Percentage of patients with AD to whom geriatricians would recommend the twice-weekly rivastigmine patch preferably than the daily use one considering the indicated circumstances.

In an effort to provide patients with AD with greater treatment convenience and management, novel formulations have been developed, leading to the development of the rivastigmine multi-day patch. This patch, designed to deliver the drug constantly for a period of up to four days, allowed twice-weekly administration with demonstrated bioequivalence to the patch for daily use.[21] Although the recommendation of this less frequent posology suggests the achievement of better drug adherence, less patient-caregiver planning, and reduced caregiver burden, patient and caregiver preferences have not been evaluated to date. In our study, the twice-weekly transdermal patch was recommended to approximately half of the patients with AD treated with rivastigmine. Neurologists and geriatricians also recommended the switch from the daily to the twice-a-week patch to 31.8% and 41% of patients, respectively, considering the higher comfort of administration, caregiver preferences, and potential improvements in drug adherence, aspects that became even more important when the cognitive impairment worsens.

Physicians considered the twice-a-week posology of rivastigmine preferential over its daily use to increase the comfort of caregivers, in circumstances of patients who do not have a caregiver during the whole week, and to improve treatment compliance. Overall, they manifested a preference for the twice-weekly patch and would recommend it to more than 80% of their patients, considering its bioequivalence with the patch for daily use. Most importantly, patients, both managed at Neurology and Geriatrics services, expressed a high degree of satisfaction with the twice-weekly posology of rivastigmine. As reported by the participating physicians, patient satisfaction with this posology was mainly triggered by a higher comfort of caregivers, easy administration of the patch (less frequent), and easier treatment compliance in those receiving polymedication. Probably as a consequence of the above, better drug adherence was reported in more than 60% of patients with the twice-weekly patch compared to the one for daily use.

Being a caregiver of an individual with AD is often associated with emotional and physical strain.[35] Care partners of patients with AD or other types of dementia experienced higher levels of stress, depression, and anxiety compared with the general population or age-matched controls.[36,37] Moreover, caregiver burden may affect the outcomes of the patient with AD, suggesting a bidirectional interplay between disease severity and the burden of the caregiver.[38] Altogether, this highlights that not only patient but also caregiver perceptions of AD burden and treatment are crucial in the management and progression of the disease. As expected, most caregivers in our study were family members of the patient with AD. Participating physicians reported greater satisfaction with the twice-daily transdermal posology than the daily patch in nearly 70% of them, suggesting reduced or optimized care work and decreased burden.

One disadvantage of transdermal delivery systems is a possible skin reaction. The IDEAL randomized multicenter trial, conducted on 1195 patients with AD to compare rivastigmine patches with capsules, showed a higher percentage of patients receiving a patch (all sizes) experiencing skin irritation and pruritus compared with those receiving placebo (skin irritation: 8% vs 4%; pruritus: 7% vs 3%).[39] Similarly, Lefevre and collaborators showed erythemic lesions in the areas of daily patch application, although they were mild and self-resolved within 24 hours of patch displacement.[40] According to the data obtained by Schurad et al, local tolerability was comparable between the daily and the twice-a-week patch, and both were well tolerated with mild skin reactions that improved over time.[21] In contrast, in our study, the perception from both neurologists and geriatricians was of better skin tolerability with the twice-weekly patch by comparison with the daily patch in more than half of patients (53.4% as reported by neurologists and 59.5% by geriatricians).

Limitations of this study include the strategy of aggregated data collection based on the experience of the participating physicians, which omitted patient opinions and data, then gathering information exposed to recall bias. In addition, results were focused on the recent experience of the neurologists and geriatricians and, therefore, could not necessarily represent all patients with AD and their caregivers. The survey design with delimited answers for certain questions also represents a limitation, as some physician opinions and preferences may be excluded. Nonetheless, to our knowledge, this is the first study that addresses the preferences and satisfaction of patients with AD and their caregivers concerning the treatment with the twice-weekly rivastigmine patch. Furthermore, our sample included 250 dementia experts with extensive experience in the field from across the country.

Conclusion

In conclusion, this study provides an overview of real-life patient and caregiver perceptions and satisfaction with the twice-a-week posology of transdermal rivastigmine patches. Neurologists and geriatricians reported that the twice-weekly posology was beneficial in terms of comfort of administration, skin tolerability, and satisfaction for both patients and caregivers. This may explain the enhanced adherence to treatment observed, a key factor in treatment effectiveness and AD symptom management. Our results also underline the need for additional research involving patient and caregiver measures of treatment preference, satisfaction, and life impact of AD, intending to improve patients' quality of life and reduce the overwhelming caregiver burden.

Data Sharing Statement

All data generated during this study are available from the corresponding author upon reasonable request.

Ethics Approval

This study was approved by the Ethics Committee of the Hospital Clínico San Carlos (Madrid, Spain). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice (GCP), and in compliance with European and local requirements.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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