Expert Opinion

Use of rivastigmine transdermal patch in the treatment of Alzheimer's disease

Bengt Winblad† & João Carlos Machado
†*Karolinska Institutet Alzheimer's Disease Research Center (KI-ADRC), S-14157 Huddinge, Sweden*

Cholinesterase inhibitors such as rivastigmine and donepezil exhibit a dose – response relationship, with higher doses of the drugs demonstrating greater efficacy. Transdermal patches provide smooth continuous drug delivery, with the potential to offer efficacious levels of drug exposure while avoiding the peaks and troughs associated with side effects. As a small, lipophilic and hydrophilic molecule, rivastigmine ($C_{14}H_{22}N_2O_2$) is chemically well-suited to transdermal delivery. The technology underlying the rivastigmine patch allows it to be discreetly small and thin. The target dose 9.5 mg/24 h rivastigmine patch has a diameter of just 3.5 cm and a surface area of 10 cm^2. A large randomized controlled trial has demonstrated that the target dose 9.5 mg/24 h rivastigmine patch provided similar efficacy to the highest rivastigmine capsule doses, yet with three times fewer reports of nausea and vomiting. Thus, the rivastigmine patch enables quick and easy access to high dose efficacy. The skin tolerability profile is good, and the patch has demonstrated excellent adhesion. The apparent success of rivastigmine patch, in terms of clinical utility and patient acceptability, suggests that it may mark the next generation of dementia treatment.

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1. Introduction

Recent epidemiological evidence suggested a year 2000 prevalence of 25 million cases of dementia worldwide: about 6.1% of the world's population aged 65 years or older were estimated to have dementia [1]. Alzheimer's disease (AD) is responsible for 60 – 70% of dementia cases in Europe [2], and incidence rates in Latin America are comparable to those reported in Western studies [3]. AD continues to be one of the most disabling and burdensome health problems worldwide. The total annual global cost of dementia, estimated to be more than US$300 billion in 2005, has been described as 'enormous' [4].

Cholinesterase inhibitors (rivastigmine, Exelon®, Novartis, Switzerland; donepezil, Aricept®, Pfizer, USA; galantamine, Razadyne®, Johnson & Johnson, USA) currently form the mainstay of AD therapy, along with the NMDA-receptor modulator, memantine (Namenda®, Merck, USA). Cholinesterase inhibitors such as rivastigmine and donepezil exhibit a dose – response relationship, with higher doses of the drugs demonstrating greater efficacy [5-7]. However, higher doses of cholinesterase inhibitors, as well as the large fluctuations in plasma concentration levels that are typical of oral drug administration, are also associated with a higher incidence of gastrointestinal side effects [8]. These side effects, which are most commonly reported during the titration phase of treatment, may act as a barrier to some patients achieving optimal therapeutic doses of oral cholinesterase inhibitors in clinical practice.

In contrast, transdermal patches provide smoother, continuous drug delivery, with the potential to offer an efficacious level of drug exposure while avoiding the peaks (C_{max}) and troughs (C_{min}) associated with side effects. Rivastigmine is the

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only agent for which a transdermal delivery system has been developed. The pharmacokinetic rationale for the development of the rivastigmine patch was that it may achieve a more gradual C_{max}, avoiding the rapid rise and fall of drug concentration seen with oral cholinesterase inhibitors [8].

Reviews of long-term cholinesterase inhibitor trials have concluded that the benefits of continued treatment may be maintained, relative to placebo, for 3 to 4 years [7,9]. However, non-compliance with oral agents has been a common problem, with the duration of AD treatment rarely exceeding even 1 year [10]. It has been proposed that patch therapy may help to enhance compliance, and have the potential to optimize clinical effectiveness in patients with dementia [10,11].

A large, randomized, controlled trial subsequently demonstrated that the target dose 9.5 mg/24 h rivastigmine patch provided similar efficacy to the highest rivastigmine capsule doses, yet with three times fewer reports of nausea and vomiting [12]. Thus, the benefits of patch delivery over oral administration of rivastigmine were demonstrated, and the rivastigmine patch has since been approved in many countries worldwide, including Europe and the Americas. This review considers the technology underlying the rivastigmine patch, with a focus on drug delivery and clinical utility, and concludes with an expert opinion on the effects that availability of the rivastigmine patch may have on future treatment paradigms.

2. Transdermal drug delivery

2.1 Skin penetration

The average adult's skin is between 2 and 3 mm thick, and is composed of three primary layers: the epidermis, the dermis and the hypodermis [13]. The epidermis is approximately 100 μm thick, and forms a waterproof, protective barrier over the body's surface. Just below the epidermis is the dermis, approximately 100 – 200 μm thick, consisting of connective tissue that cushions the body from external stresses. The hypodermis is a layer of subcutaneous fat that nourishes the dermis, conserves body heat and protects internal organs from trauma.

Any drugs penetrating the skin need to navigate the epidermis and dermis to reach the bloodstream. In order to pass through the skin, a 'concentration gradient' must be present, whereby the drug substance diffuses from an area of high concentration to an area of low concentration. In the case of a transdermal patch, the patch is 'loaded' with the drug substance at very high concentrations [14]. The drug then diffuses from the patch into the skin, and deeper into the skin layers until it reaches the bloodstream (**Figure 1**).

However, human skin has evolved over millions of years to form a barrier between the inside body and the outside world, so only certain types of molecules can be delivered in this way. Skin penetration and absorption are influenced by the physiochemical properties of a drug, including lipophilicity, molecular weight, size and structure [14,15]. For example, the lipid-rich and keratin-rich stratum corneum of the epidermis is the major rate-limiting barrier to the absorption of most drugs [16]. Hydrophobic substances transit the stratum corneum through the lipid-rich intercellular space, and more hydrophilic molecules dissolve and diffuse through the bound water of the cells [17]. Molecules that are both lipophilic and hydrophilic may take advantage of both penetration routes (both between and within cells), leading to rapid delivery to the bloodstream. In addition, small molecules pass though the skin much more easily and quickly than large molecules; a molecular weight of 500 Da is the upper limit for compounds compatible with transdermal delivery [14,15].

2.2 Transdermal absorption of rivastigmine

As a small (~ 250 Da), lipophilic and hydrophilic molecule, rivastigmine ($C_{14}H_{22}N_2O_2$) is chemically well-suited to trans dermal delivery. A low molecular weight of 250 g/mol, combined with amphiphilic (both lipophilic and hydrophilic) properties, enables rivastigmine to pass through human skin quickly and easily.

Its low molecular weight also makes rivastigmine a potent drug, in that only small doses are required to achieve therapeutic effects [5]. This means that, even with the drug loading required to create the concentration gradient needed for transdermal drug delivery, only small amounts of drug are required in each rivastigmine patch. This allows the rivastigmine patch to be small and thin, enhancing its acceptability to patients.

3. Rivastigmine patch technology

A well-designed transdermal patch needs to balance the factors of delivery, adhesion and skin tolerability, in a form that is acceptable to patients. Early patches relied on a 'reservoir' system that contained the drug in an alcohol solution [18]. Although they delivered an appropriate dosage, reservoir patches were large and indiscreet, and they were associated with a lot of skin irritation, at least in part due to the alcohol solution, as well as adherence problems. More advanced patches dissolved the drug in an acrylic adhesive, which reduced skin irritation but did not adhere well to the skin. Modern technology now offers the 'matrix patch', designed to be small and thin (making it more acceptable to patients), adhere well to the skin and demonstrate improved tolerability [18].

The rivastigmine patch is a matrix patch comprising four layers (**Figure 2**). The coloured backing layer, which is visible after the patch is applied, is made of a non-toxic, waterproof material. This layer has a low moisture – vapour transmission rate, to retain skin moisture, hydrate the local area of skin underneath the patch and increase drug penetration. It also prevents additives from leaching out of the acrylic matrix and alteration of the drug substance [14,18]. The second layer is an acrylic matrix that contains the drug

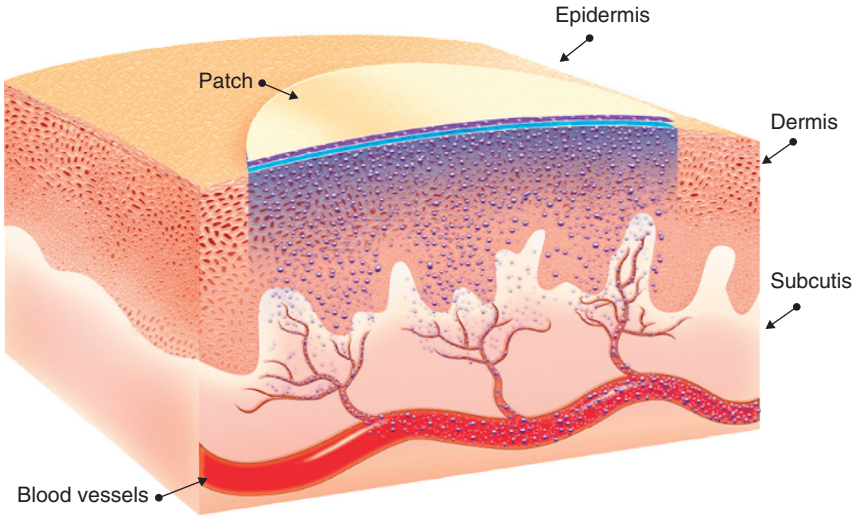

Figure 1. Illustration of skin penetration: the drug diffuses from the patch into the skin and deeper into the skin layers until it reaches the bloodstream.

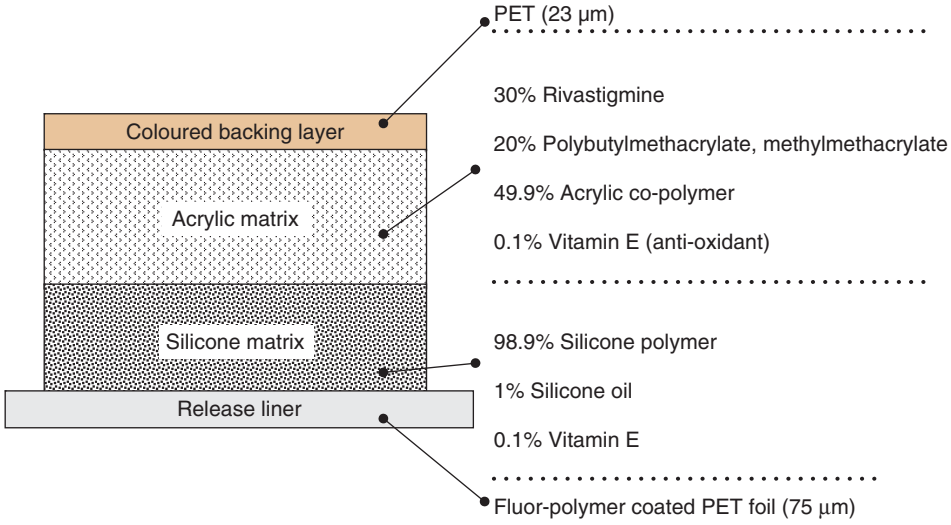

Figure 2. The four layers of the rivastigmine patch.

substance, antioxidants (e.g., vitamin E) and an acrylic polymer mixture that controls the mechanical properties of the patch such as the rivastigmine delivery rate (by including the correct ratio of constituent polymers). Below the acrylic matrix is the silicone matrix, an adhesive layer that permits optimal skin adhesion, but allows atraumatic removal of the rivastigmine patch at the end of the application period [14]. Finally, the release liner, which is removed before application to the skin, is designed to facilitate easy removal and prevent leaching of ingredients from the rivastigmine patch before it is applied to the skin.

The technology underlying the rivastigmine patch allows it to be discreetly small and thin. The target dose 9.5 mg/24 h rivastigmine patch has a diameter of just 3.5 cm and a surface area of 10 cm^2. In a large randomized controlled trial, it demonstrated good adhesion and skin tolerability [12].

4. Rivastigmine patch pharmacokinetics

4.1 Drug load and release

The rivastigmine patch is 'loaded' with drug substance to permit diffusion into the skin. In a pharmacokinetic study involving 51 AD patients, the average amount of rivastigmine absorbed from a patch over a 24-hour application period was approximately 50% of the total loading dose. The starting dose patch is loaded with 9 mg rivastigmine

and released 4.6 mg/24 h (51% of the loading dose), while the target dose patch is loaded with 18 mg rivastigmine and released 9.5 mg/24 h (53%) [19].

Absorption of any remaining rivastigmine following the 24-hour application period was shown to occur very slowly [19]. Patients should therefore not be at risk of toxic exposure should a second patch be applied without prior removal of the first.

4.2 Rivastigmine absorption

Transdermal patches are associated with smooth, continuous drug delivery, which generally means 'gentler' treatment and reduced side effects. Data from the pharmacokinetic study involving 51 AD patients [19] were used in a compartmental analysis to model rivastigmine plasma levels over a 24-hour application period following patch and oral administration [20].

All patch doses provided smoother and more continuous delivery of rivastigmine versus capsules (**Figure 3**) [20]. The 4.6 mg/24 h patch provided comparable rivastigmine exposure to a 6 mg/day capsule dose ($AUC_{24\ h}$ 64 and 60 ng·h/ml respectively, p = ns) and the 9.5 mg/24 h rivastigmine patch provided comparable exposure to a 12 mg/day capsule dose ($AUC_{24\ h}$ 166 and 207 ng·h/ml respectively, p = ns). The 4.6 mg/24 h and 9.5 mg/24 h rivastigmine patches provided significantly lower rivastigmine C_{max} and longer T_{max} (all $p < 0.001$) versus capsule doses of comparable exposure: 6 mg/day (C_{max} 3.3 versus 6.8 ng/ml; T_{max} 8.2 versus 1.2 h) and 12 mg/day (C_{max} 8.7 versus 21.6 ng/ml; T_{max} 8.1 versus 1.4 h), respectively [20].

These pharmacokinetic data, indicating similar drug exposure with a lower maximum concentration and slower absorption rate for rivastigmine patch versus capsules [20], predicted that the patch may provide similar efficacy to orally administered rivastigmine, with a more favorable tolerability profile [21].

4.3 Rivastigmine metabolism

Rivastigmine is rapidly metabolized to the inactive NAP226-90 metabolite by its target cholinesterase enzymes, with little or no interaction with the hepatic cytochrome P450 isoenzyme system [22]. However, a small amount of first-pass metabolism of orally administered rivastigmine may still occur via peripheral cholinesterases in the gastrointestinal tract. Transdermal administration bypasses this Phase I metabolism, and increases the bioavailability of rivastigmine. This is explains why the 9.5 mg/24 h rivastigmine patch may provide comparable efficacy to the highest doses of capsules [12], despite having a numerically lower $AUC_{24\ h}$ (p = ns) [20].

4.4 Rivastigmine patch application sites

The pharmacokinetic parameters of transdermal drug delivery can vary between patch application sites on the body. The optimal position would offer maximum drug exposure, be easily accessible, and avoid adhesion or tolerability issues (e.g., hirsute areas or sensitive skin). In a study in 40 healthy men or women aged 40 to 80 years, the 9.5 mg/24 h patch was applied and worn for 24 h on the upper back, chest, thigh, abdomen and upper arm [23]. At all application sites T_{max} was very slow (16 – 22 h). $AUC_{24\ h}$ and C_{max} were greatest when the patch was applied to the chest, upper back and upper arm [23]. Erythema was the only type of skin reaction reported during the study, and was least likely to occur when the patch was applied to the upper arm, chest and upper back.

Based on the findings of this study, it is recommended that the patch should be applied to clean and dry skin on the upper back, upper arm, or chest to obtain maximum rivastigmine exposure with minimal risk of skin reactions [23]. To further reduce the potential for skin irritation, the patch should be alternated daily between sites on the right and the left side of the upper body.

5. Rivastigmine patch utility

It has been proposed that a transdermal patch may offer unique utility benefits over oral therapies in the management of dementia patients [10,21]. Transdermal drug delivery systems have several advantages over oral therapies, and this is particularly true when a chronic neurological disorder is present, because cognitive or other deficits may overlap with impairments in daily living activities typical of advanced age [10,24].

5.1 Tolerability

Oral cholinesterase inhibitors have been associated with central cholinergic gastrointestinal side effects, most commonly nausea and vomiting, during the titration phase [25,26]. These side effects are thought to be a consequence of rapid increases in acetylcholine levels following effective inhibition of target enzymes in the brain [27,28], which reflect large fluctuations in plasma levels following oral administration [29]. Smooth and continuous drug delivery with the rivastigmine patch [20] has the potential to reduce fluctuations in plasma drug levels, which may lead to fewer side effects. Patch delivery also avoids the first-pass effect and minimizes the risk of drug – drug interactions in the gastrointestinal tract.

The IDEAL (Investigation of transDermal Exelon in ALzheimer's disease) study was a 24-week, randomized, double-blind trial in 1195 mild-to-moderate AD patients from 21 countries [12]. The target 9.5 mg/24 h rivastigmine patch was found to be associated with three times fewer reports of nausea and vomiting versus 12 mg/day capsules (7.2 versus 23.1%, and 6.2 versus 17.0%, respectively) [12]. There were no significant differences between the 9.5 mg/24 h patch and the placebo groups with respect to the frequencies of these side effects [12].

Concerns that specifically relate to the use of transdermal patches are problems with skin adhesion and skin irritation. However, utilizing the latest matrix technology, the risks of these events can be minimized. Throughout the course of

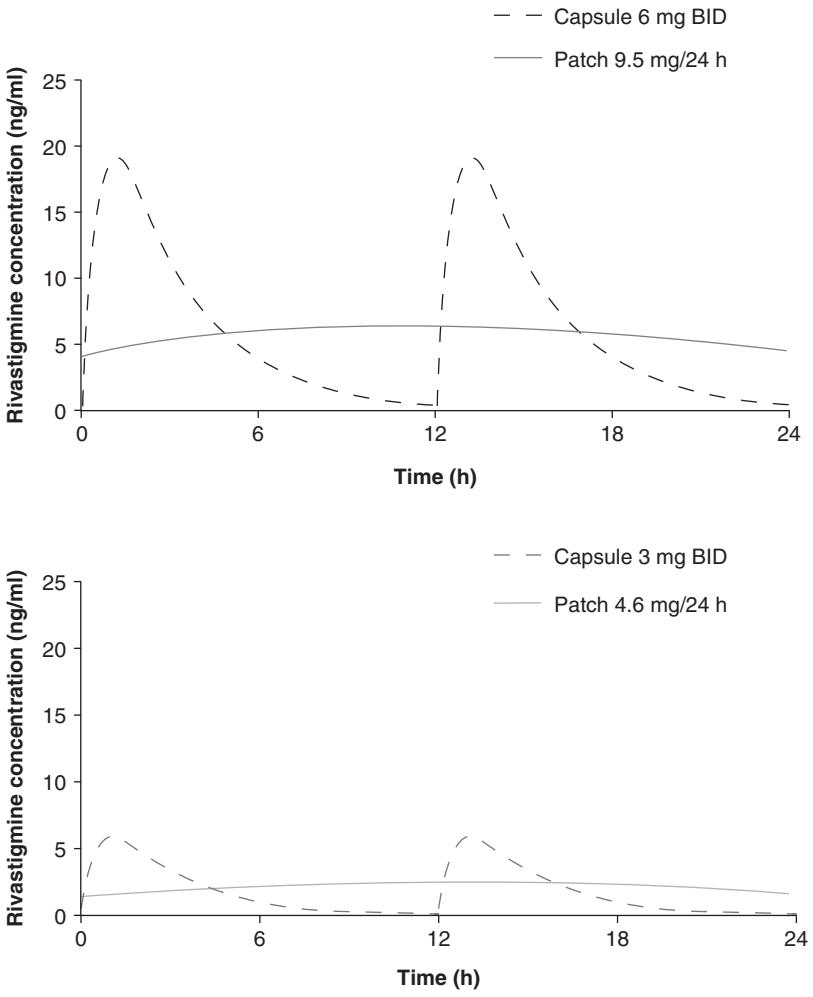

Figure 3. Steady-state rivastigmine plasma levels for a typical AD patient following application of the 9.5 mg/24 h patch versus 12 mg/day capsules, or the 4.6 mg/24 h patch versus 6 mg/day capsules.
Reproduced with permission from Mercier *et al.* [20].

the IDEAL study, adhesion properties of the 9.5 mg/24 h patch were very good [12]. The majority of patches (96%) remained either completely on or detached only at the edges by the end of the 24-hour application period [12,30]. This result was achieved even though patients were allowed to bathe with their patches on, and that the study was conducted in several countries where the climate is warm and perspiration might be expected.

During the IDEAL study, patients were asked at each visit whether they had experienced any patch application site reactions [12]. In an effort to minimize the occurrence of any skin irritation, and as recommended on the product label, patches were rotated to a different application site each day. The majority of patients receiving the target 9.5 mg/24 h patch (90%) experienced no, slight or mild skin irritation. Overall, the 9.5 mg/24 h patch was well tolerated at the site of application; skin irritation was not a problem [12].

5.2 Acceptability and compliance

Compliance with AD therapies currently represents a problem [31]. There is a clear medical need for effective, well-tolerated treatment options that have the potential to enhance compliance, thereby improving patient outcomes [10]. Transdermal patches offer a visual reminder and reassurance that treatment has been administered, and application can become part of the daily ritual, helping to improve treatment compliance by forgetful patients or caregivers [10].

Moreover, since drugs administered transdermally avoid the first-pass effect, they are less likely to interact with food intake. The rivastigmine patch may be taken at any time of the day, independent of meal times, making it a more convenient and flexible treatment option than conventional capsules (which should be taken twice daily with food).

Since compliance with AD therapy is often the responsibility of a caregiver, and medication management contributes to caregiver strain [32], it is useful to understand whether new

treatment options may help to reduce caregiver challenges and enhance their ability to provide care. In a study evaluating caregiver preferences for the rivastigmine patch versus capsules, 72% of caregivers preferred rivastigmine patches to capsules 'overall', 64% said they preferred patches to capsules for their 'ease of use', and 74% of caregivers said they preferred patches to capsules for 'ease of following the schedule' (all $p < 0.001$) [30]. Consistency of caregiver preference for the patch over capsules across participating countries, including Europe and Latin America, suggested that the advantages of a patch appeal to caregivers across a range of climates and cultures [30,33]. Although compliance was not formally assessed, caregivers were asked an open question about their opinions of the two rivastigmine treatments. Their comments suggested that a patch may help to simplify their daily medication regimens and improve treatment compliance [31].

Patches are also safer to use, reducing the possibility of accidental overdose. Therefore, patches may help to relieve some of the anxiety associated with medication management. Importantly, the potential for increased satisfaction and compliance associated with patches may in turn lead to greater and more sustained treatment outcomes for the patient.

5.3 Efficacy

There are numerous reasons to expect that transdermal patches may provide comparable, if not better, efficacy in comparison to conventional oral therapies. By minimizing plasma drug level fluctuations, a patch has the potential to provide sustained drug levels within the optimal effective therapeutic window. Since cholinesterase inhibitors exhibit a clear dose – response relationship [5,6], improved tolerability associated with transdermal administration may allow patients easier access to optimal therapeutic doses, and potentially improve the effectiveness of treatment compared with oral administration. Any gain with respect to treatment compliance resulting from the overall ease of use of a patch versus oral administration would also be expected to result in more sustained benefits.

Pharmacokinetic studies suggest that the 4.6 mg/24 h rivastigmine patch provides similar exposure to 6 mg/day capsules [20]. This means that from day 1, patients initiated on the starting dose 4.6 mg/24 h patch are receiving an effective rivastigmine dose. Comparable drug exposure provided by the target 9.5 mg/24 h patch versus the highest recommended oral dose (12 mg/day) [20] suggests that the two delivery modes may offer similar efficacy. Consistent with expectations, efficacy findings from the IDEAL study confirmed that the 9.5 mg/24 h rivastigmine patch does provide comparable efficacy to the highest capsule dose [12].

Patients in both treatment groups (9.5 mg/24 h patch and 12 mg/day capsule) experienced significant improvements over placebo on both primary outcome measures (Alzheimer's Disease Assessment Scale – Cognitive subscale [ADAS-cog] and Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change [ADCS-CGIC]). In terms of secondary efficacy outcome measures, significant improvements over placebo were also observed on the Alzheimer's Disease Cooperative Study – Activities of Daily Living (ADCS-ADL), Mini-Mental State Examination (MMSE) and Trail-making Test Part A [12].

6. Conclusion

Advanced patch technology permits administration directly into the bloodstream from a small, discreet patch with good skin adhesion and tolerability. Particularly in the elderly population with chronic neurological disorders, transdermal therapy appears to be an effective therapeutic approach [24]. Patches offer a convenient, easy-to-use alternative option to oral administration, which ensures sustained effective therapeutic plasma drug levels with improved associated systemic tolerability.

Clinical data support the rationale for development of the rivastigmine patch. The pharmacokinetic profile associated with patch delivery translates into three times fewer reports of gastrointestinal side effects compared with oral administration, while maintaining drug exposure and clinical efficacy. This may allow patients easier access to optimal effective therapeutic doses, potentially improving the effectiveness of treatment. A transdermal patch may be the optimal way to deliver rivastigmine in the pharmacological treatment of AD.

7. Expert opinion

The rivastigmine patch adds another treatment to the growing armamentarium of transdermal drug therapies. Since the rivastigmine patch was approved by health authorities in Europe and the Americas in 2007, clinical experience has already been extensive. In our own experience, most patients appear able to tolerate the target dose 9.5 mg/24 h rivastigmine patch, enabling them to reach optimal therapeutic doses and stay on treatment for longer. An interesting observation has been that we now have many patients who have not tolerated any of the oral cholinergic drugs, but are now using patches to access such a drug for the first time (see **Case studies 1** and **2**).

Most patients can tolerate the target dose 9.5 mg/24 h patch. This contrasts with our previous experience with rivastigmine capsules, when many patients had to stop titration at suboptimal oral doses, due to nausea or vomiting. What we are able to do with the rivastigmine patch is unlock the potency and efficacy of the molecule and use it in a way that optimizes clinical efficiency. Ongoing trials with even higher rivastigmine patch doses may later offer further potential to push cholinesterase inhibition to a level rarely seen before in the clinical setting, with associated clinical benefits.

Case study 1. An 80-year-old Swedish woman with AD.

Living with husband (who is also ill, with a history of stroke) at home with community support. Medical history included: anxiety; aggression; loss of appetite; low body weight; falls; hypertonia; restless legs; diverticulosis coli; osteoporosis; severe pain. Computer tomography showed generalized cortical atrophy with small right-sided ischaemic lesion, leading to a diagnosis of AD with cerebrovascular lesions. MMSE score at diagnosis was 22 points (indicating mild dementia). Donepezil tablets were initiated 2 months after diagnosis but even low-dose 5 mg donepezil tablets were associated with nausea, bad appetite and depression. Donepezil treatment was stopped and rivastigmine patch 4.6 mg/24 h was initiated (this 'starting dose' patch has a comparable exposure to 6 mg/day capsules, an effective dose). The physician in charge did not increase the dose to 9.5 mg/24 h due to low body weight* and a good response to the 4.6 mg/24 h dose. Three months after starting the rivastigmine patch, the patient regained household responsibilities for cooking and cleaning. There was no nausea and her appetite increased. The rivastigmine patch is easy to use, and the patient applies her own patches. Both she and her husband are 'very satisfied'.

*The rivastigmine patch prescribing information advises that patients with body weight < 50 kg may experience more adverse events.

Case study 2. A 76-year-old Swedish woman with AD.

Widowed 3 years ago, this woman was living alone. She drove her car every day, and her son helped her to manage her accounts. Medical history included: hypertonia; hypertension (210/110); hypercholesterolaemia; TIA episodes; asthma; increasing memory problems. Computer tomography showed small vessel disease; lumbar puncture revealed increased p-tau 125, and slightly increased tau 460 and neurofilament 890. A diagnosis of mixed dementia was made, although it was noted that most of the patient's difficulties were mainly due to AD. MMSE score at diagnosis was 27 points (indicating very mild dementia). Galantamine tablets (8 mg b.i.d.) were initiated after diagnosis but compliance was poor and treatment was stopped due to nausea and vertigo. The patient switched to donepezil tablets but vertigo and leg cramps lead to discontinuation within 2 months. The patient switched again, this time to rivastigmine patch 4.6 mg/24 h, subsequently increased to target dose 9.6 mg/24 h patch. No nausea or other discomfort was reported. The patient functioned well and a global improvement was noted. Five months after starting rivastigmine patch, the patient reported feeling well and being better able to manage living alone. Moreover, good compliance with patch therapy was reported, potentially enhancing treatment benefits.

Skin tolerability is favorable. The most common side effect is redness caused by patch removal (similar to that seen following removal of an adhesive plaster), which normally disappears after a short period of time. Nevertheless, in our experience, skin irritation has been the cause of discontinuing treatment in the few patients who have stopped using the rivastigmine patch. Anecdotally, it seems that patch size might be involved – starting dose 4.6 mg/24 h patch appears to cause less skin irritation than target dose 9.5 mg/24 h patch. Care must be taken to follow the advice in the prescribing information about application site rotation (the patch must not be applied to exactly the same place on the body every day) and the use of solvents and lotions prior to patch application; following this advice may minimize skin irritation.

The apparent success of the rivastigmine patch, in terms of clinical utility and patient acceptability, suggests that it may mark the next generation of dementia treatment. Currently, the rivastigmine patch is approved for AD and Parkinson's disease dementia (PDD) in the USA and Latin America, and for AD only in Europe. The FDA approved the rivastigmine patch for both AD and PDD on the basis of our Alzheimer trial [12]. in the belief that that since cholinergic deficits were common to both dementia types, and since rivastigmine oral was approved for both indications, it was justified to also approve the patch for PDD. However, ongoing trials in PDD are expected to address the European Medical Evaluation Agency's perceived data gap, and it is hoped that the rivastigmine patch may be approved for both indications within the next few years. Experience at the Aurus Institute of Research and Education on ageing at the University of Medical Sciences of Minas Gerais, Brazil, suggests that PDD patients may also benefit from the rivastigmine patch, as described in **Case study 3.** (the rivastigmine patch is approved for the treatment of PDD in Latin America.)

Over the next 5 years, it seems likely that other cholinesterase inhibitor patches may also become available. At least one other cholinesterase inhibitor patch is currently under investigation [34]. The suitability and utility of different agents for transdermal delivery will clearly

Case study 3. An 84-year-old Brazilian man with PDD.

Living with his wife (who has congestive heart failure) and receiving daily informal caregiver support, this man had a 6-year history of Parkinson's disease and a history of recurrent falls. He exhibited signs of minor resting tremor, bradykinesia, rigidity, poor mobility and shuffling gait (no dysphagia), which were well controlled by a combination of levodopa, carbidopa and entacapone. In addition, he had a history of depression, hypertension, type 2 diabetes, gastroesophageal reflux disease and constipation, for which he was taking escitalopram, losartan, glimepiride, pantoprazole and laxatives, respectively. When referred to the Institute, he had a recent history of cognitive decline and visual hallucinations (described by the patient as seeing dead relatives and animals, especially in the evenings, with insight). Over 13 months his MMSE score had declined from 27 to 23 (indicating mild dementia). His attention, concentration and short-term memory had also declined. He was less able to function independently in daily life, plan, organize and perform goals (dysexecutive function). He became apathetic and withdrawn from family life. MRI revealed marked atrophy but no focal lesions. Blood tests, neuropsychological and clinical evaluations led to a diagnosis of PDD. Treatment was started with rivastigmine capsules 3 mg/day, and increased to 6 mg/day after 4 weeks. Due to the occurrence of dizziness, nausea and vomiting, treatment with rivastigmine capsules was switched to rivastigmine patch 4.6 mg/24 h. The patch dose was increased to 9.5 mg/24 h after 4 weeks. After the most recent visit, 4 months after starting the treatment, the patient, his wife and caregiver reported clinically relevant benefits, reduced distress and improvement of their quality of life. Visual hallucinations had resolved. The MMSE score was found to have improved, with associated improvements in concentration, sleep quality and ability to perform activities of daily living such as eating and dressing without worsening of motor signs. Despite the large number of concomitant medications being received by the patient and the previous adverse effects with oral rivastigmine, no side effects thought to be related to drug – drug interactions or due to the rivastigmine patch were reported.

depend on the physical and chemical properties of the molecules, which need to cross the epidermis and dermis to reach the bloodstream. Investment in the development of more patch therapies for dementia would recognize current evolutions in medication management, and a movement from pills to patches in this disease setting.

When managing a patient with AD, we invariably also need to consider the caregiver. The finding that, in a clinical trial setting, 72% of caregivers appear to prefer the rivastigmine patch to capsules is a positive finding [30]. We would encourage physicians to habitually seek caregiver feedback on medication management and compliance, as well as clinical effectiveness. It will be interesting to see whether a 7/10 preference for patch is sustained in clinical practice.

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Declaration of interest

B Winblad has received honoraria for advisery board meetings for all companies with anti-dementia drugs (Novartis, Pfizer, Janssen-Cilag, Merz, Lundbeck); he has no stocks in these companies. J Carlos Machado has no conflict of interest to declare.

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Affiliation

Bengt Winblad[†1] & João Carlos Machado[2]
[†]Author for correspondence
[1]Professor
Karolinska Institutet Alzheimer's Disease Research Center (KI-ADRC),
Floor 5, S-14157,
NOVUM, Huddinge, Sweden
Tel: +46 8 585 85 474; Fax: +46 8 585 85 470;
E-mail: Bengt.Winblad@ki.se
[2]Clinical Director
Aurus – Institute of Geriatric Medicine and Gerontology, Mater Dei Hospital
Faculty of Medical Sciences of Minas Gerais,
Belo Horizonte,
Minas Gerais, Brazil