Clinical Benefits Associated with a Transdermal Patch for Dementia

a report by

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Medication management, including treatment compliance, is a widespread challenge in many therapeutic areas, particularly in chronic diseases such as hypertension, congestive heart failure, diabetes and psychiatric illnesses.[1] Older adults particularly, who typically take multiple medications for concurrent conditions,[2] tend to have difficulties with treatment compliance due to complex and complicated drug regimens, the extent to which drug regimens interfere with daily living, the lack of understanding or misinterpretation of instructions and forgetfulness.[3] The most common form of non-compliant behaviour observed in older individuals following a long-term, chronic care treatment regimen is underdosing.[4] Often this is involuntary, due to forgetfulness or misinterpretation of/confusion with the dosing regimen. However, non-compliance may also be intentional in some cases, for example when patients do not believe in the benefits of treatment or to avoid associated adverse events.

The incidence of dementia syndromes such as Alzheimer's disease (AD) or Parkinson's disease dementia (PDD) increases with age: approximately 10% of people over the age of 65 years may develop AD,[5] and dementia has been reported in as many as 80% of older PD patients (mean age 73 years).[6] These dementia syndromes are characterised by a progressive deterioration of cognition and the emergence of behavioural and psychological symptoms and functional decline, which makes conducting everyday tasks increasingly challenging. Cholinesterase inhibitors such as rivastigmine, donepezil and galantamine – which have been widely available in oral formulations – and memantine form the mainstay of treatment for AD. Currently, rivastigmine is the only treatment approved for the treatment of mild to moderate PDD. However, due to the multitude of risk factors that individuals with dementia face, i.e. typically being older, with co-morbidities, high medication burden and memory deficits, this patient population is especially vulnerable to treatment non-compliance.[7] For example, despite AD being a long-term, chronic disease, the average treatment duration for this condition seldom exceeds even one year.[8–10] Many patients continue taking low, non-therapeutic doses due to a misunderstanding of complex titration schedules; however, patients who stay on AD therapies for longer periods at adequate doses have a greater chance of slowing or delaying the progression of cognitive decline,[11] may experience fewer admissions to nursing homes and may have reduced healthcare costs.[12]

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A great deal of effort has gone into encouraging treatment compliance and developing strategies that make medication management easier. For example, it has been proposed that simplifying drug regimens and using more user-friendly modes of drug delivery or compliance packaging may improve treatment compliance.[3,13,14] Recently, the rivastigmine transdermal patch has become widely approved in Europe for the treatment of AD and in the US for AD and PDD, as well as in many other countries worldwide (including Latin America and Asia-Pacific; regional variations apply). Experts have proposed that transdermal administration using a patch may enhance compliance and thus may have the potential to optimise clinical effectiveness in patients with dementia.[7] In this article we review the reasoning underlying these suggestions, and consider how the first transdermal patch for AD (and PDD) may have the potential to advance the treatment paradigm for patients with these conditions.

Improving Treatment Compliance

Dosing of oral cholinesterase inhibitors (rivastigmine, donepezil, galantamine) is implemented in two treatment phases: a short-term titration phase during which the objective is to reach a therapeutic dose, and a maintenance phase during which the therapeutic dose is administered for longer-term therapy. The rivastigmine patch has the potential to change many aspects of medication management in both treatment phases, potentially addressing some of the concerns associated with treatment compliance in older patients.

Starting Treatment

All three cholinesterase inhibitors and memantine are always started at low, non-effective doses that must be progressively increased in titration regimes, which often become too complex for elderly patients and care-givers to understand. It is not rare to see patients remain in the first or second titration steps, consequently being undertreated for long periods. Furthermore, cholinergic events such as nausea and vomiting are the most common side effects of all oral cholinesterase inhibitors during the titration phase of treatment. In the clinical setting, these events can form a barrier that prevents some patients from reaching optimal therapeutic doses. The cholinergic side effects of cholinesterase inhibitors are most likely related to the high peak plasma drug concentrations that result from each oral dosage intake, and large fluctuations in plasma levels.[15]

Transdermal patches provide smooth and continuous drug delivery across the skin barrier and into the bloodstream. They have the potential to provide more gradual rises in maximal plasma concentration (C_{max}) and to prolong the time to C_{max} (t_{max}), thus avoiding the rapid rise and fall of concentrations seen with oral therapies.[16] Consequently, drug levels may

be maintained within the theoretical optimal 'therapeutic window', with smaller fluctuations between peaks and troughs that may be associated with side effects and reduced efficacy, respectively.[16,17] Bioavailability following transdermal administration has repeatedly been shown to be greater than with oral delivery for some drugs.[18] A drug released across the skin directly into the bloodstream is free from interactions in the gastrointestinal tract and bypasses first-pass metabolism in the liver. In the case of rivastigmine, pharmacokinetic data have shown that drug exposure in the brain over 24 hours with the target-dose patch (9.5mg/24-hour), despite being lower at face value, is comparable to that provided by 12mg/day capsules.[19] The pharmacokinetic rationale and clinical data supporting the development of the rivastigmine patch is discussed in more detail by Frölich elsewhere in this issue of *European Neurological Review*.[20]

The rivastigmine patch allows easy access to the therapeutic dose, with a simple one-step dose increase from the starting dose patch (4.6mg/24-hour) to target-dose patch (9.5mg/24-hour).[21] While it has been established that the target-dose rivastigmine patch (9.5mg/24-hour) offers comparable drug exposure and similar efficacy to the maximum recommended oral dose of 12mg/day rivastigmine capsules,[19,22] the starting-dose patch (4.6mg/24-hour) provides comparable drug exposure to an oral dose of 6mg/day.[19,20] Rivastigmine oral 6mg/day has been previously demonstrated in large clinical trials to be an effective dose,[23,24] suggesting that using the rivastigmine patch allows patients to start on an effective dose straight away. Patients may derive benefit from an effective dose immediately during the titration phase of treatment, before increasing to the target-dose rivastigmine patch (9.5mg/24-hour).

Clinical data from a trial involving more than 1,000 AD patients demonstrated that the rivastigmine patch was associated with three times fewer reports of nausea and vomiting compared with conventional capsules.[22] In fact, the incidence of cholinergic side effects was not significantly different among patients treated with the 9.5mg/24-hour patch and those receiving placebo. Moreover, the proportion of patients receiving optimal target doses was substantially higher among those in the 9.5mg/24-hour patch group of that study compared with those in the 6mg twice a day capsule group (96 and 64% of patients, respectively).[21]

Staying on Treatment

Titration schedules for cholinesterase inhibitors and memantine are complex, difficult and time-consuming for physicians to explain, and consequently hard for patients and care-givers to understand. As stated, such difficulties often lead patients to remain on low doses that are not efficacious. This is particularly true for oral rivastigmine, which requires twice-daily administration and a four-step titration schedule over four months or sometimes longer. Strategies that make scheduling and administration of medications simpler and easier may have the potential to address some of these concerns. Patches are becoming more widely used across different disease areas, and appear to offer an excellent therapeutic approach for chronic neurological disorders in the elderly, as they are undemanding and convenient to use, provide sustained therapeutic drug levels in the plasma and usually reduce systemic adverse events.[7,25]

The once-daily rivastigmine transdermal patch is easy to apply, small, discreet and comfortable to wear, requires only a one-step increase to target dose, adheres well over the 24-hour application period (while maintaining normal daily activities including bathing and swimming) and is associated with good skin tolerability.[22] Unlike other transdermal patches (e.g. those used for pain control), the rivastigmine patch does not contain any metallic elements, which means that it may be worn by patients even in the event that they need to undergo magnetic resonance imaging (MRI) procedures. Thus, the rivastigmine patch should not interfere significantly with daily living. Patches offer a visual reminder to treat, and application of a once-daily patch can be made part of the daily routine, e.g. when dressing each morning.[7] This may help to address the common problem of forgetting to apply the patch. Non-pharmacological benefits associated with transdermal patches versus conventional oral therapies for the treatment of dementia are summarised in *Table 1,* all of which may contribute to improved treatment compliance overall.[7]

Table 1: Potential Non-pharmacological Benefits of Patches for the Treatment of Dementia

Drug delivered smoothly and continuously
Sustained therapeutic drug levels in the plasma
Reduced systemic adverse events
Easier access to optimal target doses
Avoids the gastrointestinal tract
Independent of food intake – no need to administer at mealtimes
Avoids first-pass effect
Simple and convenient
Small and discreet*
Once daily*
Easy to apply
Comfortable to wear
One-step to target dose*
Empowers the care-giver
Visual reminder to treat and reassurance that medication is being taken
Avoids accidental overdosing
Compatible with magnetic resonance imaging procedures*
Easily removed in the event of an emergency
Tactile experience may enhance patient–care-giver relationship

**Applies specifically to the rivastigmine transdermal patch.*

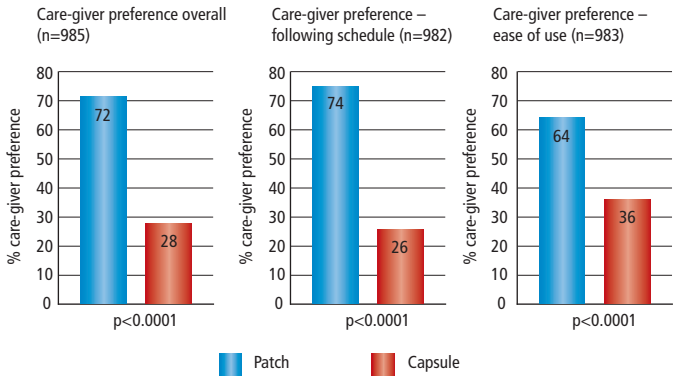
The use of a transdermal patch in dementia may have further advantages (versus conventional oral treatments) in terms of patient–care-giver communication and care, since the application of a patch is a tactile experience for both the patient and the care-giver.[26,27] A patch offers care-givers empowerment in their role of administering and managing medications, and encourages positive care-giver–patient interaction. This in turn may have a favourable impact on the patient.[28]

Preference for Patch Therapies

Transdermal patches are used as a mode of drug administration across a range of therapeutic areas, including angina, attention-deficit–hyperactivity disorder (ADHD), contraception, hormone replacement, major depression, pain management, PD and smoking cessation. Patients often prefer patches to oral therapies for their convenience, efficacy and fewer side effects.[29] A drug delivery system that is preferred for any reason is likely to promote improved compliance. Rates of compliance have been reported to be improved with transdermal contraceptive, angina, hypertension and major depression therapies versus their oral counterparts.[30–33]

A unique aspect of dementia treatment is the integral role that care-givers often play in the management of the disease. Considering that the majority of patients (~75%) require assistance with the management and/or administration of medications,[34] compliance to treatment is often care-giver-driven. Given that care-givers of individuals with AD are often older people themselves with their own medical conditions and drugs to manage, this

Figure 1: Care-giver Preference for Transdermal Patches versus Capsules[37]



Care-giver intent-to-treat population at 24 weeks.

may contribute to difficulties coping.[35] Medication responsibilities – which may include purchasing, scheduling and/or administration – can be a major concern to care-givers, particularly when medications are associated with side effects or time is limited.[36] Care-giver preference for, and satisfaction with, rivastigmine patches were investigated in a large clinical trial that showed their efficacy to treat AD patients with good tolerability and formed the basis for the approval of the rivastigmine patch.[37] The important study findings are presented in *Figure 1*. It should be remembered that all patients received both capsules and patches in this double-blind and double-dummy trial. In total, 72% of care-givers preferred rivastigmine patches to capsules "overall", while 74 and 64% of care-givers preferred patches to capsules based on "ease of use" and "ease of following the schedule", respectively (all p<0.0001).[37] Care-givers also expressed greater satisfaction overall, greater satisfaction with administration and less interference with daily life with patches versus capsules (all p<0.01).[37] Subgroup analyses revealed that care-giver preference for patches over capsules were consistent, independent of the disease severity of patients or the age, gender, patient relationship or country of residence of care-givers.[37]

Care-giver preference for a patch versus an oral approach to dementia treatment may reflect some level of relief from the pressure associated with medication management in this setting. Remarks from care-givers who participated in the study suggested that a patch helped to simplify their daily medication regimens.[38] The rivastigmine patch provides visual reassurance, as well as the ability to monitor that medication is being taken. Such benefits may in turn have a favourable impact on patient outcomes,[36] in addition to potentially improving treatment compliance for enhanced long-term clinical benefits. While the results of this sub-study provide important insight from a care-giver's perspective, in the future it would be useful to also obtain direct opinions from patients with dementia on the utility of transdermal patches versus oral therapies.

Cost-effectiveness

Apart from the obvious economic wastage associated with misused medications, a wealth of research has shown that improved treatment compliance can result in marked improvements in clinical outcomes, as well as lower overall healthcare-related costs.[1] An economic evaluation model has been developed to consider the international incremental costs and benefits associated with the rivastigmine transdermal patch versus best supportive care in the management of AD.[39,40] According to the analyses performed so far based on cost data from the UK and the US, the cost-utility per quality adjusted life year (QALY) for the rivastigmine patch is £13,042 and US$21,264 in the UK and US, respectively. This is well within the usually accepted range for cost-effectiveness as stipulated by the UK's National Health Service and health providers in the US. The cost-effectiveness of rivastigmine patch versus best supportive care appears to be due to improved cognition and functioning and delayed institutionalisation.[39,40]

Concluding Comments

Compliance to medications is a widespread problem. Individuals with dementia are a particularly susceptible population. They are usually of an advanced age and suffer numerous co-morbidities that demand multiple medications, and have memory and cognitive problems. Consequently, compliance to conventional oral cholinesterase inhibitors has typically been poor,[8–10] and it is feasible to suggest that, as a result, clinical outcomes may have been sub-optimal. Good treatment compliance – including both reaching adequate doses and maintaining medication intake over time – is an important step in obtaining maximal therapeutic benefits from any treatment.

The rivastigmine transdermal patch promises a new, effective, convenient and simple treatment option for dementia. Favoured by care-givers in terms of ease of use and following the schedule, a patch has many clinical advantages over conventional oral therapy. The rivastigmine patch offers smooth, continuous delivery of rivastigmine into the bloodstream. The starting-dose patch (4.6mg/24-hour) is believed to offer an effective level of drug exposure from the beginning of treatment, and the target-dose patch (9.5mg/24-hour) provides comparable exposure and similar efficacy to the highest recommended oral doses of rivastigmine (12mg/day).[19,20,22] However, the target-dose patch (9.5mg/24-hour) is associated with an incidence of cholinergic side effects (nausea and vomiting) that is three times lower than with conventional capsules and not different from placebo. The rivastigmine patch allows almost all patients to reach target therapeutic doses with no side effects.[21,22] Many features of the rivastigmine patch may also contribute improved compliance, potentially leading to sustained clinical benefits.[7]

Economic evaluation suggests that by improving patient outcomes in general, in terms of cognition, clinical global impression and daily activities, the rivastigmine transdermal patch represents a clinically valuable, cost-effective option for the treatment of dementia. Future studies are anticipated to provide further evidence that a transdermal patch actually improves compliance to pharmacological therapy among patients with dementia, potentially resulting in a good, cost-effective and well-perceived treatment option. ■

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Social Protection Frameworks for Dementia Sufferers in Low- and Middle-income Countries

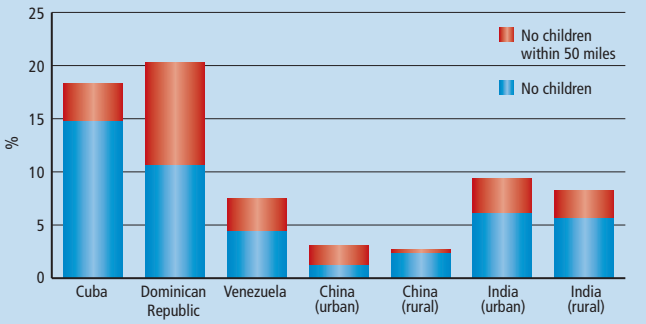
The 10/66 Dementia Research Group – co-ordinated by the Institute of Psychiatry, King's College London, and funded by the Wellcome Trust – was founded to improve population-based and social research into dementia in low- and middle-income regions. It is conducting prevalence and impact surveys in 15 catchment areas in India, China, Nigeria, Cuba, Dominican Republic, Puerto Rico, Brazil, Venezuela, Mexico, Peru and Argentina to improve epidemiological knowledge and aid future strategy. Coverage of Eastern and Central Europe is planned in the coming months.

Findings So Far

Research carried out by 10/66 suggests that dementia prevalence in low- and middle-income regions may have been underestimated, even though dementia is a dominant source of dependency and care-giver strain. Social protection for sufferers depends on a critical interaction between income, living arrangements and availability of children to provide care.

- In the Dominican Republic, social protection is compromised by both low pension coverage and a high proportion of older people having no children living locally.
- In rural China, few older people have pensions, but the large majority live with their children and are supported by them. In urban Beijing, findings reveal that many older people live alone or with their spouse, but pension coverage is good and children are available if needed.
- In all regions, primary healthcare services are used surprisingly infrequently, probably because they fail to meet the long-term needs of people with dementia and their care-givers. In the absence of any formal social care structures, families and communities shoulder a considerable burden. ■

Percentage of Demetia Sufferers without Children for Support, Selected Regions



Source: Alzheimer's Association. For more information see www.alz.co.uk/1066 or email 1066drg@iop.kcl.ac.uk