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Transdermal Treatment Options for Neurological Disorders

Impact on the Elderly

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Abstract

As people grow old, their need for medications increases dramatically because of the higher incidence of chronic pain, diabetes mellitus, cardiovascular and neurological diseases in the elderly population. Furthermore, the elderly require special consideration with respect to drug delivery, drug interactions and adherence. In particular, patients with chronic neurological diseases often require multiple administration of drugs during the day to maintain constant plasma medication levels, which in turn increases the likelihood of poor adherence. Consequently, several attempts have been made to develop pharmacological preparations that can achieve a constant rate of drug delivery.

For example, transdermal lisuride and apomorphine have been shown to reduce motor fluctuations and duration of 'off' periods in advanced Parkinson's disease, while rotigotine allows significant down-titration of levodopa without severe adverse effects. Thus, parkinsonian patients with long-term levodopa syndrome or motor disorders during sleep could benefit from use of transdermal lisuride and apomorphine. Moreover, transdermal dopaminergic drugs, particularly rotigotine, seem the ideal treatment for patients experiencing restless legs syndrome or periodic limb movement disorder during sleep, disorders that are quite common in elderly people or in association with neurodegenerative diseases.

Unlike dopaminergic drugs, transdermal treatments for the management of cognitive and behavioural dysfunction in patients with Parkinson's disease and Alzheimer's disease have inconsistent effects and no clearly established role. Nevertheless, because of their favourable pharmacological profile and bioavailability, the cholinesterase inhibitors tacrine and rivastigmine are expected to show at least the same benefits as oral formulations of these drugs, but with fewer severe adverse effects.

Transdermal delivery systems play an important role in the management of neuropathic pain. The transdermal lidocaine (lignocaine) patch is recommended

as first-line therapy for the treatment of postherpetic neuralgia. Furthermore, in patients with severe persistent pain, transdermal delivery systems using the opioids fentanyl and buprenorphine are able to achieve satisfactory analgesia with good tolerability, comparable to the benefits seen with oral formulations.

Transdermal administration is the ideal therapeutic approach for chronic neurological disorders in elderly people because it provides sustained therapeutic plasma levels of drugs, is simple to use, and may reduce systemic adverse effects. Several transdermal delivery systems are currently under investigation for the treatment of Parkinson's disease, Alzheimer's disease and neuropathic pain. Although most transdermal delivery systems treatments cannot be considered as first-line therapy at present, some of them provide clear advantages compared with other routes of administration and may become the preferred treatment in selected patients. In general, however, most transdermal treatments still require long-term evaluation in large patient groups in order to optimise dosages and evaluate the actual incidence of local and systemic adverse effects.

Transdermal drug delivery systems (TDS) have several advantages over parental and oral routes of administration, and it is the elderly who can derive the greatest benefits.[1] This is particularly true when a chronic neurological disorder is present, because motor or cognitive deficits may overlap with the impairments in daily living activities typical of advanced age. In this context, TDS may circumvent the patient's unwillingness or incapability to swallow oral preparations and remove the discomfort associated with multiple intramuscular injections or intravenous infusions. Transdermal administration of drugs also prevents problems associated with hepatic first-pass metabolism, poor absorption from the gastrointestinal tract and variable bioavailability. Constant plasma concentrations may be achieved as a result of rate-controlled delivery of particular preparations, even when the drug has a short elimination half-life. As a consequence, frequency of administration may be significantly reduced, potentially improving adherence in elderly people. The site of drug delivery can also be regularly changed, thereby reducing the risk of local adverse events.

This review examines the efficacy and tolerability of transdermal drug administrations currently under investigation for neurological diseases, with a particular focus on Parkinson's disease (PD) and restless legs syndrome (table I), Alzheimer's disease (AD) [table II] and neuropathic pain (table III).

Current available databases (MEDLINE from the US National Library of Medicine, IngentaConnect) were used for the literature search, with the main key words being: neurological diseases, movement diseases, Parkinson's disease, Alzheimer disease, dementia, restless legs syndrome, periodic limb movements, pain, transdermal, dermal, patch and elderly.

1. Motor Fluctuations in Parkinson's Disease

1.1 Motor Fluctuations and Continuous Dopaminergic Stimulation

The management of motor fluctuations in advanced PD still represents a major problem.[43-45] When the disease is recognised and dopaminergic therapy initiated, patients usually show sustained improvement after administration of medication without any deterioration in motor function.[46,47]

Table I. Transdermal delivery systems using dopaminergic drugs for the management of Parkinson's disease (PD), restless legs syndrome (RLS) and periodic limb movement disorder (PLMD) during sleep

Drug	Use	Absorption	Dosing regimen and approximate release rate	Notes	Main adverse effects	References
Bromocriptine	Preclinical studies in animals	Passive, use of penetration enhancers				2
Lisuride	Add-on therapy in PD (pilot study)	Passive	2–5 μg/cm^2/h	Reduction in motor fluctuations	Transient skin irritation	3
	Severe RLS (controlled pilot study)		3mg per patch; 7 μg/h	Improvement according to RLS severity scales and actigraphy assessments	Transient skin irritation	4
Apomorphine	Add-on therapy in PD (pilot study)	Iontophoresis and use of percutaneous absorption enhancers	15 mmol/L per patch; 98.3 ± 12.1 nmoL/cm^2/h	Improvements in rigidity, tremor and dyskinaesias during or after current application	Tingling and itching, slight erythema	5
	Add-on therapy in PD (pilot study)	Passive diffusion from microemulsion	40mg per patch; 88 μg/cm^2/h	Reduction in total duration of 'off' periods	Sleepiness, transient nausea, transient skin irritation	6
	PLMD in PD (pilot study)	Passive diffusion from microemulsion	40mg per patch	Reduction in periodic limb movement index and reduction in sleep instability	Transient skin irritation	7
Rotigotine	Add-on therapy in early and advanced PD (multicentre controlled studies)	Passive	4.5–18mg per patch	Improvements in motor scores and activities of daily living scores on the UPDRS; down-titration of daily levodopa dose allowed	Sleepiness, mild nausea and vomiting, dizziness, mild skin irritation	8-12
	Moderate and severe RLS (multicentre controlled study)		4.5mg	Improvement according to RLS severity scales	Mild skin irritation	13

UPDRS = Unified Parkinson's Disease Rating Scale.

Table II. Transdermal drug delivery systems for the management of cognitive and behavioural dysfunctions in Alzheimer's disease (AD) and Parkinson's disease (PD)

Drug	Use	Absorption	Dosing regimen	Notes	Main adverse effects	References
Physostigmine	Probable AD (multicentre controlled studies)	Passive	30–60mg	Not superior to placebo after 24 weeks, probably because of low dosages	Nausea, vomiting, abdominal cramps, headache	14,15
Tacrine	Pilot study in healthy adults	Drug release with iontophoresis from ion-exchange fibre discs	Total dose 64mg	Constant and clinically significant plasma concentrations achieved during iontophoresis	Transient skin irritation, pinching	16,17
Rivastigmine	Preclinical study in animals	Passive	18–54mg	Bioavailability 20–40 times greater than oral administration	Skin irritation	18
	Patients with AD or mild cognitive impairment (pilot study)			No deterioration in fine motor skills		19
	Probable AD (phase III study)			Efficacy in relation to cognitive dysfunctions still under evaluation		20,21
Nicotine	AD with mild-to-moderate dementia (controlled study)	Passive	14–21 mg/day	No efficacy in relation to memory deficit, verbal fluency, attention or psychomotor speed	Nausea, dizziness, sleep disturbance	22
	AD with mild-to-moderate dementia (controlled study)		5–10 mg/day	Improvement in attentional performance; performances on other tests measuring motor and memory function not improved		23
	Nondemented aged people at risk for dementia (pilot study)		5–10 mg/day	Inconsistent changes in relation to verbal learning, delayed recall and word retrieval; findings inconclusive		24
	Nondemented PD patients		7–21 mg/day	Contradictory results in relation to motor symptoms; no changes on cognitive tasks	Poorly tolerated because of nausea, vomiting, dizziness, increased blood pressure, intestinal cramps	25-28
17β-estradiol	Postmenopausal woman with AD (controlled studies)	Passive	0.05–0.10 mg/day	Improvements in attention and verbal memory; reduction of plasma concentration of toxic β-amyloid fragments (Aβ40)	Well tolerated	29,30
	Men with advanced AD (controlled study)			No effect on aggressive behaviour	Rebound in aggressive behaviour after patch removal	31

However, after a variable period of time the duration of effectiveness of a single dose of levodopa progressively decreases and it becomes necessary to increase the number of administrations to maintain the benefit. This condition characterises the 'long-term levodopa syndrome', which may also include choreiform involuntary movements that typically appear at peaks of levodopa effectiveness.[48-50] Pharmacodynamic and pharmacokinetic factors have been hypothesised to explain the genesis of motor fluctuations in patients with PD taking levodopa: impaired gastric emptying with delay in levodopa reaching its absorptive site,[51,52] interference of dietary proteins with levodopa absorption,[53] inadequate dopamine storage following progressive death of dopaminergic neurons as part of the neurodegenerative process, pulsatile dopamine receptor stimulation associated with exogenous levodopa administration,[54,55] and upregulation of nearby glutamate receptors and consequent overactivity of striatal neurons driven by cortical glutamatergic firing.[56] In order to prevent the occurrence of this pulsatile stimulation, several strategies have been proposed to provide a more continuous delivery of drug and constant levels of striatal dopaminergic activation. These strategies include levodopa administration on an empty stomach or at least separated from dietary proteins; use of medications that hasten gastric emptying such as cisapride and domperidone;[57] administration of controlled-release levodopa preparations or drugs inhibiting levodopa metabolism, such as monoamine oxidase inhibitors and catechol-*O*-methyl-transferase inhibitors;[58,59] and use of constant intravenous infusion or duodenal delivery of levodopa after placement of a percutaneous endoscopic gastrostomy tube.[60] Nevertheless, while these therapeutic approaches can reduce 'wearing-off' phenomena in some patients, further studies are needed to demonstrate their effectiveness in providing constant receptor stimulation and preventing motor fluctuations. Of the dopamine receptor agonists, apomorphine and lisuride have proved to be useful when administered by subcutaneous continuous infusion.[61,62] However, even though some patients can tolerate this treatment for years, difficulties relating to needle management and local or systemic adverse effects such as nausea, orthostatic hypotension and skin reactions[61,62] may limit the widespread use of this technique, especially in the elderly.

1.2 Continuous Dopaminergic Stimulation with Transdermal Dopamine Agonist Preparations

Currently, there is increasing interest in the potential role of TDS in the treatment of PD, as this route of administration can be considered the ideal means to achieve prolonged plasma levels of drugs and continuous dopaminergic stimulation with little discomfort for patients.[63] Several TDS have been used to deliver a variety of medications, including sex hormones and analgesics,[64,65] with resultant achievement of steady-state dose-linear plasma levels of the delivered drugs. Unfortunately, levodopa is not a good candidate for transdermal administration because of its poor solubility and stability. However, several transdermal preparations with dopamine agonists have been studied, although only a few of these still seem promising for clinical use (see section 1.2.2). Administration of most of the latter agents is based on passive diffusion of a soluble drug through the skin and capillaries, although in some cases drug passage across the skin is enhanced by the application of a small electric current (transdermal iontophoretic transport). Other promising preparations use specific microemulsions that permit a significant increase in transdermal diffusion of the agent included (see section 1.2.2).

1.2.1 Insufficiently Effective Transdermal Systems

The first attempts to develop TDS with dopamine agonists date back to the mid-1980s, when naxagolide [(+)-4-propyl-9-hydroxynaphthoxazine

(PHNO)], a potent dopamine D_2 receptor agonist, was proposed for transdermal administration because of its solubility in lipid and aqueous medium.[66] A few years later, the antiparkinsonian efficacy of naxagolide in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated squirrel monkeys[67] and in parkinsonian patients was reported.[68,69] Plasma concentrations of naxagolide were shown to begin to rise 4–6 hours after patch application and reach a steady state by 24 hours. This pharmacokinetic profile was attributed to the lag time needed for skin permeation and the reservoir action of subcutaneous tissues. Despite these preliminary results, sufficient evidence for the efficacy of this preparation as monotherapy was not obtained to justify further clinical studies.

More recently, transdermal administration of the D_2 receptor agonist nonergot piperazine derivate piribedil in a marmoset MPTP model of PD resulted in reversal of motor deficits without significant adverse effects.[70] Unfortunately, in a double-blind, placebo-controlled study of 27 patients with idiopathic PD, TDS with piribedil did not prove efficacious with respect to either the main endpoint (Unified Parkinson's Disease Rating Scale [UPDRS] motor score) or the secondary endpoints (rigidity, bradykinesia, postural and resting tremor scores), probably because of the low plasma concentrations achieved (<10 ng/mL).[71] Technical problems related to the largeness of the patch required to deliver adequate dosages of the drug stopped further developments of this TDS.

1.2.2 Promising New Transdermal Systems

At present, transdermal administration of four dopamine agonists has been evaluated with results from preliminary *in vivo* studies that warrant further efforts to confirm their effectiveness. Three of these, apomorphine, bromocriptine and lisuride, are well known dopamine agonists generally administered in past years via other routes, whereas rotigotine, introduced in clinical trials only recently, has undergone wider testing as a TDS treatment for PD.

Apomorphine (6a-β-aporphine-10,11-diol) is a well-known potent agonist at D_1 and D_2 receptors and a very useful adjunctive medication in parkinsonian patients with refractory motor fluctuations.[72,73] However, despite its favourable pharmacological characteristics, clinical use of apomorphine in the treatment of PD has been somewhat limited by its pharmacokinetic profile, i.e. short half-life of approximately 30 minutes, rapid clearance from plasma, absence of storage or retention in brain regions, poor bioavailability (5%) and high first-pass metabolism after oral administration.[74] To overcome these limitations, subcutaneous, sublingual, rectal and intranasal routes of administration were studied,[75-78] but none of these demonstrated the capability for prolonged dopaminergic stimulation. Only subcutaneous administration of apomorphine by means of a microinfusor can produce constant therapeutic plasma levels of the drug.[79,80] However, this treatment may become impractical for chronic use in most patients because of development of local subcutaneous nodules or systemic adverse effects (e.g. hypotension, nausea, sleepiness and hallucinatory phenomena), especially in the elderly.[81]

In order to exploit the favourable pharmacological characteristics of apomorphine and overcome the pharmacokinetic limitations of the drug, two different approaches have been proposed for transdermal delivery. The first approach attempted to exploit the potential of transdermal iontophoresis to deliver apomorphine continuously into systemic circulation at a well controlled rate (current-dependent delivery system).[82-84] Studies evaluating this approach demonstrated that delivery of apomorphine by the transdermal route was feasible and that the rate of delivery could be controlled by modulating current density. However, the plasma concentrations achieved were at the lower limit of the therapeutic

range (<10 ng/mL).[82-84] Recently, iontophoresis was applied after skin pretreatment for 1 hour with an aqueous mixture of three surfactants (acting as a percutaneous absorption enhancer) to overcome the limitations of iontophoretic delivery.[5] Pretreatment of the skin with this absorption enhancer, compared with iontophoresis alone, resulted in a 2-fold increase in iontophoretic transport of apomorphine *in vitro*, an approximate 10% increase in bioavailability and a near 2-fold increase in the percentage of responder patients. Moreover, the concentration-time profiles of apomorphine after transdermal iontophoretic administration with pretreatment with percutaneous absorption enhancer were similar to those obtained with constant intravenous infusions. However, pretreatment was associated with larger interindividual variations in apomorphine profiles, which suggests that this approach is not yet optimal and needs further improvement. Nevertheless, no clinically relevant systemic adverse effects were described and only brief sensations such as tingling and itching without pain during application of the current and a transient slight erythema were reported.[5]

The second approach to transdermal delivery of apomorphine consisted of the development of a novel pharmaceutical preparation of apomorphine dissolved in a thickened microemulsion.[85] In this preparation, apomorphine was present in the microemulsion as an ion pair complex with octanoate in order to increase its lipophilicity and diminish its dissociation from the microemulsion. The drug was completely dissolved in the microemulsion and relatively high concentrations could be obtained as a result of the supersolvent properties of microemulsions. The dispersed phase, also acting as a reservoir, made it possible to maintain an almost constant concentration of apomorphine in the continuous phase and pseudo-zero-order kinetics could thus be achieved *in vitro*.[85] The formation of an ion pair is presumably the main reason for the facilitated transport of apomorphine through the skin in this preparation. In a group of 21 patients affected by PD and motor fluctuations, this preparation provided therapeutic apomorphine plasma levels (>15 ng/mL) for 12 hours, corresponding to the period of time the patch was maintained on the skin.[6] The total duration of 'off' periods decreased by about 50% compared with levodopa treatment alone and by about 30% compared with levodopa plus oral dopamine agonist therapy. Systemic adverse effects (sleepiness, nausea, mild orthostatic hypotension) and local transient mild erythema occurred in about 10% and 70% of patients, respectively, but the overall tolerability was good and only one patient needed to discontinue treatment because of severe nausea not controlled by domperidone.[6] These preliminary results seem encouraging and suggest that this preparation could be a useful treatment for PD patients, particularly for those experiencing uncontrolled 'wearing-off' and prolonged 'off' phenomena. Use of a patch on the skin that can be easily applied by patients or relatives together with a long duration of clinical efficacy might be particularly advantageous for elderly subjects, especially during the night, and would also be associated with little discomfort while reducing the number of oral levodopa administrations required. Conversely, because about 1 hour is required for this preparation to achieve therapeutic plasma concentrations of apomorphine, it would not appear to be the 'ideal' preparation for rapid relief of the 'off' condition: in this case, apomorphine administered by the subcutaneous route, which provides the most rapid absorption, still remains the best choice. However, because local adverse effects are likely to be a major problem arising with chronic treatment, this preparation requires further investigation in a larger group of patients and greater optimisation of apomorphine dosages and application areas.

Bromocriptine, a semi-synthetic ergot alkaloid with a preferential effect on the D_2 receptor subtype,

has been widely used in previous years for the treatment of PD in oral formulations. However, similarly to apomorphine, the pharmacokinetics of bromocriptine administered via the oral route are not favourable because of the drug's low bioavailability as a result of the hepatic first-pass effect.[86] Alternative delivery routes such as intramuscular[87] or vaginal application[88] have been reported but also shown to be expensive or not practical for chronic use. A transdermal formulation of bromocriptine using a polycationic polymer and penetration enhancers has been tested in rabbit skin, showing that sufficient penetration of the drug could be achieved.[2] However, it should be noted that rabbit tissue is more permeable than human skin, and further studies are expected to verify if this formulation will work in the same way with human skin.

Recently, a pilot study of a novel formulation of another potent D_2 receptor agonist, lisuride, demonstrated adequate drug release in mice and encouraging results as add-on therapy in eight patients with advanced PD.[3] The additional lisuride patch application was reported to significantly improve motor function according to a patient's self-rating scale, with mild adverse effects in half of the patients resulting in transient skin irritations.[3]

Rotigotine, a novel lipid-soluble, non-ergot D_3/D_2/D_1 receptor agonist, has undergone more testing than any other dopamine agonist as a transdermal preparation for PD treatment. Rotigotine has been shown to be effective in preclinical studies with animal models of PD[89,90] and, formulated as a skin patch, has also been shown to be a promising treatment in recent clinical studies.[8-12] In these studies, administration of rotigotine led to significant improvement in motor symptoms both in advanced and early stages of PD, although the optimal dose has yet to be determined because of use of two different TDS (the more recent system increased drug delivery 3-fold compared with the earlier patch of the same size) and different study designs and durations (from 3 weeks up to 27 weeks).[9,10] Rotigotine at dosages of 13.5–36 mg/day was associated with statistically significant improvements in motor scores and activities of daily living scores on the UPDRS, and a dosage of 18 mg/day was reported to be well tolerated by about 80% of patients.[9-11] Application site reactions, occurring in about half of patients, and systemic adverse effects (primarily nausea, vomiting and somnolence), occurring in about one-fifth of patients, were generally mild, suggesting that doses higher than those used in these studies could be given.[10,11] Transdermal delivery of rotigotine was shown to provide constant blood levels of drug over 24 hours and this sustained dopaminergic stimulation allowed down-titration of the daily levodopa dose by >50%, with maintenance of efficacy on motor symptoms even in subjects with advanced PD. An overall beneficial effect of this transdermal dopamine agonist on drug-induced dyskinesias when given in conjunction with levodopa was also described.[9,12]

These encouraging preliminary pharmacokinetic, pharmacodynamic and efficacy data for dopamine agonists administered via the transdermal route mandate continued exploration of this therapeutic modality, particularly in the elderly, given the relatively simple administration, lack of invasiveness, long duration of clinical benefits and good tolerability associated with this approach. At present, these preparations have been used as adjuvant therapy in advanced PD, but future studies will define whether continuous dopaminergic stimulation from the start of antiparkinsonian therapy is efficacious and prevents motor fluctuations typical of intermittent therapy. Because orthostatic hypotension, which is not uncommon in the elderly, hallucinations and persistent local erythema could prove limitations to use of this type of therapy in the elderly, prudent selection of patients will be required. However, it must be emphasised that a further advantage of transdermal

therapy consists of the relatively rapid reversibility of adverse effects by patch removal.

2. Restless Legs Syndrome and Periodic Limb Movement Disorder During Sleep

Restless legs syndrome is a frequent cause of insomnia in the elderly because its incidence increases sharply with age and it may be associated with several diseases common in the elderly, such as neuropathies, iron deficiency, renal failure and neurodegenerative diseases. Typically, patients report a history of inability to keep their legs still when trying to fall asleep because of continuous dysaesthesias, coupled with an urge to get out of bed and walk around in an attempt to obtain transient relief. This syndrome is frequently associated with periodic jerks involving the lower limbs during sleep documented by polysomnography. The consequences of this condition include difficulties in sleep onset and maintenance, sleep disruption, low sleep efficiency and daytime excessive somnolence.

Oral dopamine agonists are the therapy of choice for restless legs syndrome and in most patients they are very efficacious at lower dosages than those used in PD.[91] Nevertheless, some patients with dysaesthesias or periodic limb movements persisting through the night may require excessively high dosages or may experience only short-lasting benefit from oral treatment.[91] Moreover, many patients may experience symptoms not only at bedtime but also during the day or according to variable circadian patterns.[92] In these cases, transdermal preparations of dopamine agonists are expected to be the best choice.

In a recent double-blind, placebo-controlled, 1-week pilot study, the novel nonergot D_2 receptor agonist rotigotine, formulated as a skin patch, was shown to be efficacious in patients with moderate-to-severe idiopathic restless legs syndrome when administered at a dosage of 4.5 mg/day.[13] The skin tolerability of the patches and systemic adverse effects for rotigotine and placebo were similar. Similarly, in a controlled pilot study, symptoms of severe restless legs syndrome were clearly improved by lisuride 3mg patch, without clinically relevant adverse effects.[4] Moreover, sleep analysis in 12 PD patients during night-time transdermal apomorphine treatment revealed a 15% reduction in the periodic limb movement index together with a significant reduction in sleep instability.[7] Future trials will verify the efficacy of these TDS in the treatment of periodic limb movement disorder during sleep and, as with PD, further efforts will be directed at evaluating the optimal dosages and possible adverse effects associated with prolonged treatment.

3. Cognitive Dysfunctions in Neurodegenerative Diseases

3.1 Behavioural Problems and Cognitive Dysfunctions in Dementia

Behavioural and cognitive problems in neurodegenerative disease, primarily AD, are difficult to control and are recognised as leading causes for institutionalisation. However, cognitive deficits resulting from progression of degenerative processes, together with advanced age, make repeated administration of doses of drug often impracticable. Currently available therapies for AD are limited to cholinergic drugs according to the hypothesis that cognitive impairment in AD results from the death or deficit of cholinergic neurons in the basal forebrain.

3.1.1 Anticholinesterase Drugs

Studies conducted in the 1980s[93-96] made up the initial phase of clinical trials that evaluated anticholinesterase drugs. These studies were designed to test the efficacy and safety of physostigmine by oral and intravenous administration, but the short half-life of about 30 minutes and rapid hepatic clearance of the drug proved to be serious disadvantages.[93]

Unfortunately, more recent trials[14,97-99] using controlled-release formulations of physostigmine had serious methodological problems that did not permit the correct identification of responders.[14] In order to overcome these limitations, a physostigmine transdermal therapeutic system was developed and tested in a large study that included patients with probable AD and mild-to-moderate cognitive impairments.[15] In contrast to expectations, the efficacy of physostigmine was not superior to placebo in this study, but, as noted by the investigators, the doses delivered (up to 60mg) were probably too low to evaluate efficacy. Physostigmine plasma concentrations showed a high degree of interindividual variability without linear correlation with dosages and appeared to be insufficient to compensate for cholinergic deficiencies in brain areas. The very low occurrence of adverse effects was also consistent with this interpretation.[15] Clearly, modification of this patch system is mandatory in order to achieve higher physostigmine plasma concentrations and allow evaluation of the clinical efficacy of this approach during long-term therapy.

Similarly to physostigmine, tacrine (1,2,3,4 tetrahydro-9-acridinamine), a reversible cholinesterase inhibitor used for AD treatment, has low bioavailability because of the hepatic first-pass effect and a relatively short elimination half-life (2–4 hours).[100] Moreover, tacrine has the potential for dose-dependent hepatotoxicity and peripheral cholinergic adverse effects.[100] Interest in transdermal delivery of tacrine for AD derives not only from the possibility of reducing toxicity but also from the hypothesis that constant levels of tacrine in the brain may maximise its effects on memory enhancement.[16] In a recent preclinical study,[17] control of transdermal drug delivery was obtained using a novel ion-exchange fibre and iontophoresis. The ion-exchange fibres acted as a drug reservoir, controlling the release and iontophoretic transdermal delivery of the drug. Pharmacokinetic data from a pilot study involving ten healthy adults who were given tacrine 64mg delivered from the ion-exchange fibre for 3 hours by iontophoresis, and for 1 hour passively, were also encouraging.[101] Therapeutically relevant plasma concentrations of tacrine were achieved, the plasma profile reached a plateau after the first 30 minutes of current delivery and inter-subject variations were quite small. The flux remained constant until the current was turned off. Moreover, even during passive permeation, tacrine plasma concentrations decreased slightly as a consequence of formation of a reservoir of the drug in the skin. Local irritation was present in all patients and was reported to be directly related to the iontophoretic current density.[101] On the basis of these data, this system appears to be a promising novel treatment for AD, although the optimal current density, possible effects of long treatment on liver function and clinical efficacy of this approach need to be investigated.

Rivastigmine, another acetylcholinesterase inhibitor, also seems to hold promise for TDS use in neurodegenerative disease. Dermal administration of rivastigmine in animals was associated with a markedly greater bioavailability than with the oral route,[18] and clinical studies in patients are still under way to verify a possible role in the management of AD.[19] In particular, a large multicentre, controlled, phase III study evaluating the safety and efficacy of the rivastigmine TDS in patients with probable AD, started in 2003, has recently been completed and data will soon be available.[20,21]

3.1.2 Nicotine

Demonstration of deficient nicotinic-cholinergic receptor binding in AD brain[102] in the past decade encouraged studies investigating the efficacy of the alkaloid nicotine in the management of behavioural problems in AD patients. Moreover, recent research has indicated that nicotine can limit verbal outbursts in Tourette syndrome[103] and reduce the inattentiveness of attention-deficit hyperactivity disorder.[104]

Short-term nicotine injections were found to improve attentional performance in AD,[105] but could not be of practical use in the long-term treatment of AD. However, transdermal nicotine patches offer a way of delivering measured doses of nicotine in a safe fashion and for a longer period of time.

Preliminary reports of use of transdermal nicotine patches for AD did not provide homogeneous results. One study described three AD patients and one patient with vascular dementia who became less agitated during treatment with transdermal nicotine 7–14mg and experienced deterioration of their clinical state when the patch was discontinued.[106] However, use of complicated medical regimens, the absence of standard assessment tools and the small numbers of patients studied prevented the investigators from drawing conclusions. In another pilot study,[107] treatment with a nicotine patch for 8 days in six patients with probable AD was reported to improve learning but did not significantly affect memory, behaviour and global cognition. Sustained administration of nicotine appeared to be safe and well tolerated, although a significant decrease in sleep was reported. Similarly, a double-blind, placebo-controlled, crossover study[22] focusing on short-term memory in 18 AD patients with mild-to-moderate dementia did not find any significant difference between placebo and treatment with a dermal nicotine plaster at dosages of 14–21 mg/day for 4 weeks. A more recent double-blind, placebo-controlled study[23] in eight AD patients with mild-to-moderate dementia, consisting of two periods of 4-week transdermal nicotine up to 10 mg/day separated by a 2-week washout period, reported a significant improvement in attentional performance, but did not show improved performance in other tests measuring motor and memory functions. The discrepancies among these reports may reflect the small number of patients studied, which limits the statistical power of these studies to detect more subtle but clinically significant cognitive improvements. Higher doses of nicotine or combining nicotine with other therapies may provide greater efficacy. Interestingly, a potential therapeutic role for nicotine treatment in nondemented aged patients at risk of dementia has recently been suggested, although further studies are needed to confirm these data.[24] In this study, significant changes in verbal learning, object learning, delayed recall and word retrieval were reported, particularly in patients at the lower end of baseline test performance on the tasks used.

In the future development of nicotinic treatments, animal models will become important for investigating the neurobiological basis of nicotine involvement in cognitive functions. Local nicotine infusion in rats showed that the hippocampus and amygdala are important substrates for nicotine effects on working memory function.[108,109] Both $\alpha 7$ and $\alpha 4\beta 2$ nicotine receptors have been reported to be involved in working memory, and nicotine interactions with dopaminergic and glutamatergic systems may also play a role.[110] At the molecular level, nicotinic receptor agonists have been shown to induce long-term potentiation, as shown by strengthening of synaptic connections associated with learning and memory formation and enhanced neurotransmitter release.[111] The study of neural nicotinic mechanisms related to cognitive functions may lead to the development of more selective nicotinic analogues for the treatment of behavioural and cognitive dysfunctions with fewer adverse effects.

3.1.3 Muscarinic Receptor Agonists

Similarly to nicotine agonists, muscarinic cholinergic drugs, particularly muscarinic M_1 agonists, are potentially useful for AD treatment and may reduce the need for free choline in acetylcholine synthesis. In AD, cholinergic neurons are believed to compensate for a deficiency of choline required for acetylcholine synthesis by degrading membrane phosphatidylcholine.[112] In a recent placebo-controlled study[113] that analysed brain proton magnetic

resonance spectroscopy in patients with mild-to-moderate AD receiving a 16-week treatment with transdermal xanomeline, it was claimed that this M_1/M_4 receptor agonist improved both the cognitive deficits and behavioural symptoms of AD. These interesting preliminary data suggested a relationship between levels of parietal lobe grey-matter cytosolic choline, the precursor pool for acetylcholine synthesis, and cognitive performances during treatment. Further large-scale studies[114] are under way to confirm the capacity of xanomeline to attenuate the membrane degradation process and to define its safety and efficacy profile in the treatment of AD.

3.1.4 Estrogens

Besides cholinergic drugs, evidence from clinical, epidemiological and basic neuroscience research suggests that estrogens should modify the pathobiology of AD and improve some symptoms of the disease. Some studies have suggested that hormone replacement therapy (HRT) has cognition-enhancing effects in women with AD.[115,116] Estradiol has shown a variety of neurotrophic and neuroprotective properties, increases the function of several neurotransmitters, increases cerebral blood flow, facilitates long-term potentiation in the hippocampus and has antioxidant activities.[117] Moreover, cell-culture studies support the ability of estradiol to favourably alter the processing of amyloid-precursor protein, the protein that plays the main role in the pathobiology of AD.[118] Unfortunately, contradictory reports do not allow a definite conclusion to be drawn as to whether or not HRT could reduce the risk of development of dementia in postmenopausal women, probably because of the heterogeneity of therapeutic protocols and populations studied.[119] A placebo-controlled, double-blind, pilot study[29] in postmenopausal women with mild-to-moderate AD treated for 8 weeks with 17β-estradiol 0.05 mg/day, delivered via a skin patch, provided clinical evidence of a specific improvement in attention and verbal memory. Indeed, the latter improved rapidly after 1 week of treatment, and the improvement was positively correlated with plasma levels of estradiol. Moreover, the improvements in attention and memory decreased as soon as treatment was discontinued. The dosages used were similar to those commonly employed to treat symptoms associated with menopause, but with the advantages of achieving steady-state plasma levels of the drug similar to those found during the early to mid-follicular phase of the menstrual cycle and low risks of venous thrombosis and hypertension. Other investigators have also reported similar beneficial effects for estrogen on other selective cognitive domains;[120,121] conversely, however, some studies were unable to demonstrate persistent effects of estrogen on cognitive functions.[122,123] These inconsistencies may reflect the use of different cognitive assessment tools, different potencies of estrogen formulations or qualitatively different population samples. Nevertheless, interest in HRT has been reinforced by the demonstration that transdermal 17β-estradiol 0.10 mg/day administered for 8 weeks to HRT-naive postmenopausal women with probable AD reduced the plasma concentration of toxic β-amyloid fragments (Aβ40) associated with AD pathology.[30] Although a clear correlation between Aβ40 concentrations and cognitive status is lacking, these data are particularly interesting because potentially this treatment could slow disease progression by reducing β-amyloid toxicity and delaying senile plaque formation. In this context, where prolonged treatment is needed, transdermal administration of hormone appears the best option.

Large studies of the efficacy of estrogens via the transdermal route in males with dementia are still lacking. A single 8-week, randomised, controlled study investigated the efficacy and tolerability of transdermal estrogen patches as adjunctive treatment for aggressive behaviour in 27 male patients with advanced dementia.[31] Use of the patch was well tolerated and produced a significant rise in

serum estrogen but not a decrease in serum testosterone. Aggressive behaviour was not influenced by estrogen treatment, but a rebound in aggressive behaviour after patch removal was described. This finding is difficult to interpret, and larger studies are therefore needed to verify any effect of transdermal estrogen treatment in males with dementia.

3.2 Cognitive Dysfunctions in Parkinson's Disease

Studies assessing the efficacy of nicotine in PD patients have produced contradictory results. The rationale for using this drug derives from animal studies that showed decreased dopaminergic cell loss in the MPTP experimental model[124] and slowed age-associated dopaminergic receptor loss[125] with administration of nicotine. The dopaminergic nigrostriatal pathway is rich in nicotine receptors and *in vitro* studies have shown that local application of nicotine at the nigrostriatal terminals increases the exocytosis of dopamine.[126] Moreover, cholinergic cell loss has been described in the basal forebrain, parietal, frontal and temporal cortices as well as in the hippocampus of patients with PD,[127] and it has been suggested that this depletion could be associated with cognitive deficits frequently observed in this disease.[128] Three controlled studies[25-27] have evaluated the effect of transdermal nicotine on motor symptoms of PD, but their results were not encouraging, as only a single study reported an improvement.[25] The other studies reported no effect or even a worsening of motor symptoms.[26,27] Because the positive study also reported improved attention and processing speed in PD,[25] further research has focused on the effects of nicotine on cognition, using a more rigorous methodological design and a larger number of cognitive tests.[28] According to this study, transdermal nicotine treatment over 25 days, at doses up to 21 mg/day, neither improved nor worsened cognitive functioning in 22 nonsmoking PD patients. The treatment was also poorly tolerated because of acute adverse effects such as dizziness, nausea and increased blood pressure, with about 60% of patients withdrawing from therapy. The poor tolerability and lack of efficacy might have been related to a possible lack of specificity of nicotine in targeting critical nicotinic receptors involved in the pathophysiology of PD, suggesting the need for more selective nicotine agonists for PD treatment.

4. Neuropathic Pain and Limb Dysaesthesias

Chronic pain syndromes and dysaesthesias caused by peripheral neuropathies are a common complaint in the elderly and may result in poor quality of life and depression. In particular, postherpetic neuralgia in aged people often presents as continuous burning or intense paroxysmal pain lasting several months and may become severe and disabling. Treatments such as tricyclic antidepressants, antiepileptics and opioids are sometimes useful for these conditions but not devoid of adverse systemic effects, particularly in aged patients. Nausea, constipation, urinary difficulties, sedation and dizziness are frequent complaints in patients taking these medications and may lead to drug withdrawal. Conversely, use of topical analgesics or anaesthetics may provide pain relief with minimal risk of systemic toxicity. Of these drugs, lidocaine (lignocaine) in a 5% concentration patch has been shown to act as a targeted peripheral analgesic and is specifically indicated for the treatment of postherpetic neuralgia.[32] Lidocaine acts locally as a sodium channel antagonist, reducing the frequency of spontaneous ectopic nerve discharges generated as a consequence of sensory nerve fibre damage.[33] Lidocaine patch 5% (700 mg/patch), at a dosage of up to three patches applied for 12 hours/day for 1–28 days, demonstrated efficacy in patients with moderate-to-severe postherpetic neuralgia, significantly improving pain relief scores and items of the Neuropathic

Table III. Transdermal delivery systems for the management of neuropathic pain and limb dysaesthesias

Drug	Use	Absorption	Dosing regimen	Comments	Main adverse effects	References
Lidocaine (lignocaine)	Moderate-to-severe chronic pain resulting from postherpetic neuralgia or painful diabetic neuropathy (controlled studies)	Passive	700mg per patch; 1–4 patches/day	Significant improvement in pain relief scores and items of the Neuropathic Pain Scale	Mild skin rashes or irritations at the application site	32-37
Ketamine	Intractable neuropathic pain caused by lesions in the CNS (controlled study)	Iontophoresis	50–75mg	Improvements on the Pain Disability Index and quality of life scales	Sedation, mild erythema	38
Fentanyl	Severe chronic pain unresponsive to nonopioid analgesics	Passive	25 µg/h	Allows continued and sustained analgesia in chronic cancer pain; under evaluation for moderate to severe neuropathic pain	Transient erythema, nausea, vomiting, constipation, somnolence	39,40
Buprenorphine	Severe chronic pain unresponsive to nonopioid analgesics	Passive	20–40mg	Effective in the treatment of chronic cancer and noncancer pain without clinically relevant development of tolerance; under evaluation for moderate to severe neuropathic pain	Transient erythema, pruritus, nausea, vomiting, dizziness, constipation	41,42

Pain Scale.[34,35] The most frequent adverse effects (affecting about 30% of patients) were self-resolving mild skin rashes or irritation at the application site. Up to four patches applied for 18 hours/day or 24 hours/day for 3 consecutive days were safe and well tolerated.[36] An open-label study of 20 patients,[37] mean age 75 years, using up to five lidocaine patches/day for 4−15 years in a compassionate programme, confirmed the tolerability of this treatment and its long-term efficacy in the elderly. Interestingly, only 40% of these patients reported concomitant use of opioids, antiepileptics, corticosteroids or tricyclic antidepressants, which meant the risks of adverse effects or drug-drug interactions were minimised significantly. Because of these data, a lidocaine patch is recommended as first-line therapy for the treatment of postherpetic neuralgia, although further studies are needed to compare this treatment with other active therapies and to determine the pain characteristics of 'responder' patients (e.g. presence or absence of allodynia).

It is important to note that unsuccessful treatment of chronic neuropathic pain may be due to the occurrence of central sensitisation that may perpetuate the pain even when peripheral sensory input is absent. In this case, hyperalgesia and hyperpathia are often the main complaints. Because glutamate is supposed to play a role in central sensitisation, ketamine, an NMDA receptor antagonist with opioid receptor activity, has been proposed for the treatment of chronic neuropathic pain and postherpetic neuralgia.[129,130] In a double-blind, placebo-controlled study[38] ketamine 50mg and 75mg were administered daily by an iontophoretic-assisted TDS in patients with central neuropathic pain. Although no significant difference in pain scores was observed between the ketamine and placebo groups after 1 week of treatment, ketamine 75mg was reported to improve scores on the Pain Disability Index and quality of life scales in this study. Therefore, until further information is available, this therapy can be

recommended only for refractory chronic neuropathic pain for which primary and secondary options have been exhausted.

In some patients, severe and persistent pain, including cancer pain and neuropathic pain, may require continuous analgesia. In this case, sustained-release formulations of opioids are the main therapeutic choice when pain is unresponsive to non-opioid analgesics. Recently, transdermal therapeutic systems including the opioids fentanyl[39,40] and buprenorphine[41,42] have became available and have been shown to achieve satisfactory analgesia with minimal requirement for rescue medication in almost half of patients. Tolerability was good and adverse effects typical of opioids, such as nausea, vomiting, constipation and dizziness, were reported to be comparable with those reported with oral administration. While transdermal fentanyl uses the reservoir patch technology, transdermal buprenorphine is a matrix system in which the substance is an integral part of the polymer structure of the patch. The latter technology is preferable because damage to the patch cannot interfere with the controlled release of the drug and the possibility of overdosing is prevented. Its long-lasting effects and potential to reduce medication overload and discomfort associated with multiple injections or frequent oral administration make transdermal opioid delivery an option for severe and intractable chronic pain, thereby contributing to improved quality of life in the elderly.

5. Conclusions

In recent years technologies for the development of TDS have made great progress and more molecules for therapeutic use can now be included in media for transdermal absorption. In some cases, clinical studies show that TDS provide a reliable, constant delivery of drugs and persistent therapeutic plasma levels with good overall tolerability. The elderly are the group of patients that can benefit the most from this particular route of administration for a number of reasons. First, several transdermal therapeutic options treat diseases typical of old age or which have an age-related incidence. Secondly, transdermal delivery significantly improves patients' adherence[1,63] as it reduces the discomfort associated with multiple administration of drugs and eliminates problems with swallowing oral preparations. Thirdly, sustained and constant therapeutic plasma concentrations increase drug efficacy and reduce the need for repeated doses. Finally, the risk of systemic adverse effects can be significantly reduced. Most transdermal treatments, however, still need to be evaluated in long-term studies of larger groups of patients in order to optimise dosage and administration regimens and to evaluate local and systemic adverse effects associated with prolonged therapy.

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References

1. Stahl SM, Wets KM. Recent advances in drug delivery technology for neurology. Clin Neuropharmacol 1988; 11: 1-17
2. Degim IT, Acarturk F, Erdogan D, et al. Transdermal administration of bromocriptine. Biol Pharm Bull 2003; 26: 501-5
3. Woitalla D, Muller T, Benz S, et al. Transdermal lisuride delivery in the treatment of Parkinson's disease. J Neural Transm Suppl 2004; 68: 89-95
4. Benes H. Transdermal lisuride: short-term efficacy and tolerability study in patients with severe restless legs syndrome. Sleep Med 2006; 7: 31-5
5. Li GL, de Vries JJ, van Steeg TJ, et al. Transdermal iontophoretic delivery of apomorphine in patients improved by surfactant formulation pretreatment. J Control Release 2005; 101: 199-208
6. Priano L, Albani G, Brioschi A, et al. Transdermal apomorphine permeation from microemulsions: a new treatment in Parkinson's disease. Mov Disord 2004; 19: 937-42
7. Priano L, Albani G, Brioschi A, et al. Nocturnal anomalous movement reduction and sleep microstructure analysis in parkinsonian patients during 1-night transdermal apomorphine treatment. Neurol Sci 2003; 24: 207-8

8. The Parkinson Study Group. Defining responder status in a clinical trial of the rotigotine transdermal system (SPM-962) in early Parkinson's disease. Mov Disord 2001; 16: 981-2
9. Metman LV, Gillespie M, Farmer C, et al. Continuous transdermal dopaminergic stimulation in advanced Parkinson's disease. Clin Neuropharmacol 2001; 24: 163-9
10. Poewe W, Luessi F. Clinical studies with transdermal rotigotine in early Parkinson's disease. Neurology 2005; 65 Suppl. 1: S11-4
11. Guldenpfennig WM, Poole KH, Sommerville KW, et al. Safety, tolerability, and efficacy of continuous transdermal dopaminergic stimulation with rotigotine patch in early-stage idiopathic Parkinson disease. Clin Neuropharmacol 2005; 28: 106-10
12. Pfeiffer RF. A promising new technology for Parkinson's disease. Neurology 2005; Suppl. 1: S6-10
13. Stiasny-Kolster K, Kohnen R, Schollmayer E, et al., for the Rotigotine Sp 666 Study Group. Patch application of the dopamine agonist rotigotine to patients with moderate to advanced stages of restless legs syndrome: a double-blind, placebo-controlled pilot study. Mov Disord 2004; 19: 1432-8
14. Coelho F, Birks J. Physostigmine for Alzheimer's disease. Cochrane Database Syst Rev 2001; (2): CD001499
15. Moller H-J, Hampel H, Hegerl U, et al. Double-blind, randomized, placebo-controlled clinical trial on the efficacy and tolerability of a physostigmine patch in patients with senile dementia of the Alzheimer type. Pharmacopsychiatry 1999; 32: 99-106
16. Sathyan G, Ritschel WA, Hussain AS. Transdermal delivery of tacrine: I. identification of a suitable delivery vehicle. Int J Pharm 1995; 114: 75-83
17. Jaskari T, Vuorio M, Kontturi K, et al. Controlled transdermal iontophoresis by ion-exchange fiber. J Control Release 2000; 67: 179-90
18. Tse FL, Laplanche R. Absorption, metabolism, and disposition of [14C] SDZ ENA 713, an acetylcholinesterase inhibitor, in minipigs following oral, intravenous, and dermal administration. Pharm Res 1998; 15: 1614-20
19. Muhlack S, Przuntek H, Muller T. Transdermal rivastigmine treatment does not worsen impaired performance of complex motions in patients with Alzheimer's disease. Pharmacopsychiatry 2006; 39: 16-9
20. ClinicalTrials.gov. A service of the U.S. Institutes of Health developed by the National Library of Medicine [online]. Available from URL: http://clinicaltrials.gov/ct/showNCT00099242 [Accessed 2006 Jun 12]
21. Novartis. Clinical trials information [online]. Available from URL: http://www.novartisclinicaltrials.com/etrials/home.do [Accessed 2006 Jun 12]
22. Snaedal J, Johannesson T, Jonsson JE, et al. The effects of nicotine in dermal plaster on cognitive functions in patients with Alzheimer's disease. Dementia 1996; 7: 47-52
23. White HK, Levin ED. Four-week nicotine skin patch treatment effects on cognitive performance in Alzheimer's disease. Psychopharmacology 1999; 143: 158-65
24. Howe MN, Price IR. Effects of transdermal nicotine on learning, memory, verbal fluency, concentration, and general health in a healthy sample at risk for dementia. Int Psychogeriatr 2001; 13: 465-75
25. Kelton MC, Kahn HJ, Conrath CL, et al. The effects of nicotine on Parkinson's disease. Brain Cogn 2000; 43: 274-82
26. Vieregge A, Sieberer M, Jacobs H, et al. Transdermal nicotine in PD: a randomized, double-blind, placebo-controlled study. Neurology 2001; 57: 1032-5
27. Ebersbach G, Stock M, Muller J, et al. Worsening of motor performance in patients with Parkinson's disease following transdermal nicotine administration. Mov Disord 1999; 14: 1011-3
28. Lemay S, Chouinard S, Blanchet P, et al. Lack of efficacy of a nicotine transdermal treatment on motor and cognitive deficits in Parkinson's disease. Prog Neuropsychopharmacol Biol Psychiatry 2004; 28: 31-9
29. Asthana S, Craft S, Baker LD, et al. Cognitive and neuroendocrine response to transdermal estrogen in postmenopausal women with Alzheimer's disease: results of a placebo-controlled, double-blind, pilot study. Psychoneuroendocrinology 1999; 24: 657-77
30. Baker L, Sambamurti K, Craft S, et al. 17β-estradiol reduces plasma Aβ40 for HRT-naive postmenopausal women with Alzheimer disease: a preliminary study. Am J Geriatr Psychiatry 2003; 11: 239-44
31. Hall KA, Keks NA, O'Connor DW. Transdermal estrogen patches for aggressive behavior in male patients with dementia: a randomized, controlled trial. Int Psychogeriatr 2005; 17: 165-78
32. Davies PS, Galer BS. Review of lidocaine patch 5% studies in the treatment of postherpetic neuralgia. Drugs 2004; 64: 937-47
33. Chabal C, Russell LC, Burchiel KJ. The effect of intravenous lidocaine, tocainide, and mexiletine on spontaneously active fibers originating in rat sciatic neuromas. Pain 1989; 38: 333-8
34. Argoff CE, Galer BS, Jensen MP, et al. Effectiveness of the lidocaine patch 5% on pain qualities in three chronic pain states: assessment with the Neuropathic Pain Scale. Curr Med Res Opin 2004; 20: S21-8
35. Galer BS, Jensen MP, Ma T, et al. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, 3-week efficacy study with use of the neuropathic pain scale. Clin J Pain 2002; 18: 297-301
36. Gammaitoni AR, Alvarez NA, Galer BS. Safety and tolerability of the lidocaine patch 5%, a targeted peripheral analgesic: a review of the literature. J Clin Pharmacol 2003; 43: 111-7
37. Galer BS, Gammaitoni AR. More than 7 years of consistent neuropathic pain relief in geriatric patients [letter]. Arch Intern Med 2003; 163: 628
38. Vranken JH, Dijkgraaf MG, Kruis MR, et al. Iontophoretic administration of S(+)-ketamine in patients with intractable central pain: a placebo-controlled trial. Pain 2005; 118: 224-31
39. Mystakidou K, Katsouda E, Tsilika E, et al. Transdermal therapeutic fentanyl-system (TTS-F). In Vivo 2004; 18: 633-42
40. Mystakidou K, Parpa E, Tsilika E, et al. Long-term management of noncancer pain with transdermal therapeutic system-fentanyl. J Pain 2003; 4: 298-306

41. Sittl R. Transdermal buprenorphine in the treatment of chronic pain. Expert Rev Neurother 2005; 5: 315-23
42. Likar R, Sittl R. Transdermal buprenorphine for treating nociceptive and neuropathic pain: four case studies. Anesth Analg 2005; 100: 781-5
43. Olanow CW, Watts RL, Koller W. An algorithm (decision tree) for the management of Parkinson's disease: treatment guidelines. Neurology 2001; 56: S1-88
44. Albanese A, Bonuccelli U, Brefel C, et al. Consensus statement on the role of acute dopaminergic challenge in Parkinson's disease. Mov Disord 2001; 16: 197-201
45. van Laar T, van der Geest R, Danhof M, et al. Stepwise intravenous infusion of apomorphine to determine the therapeutic window in patients with Parkinson's disease. Clin Neuropharmacol 1998; 2: 152-8
46. Nutt JG, Carter JH, Van Houten L, et al. Short- and long-duration responses to levodopa during the first year of levodopa therapy. Ann Neurol 1997; 42: 349-55
47. Hauser RA, Koller WC, Hubble JP, et al. Time course of loss of clinical benefit following withdrawal of levodopa/carbidopa and bromocriptine in early Parkinson's disease. Mov Disord 2000; 15: 485-9
48. Hughes AJ, Frankel JP, Kempster PA, et al. Motor response to levodopa in patients with parkinsonian motor fluctuations: a follow-up study over three years. J Neurol Neurosurg Psychiatry 1994; 57: 430-4
49. Fahn S, Oakes D, Shoulson I, et al., for the Parkinson Study Group. Levodopa and the progression of Parkinson's disease. N Engl J Med 2004; 351: 2498-508
50. Calon F, Grondin R, Morissette M, et al. Molecular basis of levodopa-induced dyskinesias. Ann Neurol 2000; 47: S70-8
51. Hardoff R, Sula M, Tamir A, et al. Gastric emptying time and gastric motility in patients with Parkinson's disease. Mov Disord 2001; 16: 1041-7
52. Djaldetti R, Baron J, Ziv I, et al. Gastric emptying in Parkinson's disease: patients with and without response fluctuations. Neurology 1996; 46: 1051-4
53. Pincus JH, Barry K. Protein redistribution diet restores motor function in patients with dopa-resistant 'off' periods. Neurology 1988; 38: 481-3
54. DeLong MR, Crutcher MD, Georgopoulos AP. Relations between movement and single cell discharge in the substantia nigra of the behaving monkey. J Neurosci 1983; 3: 1599-606
55. Nutt JG, Obeso JA, Stocchi F. Continuous dopamine-receptor stimulation in advanced Parkinson's disease. Trends Neurosci 2000; 23: S109-15
56. Chase TN, Konitsiotis S, Oh JD. Striatal molecular mechanisms and motor dysfunction in Parkinson's disease. Adv Neurol 2001; 86: 355-60
57. Soykan I, Sarosiek I, Shifflett J, et al. Effect of chronic oral domperidone therapy on gastrointestinal symptoms and gastric emptying in patients with Parkinson's disease. Mov Disord 1997; 12: 952-7
58. Kurth MC, Adler CH. COMT inhibition: a new treatment strategy for Parkinson's disease. Neurology 1998; 50: S3-14
59. Kurth MC, Adler CH, Hilaire MS, et al. Tolcapone improves motor function and reduces levodopa requirement in patients with Parkinson's disease experiencing motor fluctuations: a multicenter, double-blind, randomized, placebo-controlled trial. Tolcapone Fluctuator Study Group I. Neurology 1997; 48: 81-7
60. Syed N, Murphy J, Zimmerman T, et al. Ten years' experience with enteral levodopa infusions for motor fluctuations in Parkinson's disease. Mov Disord 1998; 13: 336-8
61. Colzi A, Turner K, Lees AJ. Continuous subcutaneous waking day apomorphine in the long term treatment of levodopa induced interdose dyskinesias in Parkinson's disease. J Neurol Neurosurg Psychiatry 1998; 64: 573-6
62. Stocchi F, Ruggieri S, Vacca L, et al. Prospective randomized trial of lisuride infusion versus oral levodopa in patients with Parkinson's disease. Brain 2002; 125: 2058-66
63. Pfeiffer RF. Potential of transdermal drug delivery in Parkinson's disease. Drugs Aging 2002; 19: 561-70
64. Sitruk-Ware R. Transdermal application of steroid hormones for contraception. J Steroid Biochem Mol Biol 1995; 53: 247-51
65. Berner B, John VA. Pharmacokinetic characterisation of transdermal delivery systems. Clin Pharmacokinet 1994; 26: 121-34
66. Martin GE, Williams M, Pettibone DJ, et al. Pharmacologic profile of a novel potent direct-acting dopamine agonist, (+)-4-propyl-9-hydroxynaphthoxazine [(+)-PHNO]. J Pharmacol Exp Ther 1984; 230: 569-76
67. Rupniak NMJ, Tye SJ, Jennings CA, et al. Antiparkinsonian efficacy of a novel transdermal delivery system (+)-PHNO in MPTP-treated squirrel monkeys. Neurology 1989; 39: 329-35
68. Coleman RJ, Lange KW, Quinn NP, et al. The antiparkinsonian actions and pharmacokinetics of (+)-4-propyl-9-hydroxynaphthoxazine (+PHNO): preliminary results. Mov Disord 1989; 4: 129-38
69. Ahlskog JE, Muenter MD, Bailey PA, et al. Parkinson's disease monotherapy with controlled release MK-458 (PHNO): double-blind study and comparison to carbidopa/levodopa. Clin Neuropharmacol 1991; 14: 214-27
70. Smith LA, Jackson MG, Bonhomme C, et al. Transdermal administration of piribedil reverses MPTP induced motor deficits in the common marmoset. Clin Neuropharmacol 2000; 23: 133-42
71. Montestruct JL, Ziegler M, Rascol O, et al. A randomized, double-blind study of a skin patch of a dopamine agonist, piribedil, in Parkinson's disease. Mov Disord 1999; 14: 336-41
72. MacMahon DG. Use of apomorphine in clinical practice. Adv Neurol 1999; 80: 529-33
73. Poewe W, Wenning GK. Apomorphine: an underutilized therapy for Parkinson's disease. Mov Disord 2000; 15: 789-94
74. Gancher S. Pharmacokinetics of apomorphine in Parkinson's disease. J Neural Transm Suppl 1995; 45: 137-41
75. Ondo W, Hunter C, Almaguer M, et al. A novel sublingual apomorphine treatment for patients with fluctuating Parkinson's disease. Mov Disord 1999; 14: 664-8
76. van Laar T, Jansen EN, Essink AW, et al. Intranasal apomorphine in parkinsonian on-off fluctuations. Arch Neurol 1992; 49: 482-4
77. Hughes AJ, Bishop S, Lees AJ, et al. Rectal apomorphine in Parkinson's disease [letter]. Lancet 1991; 337: 118
78. van Laar T, Jansen EN, Neef C, et al. Pharmacokinetics and clinical efficacy of rectal apomorphine in patients with Parkin-

son's disease: a study of five different suppositories. Mov Disord 1995; 10: 433-9
79. Nyholm D. Pharmacokinetic optimisation in the treatment of Parkinson's disease: an update. Clin Pharmacokinet 2006; 45: 109-36
80. Stocchi F, Berardelli A, Vacca L, et al. Apomorphine infusion and the long-duration response to levodopa in advanced Parkinson's disease. Clin Neuropharmacol 2003; 26: 151-5
81. Colzi A, Turner K, Lees AJ. Continuous subcutaneous waking day apomorphine in the long term treatment of L-dopa induced interdose dyskinesias in Parkinson's disease. J Neurol Neurosurg Psychiatry 1998; 64: 573-6
82. van der Geest R, Danhof M, Bodde HE. Iontophoretic delivery of apomorphine. I: in vitro optimization and validation. Pharm Res 1997; 14: 1798-803
83. van der Geest R, van Laar T, Gubbens-Stibbe JM, et al. Iontophoretic delivery of R-apomorphine. II: an in vivo study in patients with Parkinson's disease. Pharm Res 1997; 14: 1804-10
84. van Laar T, van der Geest R, Danhof M. Future delivery systems for apomorphine in patients with Parkinson's disease. In: Stern GM, editor. Parkinson's disease. Advances in Neurology, Vol 80. Philadelphia (PA): Lippincott Williams and Wilkins, 1999: 535-44
85. Peira E, Scolari P, Gasco MR. Transdermal permeation of apomorphine through hairless mouse skin from microemulsions. Int J Pharmaceutics 2001; 226: 47-51
86. Cedarbaum JM. Clinical pharmacokinetics of anti-parkinsonian drugs. Clin Pharmacokinet 1987; 13: 141-78
87. Staal-Schreinemachers AL, Lakke JP. Bromocriptine long acting (LA) 50mg intramuscular (IM) for the on-off phenomenon in Parkinson's disease [letter]. Acta Neurol Scand 1987; 75: 441
88. Vermesh M, Fossum GT, Kletzky OA. Vaginal bromocriptine: pharmacology and effect on serum prolactin in normal women. Obstet Gynecol 1988; 72: 693-8
89. Domino EF. Selective full dopamine D1-like (SKF-82958) and D2 like (N-0923) agonist combination in the MPTP monkey model of hemiparkinsonism. Brain Res Bull 1997; 43: 93-5
90. Belluzzi JD, Domino EF, May JM, et al. N-0923, a selective dopamine D2 receptor agonist, is efficacious in rat and monkey models of Parkinson's disease. Mov Disord 1994; 9: 147-54
91. Happe S, Trenkwalder C. Role of dopamine receptor agonists in the treatment of restless legs syndrome. CNS Drugs 2004; 18: 27-36
92. Michaud M, Dumont M, Paquet J, et al. Circadian variation of the effects of immobility on symptoms of restless legs syndrome. Sleep 2005; 28 (7): 843-6
93. Becker R, Giacobini E, Elble R, et al. Potential pharmacotherapy of Alzheimer disease: a comparison of various forms of physostigmine administration. Acta Neurol Scand Suppl 1988; 116: 19-32
94. Stern Y, Sano M, Mayeux R. Long-term administration of oral physostigmine in Alzheimer's disease. Neurology 1988; 38: 1837-41.
95. Beller SA, Overall JE, Rhoades HM, et al. Long-term outpatient treatment of senile dementia with oral physostigmine. J Clin Psychiatry 1988; 49: 400-4
96. Gustafson L, Edvinsson L, Dahlgren N, et al. Intravenous physostigmine treatment of Alzheimer's disease evaluated by psychometric testing, regional cerebral blood flow (rCBF) measurement, and EEG. Psychopharmacology (Berl) 1987; 93: 31-5
97. Thal LJ, Lasker B, Sharpless NS, et al. Plasma physostigmine concentrations after controlled-release oral administration [letter]. Arch Neurol 1989; 46: 13
98. Jenike MA, Albert MS, Heller H, et al. Oral physostigmine treatment for patients with presenile and senile dementia of the Alzheimer's type: a double-blind placebo-controlled trial. J Clin Psychiatry 1990; 51: 3-7
99. Harrell LE, Jope RS, Falgout J, et al. Biological and neuropsychological characterization of physostigmine responders and nonresponders in Alzheimer's disease. J Am Geriatr Soc 1990; 38: 113-22
100. Wagstaff AJ, McTavish D. Tacrine: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy in Alzheimer's disease. Drugs Aging 1994; 4: 510-40
101. Kankkunen T, Sulkava R, Vuorio M, et al. Transdermal iontophoresis of tacrine in vivo. Pharm Res 2002; 19: 705-8
102. Newhouse PA, Whitehouse PJ. Nicotinic-cholinergic systems in Alzheimer's and Parkinson's disease. In: Piasecki M, Newhouse PA, editors. Nicotine in psychiatry: psychopathology and emerging therapeutics. Washington, DC: American Psychiatric Press, 2000: 149-181
103. Sanberg PR, Silver AA, Shytle RD, et al. Nicotine for the treatment of Tourette's syndrome. Pharmacol Ther 1997; 74: 21-5
104. Levin ED, Simon BB, Conners CK. Nicotine effects and attention-deficit/hyperactivity disorder. In: Piasecki M, Newhouse PA, editors. Nicotine in psychiatry: psychopathology and emerging therapeutics. Washington, DC: American Psychiatric Press, 2000: 203-214
105. Jones GM, Sahakian BJ, Levy R, et al. Effects of acute subcutaneous nicotine on attention, information processing and short-term memory in Alzheimer's disease. Psychopharmacology 1992; 108: 485-94
106. Rosin RA, Levine MD, Peskind E. Transdermal nicotine for agitation in dementia. Am J Geriatr Psychiatry 2001; 9: 443-4
107. Wilson AL, Langley LK, Monley J, et al. Nicotine patches in Alzheimer's disease: pilot study on learning, memory, and safety. Pharmacol Biochem Behav 1995; 51: 509-14
108. Barros DM, Ramirez MR, Izquierdo I. Modulation of working, short- and long-term memory by nicotinic receptors in the basolateral amygdala in rats. Neurobiol Learn Mem 2005; 83: 113-8
109. May-Simera H, Levin ED. NMDA systems in the amygdala and piriform cortex and nicotinic effects on memory function. Brain Res Cogn Brain Res 2003; 17: 475-83
110. Levin ED, Tizabi Y, Rezvani AH, et al. Chronic nicotine and dizocilpine effects on regionally specific nicotinic and NMDA glutamate receptor binding. Brain Res 2005; 1041: 132-42
111. Buccafusco JJ, Letchworth SR, Bencherif M, et al. Long-lasting cognitive improvement with nicotinic receptor agonists: mechanisms of pharmacokinetic-pharmacodynamic discordance. Trends Pharmacol Sci 2005; 26: 352-60

112. Wurtman R, Blusztajn J, Maire J-C. 'Autocannibalism' of choline-containing membrane phospholipids in the pathogenesis of Alzheimer's disease: a hypothesis. Neurochem Int 1985; 7: 369-72

113. Frederick B, Satlin A, Wald LL, et al. Brain proton magnetic resonance spectroscopy in Alzheimer disease: changes after treatment with xanomeline. Am J Geriatr Psychiatry 2002; 10: 81-8

114. Bodick NC, Offen WW, Shannon HE, et al. The selective muscarinic agonist xanomeline improves both the cognitive deficits and behavioral symptoms of Alzheimer disease. Alzheimer Dis Assoc Disord 1997; 11 Suppl. 4: S16-22

115. Henderson V, Paganini-Hill A, Emanuel C, et al. Estrogen replacement therapy in older women: comparison between Alzheimer's disease cases and nondemented control subjects. Arch Neurol 1994; 51: 896-900

116. Baldereschi M, Di-Carlo A, Lepore V, et al. Estrogen-replacement therapy and Alzheimer's disease in the Italian Longitudinal Study on Aging. Neurology 1998; 50: 996-1002

117. McEwen B, Woolley C. Estradiol and progesterone regulate neuronal structure and synaptic connectivity in adult as well as developing brain. Exp Geront 1994; 29: 431-6

118. Xu H, Gouras GK, Greenfield JP, et al. Estrogen reduces neuronal generation of Alzheimer β-amyloid peptides. Nature Medicine 1998; 4: 447-51

119. Ancelin ML, Berr C. Hormonal replacement therapy and Alzheimer's disease. All quiet on the western front? Psychol Neuropsychiatr Vieil 2003; 1: 251-7

120. Shneider L, Farlow M, Pogoda J. Potential role for estrogen replacement in the treatment of Alzheimer's dementia. Am J Med 1997; 103: 46S-50S

121. Wang P, Liao S, Liu RS, et al. Effects of estrogen on cognition, mood, and cerebral blood flow in AD. Neurology 2000; 54: 2061-6

122. Mulnard RA, Cotman CW, Kawas C, et al. Estrogen replacement therapy for treatment of mild-to-moderate Alzheimer disease: a randomized controlled trial. JAMA 2000; 283: 1007-15

123. Henderson VW, Paganini-Hill A, Miller BL, et al. Estrogen for Alzheimer's disease in women: randomized, double-blind, placebo-controlled trial. Neurology 2000; 54: 295-301

124. Parain K, Marchand V, Dumery B, et al. Nicotine, but not cotinine, partially protects dopaminergic neurons against MPTP-induced degeneration in mice. Brain Res 2001; 890: 347-50

125. Prasad C, Ikegami H, Shimizu I, et al. Chronic nicotine intake decelerates aging of nigrostriatal dopaminergic neurons. Life Sci 1994; 54: 1169-84

126. Wonnacott S, Kaiser S, Mogg A, et al. Presynaptic nicotinic receptors modulating dopamine release in the rat striatum. Eur J Pharmacol 2000; 393: 51-8

127. Rinne JO, Myllykyla T, Lonnberg P, et al. A postmortem study of brain nicotinic receptors in Parkinson's and Alzheimer's disease. Brain Res 1991; 547: 167-70

128. Shinotoh H, Namba H, Yamaguchi M, et al. In vivo mapping of brain cholinergic function in Parkinson's disease and progressive supranuclear palsy. Adv Neurol 2001; 86: 249-55

129. Gammaitoni A, Gallagher RM, Welz-Bosna M. Topical ketamine gel: possible role in treating neuropathic pain. Pain Med 2000; 1: 97-100

130. Quan D, Wellish M, Gilden DH. Topical ketamine treatment of postherpetic neuralgia. Neurology 2003; 60: 1391-2

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