Transdermal patches: the emerging mode of drug delivery system in psychiatry

Ther Adv Psychopharmacol
(2012) 2(6) 255–263
DOI: 10.1177/2045125312458311

Miriam Isaac and Carl Holvey

Abstract: Adherence to prescribed psychiatric and nonpsychiatric medication is a serious issue in people with mental illness that can contribute to poor health outcomes. Some of the factors influencing adherence include side effects of medication and the ease of use. With mental healthcare provision increasingly focusing on a community model of health delivery, there seems to be a renewed interest in addressing complex dilemmas of safety and adherence to treatment. The use of alternative methods of safely delivering medication in innovative ways may resolve some of these difficulties. There has been little discussion about the wider use of transdermal patches in the field of psychiatry in published literature. This article describes the findings from the literature on key principles underlying transdermal delivery strategies, the scope of clinical use in psychiatric illness and explores its challenges and advantages.

Keywords: Adherence, patches, psychotropics, safety, transdermal

Correspondence to:
Miriam Isaac,
SouthWest London and St George's Mental Health Trust, Tooting, London, UK
miriam.thomas@mac.com

Carl Holvey
South West London and St George's Mental Health Trust, London, UK

Introduction

Adherence to medications and dose optimization can be affected by several physiological and psychological factors such as undesirable side effects, dosing regimen, route of administration, nature of illness, belief systems and personal attributes [Griffith, 1990]. Innovations in transdermal delivery systems (TDS) have made important contributions to medical practice by providing advances in the delivery of treatment with existing and novel drugs. TDS have significant advantages (see Table 1) over other routes of administration, such as providing prolonged and steadier drug levels [Mercier *et al*. 2007], the ability to interrupt treatment abruptly by removing the patch and less frequent dosing. Drug delivery through skin means avoidance of gastrointestinal incompatibility and hepatic first pass metabolism, without the unpleasant and painful experiences with injections or rectal applications.

Factors affecting transdermal drug delivery

Human skin is an efficient protective barrier. Choosing a candidate drug that is suitable for making transdermal formulations can be difficult. Several variables influence the transdermal transport and bioavailability of drugs as the drug traverses various structural layers of the skin (see Table 2). Preferred candidate drugs for transdermal delivery are those with low molecular weight and lipophilicity, which correlate with good solubility and penetration through the skin. In addition, drugs that are more volatile and have lower melting points tend to be more easily formulated into a transdermal patch as they permeate the skin more efficiently [Vecchia and Bunge, 2003]. There is limited availability of commonly used medications as transdermal formulations. Recent advances in methods for modulating skin penetration to enhance transdermal transport of drugs may enable a wider choice of medications available as TDS. These modulations can be a chemical modification of the drug molecules or through direct action on the skin to enhance permeation. This may involve modification of the structure and composition of skin lipids and proteins by using methods such as micro needles causing micro abrasions, ultrasound, transdermal pumps or delivery through hair follicles [Benson, 2005; Touitou, 2002].

Psychotropic medication and transdermal patches

Medical specialties such as general practice, palliative care and endocrinology frequently use

Table 1. Advantages *versus* disadvantages of transdermal drug delivery.

Advantages
Patient and carer satisfaction because of ease of use and tolerability
Limiting hepatic first-pass metabolism, hence lower dose of medication can obtain desired plasma level compared with oral formulations
Reduced frequency of dosing
Constant drug serum level *versus* episodic peaks
Reduced side effects secondary to gastrointestinal intolerance and fluctuations of drug levels
Avoidance of unpleasant and inconvenient parental administration
Easier to titrate to achieve optimal therapeutic doses
Potentially reduces the risk of drug overdose
Removal of the patch stops drug delivery
Disadvantages
Slow time towards peak plasma levels
Unsuitable model for emergency treatments that requires rapid release of desired drug and rapid serum levels
Limited choice of medication that may be formulated in transdermal format
Variations in bioavailability (see Table 2)
Skin sensitivity and application allergic reactions
Steady state of drug is maintained only as long as the patch is applied
Good adherence to skin is necessary for patches to be effective. Presence of oil, hair or sweat on the patch application site can be hindrances to adherence and can cause variations in absorption.
TDS involves learning the appropriate application technique
Potential medication error such as using multiple patches
TDS can be costlier than oral formulations
Complex issues such as: monitoring cumulative effects of long-term use emerging research evidence and lack of randomized controlled trials and economic evaluation ethical and legal dilemmas in situations where capacity and consent to treatment are in question

Table 2. Factors affecting transdermal transport and bioavailability.

Nonmodifiable	Modifiable
Age	Skin permeability
Race	Patch site selection
Gender	Adhesion to skin
Individual metabolic rates	Lipid solubility of the drug
Molecular size	Structure and composition of lipids and proteins in the skin
Molecular weight	Polypharmacy
Regional variation in blood flow	
Renal clearance	
Thickness of skin	
Pharmaco-genomics	

Based on Moser et al. [2001], Hadgraft [2001], Ngawhirunpat et al. [2001], Kanikkannan et al. [2000].

transdermal formulations for pain relief, smoking cessation and hormone replacement, but the use of psychotropics as transdermal patches is less studied and underinvestigated. Advances in enhancing transdermal drug delivery have led to treatment options for various psychiatric and neuropsychiatric conditions. Conditions such as depression, attention deficit hyperactivity disorder (ADHD), Parkinson's disease and dementia benefit from long-acting formulations due to the

Table 3. Summary of various psychotropic drugs used as transdermal systems.

Medication (as transdermal systems)	Category/class	Licensed for target illness	FDA approved for clinical use	MHRA approved for clinical use	EMEA approved for clinical use
Rivastigmine	Acetylcholinesterase inhibitor	Dementia	Approved	Approved	Approved
Rotigotine	Dopamine agonist	Parkinson's disease	Approved	No	Approved
Methylphenidate	CNS stimulant	ADHD	Approved	No	No, European patent approved
Dexamphetamine	CNS stimulant	ADHD	Preclinical phase	No	No
Selegiline	MAOI	Depression	Approved	No	No, pharmaceutical company looking for EU partner
Fluoxetine	SSRI	Depression	Preclinical phase	No	No
Nicotine		Smoking	Approved	Approved	Approved
Buprenorphine	Semisynthetic opioid	Opioid detoxification	Approved	Approved	Approved
Haloperidol	Antipsychotic	Psychosis	Preclinical phase	No	No

ADHD, attention deficit hyperactivity disorder; CNS, central nervous system; EMEA, European Medicines Agency; UE, European Union; FDA, US Food and Drug Administration; MAOI, monoamine oxidase inhibitor; MHRA, Medicine Healthcare Regulatory Authority; SSRI, selective serotonin reuptake inhibitor.

nature of the symptom relief required and this can be achieved through constant plasma levels of medication against episodic peaks. TDS may be of particular use in patients who are unable or unwilling to take oral or intramuscular medicines. Offering patients another formulation also facilitates control and choice over their treatment. An appropriately administered patch which is visible and potentially easy to monitor offers clinicians reassurance in patients who are noncompliant that a medicine is administered without the need for invasive and often injurious intramuscular injections when given under restraint. Table 3 summarizes the psychotropics that are currently approved by the US Food and Drug Administration (FDA) and the UK Medicine Healthcare Regulatory Authority (MHRA).

Dementia

Dementia is a chronic condition that has significant impact on an individual's health and social care [Harada and Vanderplas, 2006]. The cost of dementia care in the UK is expected to rise to approximately £28 billion by 2018 [All Party Parliamentary Group on Dementia, 2011]. In a time of increasing financial constraints, the demand to implement a more efficient approach to the delivery of community-based healthcare is increasing. In patients receiving antidementia therapies for longer periods at adequate doses there is a greater chance of slowing or delaying the progression of cognitive decline, leading to fewer admissions to nursing homes and reduced healthcare costs [Harada and Vanderplas, 2006]. However, misunderstanding complex titration schedules can result in people with dementia receiving subtherapeutic doses [Bernabei and Lage, 2008]. Medications featuring less frequent dosing schemes, such as extended-wear transdermal patches, are capturing the interest of providers and healthcare purchasers.

Rivastigmine is a cholinesterase inhibitor used for treating Alzheimer's disease and dementia associated with Parkinson's disease. It is the only antidementia drug currently available as a transdermal formulation. All orally administered cholinesterase inhibitors are associated with central cholinergic gastrointestinal side effects, particularly during the titration phase, believed to be caused by a rapid increase in brain acetylcholine levels

after effective inhibition of the target enzymes. Pharmacokinetic studies have shown that transdermal administration of rivastigmine prolongs the time to reach the peak concentration and reduces fluctuations in plasma concentration. It is these differences in peak and trough plasma concentrations that are in part responsible for the decreased side effects associated with the patches in comparison to the capsules [Mercier *et al*. 2007; Cummings *et al*. 2007]. Unlike other acetylcholinesterase inhibitors, rivastigmine is largely interaction free. It is metabolized by hydrolysis, avoiding possible interaction with numerous other medicines metabolized by the cytochrome P450 system. Administering medicines to people with dementia that is progressing can be difficult and may result in increased burden of care. Studies have shown an overall satisfaction with respect to ease of use of the rivastigmine patch over capsules and less interference with daily life [Blesa *et al*. 2007]. TDS offer carers and families an easy way of ensuring that the prescribed medication is administered in the least restrictive way.

Parkinson's disease

Depression, disability, postural instability and cognitive impairment have been shown to have the greatest influence on quality of life in patients with Parkinson's disease [Schrag *et al*. 2000]. Improvement of these features therefore becomes an important clinical target in the treatment of the disease. Studies on Parkinson's disease implicate intermittent or pulsatile stimulation of dopamine receptors as one potential mechanism of treatment-related complications of levodopa that limits its effectiveness. Continuous administration of medication via the transdermal route offers a potential avenue to circumvent pulsatile drug delivery, thus deflecting the development of dyskinesia and motor fluctuations [Pfeiffer, 2007]. Rotigotine is a non-ergot dopamine agonist which has been formulated and available as a once-daily transdermal patch that offers continuous release of dopamine. Review studies suggest high adherence and tolerability, and side effects reported were of mild to moderate intensity, mostly local skin reaction and nausea [Boroojerdi *et al*. 2010].

Attention deficit hyperactivity disorder

ADHD is characterized by core symptoms of hyperactivity, impulsivity and inattention. Sympathomimetic medications such as methylphenidate have been recognized as the best documented pharmacological treatment for ADHD. Children with ADHD often need varying dosage for overall coverage of their symptoms throughout the day. The concept of a flexible delivery of drug (mg/h) rather than a fixed dose (mg/dose or mg/day) can offer a potential solution for symptom control over a desired time and reduce the need for frequent dosing. Methylphenidate transdermal system (MTS) patch has FDA approval for use in children aged 6–12 years with ADHD. Most studies on MTS patches are placebo-controlled double-blind studies and they report effectiveness and tolerability in children with ADHD [McGough *et al*. 2006; Findling *et al*. 2008]. MTS patches show good absorption of the drug with a peak plasma concentration occurring 7–9 h after patch placement. Onset of therapeutic action is around 2 h after patch placement. Most adverse events reported are mild to moderate in severity and the most frequent adverse events reported are nausea, vomiting, insomnia and decreased appetite [Findling *et al*. 2008]. A randomized controlled trial (RCT) including nine children with ADHD conducted by Pelham and colleagues compared patches with three times daily oral methylphenidate. Both methods of delivery demonstrated comparable efficacy and tolerability, with MTS patches producing consistent symptom relief during the course of the day but the patches had a delayed onset compared with the oral medication [Pelham *et al*. 2011]. Duration of the medication effect is related to the wear time of the patch and may be tailored to accommodate specific needs, thus enabling individualized control over effect duration [Wilens *et al*. 2008]. MTS patches can also be a useful treatment option in children with difficulties swallowing tablets or capsules.

Research is ongoing into developing a long-acting patch for dexamphetamine to treat refractory ADHD.

Depression

Selegiline is a second-generation monoamine oxidase inhibitor (MAOI) with unique pharmacodynamic properties used for the treatment of depression and Parkinson's disease. It is selective for MAO (B) enzyme at oral doses up to 10 mg/day and is effective for improving symptoms in Parkinson's disease. At higher doses, selegiline loses selectivity and inhibits both MAO (A) and MAO (B) enzymes. MAO (A) inhibition and

tyramine presser effects in the brain result in the antidepressant effects of selegiline. However, MAO (A) inhibition in the gastrointestinal mucosa leads to dietary tyramine breakdown in the gastrointestinal tract, which can result in potentially fatal hypertensive crisis. This means that people taking MAOIs need to make lifestyle choices, avoiding food and drinks high in tyramine. An ideal formulation would optimize the dose while minimizing the adverse effects of MAO (A) inhibition. Efforts to optimize the dosing of MAOIs so that they are less likely to cause side effects have led to the selegiline transdermal system (STS). STS was approved by the FDA in 2006, making it the first skin patch to be approved for treatment of major depression [FDA, 2006]. The literature suggests an improved safety margin for STS compared with orally administered MAOIs [Robinson and Amsterdam, 2008] and it is well tolerated, with the most common side effects being application site reactions and insomnia. A tyramine-restricted diet is recommended for higher doses of 9 mg and 12mg STS [FDA, 2006].

The feasibility of developing a TDS for fluoxetine is under investigation. A study on human skin cells showed that permeation of the drug could be enhanced to sufficiently deliver doses between 20 and 80 mg from TDS [Parikh and Ghosh, 2005].

Management of substance misuse

The transdermal effects of tobacco have been studied [Rose *et al*. 1985], which has led to the innovation of nicotine patches, now widely used for smoking cessation since FDA approval in 1992. A Cochrane review showed nicotine replacement therapy (NRT) increases the rate of quitting by 50–70%, regardless of the setting. The effectiveness of NRT appears to be largely independent of the intensity of additional support provided to the individual. Nicotine patches are considered to be cost effective and less costly per year of life saved [Wasley *et al*. 1997]. One of the shortfalls of NRT patches is that it does not offer smokers the 'hit' they seek from smoking. The evidence suggests that combining a nicotine patch with a rapid delivery form of NRT, such as a gum or nasal spray, is more effective than a single type of NRT. The nicotine patch provides the steady supply of nicotine levels to prevent craving and the short-acting product gives the immediate 'hit' and control [Stead *et al*. 2008].

At high doses (>2 mg) this semisynthetic opioid is recommended as a therapeutic option for opioid dependence. Providing relief from opiate withdrawal, while having less potential for illicit selling and abuse, can be clinically significant in managing dependence. An open-label trial showed good tolerance and safety of transdermal buprenorphine formulation. The significant biodelivery of buprenorphine and the suppression of the opiate withdrawal syndrome during patch application and its reappearance after patch removal indicated clinically useful pharmacodynamic activity [Lanier *et al*. 2007, 2008].

Organic dementia

The clinical features of human immunodeficiency virus (HIV) dementia include psychomotor retardation, apathy, bradykinesia and abnormalities in posture and gait features of subcortical dementia. The sensitivity of many patients to dopamine receptor blockade suggests a significant and perhaps selective abnormality of striatal dopaminergic systems. Selegiline, a MAOI, reduces dopamine metabolism by inhibiting the MAO (B) enzyme and increasing levels of dopamine in the brain. Transdermal selegiline (3.1 mg/24 h) appears to be well tolerated, with improvement in cognitive function and psychometric scores on delayed recall in HIV dementia [Sacktor *et al*. 2000].

Antipsychotics

Limited scientific evidence is available on the use of antipsychotics in transdermal formulations. There are emerging data from preclinical studies looking at the feasibility of increasing the permeability of haloperidol gel patches [Elgorashi *et al*. 2008]. Although most of the antipsychotics are extremely lipophilic, which is one of the molecular properties that promotes transdermal transport, it may be that the challenges are in finding and modulating the drug with the right characteristics. With high incidences of nonadherence to medications and relapse in patients with serious mental illness, the prospect of having antipsychotics as a transdermal patch is exciting.

Role of psychoeducation

Achieving medication adherence and therapeutic effect using TDS requires understanding several facets. Patch-site selection, management of wear time to optimize the daily time course of clinical benefits, skin hygiene, social support and

Table 4. What to consider when prescribing transdermal patches.

Transdermal patch is a useful alternative when other routes are unacceptable
Patch strength can be titrated, oral tablets can be safely switched to patches
Optimal dosing can be achieved by controlling duration of patch wear and patch size
Using patches may reduce abuse potential of the prescribed medication
Patches are often not useful when immediate results are required, e.g. emergencies
Proper site preparation is required for improved adhesion, rotating application sites can reduce hypersensitive skin reactions
Humid and warm climate can influence adhesion
A secondary adhesive dressing can be useful when skin adhesion is problematic
Patients with severe side effects should be monitored even after patch removal
Patients/carers should be given practical guidance on applying and caring for patches and on avoiding accidental overdose (e.g. avoiding hot showers of baths while wearing patches)

education on application techniques (e.g. avoiding hot baths and showers while wearing a patch) all have implications for achieving the desired therapeutic effect. A failure to consider time-varying clearance can lead to biased estimates of *in vivo* transdermal drug delivery rates. In clinical situations, when a precise concentration of a drug is required, the effect of circadian changes of that particular drug should be considered [Gries *et al*. 1998]. These findings reinforce the need to study the impact of periodic *versus* constant dosing. Clinicians may require a paradigm shift in clinical thinking in addition to refinement of clinical skills to obtain optimal dosing with transdermal patches (mg/h) compared with oral medication (mg/day or per dose) [Arnold *et al*. 2007]. Patients and carers must be given sufficient instructions on the method of administration and related techniques. Advice on the risks of abuse potential and from accidental or nonaccidental overdose should be provided. Reports from single case studies on fentanyl patches describe the abuse potential and risk of overdose through chewing and transmucosal use [Liappas *et al*. 2004; Dale *et al*. 2009].

Medication errors with rivastigmine patches have been reported. The most common cause reported was lack of removal of patch and application of more than one patch at the same time [MHRA, 2010).

Ethical dilemmas

For complex clinical and social situations in which consent and capacity are challenged, especially in older patients, those with dementia, cognitive impairment and learning disability, prescribing transdermal formulations should be carefully analyzed as it would be with any other treatment modality. Possibilities of medication abuse, concealing, withholding or enforcing medications should be considered. Some of these issues are discussed in the case vignettes. Table 4 summarizes some of the considerations that may assist clinical decisions.

Case vignettes

The following case vignettes illustrate some of the ethical and legal dilemmas.

Case vignette 1

P is a 75-year-old man diagnosed with Alzheimer's dementia of moderate severity. He has shown adherence on cholinesterase tablets for a year. He lives on his own in a warden-controlled flat with carer support. P was admitted to hospital with significant difficulties with swallowing. Following specialist advice from the old age psychiatrist, P was started on cholinesterase patches instead of tablets with the view of reducing the risk of aspiration. P was deemed to have capacity to make an informed choice on his medication and he consented to the patches. His carers were instructed on the use of the new medication and administering techniques and he was referred for follow up at the dementia clinic. He made good progress on the patches which were well tolerated with no further deterioration in cognitive skills. It was considered clinically appropriate to continue on the patches.

Reflective notes to consider

(1) Suitability of patch over oral preparation.
(2) Patient preference.
(3) Analysis of nature and reliability of carer support.

(4) Analysis of any ongoing or planned changes to social factors, for example, will P be moving to a residential/nursing home?
(5) Risk assessment around medication administration and storage.
(6) Reviewing capacity to consent, any advance directives and future choices of medication.
(7) Review of improvement on cognition, daily living and patient experience.
(8) Specialist follow up at dementia clinic.

Case vignette 2

J is a 50-year-old woman with moderate learning disability (LD) and autism. She lives in a residential care setting. Following investigation for postmenopausal bleeding, J was recommended for hormone replacement therapy (HRT) and was prescribed HRT patches. After a period of initial adherence on the patch, J started refusing to wear them as prescribed by the physician. It was reported later on that some of the carers at the residential home were seen to be forcing J to wear the patches .The manager of the residential home is now seeking advice management on issues around the patient's capacity to refuse HRT patches.

Reflective notes to consider

(1) Face-to-face interview and collect factual details from all parties involved, preferably using a multiprofessional team.
(2) Individuals with social and communication disorder such as autism may require specialist analysis and input from a speech and language therapist or an occupational therapist to identify communication difficulties and sensory problems such as tactile hypersensitivity.
(3) Using visual cues such as pictures or picture exchange communication systems may facilitate J's understanding of the need for a particular medication.
(4) Medical basis of prescribing patch, what are the alternatives?
(5) Consider patient choice.
(6) Capacity to consent is context and issue specific.
(7) Make reasonable adjustments and appropriate measure to improve capacity, for example, providing accessible information, treatment of underlying physical or mental illness, if any.
(8) If J is deemed to have no capacity to consent to treatment, initiate a best interest meeting and consider involvement from independent mental capacity advocates.
(9) Involving specialist mental health services or family physicians can help facilitate complex decisions.
(10) If in doubt, seek advice on procedure for safe guarding vulnerable adults procedure.

The future of transdermal patches in psychiatry

Understanding how the use of TDS patches may alter the treatment paradigm for patients is important. The effectiveness of patches in the treatment of illnesses that have a chronic pattern compared with those with an acute presentation is yet to be elucidated. The effects of regional blood flow and permeability of skin, dose titrations, combination treatment with patches and tablets, cumulative effects of long-term TDS use and drug interactions are yet to be fully understood. There are identifiable gaps in the literature on legal and ethical implications of use of transdermal patches in specific scenarios when limited capacity or lack of capacity to consent to treatment and issues around vulnerability can be an issue.

In economically driven health markets, the cost of prescribed treatment is almost always debated. There are cost implications for developing transdermal formulations, such as the patented design and technology. Patches are more expensive compared with the parent oral drug: the primary care cost of rivastigmine (Exelon) 4.6 mg patches is twice as expensive compared with 4.5 mg of rivastigmine capsules [Joint Formulary Committee, 2011]. The availability of cheaper generic formulations can deter pharmaceutical companies investing in TDS. The cost difference between TDS and generic oral formulations can also be a deterrent for prescribers who must justify choosing a high-cost alternative of the same medication. With increasing emphasis on cost-effective drug therapy, having a wider range of research evidence such as patient and carer preferences, quality of life studies, RCTs with large sample sizes and economic evaluation studies will provide better clinical guidance on the use of TDS and provide the impetus to develop cost-effective solutions.

Despite these uncertainties, TDS have opened opportunities to explore the capabilities of new drugs and use existing drugs to a new level in the treatment of psychiatric disorders. TDS benefits over traditional methods are ease of titration, adherence to medications, optimal constant dosing and carer satisfaction. Increasingly, clinicians, policymakers and the public are becoming aware of the advantages of adherence to treatment and in maintaining wellbeing. The positive preliminary responses from patients and carers may bring focused attention to create an impact on targeted research and new ways of clinical practice in managing mental health disorders.

Acknowledgements

The authors would like to thank Asim Naeem, Denise Alberg and Raja Mukherjee for their valuable comments.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

The authors declare that there is no conflict of interest.

References

All Party Parliamentary Group on Dementia (2011) The £20 billion question: an inquiry into improving lives through cost-effective dementia services. London: All Party Parliamentary Group on Dementia.

Arnold, L., Lindsay, R., López, F., Jacob, S., Biederman, J., Findling, R. *et al.* (2007) Treating attention-deficit/hyperactivity disorder with a stimulant transdermal patch: the clinical art. *Pediatrics* 120: 1100–1106.

Benson, H. (2005) Transdermal drug delivery: penetration enhancement techniques. *Curr Drug Deliv* 2: 23–33.

Bernabei, R. and Lage, P. (2008) Clinical benefits associated with a transdermal patch for dementia. 1, 24–27.

Blesa, R., Ballard, C., Orgogozo, J., Lane, R. and Thomas, S. (2007) Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease. *Neurology* 69: S23–S28.

Boroojerdi, B., Wolff, H., Braun, M. and Scheller, D. (2010) Rotigotine transdermal patch for the treatment of Parkinson's disease and restless legs syndrome. *Drugs Today* 46: 483–505.

Cummings, J., Lefèvre, G., Small, G. and Appel-Dingemanse, S. (2007) Pharmacokinetic rationale for the rivastigmine patch. *Neurology* 69: S10–S13.

Dale, E., Ashby, F. and Seelam, K. (2009) Report of a patient chewing fentanyl patches who was titrated onto methadone. Case Reports 2009, bcr0120091454–bcr0120091454.

Elgorashi, A., Heard, C., Niazy, E., Noureldin, O. and Pugh, W. (2008) Transdermal delivery enhancement of haloperidol from gel formulations by 1,8-cineole. *J Pharm Pharmacol* 60: 689–692.

FDA (2006) FDA approves emsam (Selegiline) as first drug patch for depression. News release, February 2006. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108607.htm (accessed 31 July 2012).

Findling, R., Bukstein, O., Melmed, R., López, F., Sallee, F., Arnold, L. *et al.* (2008) A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. *J Clin Psychiatry* 69: 149–159.

Gries, J., Benowitz, N. and Verotta, D. (1998) Importance of chronopharmacokinetics in design and evaluation of transdermal drug delivery systems. *J Pharmacol Exp Ther* 285: 457–463.

Griffith, S. (1990) A review of the factors associated with patient compliance and the taking of prescribed medicines. *Br J Gen Pract* 40: 114–116.

Hadgraft, J. (2001) Skin, the final frontier. *Int J Pharm* 224: 1–18.

Harada, A. and Vanderplas, A. (2006) PNL27 the effect of adherence to Alzheimer's disease treatment on health care costs in managed care. *Value in Health* 9: A87–A88.

Joint Formulary Committee (2011) Rivastigmine. In: *British National Formulary*. London: Joint Formulary Committee, section 4.11.

Kanikkannan, N., Kandimalla, K., Lamba, S. and Singh, M. (2000) Structure–activity relationship of chemical penetration enhancers in transdermal drug delivery. *Curr Med Chem* 7: 593–608.

Lanier, R., Umbricht, A., Harrison, J., Nuwayser, E. and Bigelow, G. (2007) Evaluation of a transdermal buprenorphine formulation in opioid detoxification. *Addiction* 102: 1648–1656.

Lanier, R., Umbricht, A., Harrison, J., Nuwayser, E. and Bigelow, G. (2008) Opioid detoxification via single 7-day application of a buprenorphine transdermal patch: an open-label evaluation. *Psychopharmacology (Berl.)* 198: 149–158.

Liappas, I., Dimopoulos, N., Mellos, E., Gitsa, O., Liappas, A. and Rabavilas, A. (2004) Oral transmucosal abuse of transdermal fentanyl. *J Psychopharmacol* 18: 277–280.

McGough, J., Wigal, S., Abikoff, H., Turnbow, J., Posner, K. and Moon, E. (2006) A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system in children with ADHD. *J Atten Disord* 9: 476–485.

Mercier, F., Lefèvre, G., Huang, H., Schmidli, H., Amzal, B. and Appel-Dingemanse, S. (2007) Rivastigmine exposure provided by a transdermal patch versus capsules. *Curr Med Res Opin* 23: 3199–3204.

MHRA (2010) *Drug Safety Update*, June. London: Medicines and Healthcare Products Regulatory Agency.

Moser, K., Kriwet, K., Naik, A., Kalia, Y. and Guy, R. (2001) Passive skin penetration enhancement and its quantification in vitro. *Eur J Pharm Biopharm* 52: 103–112.

Ngawhirunpat, T., Yoshikawa, H., Hatanaka, T., Koizumi, T. and Adachi, I. (2001) Age-related changes in skin permeability of hydrophilic and lipophilic compounds in rats. *Pharmazie* 56: 231–234.

Parikh, D. and Ghosh, T. (2005) Feasibility of transdermal delivery of fluoxetine. *AAPS PharmSciTech* 6: E144–E149.

Pelham, W., Waxmonsky, J., Schentag, J., Ballow, C., Panahon, C., Gnagy, E. *et al.* (2011) Efficacy of a methylphenidate transdermal system versus t.i.d. methylphenidate in a laboratory setting. *J Atten Disord* 15: 28–35.

Pfeiffer, R. (2007) Transdermal drug delivery in Parkinson's disease. *Aging Health* 3: 471–482.

Robinson, D. and Amsterdam, J. (2008) The selegiline transdermal system in major depressive disorder: a systematic review of safety and tolerability. *J Affect Disord* 105: 15–23.

Rose, J., Herskovic, J., Trilling, Y. and Jarvik, M. (1985) Transdermal nicotine reduces cigarette craving and nicotine preference. *Clin Pharmacol Ther* 38: 450–456.

Sacktor, N., Schifitto, G., McDermott, M., Marder, K., McArthur, J. and Kieburtz, K. (2000) Transdermal selegiline in HIV-associated cognitive impairment: pilot, placebo-controlled study. *Neurology* 54: 233.

Schrag, A., Jahanshahi, M. and Quinn, N. (2000) What contributes to quality of life in patients with Parkinson's disease? *J Neurol Neurosurg Psychiatry* 69: 308–312.

Stead, L., Perera, R., Bullen, C., Mant, D. and Lancaster, T. (2008) Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* CD000146.

Touitou, E. (2002) Drug delivery across the skin. *Expert Opin Biol Ther* 2: 723–733.

Vecchia, B. and Bunge, A. (2003) Evaluating the transdermal permeability of chemicals. In: Hadgraft, J. and Guy, R. (eds), *Transdermal Drug Delivery*. New York: Marcel Dekker, pp. 25–57.

Wasley, M., McNagny, S., Phillips, V. and Ahluwalia, J. (1997) The cost-effectiveness of the nicotine transdermal patch for smoking cessation. *Prev Med* 26: 264–270.

Wilens, T., Boellner, S., López, F., Turnbow, J., Wigal, S., Childress, A. *et al.* (2008) Varying the wear time of the methylphenidate transdermal system in children with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 47: 700–708.