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PSYCHOTROPIC DRUGS AND TRANSDERMAL DELIVERY: AN OVERVIEW

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ABSTRACT

Optimum therapeutic outcomes require not only proper drug selection, but also effective drug delivery. Scientists are exploring new methods of drug administration to improve patient compliance and enhance drug response. In many instances, oral administration of psychotropics is considered a less than optimal medication delivery system due to non-compliance. One potential method to help promote compliance is to develop psychotropic medications that can be delivered via a transdermal patch. Transdermal patches are used for treatment of various indications including pain, pregnancy prevention, and hormone replacement. In many cases, transdermal medication delivery is believed to offer many advantages over conventional oral therapies. Transdermal patches may help to improve tolerability by providing smoother continuous drug delivery. Selegiline, fluoxetine, haloperidol, imipramine, methylphenidate and rivastigmine transdermal systems have already been developed and may provide a promising new approach for other psychotropic drugs. Recent improvements in transdermal drug delivery through the use of permeation enhancers, transdermal gels, iontophoresis, electroporation and sonophoresis appear to be promising technologies for future psychotropics utilizing transdermal medication delivery.

KEY-WORDS

Transdermal drug delivery, psychotropic drugs, methylphenidate, rivastigmine.

INTRODUCTION

Mental illness has always been a part of the human experience and so has the quest to understand and treat it. As in other medical fields, the preferred treatments for mental illness have gone hand in hand with changing theories about its causes[1-2]. However pathophysiology of mental illness is not clear, though some ideas have been formed, *e.g.* dopaminergic overactivity in the limbic system may be involved in schizophrenia and deficiency of monoamines, such as norepinephrine and serotonine, at certain key sites in the brain may underlie depression. Conversely mania is caused by an overproduction of these neurotransmitters and anxiety occurs due to abnormal functions in several neurotransmitter systems, including norepinephrine, γ- aminobutyric acid (GABA) and serotonine. Treatment is empirical, symptom oriented, and not disease specific, however can be highly effective in many situations. Depending on the primary use, the psychotropic drugs may be grouped into[3]:

Antipsychotics

useful in treating schizophrenia and schizoaffective disorder. The chemical revolution in the treatment of

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mental illness began with the release of chlorpromazine in 1954. Within 8 months of its appearance on the market, the drug had been administered to over 2 million patients[4-5]. Now a number of antipsychotic drugs are available like phenothiazines, butyrophenones (haloperidol, trifluperidol, droperidol, penfluperidol), thioxanthines (Thiothixene, flupenthixol), other heterocyclics (pimozide, loxapine, reserpine, molindone) and atypical neuroleptics (clozapine, risperidone, olanzapine, quetiapine and ziprasidone), which have transformed the treatment of psychosis. The benefits of these drugs for patients are clear: Frightening hallucinations are eliminated or reduced, the patients feel more relaxed and in control, and a return to home and family life is often possible. But there are downsides with all psychotropic drugs. Some patient complaint of feeling drugged or lethargic. Others experience restlessness, muscle rigidity or dystonia. Negative symptoms such as social isolation and flat affect, often remain. In addition, these drugs do not offer a cure, patients must continue to take them to maintain benefits. Many patients stop taking the medication after some time resulting in a return of symptoms[1].

Antianxiety agents

useful in treating anxiety disorders. Many pharmacological agents have been used to alleviate anxiety. The first were barbiturates, widely prescribed before 1960s. But they were highly sedating and addictive and didn't always work. Meprobamate in 1954 aroused the hope that anxiety could be tackled without producing marked sedation. The goal has been realized more completely by the development of chlordiazepoxide and other benzodiazepines from 1960 to 1980[6].

Antidepressants

used for minor as well as major depressive illness, phobic states, and different anxiety disorders. Tricyclic and monoamine oxidase inhibitor (MAOI) antidepressants were found to be useful in 1957-58[1]. Now a days drugs like selective serotonine reuptake inhibitors (Fluoxetine, paroxetine, esitalopram, citalopram, sertaline), serotonine-norepinephrine reuptake inhibitors (venlafaxine, duloxetine), noradrenergic and specific serotonergic antidepressants (mirtazapine), norepinephrine reuptake inhibitors (reboxetine) and norepinephrine dopamine reuptake inhibitors (bupropion) play important role in treatment of depression[7].

Antimanic mood stabilizers

used to control mania and to break into cyclic affective disorders. Australian psychiatrist John F. J. Cade in 1949 discovered that lithium is beneficial in maniac - depressive disorder[1].

Optimum therapeutic outcomes require not only proper drug selection, but also effective drug delivery. The emergence of the new technologies provides unique opportunities to exploit novel approaches in drug delivery. It is clear that oral administration is often not the optimal delivery system for most psychotropics because of large and diverse array of side effects of some drugs like lithium, drug adherence problems in case of chronic neurologic disorders and limitations of oral route as in case of antidepressants[8]. Researchers are exploring new methods of drug administration to improve patient compliance, adherence to medication and delay relapse. Advances in oral drug delivery have come in the form of sustained release formulations of psychotropic drugs, which typically produce lower maximum concentrations and higher trough concentrations, thus reducing side effects and improving tolerability[9]. The future of pharmacologic treatment for psychiatric disorders may be in part dependent on non-oral drug delivery systems such as small pumps that can inject drugs directly into the brain, electrical devices that stimulate discrete brain regions, implants and transdermal delivery systems[6, 9]. These systems have been developed to address suboptimal therapy outcome by enhancing drug

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delivery, assuring safety of treatment, reducing side effects and improving compliance. In particular, patients with chronic neurological diseases often require multiple administrations of drug during the day to maintain constant plasma medication levels, which in turn increases the likelihood of poor adherence[10]. In these cases, long acting psychotropic drugs can eliminate the need for multiple dosing[11]. The evidence that continued medication is beneficial to chronic psychiatric patients is now almost universally acceptable[12-13]. Effective treatment of patients with psychiatric disorders is often compromised by patient non-adherence followed by relapse that leads to hospitalization which is the largest financial expenditure for this disease[14]. There have been reports in the literature that long acting dosage forms of psychotropic medications are able to improve adherence, delay relapse and lower overall treatment costs[15].

Transdermal Drug Delivery

Drug delivery systems such as patches that are more patient and caregiver-friendly may enable patients to continue treatment for longer periods and to attain greater, more sustained treatment benefits[16]. Delivering medicine into the general circulation through the skin is seen as a desirable alternative to oral administration. Not all drugs are easily absorbed through the skin but, for those that are or can be altered or enhanced to be so, transdermal delivery offers distinct advantages[17]. In addition to increasing convenience, transdermal delivery can change the metabolism and bioavailability of compounds and their metabolites and thus alter the therapeutic index of a particular drug. Because of the reduced frequency of administration, compliance should be enhanced with transdermal delivery. Delivery of drug via a transdermal route also avoids the hostile environment of gastrointestinal tract, where drugs can be inactivated and absorption can vary depending on pH, food ingestion/interaction, and other factors. In addition oral medications may cause nausea because of local effects, and some cannot be taken if the patient is already nauseated. Transdermal route also avoids hepatic first-pass metabolism and associated side effects. This can be exemplified with oxybutynin, a drug useful in treatment of overactive bladder. Oxybutynin undergoes presystemic metabolism within small intestine and then primarily through hepatic first pass metabolism, before it enters the circulatory system. So a percentage of the parent drug is converted to metabolite before reaching the target site *i.e.*, bladder or other organs responsible for side effects – primarily, the salivary gland, bowel, eye and brain. Transdermal administration essentially bypasses this initial presystemic metabolism and causes fewer side effects than oral form of the drug[18]. Transdermal delivery offers convenience, especially notable in patches that require only once weekly application. It has been observed that many psychotropic drugs are non compliant because of large and diverse array of adverse effects and drug adherence problems and transdermal drug delivery may be useful in achieving patient compliance[8, 19].

We might better understand the potential benefits and role of transdermal systems by considering the experience already gained with those currently available, particularly with respect to patient and physician satisfaction. It is important for the psychiatrists to understand the advantages and disadvantages of transdermal therapy in general and for psychotropic drugs specifically. Furthermore, some insights into how transdermal therapy can be enhanced in the future will provide an even greater understanding of its potential.

Transdermal hormone replacement therapy (HRT) has been available for years and is accepted alternative to oral therapy. There have been numerous studies comparing transdermal versus oral HRT with respect to a variety of efficacy variables[20-21]. Ettinger and colleagues[22] found that 25% of women who started on oral therapy of estrogens switched to transdermal estradiol versus 0.9% who

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switched from transdermal to oral therapy. Lake and Pinnock[23] compared 2 different types of estradiol, matrix versus reservoir, in 35 hysterectomized women who received 4 weeks of each therapy. 87% of patients selected the matrix patch because it was easy to apply, open and had better adhesion and cosmetic appearance. Of 27 subjects who stated a preference, 74% preferred transdermal to oral therapy. Transdermal delivery of contraception is also becoming popular. Since its introduction in 2002, the Ortho Evra™ once weekly patch has become the fastest growing contraceptive on the market. Various trials showed superior compliance with patch as compared to oral contraceptives[24-25]. Another data showed that compliance with the patch was consistent across age groups but differed significantly by age for oral therapy, with younger patients having a lower percentage of cycles with perfect compliance[26]. Transdermal delivery has also become popular for the treatment of chronic cancer related and non cancer pain. Two studies on chronic pain in patients with advanced cancer showed a patient preference for transdermal fentanyl versus sustained release oral morphine. Although both treatments resulted in similar relief of pain, but transdermal delivery of fentanyl was associated with a lower frequency and reduced side effects[27-28]. Allan and Colleagues studied transdermal fentanyl versus oral sustained release morphine for the treatment of non cancer pain. Preference was assessed in 85% of 256 patients, of which 65% preferred transdermal therapy and 28% preferred oral therapy and 7% expressed no preference. Quality of life scores were higher in the group receiving transdermal therapy[29]. Available data suggests the acceptance of transdermal therapy for various diseased conditions because of its convenience and decreased incidence and impact of side effects.

Potential of Transdermal Delivery in Psychiatric Patients

In the case of psychotropic drugs, side effects are particularly troublesome and compliance with rigorously regular medication schedules is of great clinical importance for many psychiatric patients. Transdermal drug delivery may be helpful in achieving compliance with a regular medication schedule for certain classes of psychotropic agents. Such classes of psychotropic agents are selective serotonine reuptake inhibitors (*e.g.* sertaline, paroxetine, fluoxetine, fluvoxamine) and serotonine-norepinephrine reuptake inhibitors (*e.g.* venlafaxine), which are commonly prescribed for patients with diagnosis of mood disorders, some forms of anxiety disorders, some form of menopausal disorders and eating disorders (especially bulimia nervosa).. Although many patients tolerate oral administration of these drugs, a certain population of patients experience gastrointestinal side effects such as alteration of gastric motility, nausea and diarrhea[30]. So patients with gastric or duodenal ulcer, ulcerative colitis, irritable colon syndrome or regional enteritis may not be able to tolerate the oral form of these medications and thus transdermal drug delivery may be used for these drugs. Another class of psychotropic agents which include antidepressants such as buproprion, nefazadone and trazadone has resulted in malabsorption problems or idiosyncratic side effects with oral preparation, which may be avoided by transdermal administration[31]. Oral administration of amitryptiline and doxepine may be suboptimal when high local tissue concentrations are desired. In these cases transdermal drug delivery may be useful. Certain other psychotropic agents such as carbamazepine and valproic acid, which are used frequently in psychiatric practice as mood stabilizing and antimanic agents, can cause nausea as a gastrointestinal side effect[32]. It has been seen that oral administration of lithium, a mood

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stabilizing agent, is predictably associated with a large number of adverse effects that effects negatively on patient compliance and safety. These events are in turn well related to the pharmacokinetics of orally administered formulations. Symptomatic states related to interdose concentration 'troughs' or inadvertent noncompliance further exacerbates noncompliance. The development of sustained or slow release lithium preparations represents a direct response to the limitations of oral routes of lithium salt administration. However the performance of these preparations varies between manufacturers and between batches and they are often used in divided daily dosing strategies similar to nonsustained release preparations. Extremely slow release preparations are furthermore associated with pronounced gastrointestinal irritation. These sustained release preparations represent an imperfect solution to the limitations of oral lithium dosing. Thus there is clinical need for an alternative dosing strategy like transdermal delivery for lithium that is not met by currently available preparations[8].

Transdermal drug delivery systems of psychotropic drugs like haloperidol, imipramine, fluoxetine, selegiline and lithium have already been studied[33-34]. Transdermal drug delivery system of Selegiline, which is a monoamine oxidase inhibitor, is approved by FDA with unique pharmacokinetic and pharmacodynamic properties. This was developed to overcome limitations of orally administered MAO's, particularly dietary tyramine restrictions and was found to be suitable in long term treatment of major depressive disorder[35]. It is well known that oral MAOI antidepressants pass through the digestive tract, thus inhibiting intestinal MAO-A, which is needed to break down tyramine[36], a substance found in certain foods and beverages such as aged cheese and tap beer[37]. If a large amount of tyramine is absorbed systemically it can lead to a sudden and large increase in blood pressure called a hypertensive crisis, which is potentially life threatening and requires immediate medical treatment. A few food products may contain large amounts of tyramine that represents a potential risk for patients with significant inhibition of intestinal MAO-A resulting from administration of MAO inhibitors. As a result, patients taking oral MAOIs for major depression are required to avoid foods high in tyramine[38]. Through transdermal delivery, selegiline is directly and continuously absorbed into the bloodstream over a 24h period. As a result, initial exposure of the drug to the digestive tract is minimized. It is indicated in animal studies, that transdermal delivery of selegiline (6 mg/24 h patch) allows for levels of medicine to inhibit MAO in the brain thought to be necessary for antidepressant effect while sufficiently preserving MAO-A in the digestive tract to break down tyramine. The data for 6 mg/24 h patch support the recommendation that tyramine dietary modifications are not needed. To reduce the risk of hypertensive crisis, dietary modifications are required with 9 mg/24 h and 12 mg/24 h selegiline transdermal patches[39]. Transdermal drug delivery system of haloperidol, a typical antipsychotic has also been studied by Samanta *et al.* The neuroleptic efficacy of transdermal system was confirmed by maximum graded response in a rotarod apparatus. Minimum extrapyramidal side effects in albino rats were found with a score of zero over a 72 h study. The pharmacokinetic parameters in rabbit model showed a very significant prolongation of action upto 72 h. Thus, transdermal delivery of haloperidol improved the therapeutic profile by preventing the neuroleptic induced extrapyramidal side effects and might be a better alternative during its long period of psychiatric treatment over conventional dosage form[12].

Transdermal patches are also used for treatment of other diseases including neurologic and psychiatric disorders like Parkinson disease and ADHD. ADHD is the most common psychiatric disorder in children. Currently the most widely prescribed therapy for

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ADHD is methylphenidate. Methylphenidate has a short plasma half life and thus needs to be frequently administered for effective therapy. Such therapy has limitations in term of patient compliance, particularly in young children[40]. Innovative research has resulted in development of several formulations of methylphenidate which can modify the delivery of drug in the body. These include modified release preparations like sustained release tablets, controlled release tablets and capsules and transdermal delivery system. The rationale for the development of various delivery systems of methylphenidate stems from the need for drug coverage for at least 8 hours for ADHD patients. This can maintain efficacy over the entire school day and can eliminate the need for repeated administration while the patient is at school[41]. Among these modified drug delivery systems, a methylphenidate transdermal system represents the current status of promising treatment options that may help to shape the future of psychiatric treatment as transdermal patch is convenient to use and can reduce side effects related to oral delivery[42-43].

Rivastigmine is indicated for treating symptoms of mild to moderate alzheimer's disease and dementia in Parkinson's disease as cholinesterase inhibitor. A rivastigmine patch has been developed which may provide a promising new approach to dementia therapy. It has been found that transdermal delivery of rivastigmine in patients with alzheimer's disease significantly reduces the nausea and vomiting commonly associated with oral cholinesterase inhibitor therapy and is as effective as oral therapy. This patch is better tolerated by patients and is preferred by caregivers as it is easier to follow the treatment schedule and it interferes less with daily activities[16]. Table 1 enlists the psychotropic drugs which are approved by FDA as transdermal drug delivery systems.

TABLE 1.
RECENT FDA APPROVED PSYCHOTROPIC DRUGS AS TRANSDERMAL DELIVERY SYSTEMS

Drug	Application	Company and Approval	Reference
Selegiline (Emsam)	Depression	Somerset Pharmaceuticals, Feb. 2006	34
Rivastigmine (Exelon)	Alzheimer disease and Parkinson's Dementia	Novartis Pharmaceuticals, July, 2007	61
Methylphenidate (Daytrana)	Attention deficit hyperactive disorder (ADHD)	Noven Pharmaceuticals, April, 2006	62

Improved Transdermal Technologies for Psychotropic Drugs

The efficacy of transdermal drug delivery may be improved by altering the system to enhance the bioavailability. The main limitation of transdermal drug delivery is the lipoidal barrier of stratum corneum[44]. It is generally accepted that the best drug candidates for transdermal patches must be non-ionic, low molecular weight (less than 500 Daltons), have adequate solubility in oil and water (log P in the range of 1-3), a low melting point and are potent (dose less than 50 mg per day). But when a drug does not have suitable characteristics of penetration (*e.g.* if partition coefficient is too low), a suitable prodrug can be used[45]. The prodrug is activated after initial penetration. Other modifications include the

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use of liposomes or vesicles which can be used to entrap drug molecules for easier transport through the lipid bilayer of the stratum corneum[46]. The stratum corneum can be modified by hydration or through the use of chemical penetration enhancers, which improve penetration through lipid disruption, protein interaction or portioning promotion[47]. Costa *et al.*, studied transdermal therapeutic system containing lorazepam, an antianxiety benzodiazepine. To increase the permeation rate of lorazepam, three permeation enhancers' *viz*., tween 80, sodium lauryl sulphate and benzalkonium chloride were used in different concentrations. Results showed the increase in penetration with all permeation enhancers and the best permeation enhancement results were obtained using benzalkonium chloride in concentration of 5%[48]. Prikh and Ghosh investigated the feasibility of transdermal drug delivery of fluoxetine, an antidepressant, across human cadaver skin using either salt or base form of fluoxetine along with permeation enhancers like azone and ethanol. The studie indicated that permeation of fluoxetine free base was significantly enhanced from a vehicle system containing 65% v/v ethanol and the results seem promising for developing a transdermal drug delivery system of fluoxetine[19]. Thus psychotropic drugs can be used in transdermal system along with various permeation enhancers so that transdermal delivery of these drugs could be regarded as feasible[49-50].To expand the number of compounds that can be delivered via the skin, researchers are developing novel transdermal technologies, including iontophoresis which uses an electric current to cause charged particles to move, electroporation involves the creation of aqueous pores in lipid bilayers by the application of a short (microseconds to milliseconds) electric pulse and low frequency sonophoresis, which enhances the transport of permeants, such as drugs through cell membranes as a result of ultrasonic energy[51-54]. With these technologies molecular size, solubility, melting point and dose size is not a limiting factor. Iontophoretic transdermal delivery of haloperidol across pig skin was studied by Alvarez-Figueroa *et al*. The results indicated that iontophoresis may be used to improve the topical application of haloperidol for the treatment of chronic psychosis[55]. Singh *et al* studied transdermal iontophoretic delivery of methylphenidate. This study was undertaken to evaluate the passive and electrically assisted transport (iontophoresis) of methylphenidate from aqueous methylphenidate hydrochloride solutions across excised human skin. It was observed that iontophoresis significantly enhanced protonated methylphenidate transport as compared with passive delivery[40]. Simon *et al.*, applied a mathematical model of iontophoretic transdermal drug delivery to study the effects of physical parameters on the cumulative amount of amitriptyline HCl collected. The results supported that the increase in the iontophoretic transdermal delivery of some drugs is mainly due to a rise in the surface concentrations of the drug[56]. Iontophoretic transdermal patch of lithium was developed by Nerneroff and Kilts. This method involved the attachment of a dermal patch to the patient, wherein the patch delivered lithium in response to a current. The device and method of the invention allowed the administration of lithium ion to the bloodstream within therapeutic window without peaks (creating damage of toxicity) and troughs (creating the danger of breakthrough symptoms and decreased patient compliance) experienced with conventional methods of lithium administration[8]. Clearly the opportunities for transdermal drug delivery have been greatly expanded through application of new formulation technologies[57]. Iontophoresis appears to be a promising and perhaps the most efficient assisted delivery technique for future transdermal therapy of psychotropic drugs[9, 55].

Transdermal gels represent an improvement compared with transdermal delivery by patches because they offer more dosage flexibility, less

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irritation potential and a better cosmetic appearance. Advanced transdermal delivery gel technology was developed in order to provide enhanced passive skin permeation of various active drugs for treatment of anxiety and psychosis[58-60]. A list of psychotropic transdermal formulations that are reported in various research publications is shown in Table 2.

TABLE 2.
PSYCHOTROPIC DRUGS STUDIED AS TRANSDERMAL DELIVERY SYSTEMS REPORTED IN LITERATURE

Drug	Transdermal drug delivery technology	Category	Reference
Aripiprazole	Reservoir Patch	Atypical antipsychotic	63
Haloperidol	Matrix patch	Typical Antipsychotic	10
Lorazepam	Matrix Patch	Antianxiety	21
Oxazepam	Matrix Patch	Antianxiety	64
Clonazepam	Gel	Antianxiety	32
Propranolol	Matrix Patch	Antianxiety	65
Imipramine	Gel	Antidepressant	17
Amitryptiline	Gel	Antidepressant	66
Selegiline	Reservoir Patch	Antidepressant	20
Fluoxetine	Microemulsion	Antidepressant	15
Lithium	Iontophoresis	Antimanic	8
Bupropion	Reservoir Patch	Antidepressant	31

CONCLUSION

It is desired to develop low dose maintenance therapy of psychotropic drugs which can minimize the risk of major side effects and address the problems of poor compliance in patients. Transdermal drug delivery of psychotropic drugs is able to provide optimum amount of drug to control the disease condition along with minimum side effects. This can lead to cost effectiveness of healthcare treatment for long term management of psychiatric disease. But the successful development of the transdermal system depends upon the choice of drug. The drug should permeate the skin in adequate amount to produce the desired therapeutic effect. The opportunities for transdermal drug delivery are expanding through the application of new formulation technologies and active delivery systems. However, for these novel delivery methods to succeed and compete with those already on the market, the primary issues that require consideration include device design and safety, efficacy, ease of handling and cost effectiveness. Today, a large number of candidates for transdermal delivery have evolved along with greater acceptance. Transdermal drug delivery market is growing and there is a prospect of higher growth in this market over the next several years. Transdermal drug delivery of psychotropic drugs is expected to have a profound impact on patient care.

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