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Review Article

The Use of Transdermal Therapeutic Systems in Psychiatric Care: A Primer on Patches

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Background: *Numerous currently available medications that act in the central nervous system can be delivered transdermally. Such medications include cholinesterase inhibitors for dementia, methylphenidate (MPH) for attention-deficit hyperactivity disorder, monoamine oxidase inhibitors (MAOIs) for depression, dopamine agonists for Parkinson disease and restless leg syndrome, and clonidine for attention-deficit hyperactivity disorder and impulse-control disorders.* **Objective:** *This article aims to review the literature related to transdermal delivery systems from the perspective of clinical practice and research related to their use in the treatment of psychiatric conditions.* **Results:** *Most of the currently available transdermal systems have psychotropic properties or utility in the behavioral health arena and, therefore, are of clinical relevance to consultation-liaison psychiatrists or practitioners of psychosomatic medicine. We discuss their efficacy and safety profiles. We provide a table of these agents and their uses.* **Conclusions:** *Transdermal delivery (i.e., patches) for medicines with psychotropic properties allows mental health providers to customize therapy for patients by altering the duration of therapy, minimizing first-pass metabolism and the potential for drug–drug interactions, and decreasing the risk for gastrointestinal irritation.*

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INTRODUCTION

Transdermal delivery increasingly offers a promising alternative route for drug administration. Indeed, for thousands of years, humans have placed substances on their skin to achieve therapeutic effects. Following the development of the first transdermal system of drug delivery in 1979—a 3-day patch containing scopolamine to treat motion sickness—research on this route of drug delivery has increased. The potential benefits of transdermal drug delivery include convenience for patients, enhanced medication adherence, and the ability of medications to be delivered in a rate-controlled manner (by avoiding first-pass metabolism and fluctuating plasma concentrations often seen with orally-administered medicines). Another potential advantage of this mode of delivery is the ease of use; patches may be applied to the skin once a day or even once a week—depending on the medicine—simplifying the treatment regimen for those taking multiple daily doses of oral preparations. Transdermal systems are

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noninvasive and can be self-administered. They provide a visual reminder for patients and caregivers that treatment has been dispensed.[1] Transdermal delivery can also be helpful for patients with certain medical conditions (e.g., swallowing difficulties). Currently, there are more than 20 transdermal therapeutic systems (TTSs) approved for use in the United States. These include patches for angina, hypertension, pain relief, nausea, and hormone replacement.

A growing array of transdermal technologies that act in the central nervous system (CNS) are available, with several TTSs approved specifically for psychiatric diagnoses (e.g., MPH for attention-deficit hyperactivity disorder [ADHD] or selegiline for major depressive disorder).[2] Most of the currently available agents administered via transdermal systems have psychotropic properties or utility in the behavioral health arena and, therefore, are of clinical relevance to consultation-liaison psychiatrists or practitioners of psychosomatic medicine. Unfortunately, reviews of transdermal medicines are usually considered in a piecemeal fashion, which hampers development of a comprehensive view of their efficacy and potential. A few broad analyses of patches are available, and they approach the subject from the perspective of chemical or bimolecular engineering and the challenges of overcoming the technological barrier of skin permeability.[3,4] Our review takes a different approach; it views transdermal technology through the prism of clinical practice and research related to its use in the treatment of psychiatric conditions.

TYPES OF TTSs

TTSs, commonly called "patches," generally consist of 3 parts: an adhesive, an active pharmacologic agent, and enhancing agents. A number of types of TTSs are currently available, and these include reservoir, matrix, and iontophoretic patches.[5]

The original patch design was a liquid reservoir system where the patch consisted of a backing material (that was both protective and adhesive), a liquid drug reservoir, and a release membrane. Transdermal systems of scopolamine, clonidine, estrogen, and testosterone use such a liquid-reservoir design. A more recent design has an adhesive matrix system (where the adhesive and the drug are combined in the same layer leaving only 3 layers to the patch)—the backing layer, the drug and adhesive layer, and the protective layer that would be removed before applying the patch to the skin. Most currently available patches, except those previously mentioned, employ the adhesive matrix design (Figure).

With the passive designs of either the reservoir or matrix designs, once a patch is applied to the skin a diffusion gradient is established and the drug moves into the stratum corneum (or outer layer of the skin). Transit through the stratum corneum occurs by diffusion through intercellular lipids.[3] This is the rate-limiting step in passive transdermal drug delivery. Therefore, medicines that are suited for passive patch technology have a small molecular mass (<500 Da) and are lipophilic.[6] These drugs must also be chemically stable during patch storage and during transdermal diffusion once the patch is applied.

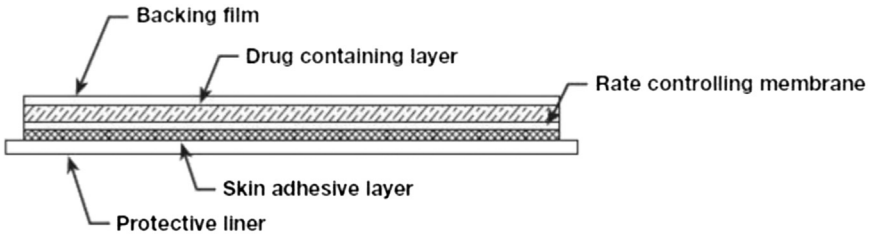
One recently approved patch, the sumatriptan iontophoretic transdermal system, uses low-voltage electric current as a driving force for transport across the stratum corneum. Iontophoresis has been studied for more than a century; it involves the movement of charged molecules via electrophoresis, whereas weakly and uncharged molecules move via electroosmotic flow.[3] One benefit of iontophoretic patches is that the rate of drug delivery correlates with the electric current delivered. Therefore, drug delivery can be turned on and off by a microprocessor—or in the case of the sumatriptan iontophoretic transdermal system—the patient.

LIMITATIONS AND SAFETY CONCERNS FOR TRANSDERMAL MEDICATIONS

Skin Irritation

One of the most common side effects associated with any transdermally-administered medication is the skin irritation that results from either exposure to the agent being administered or to the structural components of the patch itself. A review of 7 different TTSs found that skin irritation (usually mild) developed in 20%–50% of users.[7] Contact dermatitis is the most common type of reaction seen at the site of patch application; this inflammatory response is generally localized and characterized by erythema, pruritus, and mild edema. This classic irritant reaction presents as a sharply demarcated rash that conforms to the area of the TTS application.[8] Ingredients that are often implicated in irritant reactions include ethanol and glycerin; however, the accumulation of sweat and the resulting occlusion of sweat ducts is another factor associated with the skin irritation often seen with TTSs.[8] Contact dermatitis

FIGURE. Schematic of an Adhesive Matrix Patch



generally resolves without treatment after the removal of the irritant. In some cases, removal of the patch itself can cause transient erythema alone or may be accompanied by flare and edema (i.e., the triple response of Lewis).[7]

Although cutaneous reactions are common with TTSs, they can be managed by several strategies, including rotation of the application sites, placement of the TTS on the buttocks, reduction of the duration of patch adhesion, or pretreatment of the skin with topical corticosteroids. In a study comparing woman receiving an estrogen-TTS with those receiving a control adhesive, rotation of patch application sites and placement of the patch on the buttocks (rather than the abdomen or lower back) led to a 92% reduction in the cumulative irritation score.[9] In a cohort of patients receiving clonidine-TTS for more than 3 months, dermatologic side effects were minimized by decreasing the patch-wear time from 7 days (as is typically recommended for clonidine) to 5 or even 3 days.[10] Several authors[11,12] have advocated for pretreatment with topical steroids (to decrease skin irritation and allergic contact dermatitis at patch application sites). For example, pretreatment of testosterone TTS placement sites with triamcinolone acetonide 0.1% cream[13] or clobetasone butyrate 0.05% cream[14] decreased both the incidence and severity of skin irritation. Therefore, for those patients who experience allergic contact dermatitis despite rotation of patch sites or shorter duration of patch placement, pretreatment with topical corticosteroids may provide relief for localized skin irritation (Table 1).

Patch Adhesion

Another limitation common to transdermal delivery systems is the efficacy of patch adhesion. Absorption of the medicine can be compromised if a patch does not remain in contact with the skin. One study examined patch adhesion over 12 hours of wear time (during a summer day, including swimming and engaging in other physical activities) for children with ADHD. In this study of the MPH transdermal system, among 36 participants over an 8-day period, 18 patches fell off and another 18 required additional taping.[15]

Although loss of patch adhesion can result in subtherapeutic medication dosing, accidental dermal application or ingestion of transdermal medicines can cause toxicity. Patches may be mistaken for harmless Band-Aids or be accidentally transferred while bathing or sleeping in close proximity to a patch wearer.[16] Infants and toddlers have unique risks of accidental exposure to the active ingredients in patches. Infants

TABLE 1. Key Points to Discuss With Patients When Prescribing a Transdermal Patch[16]

- Avoid touching the sticky (adhesive) surface while handling a patch
- In general, do not tear, cut, or put holes in the patch (for some patches this can result in overdose)
- Before application, it is good practice to write, using a waterproof marker (Sharpie), the date of application and date to be removed on each patch
- Apply the patch to a dry, clean, flat area on the body; choose an area of the skin without cuts, scars, burns, or other skin irritation
- Avoid the practice of applying oils or alcohols before patch use
- If a patch loses adhesiveness or falls off, dispose it off and apply a new patch on a different area
- Do not apply heat over the patch any time during use (this may increase medication absorption)
- To discard the patch, fold the adhesive subsides together and discard it, keeping it out of the reach of children
- Wash hands thoroughly with soap and water after application of the patch
- Keep unused patches in a locked area to prevent unintentional misuse or diversion

are often held by adults, increasing the chances that a partially detached patch could be transferred from adult to child.[17] Toddlers are more likely to find lost, discarded, or improperly stored patches and ingest them or stick them on themselves.

Limitations in Range

The types of molecules that can currently be delivered through the skin are organic and are lipid soluble. Traditional patch systems are limited by the small, relatively lipophilic molecules that can pass through the lipid bilayer of the stratum corneum. Nicotine is the smallest molecule represented, with a molecular weight of only 162.24 g/mol. Although hormones, or a molecule like fentanyl, with a molecular weight more than 300 g/mol, are considered large organic molecules, they are still much smaller than even a small protein, such as insulin. Most psychotropics, on the contrary, are larger and more complex molecules that will require newer technologies to be delivered through the skin.[3]

CURRENTLY AVAILABLE TRANSDERMAL THERAPEUTIC SYSTEMS

Buprenorphine (Butrans)

Buprenorphine is a semisynthetic, highly lipophillic, mixed opiate agonist-antagonist. In its various formulations, buprenorphine is indicated for the treatment of both acute and chronic pain as well as for opioid dependence and withdrawal. It acts as a partial agonist at the mu-opioid receptor, an antagonist at the kappa-opioid receptor, an agonist at the delta-opioid receptor, and a partial agonist at the ORL-1 (nociceptin/orphanin FQ) receptor. As a partial mu-agonist, buprenorphine exhibits a ceiling to its pharmacologic effects when compared with full opioid agonists.[18]

In the buprenorphine transdermal system, the proportion of buprenorphine contained within the adhesive matrix is the same for each patch strength; therefore, the amount of medication released per hour is dependent on active surface area in the system. The patches are available in 5-, 10-, and 20-μg/hour strengths and are designed to be worn for 7 days. The median time for a 10-μg/hour patch to deliver quantifiable levels of buprenorphine is approximately 17 hours; the time to peak concentration ranges from 24–72 hours.[19] Similar to another transdermal opioid formulation, fentanyl, application of a heating element directly to the patch increases blood concentrations significantly. The patch should be applied to clean, dry, intact skin on the upper outer arm, upper chest, upper back, or on the side of the chest, and it should be rotated with each application allowing 21 days before reapplication to the same site (Table 2).

A number of studies have demonstrated that the buprenorphine transdermal system is well tolerated during the treatment of various types of chronic pain, particularly in sensitive populations, including the elderly.[20] There are 2 small, open-label trials that have explored the application of the buprenorphine patch for the purpose of opioid detoxification—one in which the participants wore the patch for only 3 days[21] and one in which the participants wore the patch for the full 7 days.[22] Both studies indicated that the patch appears to be safe and effective for suppressing opioid withdrawal symptoms; however, the long-term application appeared to be more comfortable and successful in this regard. Buprenorphine, owing to its partial agonist action, is thought to have a limited effect on respiratory drive, unlike morphine and fentanyl (which both have been shown to have no ceiling for analgesia but also to induce severe respiratory depression at higher doses). Also of importance in the elderly, the plasma concentration of buprenorphine does not increase in patients with chronic renal disease or decrease in patients receiving hemodialysis.[23,24] This is particularly relevant to the treatment of elderly individuals with dementia, as studies have indicated that improved pain management may decrease agitation and other mood symptoms in those with dementia, many of whom might otherwise have received antipsychotic medicines.[23,25]

Contraindications to use of buprenorphine include paralytic ileus, severe respiratory disease, or severe hepatic disease. In addition, buprenorphine has been known to induce QT prolongation at higher doses, and therefore, it should not be administered to patients with a known long QT syndrome and should be used with caution when given with other QT-prolonging medications (e.g., class IA or class III antiarrhythmics, tricyclic antidepressants, and certain antipsychotics). Buprenorphine is dependent on cytochrome P450 3A4 (CYP 3A4) for metabolism, and medications that either potently inhibit (e.g.,

TABLE 2. Transdermal Medicines Currently Available and Their Uses*

Generic name	Trade name	Patch technology	Approved indication	Dosages available	Special precautions	Potential (off-label) psychiatric uses
Scopolamine	Transderm Scop	Liquid reservoir	Motion sickness	1.5 mg changed every 72 hour		Hypersalivation (sialorrhea) associated with clozapine therapy
Nitroglycerine	Transderm-Nitro	Adhesive matrix	Angina pectoris	0.2–0.4-mg/hour patch for 12–14 hour/day		Restless leg syndrome
Clonidine	Catapres-TTS	Liquid reservoir	Hypertension	0.1, 0.2, and 0.3 mg changed weekly		ADHD, oppositional defiant disorder, posttraumatic stress disorder, sleep disturbances, substance-induced withdrawal (particularly withdrawal from opioids), Tourette syndrome, chronic headaches, and impulse-control disorders in patients with autism
Estradiol	Estraderm	Liquid reservoir	Menopausal symptoms	0.05 mg/day		
Estradiol/ norethindrone Ethinyl	CombiPatch	Adhesive matrix		0.05–0.14 mg/day, 0.05–0.25 mg/day		
Estradiol/ norelgestromin	Ortho Evra	Adhesive matrix	Contraception	0.75–6 mg		
Estradiol/ levonorgestrel	Clima Pro	Adhesive matrix	Menopausal symptoms	0.045-0.015 mg/day		
Fentanyl	Duragesic	Adhesive matrix	Chronic pain	12, 25, 50, 75, and 100 μg/hour	Nonmedical use by individuals without opiate tolerance can be dangerous and may result in death; even those with opiate tolerances are at high-risk for potential overdose	
Nicotine	Nicoderm CQ	Adhesive matrix	Smoking cessation	7, 14, and 21 mg/ 24 hour		Potentiation of neuroleptic effect in patients with Tourette syndrome; ADHD and depression?
	Habitrol	Adhesive matrix		7, 14, and 21 mg/24 hour		
Testosterone	Androderm	Liquid reservoir	Delayed puberty, hypogonadism, and palliative treatment of breast cancer	2 mg/day, 4 mg/day		Depression, especially in patients with hypogonadism, elderly men, and those with HIV/AIDS
Lidocaine	Lidoderm	Adhesive matrix	Postherpetic neuralgia	5% lidocaine patch changed every 12 hour		Diabetic polyneuropathy, cancer pain with a neurogenic component, and postoperative pain
Lidocaine/ tetracaine	Synera	Adhesive matrix	Local dermal analgesia	70/70 mg applied for 30 minute		
Oxybutynin	Oxytrol	Adhesive matrix	Overactive bladder	3.9 mg/day	Risk of adverse CNS events, including delirium (oral > transdermal form)	
Methylphenidate	Daytrana	Adhesive matrix	ADHD in children and adolescents	10, 15, 20, and 30 mg changed after 9 hour		ADHD in adults and depression

TABLE 2. Continued

Generic name	Trade name	Patch technology	Approved indication	Dosages available	Special precautions	Potential (off-label) psychiatric uses
Selegiline	Emsam	Adhesive matrix	Depression in adults	6, 9, and 12 mg changed after 24 hours	FDA recommendation for dietary modifications for the 9- and 12-mg doses	Depression in adolescents?
Rotigotine	Neupro	Adhesive matrix	Parkinson disease	1, 2, 3, 4, 6, and 8 mg/24 hours	Patch contains sodium metabisulfite, which may cause allergic reactions in those with sulfite sensitivity	
Rivastigmine	Exelon	Adhesive matrix	Dementia	4.6, 9.5, and 13.3 mg/24 hours		
Granisetron	Sancuso	Adhesive matrix	Chemotherapy-induced emesis	3.1 mg/24 hours changed weekly		
Buprenorphine	Butrans	Adhesive matrix	Chronic pain	5, 10, and 20 μg/hour changed weekly	Contraindicated in the setting of paralytic ileus, severe respiratory disease, or severe hepatic disease; lower potential for abuse and overdose than other opiates but may still be misused by chewing it, by swallowing it, or by intentionally applying heat to the patch	Pain in elderly or patients with dementia
Sumatriptan	Zecuity	Iontophoretic	Migraine with or without aura	6.5 mg/4 hour	System contains 2 lithium coin cell batteries; this patch should not be worn over an active implantable medical device or while a person undergoes MRI	

ADHD = attention-deficit hyperactivity disorder; FDA = Food and Drug Admnistration; MRI = magnetic resonance imaging.

* This list includes transdermal patches and delivery systems approved by the FDA. Patches discontinued or withdrawn from the market are not included. Patches are organized chronologically based on the first-approved product for a given drug or drug combination. Topical creams, ointments, gels, and sprays are not included.

fluoxetine and all protease inhibitors) or induce (e.g., carbamazepine, St John's wort, or phenobarbital) this metabolic enzyme may alter buprenorphine's metabolism.

Although buprenorphine has a lower potential for abuse and overdose than other opiates, in certain instances, the patch may still be misused by placing it in the mouth, by chewing it, by swallowing it, or by the intentionally applying heat to the patch. The risk of overdose becomes much greater when buprenorphine is administered with another medication (such as a barbiturate or a benzodiazepine) that suppresses the respiratory drive.[24]

Clonidine (Catapres-TTS)

Clonidine is a centrally acting α_2-agonist which stimulates α-adrenoreceptors of the brainstem, thereby inhibiting norepinephrine release. Diminution of norepinephrine results in decreases in peripheral resistance, renal vascular resistance, heart rate, and blood pressure. Clonidine is available as oral tablets or in a TTS form. Clonidine is indicated for the treatment of hypertension in adults, but has a broad range of psychiatric uses. In 2010, an extended-release oral preparation of clonidine (marketed as Kapvay) was approved for ADHD as monotherapy or as adjunctive therapy to stimulant medications.[26] Before the development of this extended-release preparation, oral dosing of clonidine was limited by wide fluctuations in clonidine plasma concentrations, which were often associated with adverse effects (e.g., sedation or dry mouth).[10] Although the incidence of these effects is limited with transdermal therapy, the proportion of patients who experience skin reactions to clonidine-TTS (observed in as many as 40% of children wearing the patch) may offset some of its benefits.[27]

Clonidine-TTS was developed to provide steady-state clonidine plasma concentration. It is unique in the length of the therapeutic efficacy; it is available in doses of 0.1, 0.2, and 0.3 mg per day (or 3.5, 7.0, and 10.5 cm^2), lasting 7 days. The patches contain 2.5, 5, and 7.5 mg of clonidine content, respectively. Transdermal doses of approximately 0.5–0.5 mg/day produce mean plasma concentrations of 0.2–2.1 mg/L, covering the theoretical "therapeutic window" for clonidine of 0.2–2.0 μg/L.[4] In our experience, patients are usually started on oral clonidine and then switched to an approximately equivalent transdermal dose. After removing the patch, the clonidine plasma concentration declines slowly, with a half-life of approximately 20 hours.[4]

In psychiatry, administration of oral clonidine has improved ADHD, oppositional defiant disorder, posttraumatic stress disorder, sleep disturbances, substance-induced withdrawal (particularly withdrawal from opioids), Tourette syndrome, chronic headaches, and hyperactive/impulsive behaviors in patients with autism spectrum disorders. The clinical literature involving psychiatric applications of transdermal clonidine, however, is considerably smaller. The clonidine patch (5 μg/kg/d) was evaluated in a small double-blind, placebo-controlled, crossover study in boys and men with autism.[28] The study recorded significant improvement in hyperactivity and anxiety, with only mild adverse effects (e.g., sedation and fatigue). A head-to-head comparison between the clonidine patch and oral haloperidol in the treatment of children with Tourette syndrome found a higher reduction in the overall tic symptom scores in the transdermal clonidine group than the oral haloperidol group.[29] The clonidine patch was effective in appropriately 80% of patients, and its side effects were mild and rare.

Estradiol TTS (Estraderm); Norelgestromin/Ethinyl Estradiol Transdermal System (Otho Evra); Estradiol/Norethindrone Acetate Transdermal System (CombiPatch); and Estradiol/Levonorgestrel (Climara Pro)

Exogenous estrogen is currently available in 4 transdermal forms. Estraderm (estradiol TTS) is an estrogen-only therapy, whereas CombiPatch (estradiol/norethindrone acetate transdermal system), Ortho Evra (norelgestromin/ethinyl estradiol transdermal system), and Climara Pro (estradiol/levonorgestrel transdermal system) contain estrogen plus a progestational agent.

Estraderm, CombiPatch, and Climara Pro are indicated for women with a uterus for treatment of moderate to severe vasomotor symptoms due to menopause, moderate to severe symptoms of vulvar and vaginal atrophy due to menopause, and hypoestrogenism due to hypogonadism or primary ovarian failure. Estraderm is also indicated for the prevention of postmenopausal osteoporosis. Estrogens bind to nuclear receptors in estrogen-responsive tissues and modulate the pituitary secretion of luteinizing hormone and follicle-stimulating hormone.

Ortho Evra is indicated for the prevention of pregnancy in women of reproductive age who choose a transdermal patch as a method of contraception. It is not indicated for use as a method of emergency contraception. Ortho Evra's mechanism of action is suppression of gonadotropins, thus inhibiting ovulation and changing the character of cervical mucus and the endometrium.

Although none of these agents is commonly prescribed by psychiatrists, there are a number of important clinical considerations when managing neuropsychiatric disorders in women who wear an estrogen-containing patch. First, estrogens are metabolized partially by CYP 3A4. Metabolic inducers of the CYP 3A4 system include barbiturates, carbamazepine, efavirenz, modafinil, oxcarbazepine, phenytoin, ritonavir, topiramate, and St. John's wort. Concomitant use of these agents is likely to decrease the effectiveness of hormonal therapies. Therefore, women who are prescribed medicines that interact with hormonal contraceptives should be advised to use nonhormonal contraceptive methods.[30] Metabolic inhibitors include certain antibiotics (e.g., erythromycin, clarithromycin, ketoconazole, and itraconazole), fluoxetine, grapefruit juice, and protease inhibitors. In addition, cigarette smoking increases the risk of serious cardiovascular side effects (e.g., venous thromboembolism) from hormonal therapies.

Second, estrogen therapy may be associated with exacerbations of epilepsy and migraine, as well as with various neuropsychiatric side effects, including emotional lability, depressed mood, nervousness, and headache.[31] Discontinuation of the hormonal agent results in resolution of these adverse effects. Importantly, the Women's Health Initiative Memory Study reported an increased risk (overall relative risk of approximately 1.76, 95% CI: 1.19–2.60) of developing probable dementia in postmenopausal women ≥ 65 years of age during 4 years of treatment with daily estrogen-only or daily estrogen-plus-progestin therapy, relative to placebo.[32–35] These and other findings from the WHI studies (e.g., increased risk of cardiovascular events and uterine cancer) are important topics for patients and providers to discuss before beginning therapy.

Finally, all 4 agents can be dangerous in overdose owing to the effects of estrogen. Estrogen toxicity may cause nausea, vomiting, breast tenderness, abdominal pain, drowsiness, fatigue, and withdrawal bleeding. Treatment of overdose begins with discontinuation of the estrogen therapy and implementation of supportive measures. In general, transdermal patches are safer in overdose than are overdoses of oral pill formulations.

Fentanyl (Duragesic/Mylan)

Fentanyl is a potent synthetic opioid that mediates its analgesic effect predominately as a μ-receptor agonist. It is highly lipophilic and well suited for transdermal delivery owing to its low molecular weight, short half-life, and high metabolic clearance.[18] There are 2 types of fentanyl-based transdermal systems that are approved for the treatment of a wide variety of acute and chronic pain syndromes (e.g., as in palliative care).

The 2 fentanyl patches currently available differ in their respective delivery system—one uses a reservoir with a rate-limiting membrane (Duragesic) and the other uses a matrix or drug-in-adhesive system (Mylan). Both forms are available in the same 5 dosage strengths—12, 25, 50, 75, and 100 μg/hour—and each is designed to provide 72 hours of dosing per application. The composition per unit area is identical for all dosage strengths. Duragesic patches contain 0.1 mL of alcohol per 10 cm^2 as a penetration enhancer.[36]

Studies indicate that fentanyl patches are effective when compared with the standard forms of opioid management for both acute and chronic pain (e.g., in palliative care and with cancer pain).[18,37] Several studies have found a reduction in certain side effects (including constipation, opioid-associated pruritus, and sedation) in those receiving fentanyl patches compared with other standard pain therapies (e.g., use of extended-release oral morphine).[18,38]

Fentanyl is relatively contraindicated in opioid-naive patients, those with known or suspected paralytic ileus, or those with a history of significant respiratory disease (e.g., severe bronchial asthma, severe chronic obstructive pulmonary disease, cor pulmonale, or hypercapnia). The use of fentanyl in patients who are taking MAOIs or who are within 14 days of cessation of MAOI therapy is not recommended, based on a theoretical risk of serotonin syndrome, as fentanyl may be a weak serotonin reuptake inhibitor.[39] Although safe use of fentanyl and MAOIs has been reported, the current recommendation still remains against their use in

combination, and more data are needed. Common side effects of fentanyl are related to the CNS effects of mu-opioid receptor agonism (including sedation, "mental clouding" [e.g., apathy and concentration deficits], mood changes, nausea, and delirium).

Fentanyl is one of a small number of drugs that may be especially harmful, and in some cases fatal, with a single dose, if used by someone other than the person for whom the drug was prescribed.[40] In 2014, the Medicines and Healthcare Products Regulatory Agency—a British agency similar to the Food and Drug Administration (FDA)—issued a warning about the potential for life-threatening harm from accidental exposure to transdermal fentanyl patches, particularly in children, and advised that they should be folded, with the adhesive side in, before being discarded.[41] All fentanyl preparations should be kept in a secure location (such as a locked cabinet) that is out of children's sight and reach. Fentanyl patches should be flushed down the toilet as soon as they are removed from the body, and unused fentanyl patches should be flushed as soon as they are no longer needed.[42]

Psychiatric consultants should be aware that nonmedical use of fentanyl by individuals without opiate tolerance can be dangerous and may result in death.[43] Even those with opiate tolerances are at high-risk for potential overdose. A common route of misuse that may lead to overdose involves extraction and injection of the drug from the reservoir (Duragesic) form of the patch. Alternately, fentanyl patches may be frozen, cut up, and eaten, or the gel from inside the patch smoked.[44] Cutaneous application of multiple patches or application to the buccal membrane has also been described.[44] In addition, depending on the patch formulation, compromised skin, use of heat, or various cosmetics can all affect the release rate and skin permeation of fentanyl patches. Heat, whether because of elevated body temperature or the intentional application of exogenous heating element, may result in overdose with either type of fentanyl delivery system. The matrix (Mylan) patch formulations have a higher risk of increased absorption rates when applied to compromised or highly variable skin, whereas the reservoir (Duragesic) formulations have an increased risk of drug leakage.[36]

Granisetron (Sancuso)

Granisetron is a 5-hydroxytryptamine subtype 3 (5-HT_3) receptor antagonist indicated for the prevention of nausea and vomiting. Transdermal granisetron is a 52-cm^2 patch containing 34.3 mg of granisetron. The patch releases 3.1 mg of granisetron per 24 hours for up to 7 days, providing exposure similar to an oral dose of 2 mg per day.[45] Therefore, transdermal granisetron is typically used in patients receiving emetogenic chemotherapy for up to 5 consecutive days.

The prophylaxis of chemotherapy-induced nausea and vomiting in patients receiving multiday chemotherapy has long presented a clinical challenge, as it is the mainstay of treatment for many cancers.[46] Current guidelines for the management of multiday chemotherapy-induced nausea and vomiting recommend 5-HT_3 receptor antagonists as a basis for treatment, to which corticosteroids (with or without a neurokinin-1 receptor antagonists) may be added.[47] Until recent years, 5-HT_3 receptor antagonists, such as granisetron, were only available in oral and intravenous preparations. Repeated administration of oral antiemetics over several days can give rise to peaks and troughs in plasma drug levels. In addition, such treatment may require a high tablet burden and complex dosing regimen, with an adverse effect on treatment adherence.[48] Delivery of antiemetic therapy from a transdermal system may help to reduce these obstacles to chemotherapy-induced nausea and vomiting control.

A double-blind study compared the efficacy and tolerability of transdermal granisetron with daily oral granisetron for the control of chemotherapy-induced nausea and vomiting. Patients treated with transdermal granisetron displayed noninferiority to oral granisetron; there was complete control of nausea and vomiting in 60% of patients in the transdermal granisetron and 65% in the oral granisetron group. Both treatments were well tolerated; the most common adverse event was constipation.[49] In clinical trials, transdermal granisetron shows few untoward events linked to active treatment. Thus, the current literature supports the notion that the granisetron transdermal system provides effective, well-tolerated control of nausea and vomiting in association with moderately or highly emetogenic multiday chemotherapy. It offers a convenient alternative route for delivering granisetron for up to 7 days, which is as effective as oral granisetron.

Lidocaine (Lidoderm) and Lidocaine and Tetracaine (Synera)

Lidocaine is a local anesthestic of the amide class. There are 2 lidocaine-containing FDA-approved

patches at this time: Lidoderm (lidocaine only) and Synera (lidocaine and tetracaine). Lidocaine-only patches are 10 × 14 cm with an adhesive layer of lidocaine (5%), which is applied to the most painful area of the skin for 12 hours every 24 hours. Transdermal absorption of lidocaine is related to the duration of its application and the surface area over which the patch is applied. It undergoes hepatic metabolism by P450 enzymes CYP 1A2 and CYP 3A4; its metabolites are then excreted by the kidneys. When the dermal patch is used as directed, only a very small fraction is expected to be absorbed transcutaneously, with little systemic absorption.

Initially developed for their local anesthetic effects, lidocaine patches were approved by the FDA for the treatment of postherpetic neuralgia and were later listed as an orphan drug to treat diabetic neuropathy.[50] Transdermal lidocaine is thought to alleviate neuropathic pain by nonselective blockade of sodium channels in damaged nociceptors. Additionally, lidocaine patches are being investigated for use in other chronic pain syndromes (including cancer pain with a neurogenic component and even postoperative pain), as a nonaddictive alternative or adjunct to opioid pain control; promising results are evident.[51–54]

In an open-label study involving patients with painful diabetic polyneuropathy, the use of lidocaine patches for 3 weeks was associated with significant improvements in pain and quality-of-life outcome.[55] Adverse events were minimal, and systemic accumulation of lidocaine did not occur. More recently, lidocaine patches were found to be as effective as a lidocaine injections into trigger points in terms of pain control and functional disability outcomes in patients with myofascial pain syndrome.[56]

Synera is a topical patch for local anesthesia that contains lidocaine and tetracaine, an ester-type local anesthetic. Each patch contains 70 mg of lidocaine and tetracaine. It is unique in that it self-heats when the packaging is removed, and it is exposed to oxygen, for example, when applied 20-30 minutes before a venipuncture procedure. It is currently indicated for use in superficial dermatologic procedures as well as to establish superficial venous access.[57,58] Unlike lidocaine-only patches, there are currently no indications for its use in chronic, systemic pain syndromes. Side effects in studies have been limited to localized pruritus and erythema.[57]

MPH (Daytrana)

All FDA-approved ADHD medication preparations are oral, except for the MPH patch, marketed as Daytrana. The MPH transdermal system (MTS) was also the first transdermal system developed specifically for pediatric patients. This patch is applied to the skin (e.g., on the hip) before, or on, awakening,[59] and it is removed approximately 3 hours before the effect would be prudent to conclude.[60] MTS is especially advantageous for patients (or their parents) who desire having an "off switch" for controlling the delivery of active drug or for those with swallowing difficulties.

MTS is a drug-in-adhesive matrix patch containing a racemic mixture of D- and L-enantiomers of methylphenidate. The MPH dose delivered is dependent on the size of the patch, the application site, and the wear time. The design of the MTS is based on the pharmacokinetic studies showing that when a patch is worn for 9 hours, peak plasma concentrations of MPH occur approximately 8 hours after multiple patch applications, and the elimination half-life is 3–4 hours.[61] The package insert recommends application to the hip area 2 hours before the effect is needed—a slower onset of action compared with most oral stimulants. Overall, 4 patch sizes are available that deliver 10-, 15-, 20-, and 30-mg doses based on a recommended 9-hour wear time (or possibly longer, in our experience). The patch can be removed before 9 hours if a shorter duration of dose is required. Steady dosing with the patch results in higher peak MPH levels than does equivalent dosing with extended-release oral forms of methylphenidate, suggesting increased absorption.[62] Clinically, it is most common to start treatment with application of MTS at the 10-mg dose and increase to next larger system (15-mg/9-h, then 20-mg/9-h, and then 30-mg/9-h systems) at regular intervals (e.g., weekly or monthly), based on response and tolerance.

The efficacy of MTS has been established in children 6–12 years and adolescents 13–17 years of age. MTS received an indication for the use in children based on results showing efficacy in a 7-week, randomized, double-blind, placebo-controlled, and naturalistic study.[63] Commonly reported adverse effects included decreased appetite, nausea, vomiting, and insomnia—though nearly all were mild to moderate intensity. Approximately 7% of patch wearers discontinued study treatment compared with 2% taking oral

MPH and 1% wearing a placebo patch. In a 12-month open-label extension study of long-term safety and tolerability, 81% of children wearing MTS reported at least 1 adverse event, nearly all being rated at mild or moderate severity (approximately 40% were considered related to study treatment).[64] The discontinuation rate over 1 year was 9%, the majority of which (7%) were because of dermatologic reactions.

Similar benefits and tolerability with MTS has been observed in adolescents diagnosed with ADHD.[65] Frequently reported adverse events were typical of those observed in clinical trials of stimulants. Long-term safety and tolerability has been established in a 6-month, open-label extension study, with the most frequent treatment-emergent side effects being decreased appetite (15%) and headache (12%).[66] Few (7%) patients discontinued the extension study because of adverse events.

Nicotine Patches (Nicoderm, Habitrol)

Transdermal nicotine delivery systems were first FDA-approved as an adjunct to physician support for smoking cessation. Nicotine patches were the first "blockbuster" transdermal medications, raising the profile of transdermal delivery in medicine and for the public in general. In recent years, patches of various designs and differing pharmacokinetic actions have become available. The low-dose patches were designed to produce blood nicotine levels that are generally lower than those resulting from smoking.[67] The rate of nicotine absorption is maximal between 6 and 12 hours after transdermal application, with an absolute bioavailability of approximately 82%.[65] Blood nicotine levels peak after 16–24 hours and then decline. The skin may serve as a reservoir for nicotine as approximately 10% of transdermal nicotine is systemically absorbed after the patch is removed.[68]

Transdermal nicotine systems are applied in the morning and removed the next morning (i.e., they are 24-hour patches). For individuals smoking 10 or more cigarettes per day, the highest dose patch should be used to start; a lower dose can be used if the patient smokes fewer than 10 cigarettes per day.[69] Dosage reduction is usually recommended after 2–4 weeks of nicotine replacement therapy; however, a meta-analysis showed no benefit of dosage reduction on patch efficacy.[70]

The aggregate of findings from double-blind studies indicates that prescription transdermal nicotine systems are an effective aid to tobacco-dependence treatment.[71] However, the success rate varies greatly across different studies, suggesting that the results may be influenced by the nature and intensity of adjunctive smoking cessation counseling.[68] There are no significant differences in cessation rates or withdrawal symptoms between 16- and 24-hour types.[72] An analysis of over-the-counter products shows that their use resulted in greater session rates by a factor of up to 2.8 when compared with placebo and proved as effective as when given as a prescription.[73] Higher dose nicotine (e.g., 44 mg/d) can achieve blood concentrations similar to those resulting from smoking[74,75]; clinical data from more than 3000 patients suggested that smoking cessation may be enhanced.[76]

Patients who continue to smoke while using nicotine patches should be warned that they may experience nausea, abdominal pain, diarrhea, vomiting, dizziness, profuse perspiration, flushing, disturbances of hearing and vision, confusion, weakness, palpitations, altered respiration, and hypotension; these are signs and symptoms of nicotine toxicity. Some patients may confuse these symptoms as signs of nicotine withdrawal.

Transdermal nicotine has less of an effect on platelet activation and catecholamine release than does cigarette smoking, so the use of transdermal nicotine as a smoking cessation treatment in a patient with coronary artery disease is likely to be safer than cigarette smoking.[77] In 2 studies using a transdermal nicotine patch or placebo in patients with known coronary artery disease and a history of smoking more than 1 pack of cigarettes per day, nicotine replacement therapy proved safe.[78,79] Nonetheless, the Working Group for the Study of Transdermal Nicotine in Patients with Coronary Artery Disease[78] recommended against starting nicotine patches around the time of an acute myocardial infarction or in a patient who is undergoing coronary artery surgical procedures.

Beyond smoking cessation, research on combining nicotinic receptor modulation with neuroleptics in the treatment of Tourette syndrome exists. A double-blinded, placebo-controlled study found that transdermal nicotine may potentiate the effects of haloperidol and reduce the dyskinetic symptoms of Tourette syndrome.[80] Nausea and vomiting were more common adverse effects in the nicotine patch group. There is preliminary research on the use of nicotine in ADHD and cognitive enhancement.

A study of nonsmoking teenagers with ADHD demonstrated improvement in multiple cognitive domains with the administration of nicotine.[81] Finally, nicotine may also have a role as an adjunctive therapy in the treatment of depression, as studies on rats demonstrate improvement in depressive characteristics with nicotinic agonists. Open-label studies with nonsmoking human subjects diagnosed with major depression have shown improvement in mood with administration of nicotine.[82]

Nitroglycerin (Transderm-Nitro)

Nitroglycerin is primarily indicated for the treatment of exertional stable angina and acute coronary syndrome. Its effects include dilatation of the coronary vasculature, resulting in decreased cardiac preload and myocardial oxygen demand. Its core mechanism of action is through a multistep biomolecular cascade, leading to production of cyclic guanosine monophosphate in smooth muscle, which in turn leads to decreased intracellular calcium levels and ultimately smooth muscle relaxation in the walls of veins and arterioles.

Although nitrates have been used in the prevention of angina as far back as 1879, a well-known drawback of nitrate therapy is the development of tolerance. To counteract this phenomenon, intermittent therapy is employed, which is implemented by scheduling distinct time periods in the day during which the medication is withdrawn. The nitroglycerin transdermal system is a convenient approach to the delivery of nitroglycerin, especially for intermittent therapy. The patch contains either a polymer matrix or silicone gel infused with nitroglycerin as well as a semi-impermeable membrane between skin and drug, resulting in constant drug delivery. Onset of action is 30 minutes with 8- to 14-hour duration of action. The usual dose is between 0.2 and 0.8 mg/hour. The primary side effects include transient headache and local skin irritation where the patch is applied.

Research interest in the use of the transdermal nitroglycerin outside of cardiac conditions includes local uses (e.g., to relieve Raynaud phenomenon in distal appendages and tendonopathies), as well as systemic uses (e.g., in the prevention of preterm labor and to aid in healing of chronic anal fissures).[83–85] For example, nitroglycerin has been shown to be superior or equally effective to nifedipine in randomized, controlled trials to control preterm labor.[86–88] It has been associated with a significant reduction in the risk of preterm birth at <34 and <37 weeks of gestation, admission to the neonatal intensive care unit, use of mechanical ventilation, and maternal side effects. In 1 study, this resulted in lower hospital costs and reduced need for ongoing social services required for preterm babies for months to years after birth.[89]

On the horizon, nitroglycerin may emerge as an effective treatment for restless leg syndrome (RLS) based on the theory that patients with RLS have lower levels of nitric oxide than do healthy individuals. A case report described significant improvement in 3 patients with RLS treated for 1 month with transdermal nitroglycerin.[90]

Oxybutynin (Oxytrol)

Oxybutynin chloride is indicated for the treatment of overactive bladder syndrome, a condition characterized by urinary urgency and frequency in the absence of a urinary tract infection. Oxybutynin is a member of the antimuscarinic class of medications frequently used to treat overactive bladder. In a meta-analysis of 15 randomized, controlled trials, oral oxybutynin therapy was associated with a 52% average decrease in incontinence episodes and a 33% reduction in urinary frequency.[91]

Despite its recognized efficacy, oral oxybutynin therapy is hampered by its pharmacokinetics. It is absorbed by the gut and metabolized by the liver's cytochrome P450 system, primarily by the CYP 3A4 enzyme. Its active metabolite, N-DEO, is produced in significant amounts by this first-pass hepatic metabolism, and it is likely responsible for the drug's anticholinergic side effects. Up to 80% of patients treated with immediate-release oral oxybutynin experience side effects (including dry mouth, constipation, and dizziness).[92] These effects may be lessened by using an extended-release form of oral oxybutynin, but they remain quite common.[93]

The oxybutynin transdermal delivery system was developed to circumvent these adverse consequences. This 39-cm^2 skin patch contains a matrix of oxybutynin as well as triacetin, which controls the rate of absorption into the skin. The patch delivers 3.9 mg of oxybutynin daily, and steady-state plasma concentrations are maintained for approximately 96 hours. Patients typically apply 2 patches over the course of

a week. Transdermal oxybutynin results in less production of N-DEO and therefore minimizes anticholinergic side effect burden.[94]

For the consultation-liaison psychiatrist, it is important to recognize the potential for oxybutynin to be a contributing factor to the development of delirium. Oral delivery of oxybutynin, especially in the elderly, may produce agitation, hallucinations, cognitive impairment, ataxia, delirium, seizures, or coma.[95] In 2008, the FDA specifically labeled oral oxybutynin as a cause of adverse CNS events.[96] The oxybutynin patch offers an approach to the treatment of an overactive bladder that poses fewer CNS effects than oral oxybutynin administration.

Rivastigmine (Exelon)

Rivastigmine is a reversible acetylcholinesterase inhibitor indicated for the treatment of mild, moderate, and severe dementia of the Alzheimer type, and mild to moderate dementia associated with Parkinson disease. Although its precise mechanism of action is not fully understood, rivastigmine is presumed to exert its therapeutic effects by inhibiting the hydrolysis of acetylcholine, thereby increasing its concentration.

Exelon is a transdermal application of rivastigmine that is applied to the skin once daily at a consistent time. The manufacturer suggests that it is helpful to apply the patch to the upper or lower back where it is less likely to be removed by the patient. It can be worn safely during baths and showers. At least 1 study suggested that caregivers express a preference for the transdermal application of rivastigmine over the oral formulation for ease of use, ease of following the dosing schedule, and reduced interference with daily life.[97]

Dosing starts at 4.6 mg/24 hours for 4 weeks. If the drug is tolerated over this period, the dose is increased to 9.5 mg/24 hours, which is the minimum effective dose for mild to moderate Alzheimer disease and for Parkinson disease. After an additional 4 weeks, the dose can be increased to 13.3 mg/24 hours, which is the minimum effective dose for severe Alzheimer disease. Although the daily application minimizes dosing complexity, the dose should be adjusted in those with hepatic impairment or with low body weight (<50 kg). Interruptions in treatment lasting longer than 72 hours should be followed by retitration from the initial starting dose. A patient receiving 6–12 mg of oral rivastigmine can be switched to the 9.5-mg/24-hour transdermal formulation on the day following the last oral dose.[98] As with other cholinesterase inhibitors, it can be safely coadministered with memantine, an N-methyl-D-aspartate antagonist.[99]

The efficacy of the rivastigmine transdermal system is established in multiple randomized, double-blind, placebo-controlled clinical trials in persons with Alzheimer disease[100–103] and 1 controlled trial of the oral formulation of rivastigmine in persons with dementia associated with Parkinson disease.[104]

In controlled trials, the adverse effects most commonly reported were nausea, vomiting, and diarrhea, which were dose-related and also more frequently reported in patients receiving the capsule formulation. The next most common side effects reported were depression, anxiety, and headache. At higher doses, the patch was associated with agitation, falls, insomnia, anorexia, weight loss, urinary tract infections, and application-site reactions. Severe adverse reactions, including death, were reported in association with the application of more than 1 patch at the same time.

Rotigotine (Neupro)

Rotigotine is a potent dopamine agonist indicated for the treatment of idiopathic Parkinson disease and of moderate to severe primary RLS. Rotigotine is a highly lipophilic, nonergolinic compound that has high affinity for dopamine D_3 receptors. It also behaves as an antagonist at the α_{2B}-adrenergic receptor and as a partial agonist at the 5-HT_{1A} receptor. Its precise mechanism of action is not fully understood.

The rotigotine transdermal system provides consistent, 24-hour delivery of rotigotine. For individuals with Parkinson disease, this effect can reduce "off" time and improve nighttime and early morning symptoms.[105] Similarly, for persons with RLS who have symptoms during the day as well as at night, the continuous delivery system provides 24-hour symptom improvement. The patch minimizes dosing complexity and prevents the need for dose adjustments in those with renal or hepatic impairment. The patch should be applied around the same times every day to an area of clean, dry skin over the abdomen, flank, hip, thigh, shoulder, or upper arm (alternating sites each day).

For persons with early-stage Parkinson disease, dosing starts at 2 mg/24 hours, typically titrating

weekly by 2-mg/24-hour increments (to a maximum dose of 6 mg/24 hours). For those with advanced-stage disease, dosing starts at 4 mg/24 hours with an equivalent titration schedule up to a maximum of 8 mg/24 hours. For individuals with RLS, the initial starting dose is 1 mg/24 hours, titrating weekly by 1-mg/24-hour increments to a maximum of 3 mg/24 hours. Discontinuation of the drug should involve reducing the dose by no more than 2 mg/24 hours every other day.

The efficacy of the rotigotine transdermal system as monotherapy for the treatment of the signs and symptoms of early-stage Parkinson disease has been established in 3 randomized, double-blind, placebo-controlled trials, each of which enrolled adults who were not also receiving levodopa.[106–108] Its efficacy as combination therapy in advanced-stage Parkinson disease was established in 2 randomized, double-blind, placebo-controlled trials that enrolled adults also on levodopa.[109,110] The efficacy of rotigotine for treating the signs and symptoms of RLS was established in 2 randomized, double-blind, placebo-controlled clinical trials,[111,112] as well as in other well-designed clinical trials.[113]

In controlled trials, the side effects most commonly reported were nausea, somnolence, dizziness, and mild application-site reactions. Additional side effects reported were similar to those of other dopamine agonists and included hallucinations, agitation, delusions, delirium, and impulse-control problems. These adverse neuropsychiatric effects appear to be dose related. Of note, neuroleptic malignant syndrome has been observed in patients treated for parkinsonism in the setting of withdrawal of dopamine agonist therapy,[114] as well as with dose reductions and a switch from one agent to another.

A contraindication to the rotigotine transdermal is a history of sulfite sensitivity (which is not the same as a sulfa allergy). The patch contains sodium metabisulfite, which may cause allergic reactions, such as anaphylaxis.

Scopolamine (Transderm Scop)

Scopolamine is available as an oral tablet, as an injectable solution, and in a transdermal form. However, the oral or parenteral routes of administration are rarely used owing to pronounced dose-dependent side effects (e.g., excessive sedation, vertigo, dry mouth, agitation, or hallucinations) and a short plasma half-life. The transdermal scopolamine delivery system was the first commercially-available patch, approved for use in adults for the prevention of nausea and vomiting associated with motion sickness and anesthesia/surgical recovery. Transdermal scopolamine was successful, and remains in use today, because it circumvented the high incidence of side effects and short duration of effect that restricted the usefulness of oral or parenteral scopolamine. Scopolamine is a high-affinity selective antagonist of G protein–coupled muscarinic receptor for acetylcholine with both peripheral and central antimuscarinic effects, including sedative, antiemetic, and amnesic actions.[115] It acts on the CNS by blocking cholinergic transmission from vestibular nuclei to higher CNS centers and from the reticular formation to the vomiting center.[116]

The scopolamine transdermal delivery system, comprising a 4-layer film, controls the absorption process and rate of drug entry into the systemic circulation over a 72-hour period. It contains 1.5 mg of scopolamine base and is applied to the skin in the postauricular area. A priming dose of 140 μg is incorporated into the adhesive layer to accelerate the patch's ability to achieve steady-state blood levels. Relative to oral administration, scopolamine patches must be applied 5–6 hours before traveling (or the onset of the desired effect) owing to slow drug absorption.[117]

The adverse effects produced by transdermal scopolamine are similar to those reported for the oral and parenteral formulations of this medicine, but comparative studies suggest that the incidence is reduced with the transdermal form.[118]

In addition to preventing the nausea, vertigo, and vomiting often associated with motion sickness, scopolamine patches are effective in reducing postoperative nausea and vomiting in adults,[119] but is less effective in children.[120] There are also reports of its usefulness in the treatment of excessive respiratory secretions and the sialorrhea associated with clozapine treatment.[117]

Selegiline (Emsam)

Oral MAOIs were the mainstay of major depressive disorder treatment during the 1950s. However, reports of serious adverse events, including acute hypertensive

reactions arising owing to ingestion of tyramine-rich foods (such as aged cheese), and the subsequent need to restrict dietary intake of tyramine with MAOI therapy, led to a decline in the use of these agents. Emsam (selegiline transdermal system or STS) was designed to overcome the limitations associated with oral MAOIs, particularly those relating to dietary constraints.[121]

Monoamine oxidase (MAO) in the gastrointestinal tract (predominantly the MAO_A isoenzyme) is a key enzyme in tyramine metabolism. When MAO_A in the gastrointestinal tract is sufficiently inhibited, tyramine cannot be metabolized; it enters the systemic circulation, resulting in an elevation of blood pressure and potentially leading to a hypertensive crisis.[122] The pharmacokinetic and pharmacodynamics properties of the STSs permit the inhibition of MAO_A and MAO_B in the CNS while limiting MAO_A inhibition in the intestinal mucosa and liver. At the effective selegiline dose of 6 mg every 24 hours, the system's dermal application allows targeted inhibition of MAO enzymes in the CNS without significantly increasing sensitivity to dietary tyramine, thus eliminating the need for dietary modifications of foods containing tyramine at this dose.[123]

STS patches are available in 3 doses: 6, 9, and 12 mg every 24 hours. No dietary modifications are required at the recommended starting dose of 6-mg/24-hour regimen. Higher STS doses of 9 and 12 mg/24 hours are also effective, but studies were not designed to evaluate improved efficacy at higher doses. Based on the more limited data available for the doses of 9 and 12 mg/24 hours, food effects cannot be ruled out; therefore, the FDA advises that patients receiving these doses follow dietary modifications that include the avoidance of tyramine-rich food and beverages during treatment and for up to 2 weeks after therapy has been completed.[124] Although the FDA recommendations for dietary modifications for the 9- and 12-mg doses are largely based on theoretical concerns, there are reports of adverse events with the STS owing to diet.[125] However, some authors have used the 9 and 12-mg doses without a restricted diet, and they report no increases in blood pressure.[126] The package insert also recommends following dietary modifications for 2 weeks after a dose reduction to 6 mg/24 hours. No dose adjustment is necessary for patients with mild-to-moderate renal or hepatic impairment. The recommended daily dose for elderly patients ($\geq$65 y of age) is 6 mg/24 hours; careful monitoring of these patients is necessary if the dose is increased further.[122]

The efficacy of STS was demonstrated in 3 short-term studies of 6–8 weeks[127–129] and a relapse-prevention trial of 52 weeks involving adults with major depressive disorder.[130] A recent double-blind, placebo-controlled study of moderately to severely depressed adolescents showed that STS-treated subjects demonstrated a decline from baseline depressive symptoms, but it was not statistically different from placebo-treated patients.[131]

In the aforementioned short-term and long-term studies, transdermal selegiline was well tolerated, and there were no significant differences in treatment withdrawal rates between STS and placebo groups. No cases of hypertensive crisis were reported in any of the controlled clinical trials. The most common adverse events that occurred with long-term STS use included application-site reactions, infection, insomnia, and headache. In the 52-week study, there was a trend toward an increased incidence of insomnia in STS-treated patients.[130] Application-site reactions, which generally consisted of mild-to-moderate itching, redness, and swelling, were the most problematic adverse events associated with STS patches. However, these reactions were usually transient, of short duration, of mild to moderate intensity, and they usually resolved within several hours after removal of the patch.

As with other MAOIs, the STS should not be administered with cold medication products or weight-reducing preparations that contain vasoconstrictors, including amphetamine and other sympathomimetic agents. Other medications are also contraindicated with the STS (e.g., selective serotonin reuptake inhibitors]; selective norepinephrine reuptake inhibitors); tricyclic antidepressants; St John's wort; meperidine; analgesic agents such as tramadol, methadone, and propoxyphene; and cold or cough preparations containing dextromethorphan).[126]

Oral selegiline and other MAOIs should not be used concomitantly with the STS. Contraindications with the use of other antidepressants are largely related to CNS toxicity (i.e., "serotonin syndrome"), which has been reported in case studies.[132] Serotonin toxicity is characterized by neuromuscular excitation (hyperreflexia, myoclonus, and rigidity), autonomic stimulation (hyperthermia, tachycardia, tremor, and flushing), and an altered mental state (anxiety, agitation, and confusion).

Sumatriptan (Zecuity)

Sumatriptan, a serotonin agonist (commonly known as a triptan), is indicated for the acute treatment of migraine (with or without aura in adults). It is not intended for the prevention of migraine. Sumatriptan is a selective 5-HT receptor subtype 1B/1D agonist presumed to exert its therapeutic effects by binding to 5-$HT_{1B/1D}$ receptors on intracranial blood vessels and sensory nerves of the trigeminal system, which results in vasoconstriction and inhibition of proinflammatory neuropeptide release. It is available in oral and several nonoral formulations including suppository, subcutaneous injection, and nasal spray formulations. Current practice guidelines recommend a nonoral formulation for patients whose migraine is associated with severe nausea or vomiting.[133]

Sumatriptan iontophoretic transdermal system is a single-use, single-dose patch that uses a small amount of electrical current (iontophoresis) to deliver sumatriptan succinate through the skin at rate of 6.5 mg over 4 hours. The patch is applied to an area of clean, dry skin over the thigh or upper arm. Once the patch is applied, the patient must press the activation button, which contains a red light emitting diode indicator that will then turn on. The patient should wear the patch for approximately 4 hours or until the red light emitting diode indicator turns off. The patch should not be cut or tampered with in any way. The safety when using more than 2 patches in a single 24-hour period has not been established.

The efficacy of the sumatriptan iontophoretic transdermal system for the acute treatment of migraine (with or without aura in adults) has been established in 1 randomized, double-blind, placebo-controlled clinical trial.[134] Currently, comparative studies are needed to assess the efficacy of transdermal sumatriptan compared with other nonoral sumatriptan formulations.

In controlled trials, the most commonly reported adverse events were application-site reactions (including pain, paresthesia, and pruritus). Other potential adverse effects (such as myocardial ischemia/infarction, Prinzmetal angina, arrhythmia, stroke, pain or pressure in the chest/throat/neck/jaw, elevated blood pressure, and medication overuse headache) include those observed with other triptan agents. Like other sumatriptan formulations, Zecuity is contraindicated in persons with severe hepatic impairment, and it should not be coadministered with other 5-HT_1 agonists (owing to the risk of vasospasm), or with MAO_A inhibitors (owing to the risk of serotonin syndrome).

The sumatriptan iontophoretic transdermal system contains 2 lithium coin cell batteries that control the rate of current applied and, thus, the rate of sumatriptan delivered. Because of the presence of metal and an electrical charge, this patch should not be worn over an active implantable medical device or while a person undergoes magnetic resonance imaging.

Testosterone (Androderm)

Exogenous testosterone is currently available in a transdermal patch form: Androderm. Unlike earlier versions of transdermal testestorone, Androderm is not applied directly to the scrotum and can be applied to any healthy skin site other than the scrotum or bony areas. Daily application of 2 Androderm 2.5 mg skin patches at 10 PM results in serum testosterone concentrations that approach those of healthy young men and follow normal circadian variation. The first day of dosing with Androderm results in morning serum testosterone levels within normal range, and there is no accumulation with continued use. Hypogonadal status returns within 24 hours following removal of Androderm. Baseline serum testosterone levels may be reduced with transdermal testosterone owing to suppression of secretion of endogenous testosterone. Androderm is approved for the treatment of delayed puberty, hypogonadism, and palliative treatment of breast cancer.

A number of studies have examined the role of testosterone in treatment-resistant depressed men, though results of have been variable. The subgroups that mostly consistently show benefit with adjunctive testosterone treatment are those with detectably low serum testosterone levels.[135,136] In particular, the groups that tend to show the greatest improvement in depressive symptoms are patients with hypogonadism, elderly men, and those with HIV/AIDS.[126,137] However, a randomized control study examining the utility of intramuscular testosterone to augment SSRI therapy in a cohort of depressed men failed to show a significant separation from placebo.[138]

Testosterone has also been explored as hormonal treatment for perimenopausal and postmenopausal women, with some studies indicating improvement in

overall mood and well-being and others indicating no effect.[126,139]

Testosterone therapy is associated with a number of risks that warrant consideration before beginning supplementation therapy. Long-term treatment can cause gynecomastia, increase the signs and symptoms of benign prostatic hypertrophy, and may increase the risk of prostate cancer.[140] In addition, edema may occur owing to water and sodium retention that may exacerbate underlying medical conditions in patients who have cardiac, liver, or renal disease.[141] Finally, a small study reported that paranoid symptoms developed in several participants while receiving testosterone supplementation and tricyclic antidepressants,[142] though this reaction has not been seen in additional studies.[136–139]

FUTURE DEVELOPMENTS IN TRANSDERMAL MEDICINES

A February 2015 search of the word "transdermal" at clinicaltrials.gov returned 674 entries.[143] The focus of these trials is both novel transdermal medicines and novel delivery routes for existing products. The scope of some of these transdermal clinical trials includes the following: an insulin patch; a sufentanil patch for chronic cancer pain; a rivastigmine patch for the management of delirium in the elderly and parkinsonian-associated apathy; a varenicline patch for smoking cessation; a high-dose nicotine patch for fast metabolizers of nicotine; estrogen and testosterone patches for low libido in premenopausal and postmenopausal women; a selegiline patch for depression in the elderly and for cocaine addiction; clonidine for the treatment of delirium in patients with trauma and for symptoms of severe hyperemesis gravidarum; and a transdermal glyceryl trinitrate or nitric oxide for acute stroke therapy.

No transdermal delivery systems for larger molecules or peptides are currently approved by the FDA, though delivery systems for medicines with this profile are subject to ongoing research. Delivery systems in development include the use of electrical current to actively drive diffusion of charged molecules across the stratum corneum (iontophoresis), ultrasound (sonophoresis), microneedle, and microdermabrasion. These methods will likely expand the array of psychotropics deliverable via a patch in the future.[3]

CONCLUSION

Adherence to treatment is a challenge for those with a variety of chronic illnesses, and psychiatric disorders are no exception. The emergence of transdermal delivery for medicines with psychotropic properties has facilitated the ability to customize therapy for patients by altering the duration of therapy, minimizing first-pass metabolism and the potential for drug–drug interactions, as well as by decreasing the risk for gastrointestinal tract irritation. Steady-state absorption through the skin may provide more consistent drug exposure during dosing and avoid the unpredictability of plasma drug peaks and troughs. The reduction of peaks and troughs, in turn, increase medication efficacy and decrease the incidence of adverse effects. Long-acting patches (e.g., buprenorphine, clonidine, or granisetron) require less frequent dosing, which may reduce interference with daily life and improve adherence. Although there are many advantages to transdermal drug delivery, there are also disadvantages that must be considered. Patches can cause localized skin irritation, often have a slower onset of action than their oral or parental forms, and may fall off owing to poor skin adhesion. Most psychotropics are poorly suited for transdermal delivery because of their large size and molecular complexity; only a narrow range of molecules can be delivered through the skin using available technologies. Future advances in delivery technologies could expand the number and broaden the clinical use of available drugs with psychotropic properties, allowing clinicians to overcome the low bioavailability of many oral medicines, the pain and inconvenience of injections, and the limited controlled-release options of both.

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