

Potential New Drug Delivery Systems for Antidepressants: An Overview

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Oral administration is probably a nonoptimal delivery system for most psychotropics. Scientists are turning to optimizing drug delivery as a method for enhancing antidepressant response. Advances in oral drug delivery have come in the form of sustained-release formulations of antidepressants, which have smoothed the plasma drug concentration maxima and minima, thus decreasing side effects and increasing tolerability. The future of pharmacologic treatment for psychiatric disorders may be in part dependent on nonoral drug delivery systems such as implantable and transdermal delivery systems. Like the available sustained-release formulations of antidepressants, these alternative delivery systems will have enhanced safety, tolerability, and efficacy because of their ability to maintain a more constant circulating drug level. Implantable devices that sense, stimulate, deliver to, and record from biological systems are being developed through microtechnology and nanotechnology. Transdermal delivery techniques, such as passive diffusion, sonophoresis, electroporation, and iontophoresis, enhance the skin's permeability to drugs. Iontophoresis appears to be a promising and perhaps the most efficient assisted-delivery technique for future antidepressant transdermal delivery.

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The quest for the ideal antidepressant medication is ongoing. Efficacy and tolerability are obviously the essential criteria for such an agent. Given the recognition that remission of depression, rather than simply response, is the treatment goal,¹ depression requires antidepressants that result in sustained remission for long periods of time in a majority of patients.² Concurrently, the onset of action of the ideal antidepressant should be faster than the 2 to 8 weeks characteristic of today's available agents. Research to develop this agent, or group of agents, typically focuses on improving pharmacotherapy at the molecular site of drug action. Increasingly, however, scientists are turning to enhancing drug delivery as an equally viable method for optimizing the ideal antidepressant treatment. The ability to target drugs to specific body organs or to precisely control drug administration rates for prolonged periods of time are becoming realities. Such abilities will undoubtedly ease the immense medical and social burden posed by drug adverse effects and nonadherence.³

ADVANCES IN ORAL DELIVERY SYSTEMS

The sawtooth pattern of plasma drug concentrations following oral drug administration is associated with adverse events at maxima ("peaks") and loss of therapeutic effect at minima ("troughs") that have led to intolerability or frequent dosing of many antidepressants. As medication nonadherence represents a major determinant of nonresponse,⁴ drug reformulations aimed at reducing the pharmacokinetic inadequacies of orally dosed immediate-release preparations have been actively explored. Sustained-release formulations of lithium have been available for many years but have had minimal clinical impact. This latter fact may relate to the failure of such formulations to deliver on the promise of sustained-release.⁵ In recent years, delayed-release formulas of bupropion, venlafaxine, paroxetine, and fluoxetine have been introduced. The circulating drug concentrations of these agents fluctuate less than their immediate-release formulations, thereby providing a more uniform therapeutic effect, fewer adverse events, and decreased dosing frequency (Table 1).⁶ Enteric coatings on paroxetine controlled-release and fluoxetine weekly formulations delay medication dissolution until more distal points in the gastrointestinal tract in an attempt to lessen gastrointestinal side effects that are common to this generation of antidepressants. Although delayed-release oral formulations are a promising approach for enhancing therapy related to antidepressant treatment, the technology may be best indicated for drugs that benefit from absorption in the small intestine.

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Table 1. Delayed-Release Antidepressants^a

Antidepressant	Drug Delivery System	Comments
Paroxetine CR	Oral sustained release	Reduces nausea, improves overall tolerability
Venlafaxine XR	Oral sustained release	Reduces bid dosing to qd; reduces nausea; improves overall tolerability
Fluoxetine Weekly	Oral sustained release	Allows once-weekly dosing
Bupropion SR	Oral sustained release	Reduces tid dosing to bid; probably reduces seizures and improves overall tolerability
Bupropion XL	Oral sustained release	In testing; would reduce bid dosing to qd
Gepirone ER	Oral sustained release (serotonin-1A partial agonist)	In testing; would reduce tid dosing associated with the related agent buspirone to qd; could reduce the peak dose side effects associated with the related agent buspirone
Selegiline	Transdermal MAO-B inhibitor	In testing; changes pharmacokinetic delivery of active drug and metabolites to the brain; reduces dietary tyramine interactions

^aAdapted with permission from Stahl.⁶

Abbreviations: CR = controlled release, ER = extended release, MAO-B = monoamine oxidase-B, SR = sustained release, XL = extended release, XR = extended release.

Unfortunately, while representing an easy and well-accepted route, oral administration is a nonideal delivery system for most psychotropic medications.

ALTERNATIVE DRUG DELIVERY SYSTEMS

The future of pharmacotherapy for psychiatric disorders may lie in drug delivery routes other than oral administration. An implantable delivery system for the antipsychotic haloperidol is in the preclinical phase of development, with the aim that such a device will improve medication compliance, and therefore treatment outcomes, in patients with schizophrenia.⁷ An intranasal spray formulation of the benzodiazepine midazolam has been found to reduce anxiety in children,⁸ suggesting that intranasal delivery may be promising for rapid-acting agents such as anxiolytics that are administered on an as-needed basis. The role of this route of administration for long-term antidepressant treatment is less obvious. A transdermal delivery system for the selective monoamine oxidase-B inhibitor selegiline (Table 1) was found to be an effective and well-tolerated treatment for adult outpatients with major depression.⁹ The demonstrated advantages of the transdermal delivery of selegiline in this double-blind, placebo-controlled trial were minimal interaction with dietary tyramine (this drug-food interaction has restricted the use of monoamine oxidase inhibitors in the treatment of depression), sustained exposure to the parent compound, and faster onset of action. These findings^{8,9} support the contention that effective psychopharmacotherapy can be enhanced at the drug delivery level. Implantable and transdermal delivery systems are 2 promising alternatives to oral delivery for antidepressant therapy, while intranasal routes may be useful for anxiolysis.

Implantable

Implantable technology for psychotropic medications may have its historical beginnings in the use of haloperidol or fluphenazine depot injection formulations, which repre-

sented a crude delivery system that delayed the delivery of the drug to the circulatory system by its slow dissolution from a lipophilic matrix. Today, internal drug delivery devices that sense, stimulate, deliver to, and record from biological systems are being developed by application of the burgeoning fields of microtechnology and nanotechnology.¹⁰ Some of these devices are programmable, i.e., drugs can be stored and released on predetermined or real-time demand. Santini and colleagues¹¹ described a silicon microchip with the ability to provide on-demand controlled release of single or multiple drugs. Drugs in solid, liquid, or gel form could be stored in

microreservoirs covered by a thin anode membrane and released in controlled patterns when the anode membrane is dissolved via electrochemical dissolution. The future may also hold the development of a biodegradable microchip that, once implanted, would not require removal.¹⁰

Like the available delayed-release antidepressants, implantable drug delivery systems such as microchips will enhance drug safety, tolerability, and efficacy because of the ability to maintain a more constant plasma drug level. The advantages of implantable systems in the treatment of chronic depression are that patients are psychologically and behaviorally freed from having to continue to take medications for months or years, while clinicians retain and expand their roles in medication management.

Transdermal

As the body's largest organ, the skin is a promising target of drug delivery. However, the stratum corneum that forms the outer layer of the epidermis represents an impenetrable barrier to most drugs. Effective transdermal drug delivery thus necessitates the use of assisted-delivery techniques, such as passive diffusion, sonophoresis, electroporation, and iontophoresis, to enhance permeability. These techniques involve concentration gradients, pressure gradients, and electrical fields. All of the transdermal delivery systems focus on the following important properties of the skin: its permselectivity, its permeability for positively charged drug species that is enhanced by its net negative charge, and its large surface area available for the transport of candidate drugs.

Although currently widely accepted and used for transdermal patches for estradiol, clonidine, and nicotine, passive diffusion down concentration gradients has limited capabilities for the treatment of depression because of its relatively low capacity and its nonideal use for charged drug species such as antidepressants. Sonophoresis, or low-frequency ultrasound, refers to the transport of solutes along an applied pressure gradient. This technique is ideal

for the delivery of high molecular weight proteins in experimental settings but has limited application in the chronic treatment of depression with small, charged drugs.

Clinicians may be familiar with electroporation, a transdermal assisted-delivery technique that involves the application of large electrical potentials (in excess of 75 V) to a small epidermal area. The electrical charge forces the opening of aqueous pathways through the lipid bilayer of the stratum corneum and provides a driving force for the transport of charged molecules through these pathways. Compared with passive diffusion, electroporation enhances transdermal transport of small molecules by up to 4 orders of magnitude, which enhances the rate and capacity of transdermal drug delivery.⁹ Problems with local sensations due to stimulation of local muscles and nerves make the use of this technique unlikely for long-term treatment. However, similar to electroporation is iontophoresis, which offers more promise than other assisted-delivery techniques for transdermal delivery of antidepressant treatments.

Iontophoresis refers to the facilitated movement of ions of soluble salts through application of an electrical field. It has the advantage over passive diffusion of being able to increase the delivery of agents across the dermal barrier by 3 to 4 orders of magnitude. Much like implantable microchip drug delivery, iontophoresis-assisted transdermal drug delivery would allow for the programmable delivery of agents, resulting in continuous plasma drug delivery attained in as little as an hour.¹²

The iontophoretic patch works via the interaction of 3 basic components.¹² The aqueous drug reservoir is composed of a biocompatible gel or absorbent pad material that conforms to both the skin and the patch's electrode component. The reservoir's pH optimizes drug charge, and thus iontophoretic delivery, and is adjusted for skin tolerability, usually in the pH range of 4 to 8. Drugs with a positive charge under these conditions are placed adjacent to the anode of the patch. Drugs with a negative charge are placed within the cathode compartment. The return reservoir of such a patch device is usually filled with a saline solution that completes the electronic circuit. Inside the patch's final component, the electronic controller, are a battery and programmable microcomputer that control the iontophoresis rate. The electronic controller can be recycled several times, whereas the rest of the patch is disposable.

A mechanism by which iontophoresis assists transdermal drug delivery is electroosmosis.¹³ Electroosmosis is the flow of fluid accompanying an applied electrical field that occurs because human skin has a net negative charge of about pH 4. Therefore, positive ions are counterions in electroosmotic flow and flow occurs from anode to cathode, as is the case in iontophoresis. Since anodic delivery enhances the transport of neutral, or uncharged, species, electroosmosis is probably responsible for the enhanced transdermal flux of these species by iontophoresis.

CONCLUSION

Alternative drug delivery systems like implantable microchips and transdermal patches that use iontophoretic-assisted delivery may be key in developing the ideal antidepressant drug strategy. In both systems, the controlled delivery of a medication should improve tolerability by smoothing out the peaks and troughs of plasma drug levels associated with adverse events and symptom breakthrough. Fewer side effects and better symptom reduction may improve patient compliance, which increases the likelihood of remission of depression.¹⁴ Further, such drug delivery systems may allow medications with therapeutic action but short pharmacokinetic half-lives to be offered to a wider group of patients at perhaps decreased daily doses.⁶ More research on and development of antidepressants delivered via implantable and transdermal technologies are needed, but results⁹ thus far indicate that these alternative delivery systems have a role in the future of the treatment of depression.

Drug names: bupropion (Wellbutrin SR), buspirone (BuSpar and others), clonidine (Catapres-TTS), estradiol (Vivelle, Climara, and others), fluoxetine (Prozac Weekly), fluphenazine (Prolixin, Permitil, and others), haloperidol (Haldol and others), paroxetine (Paxil CR), selegiline (Eldepryl and others), venlafaxine (Effexor XR).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration-approved labeling.

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