At Long Last, Long-Lasting Psychiatric Medications: An Overview of Controlled-Release Technologies

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Issue: *Controlled-release technologies are being adapted in psychopharmacology at an increasing rate and can enhance the utility of numerous psychiatric drugs.*

AT LONG LAST, LONG LASTING

Technologies that can change the delivery characteristics of drugs have been around for decades,[1] but there has been a recent acceleration in the pace of their adaptation to psychiatric medications (Tables 1–3). Most notable is the increasing availability of numerous agents in oral sustained-release formulations that increase a drug's duration of action. By allowing the frequency of dosing to be reduced from 2 or 3 times a day to once a day, compliance can be greatly enhanced.[2] This development has proved to be particularly important for school-aged children receiving stimulants, since controlled-release technology now allows them to skip the hassle and stigma of receiving a middle-of-the-day dose at school (see Table 2).

I'VE GOT YOU UNDER MY SKIN

New to psychopharmacology are some drugs that can be delivered through the skin via transdermal patches; these include both an antidepressant (Table 1) and a stimulant (Table 2) being tested in a once-daily transdermal patch. Since transdermal administration avoids first-pass metabolism of the drug, the amounts of parent drug and active metabolites of transdermally administered drug are altered compared with orally administered drug. This feature may result in a more favorable side effect and efficacy outcome in some cases.[3]

It may soon be possible to administer atypical antipsychotics in long-lasting injectable forms. One version on the immediate horizon is a long-acting injectable form of risperidone that was developed by utilizing drug encapsulated in microspheres made of a biodegradable polymer that are suspended in a water-based solution and administered to patients by intramuscular injection and can last for 2 weeks.[4] This long-awaited development could greatly enhance compliance and reduce various high-cost prescribing practices, such as polypharmacy and high dosing, for patients with psychosis.

NO MORE ROLLER COASTER DRUG DELIVERY

A sawtooth pattern of rapid rises and falls in plasma drug levels can wreak havoc by causing side effects at the peak and loss of therapeutic effects at the trough. Sometimes it's the rate of rise and fall rather than the absolute level of drug that matters the most in causing side effects. It is now generally acknowledged that oral sustained-release delivery technologies have enhanced the tolerability of numerous psychotropic drugs, sometimes dramatically (Tables 2 and 3). Thus, adverse experiences associated with high peak doses, ranging from seizures to alopecia to nausea to sedation, are now widely recognized to be mitigated or even eliminated by applying controlled-release technologies to specific psychotropic drugs that cause the agents to be delivered in a manner that results in a more constant plasma level. Lowering the peaks and raising the troughs while slowing the rate of ascent and descent of drug can smooth out the roller coaster ride of drug delivery and result in important patient benefits.

IT'S ABOUT TIME FOR TIME RELEASE

In summary, new drug delivery technologies are helping to optimize the efficacy and tolerability of numerous psychotropic drugs, which should lead to greater compliance while reducing side effects. Given that many psychotropic drugs have delays in onset of action for the treatment of acute symptoms while needing to be delivered over many years to prevent relapses, it is now time to start exploiting these time-release technologies in psychopharmacology. ◆

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Table 1. Controlled-Release Antidepressants

Brand (generic)	Drug Delivery Technology	Comments
Paxil CR (paroxetine)	Oral sustained release	Reduces nausea, improves overall tolerability significantly
Effexor XR (venlafaxine)	Oral sustained release	Reduces bid dosing to qd; reduces nausea; improves overall tolerability significantly
Prozac Weekly (fluoxetine)	Oral sustained release	Allows once-weekly dosing
Wellbutrin SR (bupropion)	Oral sustained release	Reduces tid dosing to bid; probably reduces seizures and improves overall tolerability
Wellbutrin XL (bupropion)	Oral sustained release	In testing; would reduce bid dosing to qd
Ariza (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
EmSam (selegiline)	Transdermal MAO-B inhibitor	In testing; changes pharmacokinetic delivery of active drug and metabolites to the brain; reduces dietary tyramine interactions

Table 2. Controlled-Release Stimulants

Brand (generic)	Drug Delivery Technology	Comments
Concerta (methylphenidate)	Oral osmotic pump	No lunch-time dose required; delivers up to 12 hours; lesser peak, longer duration than other options
Metadate CD, Ritalin LA (methylphenidate)	New oral sustained release	No lunch-time dose required; greater and earlier peak than some other options; delivers up to 8 hours
Metadate ER, Ritalin SR, and Methylin ER (methylphenidate)	Older oral technology	Lunch-time dose is required; delivers up to 4 hours
MethyPatch (methylphenidate)	Transdermal	In testing
Adderall XR (*d*- and *l*-amphetamine)	Oral sustained release	No lunch-time dose required; delivers up to 9 hours
Dexedrine Spansules (*d*-amphetamine)	Oral sustained release	Usually no lunch-time dose required; delivers up to 9 hours

Table 3. Other Controlled-Release Psychotropics

Brand (generic)	Drug Delivery Technology	Comments
Depakote ER (divalproex)	Oral sustained release	Once-daily dosing; eliminates peak dose side effects significantly
Eskalith CR, Lithobid (lithium)	Oral sustained release	Reduces peak-dose side effects; reduces tid dosing to bid
Xanax XR (alprazolam)	Oral sustained release	Reduces tid or qid dosing to once or twice daily; could reduce "clock watching," peak dose sedation, and discontinuation symptoms
Risperdal Consta (risperidone)	Depot injection	First and only depot atypical antipsychotic microspheres; will enhance compliance; could enhance long-term efficacy
(indiplon MR)	Modified oral release	In testing; short-acting hypnotic with middle-of-the-night burst could target middle insomnia

Take-Home Points

- Psychotropic drugs can have limited utility in psychiatric practice due to their pharmacokinetic properties.
- One such limitation is short half-life requiring multiple daily doses, which often reduces compliance. Technologies that increase duration of action, ranging from once-daily oral or transdermal administration to a bimonthly depot injection, are now available for an increasing array of psychotropic drugs. Increased duration of action will hopefully lead to enhanced compliance.
- Another common limitation is the fact that undesirable side effects are associated with both peak plasma drug concentrations and the rapid rise and fall of these concentrations. Technologies that eliminate the rapid peak-and-valley pattern of drug delivery can significantly improve tolerability and make a medication with enhanced therapeutic actions available to a much wider population of patients.

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