Clinical and Economic Advantages of Modern Dosage Forms:
Improving Medication Adherence

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Overview

- Modern dosage forms can improve adherence to treatment with medications by reducing side effects and simplifying dosing regimens.

- This improved adherence can provide both clinical and economic value by improving treatment outcomes and reducing the use of medical services.

- Modern dosage forms offer meaningful therapeutic advantages that may be especially important in children and the elderly who are often sensitive to adverse effects or must adhere to complex medication regimens.

- The advantages of innovative dosage forms should be factored into decisions regarding pharmaceutical benefit design and reimbursement.

A substantial source of waste and inefficiency in health care is patient non-adherence with medications. Health and economic consequences of non-adherence include excess hospitalizations and office visits, disease progression, complications, and premature disability and death.\textsuperscript{1,2,3,4,5,6} The economic burden of deaths from coronary heart disease due to non-adherence with high blood pressure, cholesterol-lowering, and diabetes drugs is greater than $100 billion a year.\textsuperscript{7} More consistent and effective use of medications can lead to reduced use of hospital and other medical services, improved treatment outcomes and reductions in overall treatment costs.

Adherence among patients suffering from a variety of chronic diseases averages only 50 percent.\textsuperscript{8} Since the likelihood of non-adherence increases with the complexity of the dosing regimen, non-adherence is of particular concern for elderly patients who often take multiple medications.\textsuperscript{8} Discomfort due to side effects also contributes to lack of persistence with medication regimens.

Modern drug delivery technology can help improve adherence by simplifying the dosing regimen, and/or decreasing side effects. Other advantages include steadier drug concentrations in the bloodstream and targeted delivery of medication to its site of therapeutic action in the body.\textsuperscript{9,10}

### Improved Adherence through Advancements in Dosage Technology

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<tr>
<th>Technology Advancement</th>
<th>Adherence Advantage</th>
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<td>Sustained-release</td>
<td>Avoids need to take drug during other activities (school, work)</td>
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<td>Transdermal patch</td>
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<td>Melting tablets</td>
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<td>Long-lasting (depot) injections under skin or into muscle</td>
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*As with any pharmaceutical product, advanced dosage formulations can have both advantages and disadvantages. Modified-release products should not be crushed, chewed or damaged as the slow-release characteristics may be lost and toxicity may result. The larger size of some extended-release products may cause difficulties in ingestion or transit through the gut. With skin patches, irritation and allergic reactions may occur. To avoid these potential problems, patients must be informed about the proper and safe use of these products and should maintain open lines of communication with their health care providers.*
Simplified Dosing Improves Adherence

Simplified regimens associated with some advanced delivery technologies can improve adherence with medications and reduce dosing errors such as taking the wrong medication or taking medication at the wrong time.

The following examples illustrate how technologies that simplify administration of medications have improved adherence in a variety of chronic illnesses, especially those affecting older individuals and children. These technologies include long-acting pills and patches, inhalation devices, long-acting injections, and products combining two drugs in one pill.

- **Once-daily.** Adherence to anti-retroviral therapy is crucial for maintaining effective outcomes in the treatment of HIV/AIDS. Numerous once-daily formulations are now available among the many treatment options for these conditions. Patients switched to a once-daily from a twice-daily formulation of the same agent showed improved adherence after 24 weeks.11

- **Once-weekly.** Half of women with postmenopausal osteoporosis being treated with bisphosphonate therapy do not stay on their medications. One study found that 40 percent of patients taking once-weekly formulations continue to fill their prescriptions after one year, however only 20 percent of those prescribed once-daily formulations were still filling their prescriptions.12 Similarly, a once-weekly patch formulation of a blood pressure medication was associated with a 99 percent adherence rate, compared to only 64 percent of patients taking an oral blood pressure medication.13

- **Once-monthly.** Although many patients prefer the least invasive form of therapy, a survey found that nearly 25% of women taking medication for breast cancer stated a preference for a monthly injection to a daily tablet. Forty-three percent of those preferring the monthly injection cited ensuring adherence as a reason. This concern about adherence is significant since almost half of patients receiving oral cancer medications said they forgot to take their tablets once or twice each week.14

- **Combination products.** Among diabetes patients taking either metformin or glyburide who later required addition of the alternate agent, those receiving a combination pill containing both agents showed better adherence than those receiving two separate pills.16 A combination blood pressure pill containing an ACE inhibitor and a diuretic was associated with a 69 percent adherence rate after one year compared with a 58 percent adherence rate for treatment with its separate components (see figure below).16

- **Patches.** Oxybutynin is used to treat urinary incontinence and overactive bladder, but has side effects, which include dry-mouth, constipation, blurred vision, confusion, drowsiness, and cognitive impairment that can severely reduce persistence with treatment. A skin patch formulation is associated with fewer of these side effects, improvement in the condition, and improved quality of life.17 The long-duration action of the patch reduces the oral medication burden, which may be a particular advantage for elderly patients taking multiple oral medications or who depend on caregivers.18 The patch may be the only choice for patients who are unable to swallow oral medications.

Although oral contraceptives are used by an estimated 12 million women in the United States, non-adherence can have tremendous consequences since pills must be taken precisely as directed to avoid pregnancy. Adherence difficulties have been well documented; one study found that 30 to 51 percent of women skipped 3 or more dosing days per cycle.19 Lapses in therapy result in over 3.6 million unintended pregnancies annually.19 Several transdermal contraceptive patches are now available to address this problem. These patches can produce a higher rate of adherence compared with the pill.20

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**Two hypertension agents in one pill enhances adherence**

![Chart showing adherence with and without combination pill](chart.png)
Decreased Costs for Patients, Employers and Payers

Although innovative dosage forms can be more expensive than conventional pills, overall cost savings may be realized. Improved adherence can result in lower costs to patients and decreased use of expensive health care resources, including hospitalizations, nursing home stays, and labor costs.

**Combination medicines can reduce copays.** Combination medications, such as those containing two or more different drugs in the same pill, can be considerably less expensive than the sum cost of the individual components. Cost savings may accrue directly to patients with prescription insurance because one or more copayments may be eliminated each time prescriptions are refilled. Lower copayments have been associated with a greater tendency for patients to persist in refilling prescriptions for diabetes and other chronic diseases.

**Simplified regimens can save nursing home costs.** Elderly persons residing in nursing facilities, who are often frail and predisposed to adverse drug effects, often benefit from advanced-technology dosage forms. In addition to their potential for reduced side effects, the simplified regimens associated with long-acting formulations can save nursing time, improve general adherence, and allow greater independence.

Labor costs associated with more frequent administration of immediate-release products may exceed the acquisition and labor costs of long-acting products. One study examined the nursing home labor costs associated with the administration of immediate- vs. sustained-release dosage forms of a Parkinson's drug and of two cardiovascular drugs. The sustained-released products, which required less frequent dosing, were found to save labor time over the immediate-release brand and generic equivalent products, despite their higher costs.

**Improved adherence can reduce costly hospitalizations.** Long-lasting depot injections are often the treatment of choice for psychiatric patients who are not adherent to oral medications. Depot and other long-action formulations of antipsychotic drugs can improve adherence, delay relapse and lower overall treatment costs. For example, 41 percent of patients were projected to experience a relapse requiring hospitalization after one year of treatment with a conventional formulation of an antipsychotic agent compared with only 26 percent taking a long-acting injection formulation of this drug. This difference translates into an annual medical cost savings of $397 per patient.

A “melting tablet” formulation, which begins to dissolve upon contact with saliva, can facilitate drug therapy in acutely ill non-adherent patients in psychiatric hospitals. Patients' attitudes toward the medication were improved, adherence was increased, and the nursing burden was decreased when compared to patients treated with conventional tablets.

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Modern Dosage Forms: Making A Medicine Better

Why are some medications available in one form, like pills, and others as liquids or inhalers? Sometimes the difference is easy to see—medicines commonly used in treating small children or elderly persons are often available in a liquid form because these patients may have difficulty swallowing pills. In other instances the reasons may be less clear, but may actually reflect very important improvements in delivering medication where it is needed in the body, in the effectiveness of the medication, or in reducing side effects. A very early breakthrough in drug delivery technology is the hypodermic syringe, used during the Civil War to rapidly introduce morphine into the blood stream for quick pain relief.

In order to have an effect, medications must reach the appropriate area of the body. Like food, medicines are broken down and eliminated by the body’s natural processes, and many drugs are inactivated in the gastrointestinal (GI) tract. These drug molecules must be transported to the appropriate site in a way that bypasses the GI tract—such as by injection or across the skin using a patch. Other medicines must be protected from inactivation by the immune system.

Injection is problematic when medications must be given frequently over a long period of time. Insulin therapy for diabetes is one example. The oral route is not an option for insulin, since this large molecule cannot be absorbed from the GI tract. Inhaled dry-powder insulin, the first non-injectable insulin available since insulin was discovered in the 1920s, has recently come on the market. This is significant because aversion to injections keeps millions of persons with diabetes from achieving proper glucose control. Up to half of all people with type 2 diabetes who require insulin decline it; and research shows that patients are three times more likely to follow a course of insulin treatment if an inhaled option is available.

Medicines can also be coated to protect them as they travel through the body to the target site. One technique, now being used for therapy in cancer and hepatitis, is to enclose the drug in a liposome (a fat bubble), which is then coated with a material that allows it to avoid detection and destruction by the immune system. The medicine slowly leaks out as the coating dissolves, allowing the drug to reach its target site (e.g., a tumor) without being inactivated. This targeting strategy also minimizes “collateral damage,” i.e., the residual—and potentially negative—effects of these powerful medicines on other parts of the body.

For other medications, timing of the dose is important. Timed-release therapies can ensure that a constant level of medicine is released into the bloodstream. Today’s sophisticated technologies...
can also delay the release of medication from a pill or capsule until it is needed. This is important, for example, in the treatment of high blood pressure since blood pressure levels tend to rhythmically fluctuate throughout a 24-hour cycle. A delayed-onset formulation taken at bedtime can be designed to release a burst of medicine very early in the morning—when blood pressure tends to be high, and with it, the risk of angina, heart attack, and stroke. Similarly, a sleeping pill taken at bedtime can provide a "second stage" burst of medication in the wee hours of the morning to prevent early awakening.

Drug delivery via skin patches allows the medicine to enter the bloodstream without first passing through the GI tract and liver. This means that lower doses can be used to achieve the same effect because a much smaller portion of the medicine is destroyed on route to the target. Patches can have a sustained action similar to a timed-release pill, resulting in fewer side effects, and requiring less frequent dosing. Popular patches include those for motion sickness (which have less sedating effects than oral versions), nicotine withdrawal symptoms, hormone replacement, and chest pain from heart disease.

High concentrations of powerful medicines are sometimes required for an adequate therapeutic effect. However, this can result in side effects as the medication acts throughout the body. High-technology delivery systems now enable direct placement and containment of medication on a specific part of the body. This places a high dose only where it is needed and avoids or decreases whole-body side effects. Examples include drug-soaked membranes placed on the eye to treat glaucoma, or implanted in the brain to treat brain cancer.

Large-molecule medicines, including hormones, peptides, and antibodies, are not absorbed into the bloodstream from the GI tract. As new large-molecule drugs are developed to treat previously untreatable or only partially treatable diseases, suitable delivery systems must be found to deliver them to their target sites. Nasal sprays, which deliver drugs across mucosal membranes, and inhaled formulations which deliver drugs through the surface of the lung are being developed. Other innovations on the horizon include biofeedback systems that sense conditions in the body and release the drug only when needed, implanted microchips and microspheres to improve the use of proteins and virus carriers that will deliver therapeutic agents directly to cells.

Multiple dosage forms of a medication may be required to meet the needs of children as they grow and develop. Some children have trouble taking certain dosage forms—swallowing large pills or using inhalers for example. Depending on the child’s age, the choice of available formulations may include liquids, suspensions and/or chewable tablets containing different drug concentrations. Additionally, some dosage forms may be more compatible with the child’s routine.

**Child-friendly delivery.** Corticosteroid therapy for asthma has traditionally been administered via inhalers that are often difficult for young children to use correctly. Medication can now be delivered as a fine mist, produced by a user-friendly jet nebulizer, which is inhaled through a face mask or mouthpiece. Another type of delivery device allows asthma patients to use their own breath to inhale pre-measured doses of medication. Hand-breath coordination or spacers are not required.

**Medication and the school day.** Children with attention-deficit hyperactivity disorder (ADHD) can now take 12-hour formulations of methylphenidate (Ritalin) before going to school. Thus, there is no need for storage of medication at school or for the child to be summoned by the school nurse for supervised administration, thereby identifying him/her as a child on medicine. Long-acting preparations may be particularly helpful to adolescents because their day is much longer than a young child’s in terms of school and after-school activities. In addition, since a major problem for ADHD patients is the ability to remember and plan, they often do not realize the need to take another pill at a certain time and can be unaware of the medication’s decreasing effectiveness as it wears off. Long-acting preparations can help minimize this problem.

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**The transformation of insulin therapy: modern delivery devices improve dosing accuracy and quality of life**

Simply improving the delivery method for insulin—a critical component of diabetes treatment since its discovery in 1922—can substantially enhance the ability of people with diabetes to manage their disease.

Insulin-injecting pens, first introduced in 1985, offer repeatable, accurate dosing compared with syringes. They generally resemble a large pen, and use an insulin cartridge (often prefilled) rather than a vial. Accurate dosing is easier for users with poor vision since measuring the dose involves dialing a mechanical device rather than reading a syringe scale. The smallest pen needles are very short, very thin and minimize injection discomfort. Pens are easy for children to use at school or during other activities.

Inhaled insulin, first introduced in 2006, delivers insulin in reproducible, convenient doses to the deep lung. This offers some diabetics freedom from injections, which is important since aversion to insulin injections keeps millions of people with types 1 and 2 diabetes from achieving proper glucose control. Up to half of all people with type 2 diabetes who require insulin decline it. Surveys show that many patients would be more likely to adhere to treatment with inhaled insulin.
Innovative dosage forms and delivery systems can represent important advances in drug therapy, providing both clinical and economic value, often through their ability to enhance adherence with medication regimens. Access to these formulations allows physicians to personalize therapeutic regimens to facilitate adherence, thereby improving treatment outcomes.

The advantages of innovative dosage forms should be factored into decisions regarding inclusion of drug products on formularies and their assignment to co-payment tiers. These formulations can often improve adherence and treatment outcomes in children and in the elderly, where adherence may be an issue due to sensitivity to side effects or complex treatment regimens for multiple illnesses. Accordingly, innovative dosage forms should receive particular consideration for placement on Medicaid and Medicare Part D drug formularies.
References


25. Ellis JJ, Erickson SR, Stevenson JG, et al. Suboptimal statin adherence and discontinuation in primary and

26. Feinsod HM, Manyam BV. Controlled-release carbidopa-levodopa in frail elderly and long-term care

27. McCue JD. The advantages of simplicity in drug regimens for long-term care residents. Nursing Home


30. Lehman AF, Steinwachs DM. Translating research into practice: The Schizophrenia Patient Outcomes


Health Syst Pharm. 2002;59(suppl 8):S10-S15.


atypical and conventional depot formulations in Germany. Pharmacoeconomics. 2005;23(suppl 1):49-61.

36. Chue PS, Heeg BM, Buskens E, et al. Modeling the impact of compliance on the costs and effects of long-


treatment with orally disintegrating and coated olanzapine tablets – results from a prospective multi-

2000.

41. Findling RL, Manos MJ, Wilens TE, et al. Identification and discussion of key issues and advances in
pediatric ADHD. Medscape Medical Crossfire. http://www.medscape.com/viewprogram/4967_pnt,

Available at: http://www.johnratey.com/Articles/An%20Update%20On%20Medications


44. Nash DB, Koenig JB, Chatterton ML. Why the elderly need individualized pharmaceutical care. Office of