



Two-Plus Decades of Research Studies Support Improved Patient Adherence With Calendarized, Compliance-Prompting Packaging

Executive Summary

The US Healthcare System is heading for a dramatic overhaul. Projects targeting improvement of care and cost reduction are well underway. Data suggests that poor medication adherence has a detrimental effect on the healthcare, contributing to the increasing problem of poor outcomes. Improving medication adherence is critical and many organizations are looking for adherence solutions. Unfortunately, pharmaceutical prescription packaging is not often targeted in these activities and has been largely untouched for more than 55 years. Over two decades of research studies, however, support the use of modern packaging solutions, including patient prompting, also known as compliance-prompting, packaging, as a successful option for improving patient adherence.

Over two decades of research studies, support the use of modern packaging solutions.

It is the intention of the Healthcare Compliance Packaging Council to highlight the improvements in patient adherence obtained through the use of compliance-prompting packaging. By sharing the results of these nine cumulative studies, beginning with the 1984 Modulus Hormone Replacement Study, then citing the well-known Ohio State study, followed by current peer-reviewed research from a major mass merchandise pharmacy retailer, as well as results from a newly published adherence study from a major pharmaceutical supplier, the HCPC and its member companies, aspire to have compliance-prompting packaging recognized as a key tool to improving patient adherence and outcomes.

The Healthcare Compliance Packaging Council is a not-for-profit trade association whose mission is to promote the greater use of compliance-prompting packaging to improve patient adherence and patient outcomes. For more information on HCPC, please visit our website, www.hcpconline.org. To contact the HCPC, please email vickiwelch@hcpconline.org, call 804-338-5778, or write the HCPC at 2711 Buford Road, #268 Bon Air, VA 23235 USA

It should be noted that none of the data cited in this report were influenced in any way by the HCPC. The HCPC did not fund, suggest, participate in research or otherwise contribute to any of the quoted data or studies in this document.



Two-Plus Decades of Research Studies Support Improved Patient Adherence With Calendarized, Compliance-Prompting Packaging

A compilation of peer and non-peer reviewed compliance-prompting packaging studies.

The US Healthcare System is heading for a dramatic overhaul due to gross inefficiencies in current practices. Not only are we overspending for care (based on international statistics) but the quality of care we receive is not up to developed western nation standards. The World Health Organization (WHO), in 2000, ranked the U.S. healthcare system as the highest in cost, first in responsiveness, 37th in overall performance, and 72nd by overall level of health (among 191 member nations included in the study)^{[1][2]} The Commonwealth Fund ranked the United States last in the quality of healthcare among similar countries,^[3] and notes U.S. care costs the most.^[4]

One of the major but often overlooked problems in US Healthcare is the severe lack of medication adherence, a topic that is finally gaining nationwide attention as our government focuses on healthcare costs and improving outcomes. The estimated annual cost the US incurs as a result of poor medication adherence approaches \$300 billion^[5], as recently noted in the New England Healthcare Institute paper "Thinking Outside the Pillbox", 2010. Data points to poor adherence in America as being the primary cause for 125,000 deaths annually (342 people every day) and an estimated 10% - 25% of hospital and nursing home admissions.^[6] While insurance companies and managed care organizations bear the greatest economic burden from poor medication adherence, including the largest payer, Center for Medicare and Medicaid Services (CMS), everyone pays a share for the inefficiency in the form of higher taxes, grossly higher premiums, and lost productivity.

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There are many reasons for patients' non-adherence with their medication regimen, including forgetfulness, lack of understanding for the drug or the disease, or simply not filling the prescription. Many of these issues are beyond the control of the pharmaceutical and packaging industry but there is one aspect of US prescription dispensing which has gone virtually unchanged for 55 years that is well within our reach to improve - the pharmacy-filled amber vial. While other nations have moved away from pharmacy repackaging of prescription medications, the US has clung to this antiquated method that is fraught with opportunity for medication and dispensing errors and leaves the consumer with an outdated

package that offers no support for medication adherence.

The practice of pharmacy packaging started in a time when compounding pharmacists were the norm. It was the correct place to package pharmaceuticals. Today, however; pharmaceutical manufacturing takes place in multi-million dollar pharmaceutical manufacturing facilities and not in the backroom of pharmacies. These pharmaceutical companies design and test packages according to FDA and ICH guidelines to protect the product until it reaches the consumer and yet, our system discards that package in pharmacy and opts for the plain amber vial that has not been tested for the particular chemical makeup of the individual drug. Worse yet, we have a system that has ignored the successful performance demonstrated again and again by unit dose packaging with compliance-enhancing formats. Packaging that reminds people whether they have taken their medications. Birth control pills, certain antibiotics, hormone replacement therapies, and steroids are already being dispensed in compliance-prompting, unit dose packaging that has proven highly effective in helping people manage their pharmaceutical regimens. There is a wealth of data to support the idea that if more products were packaged in a these formats, patient adherence would be greatly increased and the associated improvement in health outcomes would greatly reduce healthcare costs that exist today. That is why the HCPC's goal is to inform and educate consumers, health professionals and policy makers about the role that compliance-prompting packaging can play in improving pharmaceutical adherence.

Calendarized blister packaging can have a positive impact.

There is a wealth of data to support that patient adherence would be greatly increased.

The best examples of significant patient adherence achieved through compliance-prompting packaging are birth control pill packages used in various calendarized forms since 1960. While some may object to this reference, citing that the high compliance with birth control pills is associated with known risk, data from National Council on Patient Information and Education (NCPIE) does not support that conclusion. According to NCPIE, birth control pills have a compliance rate of 92 percent (some list it as high as 95%) while organ rejection drugs (with a "known risk" of death) have an average compliance rate of 82 percent. The unprecedented 95% adherence rate experienced with birth control pills can be correlated with the calendarized blister that reminds the patient if she has taken her daily dose and not with the associated risk. Given the high rate of adherence, one can only wonder why this form of compliance-prompting packaging has not been introduced in other areas of drug therapy, particularly those dealing with chronic conditions where non-adherence can result in increased hospital admissions and poor health outcomes.

The HCPC has been tracking and informing the industry of compliance packaging research conducted over the years. Contained herein is an overview of both peer-reviewed and non-peer reviewed studies that have successfully demonstrated that compliance-prompting packaging can improve patient

adherence and outcomes. As you will see, those focusing on the issue of **medication adherence**, which is defined as the "extent to which patients follow provider recommendations about day-to-day treatment with respect to the timing, dosage, and frequency,"^[7] are realizing that calendarized blister packaging can have a positive impact. And, as recent data has shown, **medication persistence**, or the duration of medication-taking from initiation to discontinuation^[8], can also be assisted by calendarized packaging by influencing the rate at which a patient will refill their prescription.

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Modulus, Inc. Hormone Replacement Therapy

Leonard W.G., Leonard D.: Calendar oriented compliance. *Maturitas*, the international journal for the study of the climacteric. Sept. 1984, MATURITAS

A study conducted over 20 years ago, six years prior to the formation of the HCPC, still provides confirmation that calendarized blister packaging can increase patient compliance. In a study conducted by Walter Leonard, MD, and Dawn Leonard, RN, BSN, the researchers found that a "calendar-oriented, structured dosage package" increased patient compliance with estrogen-replacement therapy as compared with a two-drug regimen administered from bottles. In the article the authors describe how two groups of 50 women are each given two prescriptions of hormone therapy, one is for estrogen and the other for progesterone. The women in the control group receive their prescriptions in amber vials, one for each prescription. The other group of women, known as the research group, is provided with a compliance-prompting blister card housing both medications. The data from this research highlights that those women who received their prescription in amber vials were only 30% compliant, while those 50 women with the calendarized blister cards were 82% compliant.

Women with the
calendarized blister
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compliant.

Unit Dose Packaging and Elderly Patient Compliance

In a highly recognized study presented at the Unit-of-Use – Contemporary Issues Open Conference, Baltimore, Maryland, December 13-15, 1992, and also published in the *New Zealand Medical Journal* in 1991, it was revealed that in a study of 84 elderly patients, those using unit-dose calendar packaging were more likely to comply with their regimens than those using bottles or other noncalendarized packs. The 45 seniors using compliance-prompting calendar-packs led in compliance rates throughout the study.

Patients using unit-dose
calendar packaging were
more likely to comply
with their regimens.

Those using the compliance-prompting packs, exhibited an 86.7% compliance rate compared to the 39 seniors using amber vials, who had a 66.7% compliance rate at the start of the program. After the patients were discharged the seniors using calendarized packaging continued to lead in compliance, 68.8% versus the control group's 41.0% after 10 days, then, 64.4% to 38.5% after one month, and 48.9 to 23.1% after three months.

A Project to Increase Medication Compliance and Reduce Costs in Domiciliaries

Also in 1992, the results of the U.S. Department of Health and Human Services Grant Award 90-AM-0433, Jefferson County Office of Senior Citizens Activities, Birmingham, Alabama, were published in February of that year. In this study, bulk medications were put up in compliance-prompting formats for assisted living facilities in Alabama. The conclusion drawn at the end of this study was that "results indicated significant improvements in average compliance" . . . with "overall average compliance improved from 85 percent to 95 percent."

"Results indicated significant improvements in average compliance"

"Effect of Value-Added Utilities in Promoting Prescription Refill Compliance Among Patients with Hypertension"

The following year, Current Therapeutic Research, Vol. 53, No. 3, March, 1993, published the results of a study that focused on the adherence of 128 hypertensive patients. These patients were monitored for one entire year. The control group received no intervention in compliance and their compliance rate was only 0.64, those with a reminder card maintained a 0.71 compliance rate, those with a compliance-prompting package demonstrated a compliance rate of 0.75. Those who received their medications in compliance-prompting packaging coupled with a reminder card achieved the highest level of compliance at 0.87, demonstrating that compliance-prompting packaging can be a advantageous portion of a multi-faceted compliance enhancing program.

Compliance-prompting packaging can be an advantageous portion of a multi-faceted compliance enhancing program.

"Use of Blister Packaging to Improve Patient Medication Compliance in the Treatment of Depression"

In 1996, SmithKline Beecham, Inc. conducted research of 150 patients diagnosed with depression among 43 different sites throughout Canada. These patients were monitored for 12 weeks. The control group was provided their prescription in typical amber vials. The research group was provided

with compliance-prompting blisters. Prior to the distribution of the differing packaging, the Baseline Beck Depression Index (BID) for both groups was 27.5. At 24 weeks, the Mean BID for control group measured 13.1, while the mean BID for the research group was 11.0 and it was concluded "Patients randomized to the blister pack preferred the blister packaging scheme over traditional bottle formats."

"Patients preferred the blister packaging scheme over traditional bottle formats."

"Impact of Innovative Packaging on Adherence and Treatment Outcome in Elderly Patients with Hypertension"

(Journal of the American Pharmacists Association, Jan/Feb 2008, 48:1 pp. 58-63)

A more recent study conducted by Ohio State University compares compliance rates of an anti-hypertensive drug administered to some elderly patients in a bottle and others in a blister. The results of this study continue to prove the point that calendarized blister packaging can provide increases in patient adherence. In the OSU research, 88 adults, all 65+ years of age, were included in the study. All had blood pressure readings of at least 140/90. Forty-eight participants received Prinivil in blister packs with compliance-prompting features. These participants constituted the study group. Forty received Prinivil in traditional pharmacy vials and composed the control group. The patients were tracked for 12 months.

Over these months, the percent of on-time refills of the control group was only 66.1%, while the study group's percent of on-time refills was 80.4%. Dramatic improvements in blood pressure were also measured in the study group. The change in DBP of the control group was -17% and SBP was -40%. For the study group, DBP was -50% and SBP was -57%.

The conclusions drawn by the researchers: "Patients in the study group had better adherence as measured by: 1) Significantly more likely to refill prescriptions on time; and 2) Medication possession ratios significantly higher for study group (MRP = "proportion of days a patient has medication available to be taken") and "At 12 months, a significantly greater proportion of patients in the study group had lower diastolic blood pressure (compared to baseline) than patients in the control group."

Patients in the study group had better adherence

New Catalent/SDI Study Shows Adherence Packaging Solutions Drive Substantial Gains in Patient Persistency – April 2011

Since the highly-noted OSU study, pharmaceutical packaging suppliers have had third party research conducted in the past several months. In April 2011, Catalent Pharma Solutions, a drug delivery technology and packaging provider, announced the results of an independent study in which unit-dose patient adherence packaging was associated with a 17-point increase in patient persistency to a drug over 12 months, as compared to conventional 30-count bottle packaging. The study utilized patient data from SDI, a provider of anonymous patient-based prescription data for US retail pharmacies.

The adherence study looked at patient persistency rates over a 12-month period by analyzing a cohort of ~200,000 qualified patients from SDI who filled their prescriptions in either a traditional bottle or a patient adherence package. Persistency rates were defined as the percentage of patients who remained compliant or restarted therapy over the 12-month tracking cycle. This new study again suggests that appropriately tailored packaging can provide

Appropriately tailored packaging can provide customers with compliance solutions that positively impact patient adherence and treatment outcomes.

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“A Pharmacoepidemiologic Analysis of the Impact of Calendar Packaging on Adherence to Self-Administered Medications for Long-Term Use.”

(Clinical Therapeutics, May 2011, Vol. 33, Number 5)

Shortly after the Catalent results were revealed, MWV, a packaging manufacturer, shared their compliance-prompting packaging research results. The MWV study was conducted to assess the effect of new MWV calendar packaging technology on prescription refill adherence and persistence for daily, self-administered, long-term medication use. The study group involved 76,321 new users and 249,040 current users, aged 18 – 75 years, who filled prescriptions for oral lisinopril or enalapril (control group) at a mass merchandise study pharmacy during 1 year prior and after the switch of lisinopril packaging from vials to calendarized blister packaging.

Within the study, the use of MWV's Shellpak®, a proprietary calendarized 30-day, unit-of-use medication package, demonstrated improvement in the adjusted estimates of refill persistence and adherence as measured by length of therapy (LOT) and proportion of days covered (PDC) with medication.

Results revealed the Shellpak refill persistence benefit was especially pronounced among certain subgroups. New medication users had an average length of therapy increase of 9 days over a year.

Ongoing medication users had an average length of therapy increase of 4 days over a year. Persons taking fixed-dose combination formulations, or 2 medications in a single tablet experienced an average 17-day increase in length of therapy for new users and 12 days for ongoing medication users. In addition, the study

revealed that Shellpak users overall were more likely to reach “full refill adherence” – at least 80% of days covered with medication in a year – than vial users, with the greatest effect observed in new medication users.

A 30 day calendarized unit-of-use package demonstrated improvement in the adjusted estimates of refill persistence.

The conclusion reached by the researchers: “Calendarized Blister Packaging of medication prescribed for daily, self-administered, long-term use was associated with modest improvement in prescription refill adherence and persistence. And adherence strategy of even small effect size that is broadly implemented on a population level could significantly leverage therapeutic effect and provide substantial cumulative public health benefit.”

“Real-world impact of reminder packaging on antihypertensive treatment adherence and persistence.”

(Patient Preference and Adherence 2012: 6 499-507, Dovepress Open Access to Scientific and Medical Research)

As cited in the publication of this real-world study on the introduction of a reminder package for a Novartis hypertensive tablet, “Adherence-oriented blister packaging may improve treatment of adherence and reduce compliance barriers in community and outpatient settings. However, improved packaging has not been used widely and has rarely been studied for medications used to treat chronic and long-term illnesses.” The HCPC has always been puzzled by this lack of interest in reminder packaging for the treatment of long-term chronic illnesses, and heralds the release of recent results from the open access research from Novartis and Xcenda for the DiovanHCT blister package.

In this study, Novartis Pharmaceuticals, through Walmart pharmacies, began to distribute a single-pill combination of valsartan-hydrochlorothiazide in reminder packaging. The DiovanHCT package introduced to hypertensive patients at Walmart pharmacies consists of 30 tablets in a push-thru calendarized blister in three rows of ten. To facilitate compliance with the medication regimen, tablets are laid out with color coded days and weeks, including reminders for refilling the prescription. Diovan HCT® is offered in four strength combinations with each strength combination using a unique color

(Brown, Blue, Purple, Red) and a photograph of the unique tablet design for each strength to ensure correct dosing. This plus additional important labeling information is clearly provided on the exterior of the child-resistant MWV Shellpak™ which houses the calendarized blister. The back label provides the designated area for the patient's prescription label as well as an adhered prescription insert. The front of the pack features an extended content booklet label and the photograph of the pill. Multiple pages within the front label provide patients assistance with dosing instructions and guides to joining the BP Success Zone Program, including both the website and toll-free number, and additional regulatory information.

When 4,633 Walmart patients obtained refills of the single-pill combination in this new reminder packaging, their adherence rates were studied over 11 months by measuring the following: medication possession ratio, time to refill, proportion of days covered, and time to discontinuation. An additional 4,633 patients from the SourceLx (Wolters Kluwer) database who did not receive their single-pill combination of valsartan-hydrochlorothiazide in reminder packaging were also included in the study for the 11month period.

At the end of the study period, those who received the DiovanHCT reminder package, exhibited a medication possession ratio of 80%, while those patients not utilizing the reminder package demonstrated a lesser ratio of 73%. Proportion of days covered for the Walmart pharmacy customers was 76% versus the 63% for the non reminder package group. Those patients with the reminder package also refilled their prescriptions four days earlier, on average, than the other patients. Finally, those patients with the Diovan HCT reminder package were also more likely to continue their therapy in the long term.

Reminder packaging has a positive effect on medication possession ratio, proportion of days covered and refill rates.

It should be noted that the Novartis DiovanHCT reminder package was awarded the HCPC's highest honor in 2010 as the Compliance Package of the Year, prior to the study results being published. Even then, the independent industry panel of judges, including pharmaceutical manufacturing engineers and pharmaceutical packaging media representatives, recognized that the DiovanHCT reminder package was a well developed design that focused on the patients' adherence in order to improve their disease states. And, the results provided in this very recent study support the broad adaptation of compliance-prompting, reminder packaging throughout the industry.

The nine studies cited all draw a similar conclusion, as reiterated by the Institutes of Medicine in the National Academy of Sciences article *Preventing Medication Errors*, "***The strategy of using calendar blister packs could help large numbers of patients (including seniors, children, and those challenged by cognitive, physical, or functional impairment) take their medication more reliably***

and safely, and enhance their treatment outcomes.^[9]

The WHO identifies two categories of nonadherence. The first is **preventable** nonadherence where the patient forgets, or misunderstands. The second category is **nonpreventable** where the medication may have life-threatening adverse effects. The WHO recommends targeting tailored treatment interventions for **preventable** nonadherence^[10] and now, due to the most recent studies cited the industry's attention has refocused to relatively simple approaches, such as "reminder" packaging, that can be widely implemented for once-daily medications take for chronic diseases.^[11]

The WHO recommends targeting tailored treatment interventions for **preventable** nonadherence.

As previously mentioned, those focusing on the issue of medication adherence, or the "extent to which patients follow provider recommendations about day-to-day treatment with respect to the timing, dosage, and frequency, are realizing that calendarized blister packaging can have a positive impact and medication persistence, i.e., a patient's duration of medication-taking from initiation to discontinuation, can also be assisted by calendarized packaging by influencing the rate at which a patient will refill their prescription.

A large segment of the healthcare industry regularly uses calendarized blisters on a daily basis, the "bingo card" containing 28-30 doses is found in a large percentage of Long Term Care institutions where tracking patients daily (and often multiple) meds is critical to maintaining the health of patients in their care. It is curious that this segment of professional caregivers sees the benefit of calendarized packaging for managing daily medication regimen in a professional setting but the industry neglects to offer that same benefit to the broader home based population where similar gains in health outcomes could be realized.

Building on Technology

The referenced studies provide a great beginning, but there is much more that can be achieved through enhanced packaging developments and creative thinking. If we separate package improvements into three categories we can gauge their potential benefit. The categories are:

Passive features

Active features

Interactive features

The goals of incorporating these features are basic: communicate, remind, engage and, verify.

Passive features can take the form of simple educational graphics on the package. They are put in the path of the consumer and we hope they do some good.

Active features include the calendarized blister pack. It qualifies as an active solution since its use leaves evidence of dispensing that can provide feedback to the patient and caregiver. Also included in this category are lights, buzzers or other components that will gain patient attention with similar goals as

the passive solutions. Integrated electronics from companies such as Cypak and IMC that can record dispense events and create a real time record of adherence performance also fall into this category.

Interactive features go beyond the simple package. Certain packages with imbedded electronics provide feedback and elicit response from the patient. Some, like Vitality's Glow Caps, incorporate internet based or cellular feedback features to provide professional caregivers real time data on patient adherence. This link is critical since it provides the opportunity to intervene if a non-compliant patient is putting themselves in a dangerous situation. Call centers are another example of interactive solutions. Human to human interaction can be quite effective in prompting adherence but, unless we intend to have one half the world call the other half of the world, they are an impractical solution long term. In addition, call centers have developed due to poor primary packaging that does little to communicate or promote adherence.

The goal at the end of the day is verifiable use. Family members, caregivers and health professionals need some way to know that a drug was taken by the patient. Only with verifiable use can we prevent Adverse Drug Events (ADE's) that are responsible for as much as 28% of Emergency Room visits, 10% of hospitalizations, and 25% of Nursing Home admissions.

As well, we have a growing number of Pay-for-Performance insurance models that will pressure caregivers to improve medical outcomes for patients in their care with this performance linked to financial compensation. Programs such as Care Transitions and Patient Centered Medical Homes need improvements in medication adherence in order to meet their goals. Smarter packaging can help them reach their goals and improve the welfare of patients at the same time.

The HCPC believes all this work is leading toward broader adoption of compliance-prompting packaging for the benefit of the patient, and the healthcare industry, overall. Industry efforts to incorporate reminders and positive reinforcement cues have been introduced and tested in the form of calendarized blister packaging. By utilizing today's amazing technology additional functions such as real-time data feedback are possible. This type of compliance-prompting packaging, when used in combination with education and other reminders, has been shown to improve patient medication adherence. We, as part of the US Healthcare industry, need to put these options in the hands of the patient. Consumers need to have a choice how their prescriptions are packaged: either the standard cap and vial format that does nothing to help them manage their medications, or a compliance-style, unit dose package that will help ensure that they actually take the medication as it has been prescribed. We believe, like the World Health Organization, that "Increasing the effectiveness of adherence interventions may have a far greater impact on the health of the [world] population than any improvement in medical treatment."^[12]

The HCPC is working towards the day that calendarized blister packaging will be more widespread for the benefit of patients.

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