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Impact of push-through-packages with electronic devices for accurate drug taking

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Abstract

Improved compliance is an issue in medical care and a previous study showed noncompliance measured via a survey and by counting unused drug. However, it is difficult to assess the frequency and timing of noncompliance in real time. In order to address these issues, we developed paper-made electronic devices with press through packages (PTPs) which recorded the time and frequency when users opened the PTPs. Using these devices, we studied the actual practice of self-administration of a hypertension drug (once a day). The data of 37 subjects using PTPs with electronic devices showed a discrepancy between actual compliance and subject-reported compliance. Only one subject (2.8%) had 100% compliance. There were 11 (30%) subjects in the highest level compliance group and 8 (22%) in the lowest. In contrast, 35 subjects (95%) reported perfect compliance by their own evaluation. Using innovative devices, it is possible to observe time, frequency, missed doses, and misuse in self administration. From an analysis of the correlation between subject background and noncompliance, all subjects had an equal possibility of noncompliance. This is the first report of actual patient compliance with real evidence of timing and frequency. The innovative electronic devices are particularly necessary for accurate control of drug therapy and cost-effective therapy with expensive drug-use.

Keywords: Compliance, Medical care, Electronic devices, Evidence, Drug therapy, Cost-effective.

Introduction

Press through packages (PTPs) are widely used for prescription drug and over the counter drug (OTC) pills and capsules. However, adherence with PTP medicine has not been well-studied with objective measures.[1] We have developed and studied several types of PTPs with electronic devices, one of which has the ability to record the date and time that patients take their medicine (Figure 1). The data can be easily displayed on a computer screen in various medical settings such as an out-patient examination, hospital ward, community pharmacy, or nurse center.

Materials and Methods

Eligible subjects were patients prescribed to take same hypertension medication once a day on a regular basis; there was no specific age range. Those who required the support of other people to take the medication were not included. All enrolled subjects signed an informed consent. The electronic devices were fitted into the PTPs before being used by the subjects (Figure 2). The subjects were not informed of the recording

capabilities of the devices and were only asked to take their drugs in the usual manner. To confirm the devices were working properly, we included one subject who was informed of the mechanism of the devices to serve as a control. The control subject had very good compliance in our 2 week trial study in which we counted the used drug.

After 1 month, we evaluated actual compliance of time and frequency of their drug-taking from the data recorded by the electronic devices in the PTPs. We also summarized the subjects' personal evaluation statements. The subjects' compliance was evaluated and assigned to one of four groups according to the frequency of misuse or missed doses: Level A; 0 to 2 times/month, Level B; once/week to 3 to 4 times/month, Level C; twice/week to 3 to 10 times/month, Level D; 3 times/week to >11 times/month (Table 1).

Results

Thirty-seven subjects [10 men (including the one control), 27 women] were included in the study and the average age was 66.7 ± 14.1. No subjects had obvious dementia and all had a history of more than 3 months of taking the same hypertension drug.

The compliance results as recorded by the electronic devices are shown in Table 2. There was a wide variation in compliance among the subjects. No subject achieved 100% compliance other than the control subject. Only 30% of subjects qualified as Level A but almost all evaluated themselves at Level A (no missed doses) (Table 3).

Figure 1: PTPs with electronic devices and usage

The electronic devices combined with the PTP can be used for accurate monitoring of self-administration. The device records the date and time when users open the package. The data are easily displayed on computer or smartphone using an NFC (near-field communication) reader.

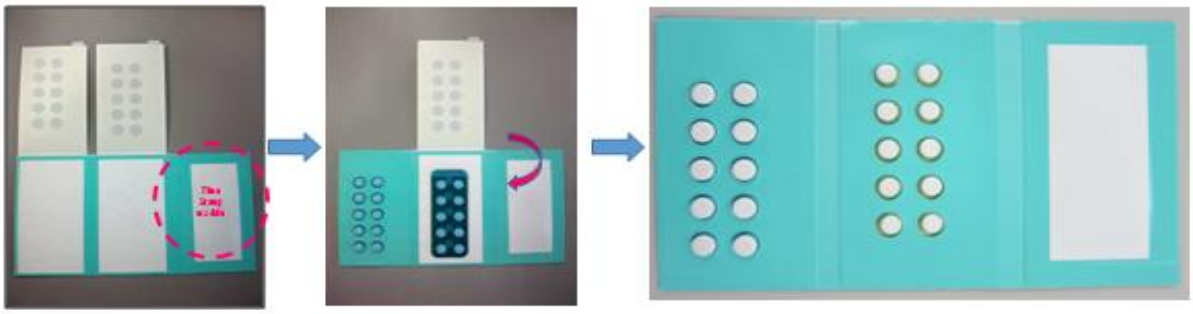

Figure 2: Equipping PTPs with electronic devices

The hypertension drug (olmesartan medoxomil) is placed into the electronic devices and patients are able to take drugs as usual. Ordinary PTPs can be equipped with the electronic devices by a pharmacist or medical provider.

Table 1: Compliance Groups

Groups	Noncompliance	Forgot to take or took with a >6-hr delay, took more than once per day
A	Good Compliance	Missed dose 0 - 2 times/month
B	Few Noncompliance	Missed dose ~1 time/week or 3 – 6 times/month
C	Middle Noncompliance	Missed dose ~2 times/week or 7 - 10 times/month
D	Severe Noncompliance	Missed dose ≥3 times/week or more than 11 times/month

Subjects were divided into four groups based on compliance level.

Table 2: Compliance by group – electronic device

Compliance Level	Number (%) of Subjects
A	11 (30%)
B	12 (32%)
C	6 (16%)
D	8 (22%)

About 40% of subjects showed poor compliance.

Table 3: Compliance by group – subject evaluation

Compliance Level	Number (%) of subjects
A	35 (95%)
B	2 (5%)
C	0 (0%)
D	0 (0%)

Subjects' self-assessment of compliance was much higher than actual compliance.

The summary of the results as recorded by the PTPs and displayed with the NFC (near-field communication) reader (Figure 1) is shown in Table 4. Although subjects were instructed to take their medicine in the morning, the actual time varied between 6:52 and 12:11 depending on the day of the week. There were also days where the dose was completely missed as well as days where it was taken twice per the data recorded by the devices (Table 4). From the results of the questionnaire administered after the study, every subject implemented more than one method in order to help them be compliant with their drug regimen (Table 5). From the subject self-assessment of compliance, those who missed a dose 0 to 2 times per month reported no missed doses (Table 6).

The data provided by the electronic devices revealed that some subjects took too many doses in 1 day while others tended to skip their drugs or took them at the wrong time

in the same pattern every day. There were also some subjects who opened several drug packages in 1 day (Table 4). There was no correlation between subject background and noncompliance, and no significant correlation between age, sex, number of other drugs taken regularly, and whether or not the subject used other methods to aid compliance (Table 7).

Table 4: Example of electronic device data

Example of electronic device data																								
Subject	1		2		3		4				5		6	7		8								
Day	5229		3215		4158		1101				2945		6389	1378		432								
2	7:44		7:08	7:08	10:04	10:06	18:33				12:16	21:57	6:42	14:20	14:21	8:00								
3	8:11		7:21	?	7:48		9:20				×		6:45	9:00		7:59								
4	7:40		4:54	4:54	7:26		8:51				×		6:55	9:47	9:47	8:29								
5	7:31		6:45		7:20		8:25				22:27		6:57	×		7:44								
6	6:52		5:38		7:25		9:03				22:00		6:49	9:28		7:33								
7	8:02		×		7:34		9:30				22:56		6:32	9:16		7:37								
8	8:43		5:04		7:12		7:31				21:05		6:42	9:07		8:12	8:12							
9	7:46		×		×		9:46				23:12		6:40	9:25		8:47	8:47							
10	8:12		4:55		7:48		11:50				22:57		6:34	9:13		9:03								
11	7:56		5:01		7:13		9:16				22:30		6:38	9:20		×								
12	9:54		5:15		7:45		×				23:39		6:38	9:12		9:42	9:43							
13	7:38		7:23		×		9:08				22:37		6:38	9:12	9:12	×								
14	7:07		6:37		7:01		9:05				×		6:32	×		7:28								
15	7:38		4:38		7:22		×				22:22		6:45	9:21	9:22	8:40								
16	7:08		4:57		×		9:34				21:01		6:44	×		7:56								
17	7:39		5:30		7:34		9:32				23:56		6:41	9:15		9:10								
18	7:32		5:16		8:11		9:52				×		6:45	9:30		8:57								
19	8:18		5:19		7:10		9:25				21:33		6:43	9:22		8:16								
20	8:34		8:13		7:13		10:08				20:15		6:33	9:31		7:18								
21	8:00		7:31		7:29		9:31				23:41		6:38	9:30		7:55								
22	12:11		5:35		7:08		6:59				23:24		6:44	9:22		8:03								
23	8:11		6:18		×		×				22:48		6:34	9:21		7:55	7:55	7:55						
24	7:00		5:37		7:22		10:29				22:00		6:19	8:56		×								
25	8:06		5:32		7:45		9:34				21:01		6:42	8:16	8:16	×								
26	7:41		5:38		6:58		9:08				22:07		6:51	×		7:25								
27	8:31		7:17		7:31		8:51				21:11		6:40	9:27		7:56								
28	8:04	8:04	8:10		9:32		9:03				×		6:32	9:17	9:17	7:56	7:56	7:57						
29	7:15		5:41		9:13		8:28				10:10	21:47	6:37	9:16		×								
30	×		5:36	15:50	7:53		×				22:55		6:39	9:24		×								
31	7:13		6:46		6:41		9:44	23:39	23:39	23:39	×		6:39			7:52								
32					7:56		×				22:13		6:36											
33					7:36		9:19				23:02		×											
34					6:55						×		×											
35											10:39	21:20	×											
													14:22											
Ending date	31		32		34		35				36		35	35										
	To determine the actual status of drug consumption (not just opening the package), including possible overdose, and checking the final date																							
Missed dose	1		2		4		5				7		3	4		6								
Too much taken	1		2		1		3				1			6		5								
Taken at wrong time	1						1				2		1	1										
Total	3		4		5		9				10		4	11		11								
Compliance level	B		B		B		C				C		B	D		D								

This is an example of data shown on the computer display. The actual time that subjects took drugs is clearly shown. In addition, it is easy to see the date when the subjects skipped taking drugs.

Table 5: Healing item and evaluation level among subjects

	Evaluation Level
Removing pill from the PTP	1. No problem: 6/34 (18%) 2. Some problems: 19/34 (56%) 3. Difficult: 9/34 (26%)
Number of drugs other than the hypertension drug	1. None: 5/34 (15%) 2. 1 – 3 drugs: 16/34 (47%) 3. More than 3 drugs: 13/34 (38%)
Methods employed to aid drug taking	1. None: 17/34 (50%) 2. Some: (50%) 2-1: small container 4/17 (24%) 2-2: other container or package 10/17 (59%) 2-3 others: 4/17 (24%)
Self assessment of noncompliance (frequency)	1. (A) 0 - 2/month 31/32 (97%) 2. (B) ~1/week 1/32 (3%) 3. (C) ~2/week 4. (D) ≥ 3/week

From the self-assessments, about 50% of subjects tried some type of method to aid compliance, and they believed their compliance was better than it actually was and that they did not have any problems taking their drugs correctly.

Table 6: Self-assessment of noncompliance and reality

	Actual compliance
Frequency of missed doses	0 - 2/month 31/32 (97%) ← Answered no missed doses when asked by the doctor.
	~1/week 1/32 (3%) ← Subjects who answered sometimes missed dose had 6 actual missed doses/month

There is a possibility that subjects' comments regarding their compliance did not always show their actual compliance. Therefore, relying on an oral interview of compliance alone does not provide sufficient information for drug therapy.

Table 7: Relationship between subject background and noncompliance

Correlation Coefficient	Missed doses	Overall*
1. Subject age and missed doses and overall noncompliance	-0.059	-0.060
2. Subject gender and missed doses and overall noncompliance	-0.099	-0.078
3. Number of other drugs taken and missed doses and overall noncompliance	0.034	0.1087
4. Created methods to aid with compliance or not and missed doses and overall noncompliance	-0.167	-0.087

* Overall noncompliance : missed doses, took too frequently, dose delayed by ≥6 hours

There was no significant correction between subject background and noncompliance.

Discussion

Accurate drug taking is very important in a variety of medical care settings such as AIDS and cancer treatment where medicine may need to be taken at regular intervals, as well as in clinical trials.[2] A previous study found that appropriate medication should be considered within the context of all medical care and is a complex matter as only 10% to 15% of patients take their drugs correctly; this highlights the necessity for improvement.[3] When medication is not taken as prescribed, it is difficult to assess the efficacy of the medical care or the therapeutic agent; therefore, adherence is a primary concern in the medical community.

To date, there have not been sufficient data evaluating actual patient compliance within an objective study. In addition, measurements of compliance (adherence) vary across studies and intervention is often complex with multiple components.[4,5] In fact, improving patient medication adherence for chronic disease requires addressing several issues such as patient behavior, improving drug regimens, reducing cost, and appropriate medication use including packaging solutions.[6] In particular, patient behavior and appropriate medication use are medical-support issues which are applicable to medical care globally. In consideration of the above situation, we presented a strategy of an innovation in medical packaging to measure actual patient self-administration habits. Without a sophisticated manufacturing system, we created a simple device combining a PTP with an electronic recording device which has the potential to monitor various medical and lifestyle activities. Using this device, we studied actual drug-taking habits for 1 month.

Tables 1, 2, and 3 show actual adherence with subjects divided into four compliance levels. Sixty-two percent of subjects were in Levels A or B which is quite similar to previous reports.[4,5] However, only our trial reports the actual dates and times including frequency and misuse. Without the PTP electronic devices, it is difficult to assess actual noncompliance. A proper evaluation of hypertension therapy is not possible among patients with poor compliance.[7] With actual compliance data and blood

pressure measurements, doctors are able to evaluate the efficacy of the prescription. Given the discrepancy between actual compliance and subject self-assessments, it is necessary to find ways to accurately measure compliance (Tables 2 and 3).[8,9]

Table 4 shows an example of how the data displays on the computer showing the actual time and frequency the subject opened the PTP by day. Using these devices, even patients who live in remote areas or who have difficulty with frequent visits to an outpatient clinic can be monitored for compliance by medical professionals using a cloud system. This allows their medical team to support or advise patients on their drug-taking in an evidence-based manner. There is flexibility in the software design of the data display so that it can be remodeled depending on the needs or preference of the user and is also available to be viewed on a smartphone.

According to the self-assessments, there was a tendency for subjects to try to appear as though there were no problems with their compliance in front of clinicians (Table 6). Usually, doctors and/or clinicians simply asked the subjects about their compliance verbally; however oftentimes subjects' comments regarding their compliance did not reflect their actual compliance (Table 6). On the other hand, most of the subjects were aware of their need for better compliance as indicated by their use of other methods to help them take their medication according to schedule (Table 5).[10,11] However, even with these methods employed, the level of actual compliance was not sufficient (Tables 2 and 3). There was no significant correlation between whether or not subjects utilized other methods and their level of compliance. Furthermore, there was no correlation between age, gender, and number of other drugs taken regularly and noncompliance, which means that every patient has equal potential to be noncompliant (Table 7). Given these data, inappropriate drug therapy and wasted cost of medical care are concerns. To develop effective and cost-effective drug therapy, it is useful to be able to monitor actual drug compliance.[12] This electronic device provides one answer for practical change in accurate measurement of adherence.

Conclusion

Actual drug compliance remains uncertain with ordinary studies. The use of a simple electronic device such as the one described here has the potential to decrease or assess noncompliance and play a role in evidence-based drug therapy.

Conflict of interest: None

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