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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

What's in a label? An exploratory study of patient-centered drug instructions

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Abstract
Objective To assess the efficacy of patient-centered label (PCL) instructions on the knowledge and comprehension of prescription drug use compared to standard instructions.
Methods A total of 94 participants recruited from an outpatient clinic in Ireland were each randomly assigned to receive: (1) standard prescription instructions written as times per day (usual care), (2) PCL instructions that specify explicit timing with standard intervals (morning, noon, evening, bedtime) or with mealtime anchors (both PCL), or (3) PCL instructions with a graphic aid to visually depict dose and timing of the medication (PCL + Graphic). The outcome was correct interpretation of the instructions.
Results PCL instructions were more likely to be correctly interpreted than the standard instructions [adjusted relative risk (RR) 1.08, 95% confidence interval (CI) 0.98–1.18]. The inclusion of the graphic aid (PCL + Graphic) decreased the rates of correct interpretation compared to PCL instructions alone (RR 0.98, 95% CI 0.91–1.05). There was a significant interaction between instruction type and health literacy (p=0.01). Those with limited health literacy were more likely to correctly interpret the PCL labels (91%) than the standard labels (66%), and those with adequate health literacy performed equally well.
Conclusion The PCL approach may improve patients' understanding and use of their medication regimen.

Keywords Health literacy · Communication · Drugs · Patient centred care · Pharmaceutical care

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Introduction

Patients frequently have difficulty correctly interpreting prescription drug label instructions [1–4], with older patients, patients taking multiple medications, and patients with limited health literacy being at a relatively greater risk for making errors [2, 3]. Multiple factors, such as unnecessarily complex and variable instructions, may contribute to patients' misunderstanding of labels [5]. The United States Institute of Medicine (IOM) highlighted the variability in the way that clinicians write prescriptions and pharmacists transcribe clinicians' instructions [6, 7], an issue which has been reported by many research studies [8, 9].

In 2007, a Universal Medication Schedule (UMS) was proposed to help standardize prescription instructions and provide explicit information in plain language to support patients in correctly dosing their medicine over the course of a day [7]. As the majority of prescription drugs are taken four times a day or less, the UMS dosing instructions specify four standard time intervals (morning, noon, evening, bedtime) [7]. Ideally, this strategy may not only help patients self-

administer their medicine, but also organize complex medication regimens for daily use.

Despite the intentions for the UMS to standardize medication use globally, its application to prescribed medications has been investigated in a U.S. sample only. In the European Union (EU), there are potentially more opportunities to revise pharmacy practices in support of the UMS compared to U.S. Food and Drug Administration (FDA) and state board of pharmacy guidance. Yet the value of the UMS among EU consumers must first be proven, as far fewer studies have examined how adults from European countries interpret existing medication label instructions. In Ireland, for instance, different system-level issues are likely to be present. Whereas U.S. pharmacies vary widely in their use of information on patient labels and place more emphasis on provider versus patient content [9], Ireland and other countries may be less likely to exhibit such variability and poor quality. However, it cannot be presumed that problems of misunderstanding prescription medication instructions are not prevalent or that the UMS principles would not enhance comprehension.

In Ireland and the rest of the EU, legislation sets minimum requirements for drug labeling [10] in terms of broad content but not specific standards that would limit the variability in dosing instructions. In this study, we investigated the potential efficacy of the UMS and take the first step towards assessing whether the UMS can in fact be a universal standard outside of the US. This study represents a significant advancement of a common goal between the US and EU, i.e., the promotion of safe and appropriate medication use.

Methods

A cross-sectional evaluation of the efficacy of patient-centered label (PCL) instructions was conducted. Partic-

Table 1 Prescription label instructions by study arm

	Regimen A	Regimen B	Regimen C
Standard	Drug1 Take one tablet once daily Dissolve or mix with water before taking	Drug 3 Take two tablets twice daily To be sucked or chewed	Drug 2 Take one tablet three times daily Take with or after food
PCL	Drug 2 Take 1 tablet at breakfast, 1 tablet at lunch,and 1 tablet at dinner Take with or after food	Drug 1 Take 1 tablet at bedtime Dissolve or mix with water before taking	Drug 3 Take 2 tablets in the morning and 2 tablets at bedtime. To be sucked or chewed
PCL + Graphic	Drug 3 Take 2 tablets in the morning and 2 tablets at bedtime Morning: 2 | Noon: | Evening: | Bedtime: 2 To be sucked or chewed	Drug 2 Take 1 tablet at breakfast, 1 tablet at lunch, and 1 tablet at dinner Morning: 1 | Noon: 1 | Evening: 1 | Bedtime: Take with or after food	Drug 1 Take 1 tablet at bedtime Morning: | Noon: | Evening: | Bedtime: 1 Dissolve or mix with water before taking

ipants were randomly assigned to receive either Regimen A, B, or C. Each regimen consisted of three drug labels of increasing complexity, each of which contained one standard prescription instruction written as times per day (once, twice, etc.) (usual care), one PCL instruction that specified explicit timing with intervals (morning, noon, evening, bedtime) or with mealtime anchors (breakfast, lunch or dinner) (both PCL), and one PCL instruction with a graphic aid to visually depict dose and timing of the medication (PCL + Graphic) (Table 1).

Study participants

Adults attending the outpatient clinic of an urban teaching hospital in Cork, Ireland, were recruited in January and February of 2010. Adults were eligible if they were aged ≥18 years and ineligible if the study research assistants (RA) identified a participant as having one of the following conditions: (1) severely impaired vision; (2) hearing problems; (3) too ill to participate; (4) non-English speaking; (5) cognitive impairment (Mini Mental State Examination [12] score of ≤17). The Clinical Research Ethics Committee of the Cork Teaching Hospitals approved the study.

Structured interview and assignment

A structured interview protocol was developed to assess participant understanding of the standard label and the PCL with and without the graphic aid. Three trained RAs collected socio-demographic information, then presented participants, one at a time, with three prescription tablet bottle containers with either standard, PCL, or PCL + Graphic drug labels attached for review. Once participants provided their interpretations, the RA administered the Rapid Estimate of Adult Literacy in Medicine (REALM) word recognition test [13]. Participants were classified as having "limited" health literacy if they attained a score of ≤60 on the REALM test.

Outcomes

Correct interpretation of the three prescription drug label instructions was evaluated by (1) subjects' verbatim response to the RA asking "In your own words, how would you take this medicine?", and (2) subjects' demonstration of understanding by a second question: "How many tablets would you take of this medicine in one day?". Participants had to respond correctly to both questions in order to be classified as having correctly interpreted a prescription instruction. This was deemed necessary as a prior study found that patients could passively repeat instructions but not operationalize them by correctly identifying the proper dose of the medication [3].

Analysis plan

A generalized linear model with a Poisson distribution and log link function was used to estimate the risk ratio of correct interpretation of dosage instructions for covariates

Table 2 Characteristics of the study sample stratified by health literacy level

Variable	All subjects (n=94)	Health literacy level		p value
		Limited (n=29)	Adequate (n=65)	
Age, years (%)				0.85
18-45	45.7	41.4	47.7	
46-60	22.3	24.1	21.5	
>60	31.9	34.5	30.8	
Male (%)	31.9	37.9	29.2	0.40
Education (%)				0.06
Primary	17.4	27.6	12.7	
During Secondary	16.3	17.2	15.9	
Junior/Intermediate Certificate[a]	22.8	34.5	17.5	
Leaving Certificate Level[b]	22.8	13.8	27.0	
Post Leaving Certificate Course	8.7	3.5	11.1	
Third Level	12.0	3.5	15.9	
Prescription medications taken daily[c] (n)	2.8 (3.4)	3.1 (3.1)	2.6 (3.6)	0.59

[a] Age 15–16 years

[b] Age 18 years

[c] Presented as the mean, with the standard deviation (SD) in parenthesis

in the model compared to each referent condition. Generalized estimating equations (GEE) with robust error estimation were used to account for repeated measures within participants and to correct for overestimation of variance resulting from using the Poisson distribution for a binomial outcome [14, 15]. The primary independent variable of interest was label type (standard, PCL, PCL + Graphic); two dummy variables (PCL=0, 1; Graphic=0, 1) were included in the model to separate the effects of the PCL and the graphic aid. The final multivariate model included the potential confounding variables age, gender, health literacy, education, and number of medications currently taken daily. Interaction terms between label type and health literacy, age group, and regimen complexity were included in models to determine whether associations varied according to these characteristics. The interaction between regimen complexity and health literacy was also tested. Statistical analyses were performed using Stata ver. 10.0 (StataCorp, College Station, TX).

Results

A total of 94 adults participated in the study. The sociodemographic characteristics of the patient group are presented in Table 2. Overall, 30.9% were classified as having limited health literacy according to the REALM test. Lower health literacy was associated with less education, although this did not reach statistical significance (p=0.06). No significant differences were reported between health literacy level, gender, age, or number of prescription medications taken daily.

Correct interpretation by label type and instruction varied among standard, PCL, and PCL + Graphic labels (Table 3). The PCL label type performed as well as the standard label type for Drugs 1 and 2; however, for the more complex regimen, Drug 3 (higher tablet load), the PCL label outperformed the standard label (97% correct interpretation vs. 79%; p=0.02).

In multivariate analyses (Table 4), prescription instructions with the PCL format were more likely to be correctly interpreted than standard instructions, although the difference did not reach statistical significance [adjusted relative risk (RR) 1.08, 95% confidence interval (CI) 0.98–1.18; p=0.12). The inclusion of the graphic aid on the label (PCL + Graphic) decreased the rates of correct interpretation compared to the PCL instructions alone (RR 0.98, 95% CI 0.91–1.05; p=0.54). Age group did affect interpretation, with participants aged ≥60 years being more likely to misinterpret label instructions (RR 0.85, 95% CI 0.75–0.96; p=0.01).

Participants with limited health literacy were more likely to misinterpret label instructions, but this did not reach statistical significance (RR 0.90, 95% CI 0.80–1.01; p=0.06). However, a significant interaction between health literacy and label type was found; participants with limited health literacy were more likely to correctly interpret PCL instructions compared to standard label instructions (91% correct interpretation of PCL labels compared with 66% correct interpretation of standard labels; p=0.01). Participants with adequate health literacy levels had comparable rates of correct interpretation of label instructions (95% standard vs. 92% PCL).

Table 3 Correct interpretation by label type and instruction

Drug	Standard (%)	PCL (%)	PCL + Graphic (%)	p value
1	88	88	89	0.99
2	91	92	88	0.86
3	79	97	96	0.02

PCL, Patient-centered label

Table 4 Generalized estimating equation (GEE) model for correct interpretation of prescription label instructions

Variable	Correct interpretation		
	RR	95% CI	p value
Instruction type			
Standard			
Patient-centered label	1.08	(0.98 – 1.18)	0.12
Use of graphic			
No graphic on label			
Graphic on label	0.98	(0.91 – 1.05)	0.54
Regimen complexity			
1 pill a day			
3 pills a day	1.03	(0.95 – 1.12)	0.46
4 pills a day	1.03	(0.93 – 1.13)	0.59
Age group			
18-45			
46-60	1.03	(0.95 – 1.11)	0.51
≥60	0.85	(0.75 – 0.96)	0.01
Gender			
Female			
Male	1.00	(0.91 – 1.11)	0.89
Health literacy level			
Adequate			
Limited	0.90	(0.80 – 1.01)	0.06
Number of medications taken daily			
None			
1–2	1.07	(0.97 – 1.19)	0.17
3–4	1.03	(0.91 – 1.17)	0.59
≥5	1.02	(0.90 – 1.15)	0.81

RR, Relative risk ratio adjusted for all variables shown; CI, confidence interval

Discussion

The PCL study conducted in the USA [11] reported findings similar to those found in our study: (1) instructions with the PCL format were more likely to be correctly interpreted compared to standard instructions; (2) participants with limited health literacy were better able to interpret PCL instructions; (3) inclusion of the graphic aid (PCL + Graphic) decreased rates of correct interpretation compared to PCL instructions alone. The combined findings of both studies suggest that similar standards for drug labeling could possibly be achieved internationally.

In this Irish study, PCL instructions that used explicit time periods performed equally well as standard instructions. For the most complex regimen (highest tablet burden), PCL labels significantly improved interpretation relative to standard instructions.

In contrast to the U.S. study, we found a significant interaction between health literacy and label type, i.e., participants who had limited health literacy were better able to comprehend the PCL instructions compared to the standard ones. Importantly, there were no differences in comprehension between the label types among those with adequate health literacy. Given the numerous studies that have indicated limited health literacy as a strong risk factor for poor medication understanding and use [1–4, 6, 7], our study provides strong evidence in support of the use of PCL instructions despite the lack of overall significance between label types.

Our study did not examine the association between misinterpretation of label instructions and actual error in taking real prescriptions. Participants' motivation, concentration, and comprehension might have been greater if they were reporting on their own medicine given by their physician. Finally, the generalizability of our findings may be limited given the small sample and the fact that participation was limited to participants who spoke English (due in part to the use of the REALM).

This is a first step in considering an international standard for prescription drug instructions; further research is needed to understand the full value and/or concerns of using the PCL instructions. While it appears that substantial improvement in patient drug use might be achieved by adopting such a standard, further enhancements may be necessary. For example, it is unclear how effective the PCL instructions would be among patients who work at night/shift workers, or for patients who fast for long periods of the day for religious reasons. Also, strategies must be developed to address instructions for medications in non-tablet form, such as suspensions, creams, inhalers, and for those taken on an "as-required" basis, such as analgesic medication. In addition, future work should examine the effectiveness of the PCL using the patient's own medication and within specific at-risk patient cohorts, such as those with an increased tablet burden (the older patient, patients with chronic diseases). Working with research groups in the US, we are learning more about the feasibility and effectiveness of the PCL to improve patients' actual use of prescription medications. We hope additional countries may become involved and consider the benefits and risks of using PCL.

Conclusion

The evidence presented here confirming the efficacy of the PCL approach should guide necessary changes to reduce variability related to prescription medication labeling. It is inconceivable that the variability in writing prescriptions to guide patient use would be tolerated in settings such as commercial aviation. We need to move to a standardized medication timing regimen. Our instructions that are evidence based and patient centered offer such an opportunity.

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Statement of conflict of interest None.

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