HEALTH CARE REFORM

Helping Patients Simplify and Safely Use Complex Prescription Regimens

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Background: There is considerable variability in the manner in which prescriptions are written by physicians and transcribed by pharmacists, resulting in patient misunderstanding of label instructions. A universal medication schedule was recently proposed for standardizing prescribing practices to 4 daily time intervals, thereby helping patients simplify and safely use complex prescription regimens. We investigated whether patients consolidate their medications or whether there is evidence of unnecessary regimen complexity that would support standardization.

Methods: Structured interviews were conducted with 464 adults (age range, 55-74 years) who were receiving care either at an academic general medicine practice or at 1 of 3 federally qualified health centers in Chicago, Illinois. Participants were given a hypothetical, 7-drug medication regimen and asked to demonstrate how and when they would take all of the medications in a 24-hour period. The regimen could be consolidated into 4 dosing episodes per day. The primary outcome was the number of times per day that individuals would take medication. Root causes for patients complicating the regimen (>4 times a day) were examined.

Results: Participants on average identified 6 times (SD, 1.8 times; range, 3-14 times) in 24 hours to take the 7 drugs. One-third of the participants (29.3%) dosed their medications 7 or more times per day, while only 14.9% organized the regimen into 4 or fewer times a day. In multivariable analysis, low literacy was an independent predictor of more times per day for dosing the regimen ($\beta = 0.67$; 95% confidence interval, 0.12-1.22; $P = .02$). Instructions for 2 of the drugs were identical, yet 31.0% of the participants did not take these medications at the same time. Another set of drugs had similar instructions, with the primary exception of 1 drug having the added instruction to take "with food and water." Half of the participants (49.5%) took these medications at different times. When the medications had variable expressions of the same dose frequency (eg, "every 12 hours" vs "twice daily"), 79.0% of the participants did not consolidate the medications.

Conclusions: Many patients, especially those with limited literacy, do not consolidate prescription regimens in the most efficient manner, which could impede adherence. Standardized instructions proposed with the universal medication schedule and other task-centered strategies could potentially help patients routinely organize and take medication regimens.

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PATIENTS FREQUENTLY MISUNDERSTAND common instructions and warnings that accompany prescription drugs, resulting in unintentional misuse and potentially adverse drug events.[1-6] This should not be surprising, as prescription labels may provide seemingly simple but often unclear directions that are confusing to most patients. In the United States, physician prescriptions and pharmacy labeling typically include vague information detailing recommended medication schedules described either in hourly intervals (eg, every 4-6 hours) or times per day (eg, twice daily). Davis et al[1] found that nearly half of patients misinterpreted common instructions when attempting to dose a single prescription medication.

Yet the problem may be more serious than these findings suggest, as patients are increasingly managing multiple prescriptions and over-the-counter medications. According to the Medical Expenditure Panel Survey, the average adult in the United States fills 9 prescriptions annually,[7] while adults older than 65 years fill on average 20 prescriptions a year. Greater regimen complexity, based on multiple medications and/or multiple daily doses per drug, may lead to poorer adherence, which in turn will lead to worse health outcomes.[8-12] From a health system perspective, the known variability and poor quality in the manner in which prescription instructions are written by physicians and translated by pharmacies impede an individual's ability to organize and properly dose multiple medications.[13,14]

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The Institute of Medicine, in its 2008 report *Standardizing Medication Labels,* recognized the need for setting standards within prescribing and dispensing practices to promote safe and accurate medication use for patients.[6] Because approximately 90% of prescriptions are taken 4 or fewer times a day,[12] a universal medication schedule (UMS) was proposed in the Institute of Medicine report specifying 4 standard times (morning, noon, evening, and bedtime) for the prescribing and dispensing of medication.[14] The UMS would describe when to take a drug in the same manner on all prescription labels, removing the current variability often found in the manner in which prescriptions are written by physicians and transcribed by pharmacists.[13-15] All prescriptions would instruct patients to take their medications using these specified times, and label instructions would subsequently be described in a single standardized fashion. This standardization was viewed with both promise and controversy by the pharmacological and medical communities. While it might help patients organize and group increasingly complex medication regimens for daily use, it was concluded that further evidence would be needed to support the need for the UMS. In the present study, we sought to fill the gap of existing literature and to investigate whether patients complicate multiple prescription regimens by taking medications more than 4 times a day. Specifically, we evaluated the accuracy and variability in the way patients implemented a typical 7-drug regimen.

METHODS

PARTICIPANTS

Adults between the ages of 55 and 74 years who received care either at an academic general internal medicine ambulatory care clinic or at 1 of 3 federally qualified health centers in Chicago, Illinois, were recruited for a National Institute of Aging study, referred to as *LitCog*, that examined performance on everyday health tasks, including medication use. Patient enrollment took place between August 2008 and December 2009. Patients were ineligible if they had severe visual or hearing impairments, were too ill to participate, or were non-English speaking. The institutional review board of Northwestern University approved the study, and all patients gave informed consent before participation. A total of 2168 patients were identified through electronic health record systems at clinic sites as initially eligible to participate in LitCog by age. A random sample of 1012 eligible patients were selected to be contacted by research staff via telephone and invited to participate in the study. Of those contacted, 479 refused to participate, 12 were deceased, and 521 ultimately consented to participate. Initial screening deemed 57 participants as ineligible because of severe cognitive or hearing impairment (n=22), limited English-language proficiency (n=11), or not being connected to a clinic physician (defined as ≥2 visits in the past 2 years [n=24]). In all, 464 patients participated in the study, for a determined response rate of 52.1%, following American Association for Public Opinion Research guidelines.[16]

DATA AND PROCEDURE

Participants completed a 2-hour, structured cognitive interview that included an assessment of their ability to perform everyday health tasks, including dosing a 7-drug medication regimen over the course of a 24-hour period. A research assistant gave patients a hypothetical drug regimen, which consisted of 7 actual prescription drug pill bottles with mock-up labels, each with a retired drug name and different dosing instruction (**Table 1**). The drug names that were chosen were specifically used to avoid the influence of participants' potential current or prior experience with an actual drug.

Table 1. Drug Names and Instructions

	Drug Name	Instruction
A	Pimvampicillin, 700 mg	Take 1 tablet by mouth twice daily for 10 d
B	Disopyramide, 400 mg	Take 2 tablets by mouth every 12 h
C	Zoplicone, 7.5 mg	Take 1 tablet by mouth at bedtime
D	Colesevelam, 1875 mg	Take 1 tablet twice daily with meals and liquid
E	Trimipramine, 100 mg	Take 1 tablet by mouth 3 times daily
F	Cephalothin, 500 mg	Take 1 tablet by mouth 3 times daily
G	Pinaverium, 50 mg	Take 2 tablets by mouth 3 times daily with food and water

The task presented to participants was to demonstrate when they would take the entire regimen by dosing fake pills contained with each prescription bottle at the times of day that they would take the drug. The research assistant gave patients a medication box, which had 24 slots labeled with every hour of the day (12 AM-11 PM), and instructed them to place the correct number of pills in the slots that identified the times when they would take a medicine. Unlike a pill organizer, the medication box was not meant to assist participants. Instead, it allowed them to demonstrate precisely at what times during the course of a day they would take each drug. The scripted verbal instruction given to patients was, "Imagine that your doctor has prescribed you these medicines. I would like you to please show me when you would take these medicines over the course of 1 day." Detailed guidance was then provided to patients on how to demonstrate, with the fake pills, how to dose the regimen using the medication box.

In addition to completing this task, patients answered basic demographic questions and completed a literacy assessment known as the Newest Vital Sign.[17] This is a 6-item measure that includes reading comprehension and numeracy items based on a nutritional facts label. The Newest Vital Sign is strongly correlated with the Short Test of Functional Health Literacy in Adults.[18]

OUTCOME AND ANALYSIS PLAN

The outcome of interest was the number of times per day that patients would propose to take the medicine, based on the manner in which they dosed the 7-drug regimen throughout a 24-hour period as demonstrated using the medication box. Descriptive statistics were calculated for each variable. The association between participant sociodemographic characteristics and the number of reported times per day that patients would take the 7-drug regimen were evaluated with *t* tests. Multivariable linear regression analyses were then conducted to examine patient characteristics that independently predicted taking medication at more times throughout a single day. Only variables that were found to be associated with the outcome with a set value of $P<.20$ were included in the multivariable model. All statistical analyses were performed using Stata version 10 (Stata Corp, College Station, Texas).

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Table 2. Mean Number of Doses Identified in a 24-Hour Period, Stratified by Patient Characteristics

Variable	No. (%)	No. of Doses per Day, Mean (SD)	*P* Value
Age, y			.55
55-59	136 (29.3)	5.9 (1.6)	
60-64	154 (33.2)	6.0 (1.9)	
≥65	174 (37.5)	6.1 (1.9)	
Sex			.47
Female	330 (71.1)	6.1 (1.7)	
Male	134 (28.9)	6.0 (1.9)	
Race			.94
African American	138 (29.7)	6.1 (2.1)	
White	282 (60.8)	6.0 (1.6)	
Other	44 (9.5)	5.9 (1.9)	
Education			.03
High school or less	82 (17.7)	6.4 (2.3)	
Some college	97 (20.9)	6.2 (1.8)	
College graduate	285 (61.4)	5.8 (1.6)	
Literacy			.03
Low	96 (20.7)	6.5 (2.4)	
Marginal	106 (22.8)	6.1 (1.7)	
Adequate	262 (56.5)	5.8 (1.6)	
Income, $			.44
<15 000	78 (16.8)	6.2 (2.0)	
15 000-49 999	99 (21.3)	6.0 (1.9)	
≥50 000	287 (61.9)	6.0 (1.8)	
No. of chronic conditions			.10
0	75 (16.2)	6.2 (1.8)	
1	145 (31.2)	6.0 (1.8)	
≥2	244 (52.6)	5.9 (1.8)	

RESULTS

The mean (SD) age of the participants was 63.3 (5.3) years; most (71.1%) were female, white (60.8%), and highly educated (61.4% college graduates), with a household income greater than $50 000 (61.9%). Nearly half of the participants, however, were identified as having either low (20.7%) or marginal (22.8%) health literacy skills. Eighty-four percent of the participants reported having 1 or more chronic health conditions (**Table 2**).

When dosing the 7-drug regimen, participants on average identified 6 times (SD, 1.8 times) in 24 hours to take medicine. Regimen dosing ranged from as few as 3 to as many as 14 times a day. Approximately one-third of the participants (29.3%) dosed the regimen 7 or more times within 24 hours, while only 14.9% organized the medication 4 or fewer times a day, as would be suggested through the proposed universal medication schedule. Examples of how patients actually dosed the regimen is shown in the **Figure**.

In multivariable analysis that included the covariates of education, health literacy, and number of self-reported chronic conditions, low health literacy was found to be the sole independent predictor of a greater number of times per day for dosing the 7-drug regimen ($\beta = 0.67$; 95% confidence interval, 0.12-1.22; $P = .02$). Interactions between all patient characteristics were examined. Patients with low health literacy and no chronic conditions on average dosed the regimen the most times daily compared with others (8.4 times a day vs range of 5.6 to 6.3 times per day among other groups by literacy and chronic conditions, $P = .005$). No other interactions by age, race, education, literacy, or chronic conditions were statistically significant.

To identify explanations for participants' failure to consolidate the medications into 4 or fewer times per day, we examined in detail how they handled 3 specific sets of drugs within the hypothetical regimen that could have been taken at the same time. Suspected root causes linked to each set were (1) overall difficulty taking multiple medications and coordinating doses (set 1); (2) distraction of secondary, or auxiliary, instructions (set 2); and (3) variability in language used to identify the interval between doses (set 3). In the first set, the dosage instructions were exactly the same (drugs E and F, Table 1). Nearly one-third of the participants (30.8%) did not take these drugs at the same hours of the day despite having identical label instructions.

In the second set, we investigated 2 drugs (F and G) that could also be taken at the same daily intervals (3 times daily), yet 1 drug included the additional instruction to be taken "with food and water." Half of the participants (49.5%) did not take these medications at the same time of day. In the final set, medications that were to be taken 2 times a day (drugs A and B) were compared; drug A expressed frequency as "twice daily," while drug B stated that it was to be taken "every 12 hours." Four of 5 patients (79.0%) did not consolidate these variable expressions of dose frequency and took the 2 drugs at different times. Notably, drug A instructions also included an auxiliary comment that the medication should be taken for 10 days, and in both the second and third sets investigated, the dose (1 or 2 tablets) also varied.

Beyond examination of the drug set scenarios described herein, **Table 3** details how long the participants demonstrated that they would wait between doses for medications that were to be taken 2 (drugs A, B, and D) and 3 (drugs E, F, and G) times a day. Considerable variability was found among participants with regard to how many hours they would allot between doses for both 2- and 3-times-a-day regimens. For drugs to be taken twice daily, participants averaged 10.3 hours (SD, 3.0 hours) between doses, with as few as 1 and as many as 18 hourly intervals (interquartile range, 0-12 hourly intervals). For regimens of 3 times a day, the hourly intervals ranged from 1 to 13 hours, with the mean (SD) being 5.4 (1.8) hours between the first and second dose (interquartile range, 4-7 hours) and 6.5 (1.5) hours between the second and third doses (interquartile range, 6-8 hours).

COMMENT

Our findings demonstrate that most patients may self-administer multidrug regimens more times a day than necessary and that those with limited literacy are at greater risk. This increased complexity, at the very least, translates to taking medication too often each day, leading to substantial interference with patients' lives. As a result, doses may be frequently missed or incorrectly administered. Given the heightened concerns of medication safety and adherence, particularly among the elderly, who take more medicine and are increasingly cognitively challenged,[19] we offer evi-

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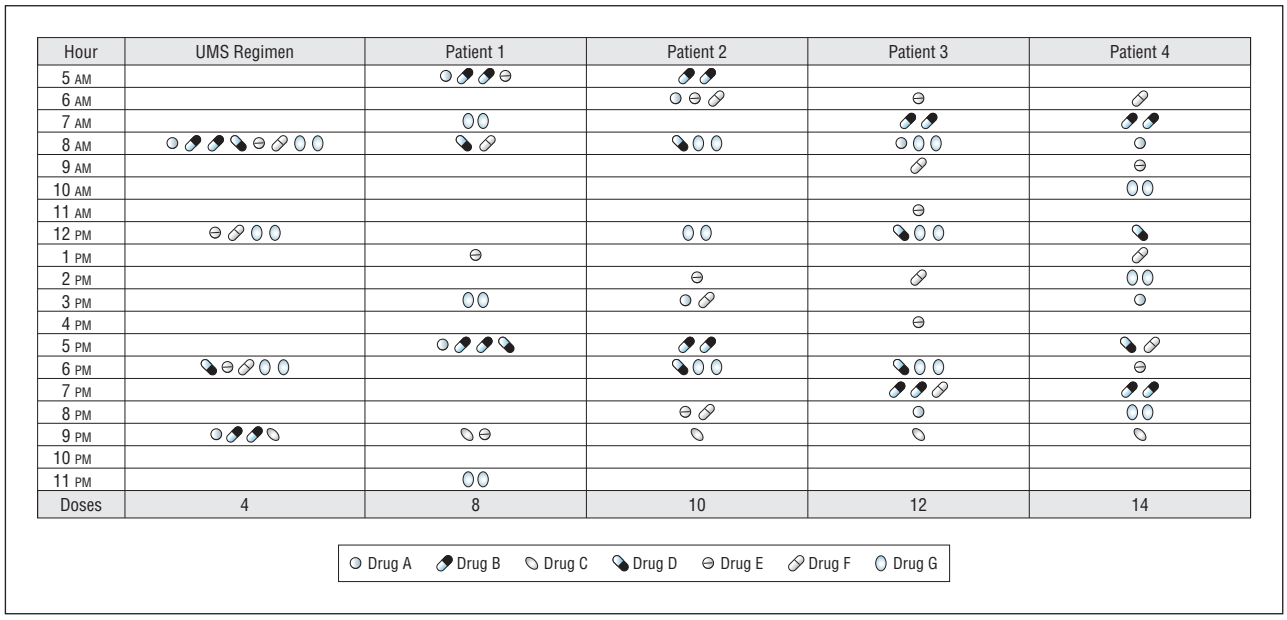

Figure. Case examples of older adults' dosing of a 7-drug regimen. UMS inidicates universal medication schedule.

dence that previously was unavailable. In particular, strategies are needed to help patients not only to understand how to take a particular medicine but also to consolidate and simplify how to take an entire drug regimen.

The inherent complexity of the task of organizing multiple medications into as few times per day may be an apparent reason that so many patients do not use more efficient consolidation strategies. This is evident in our finding that 1 in 3 older adults did not take 2 medications (drugs E and F) that had the exact same dosage instruction at the same time. Variability in how prescriptions are written, both in describing the timing of doses and the expression of auxiliary instructions, further distracts individuals from the goal of consolidating regimens. Yet many patients may not explicitly perceive finding the most efficient medication-taking strategy to be the objective. It is also possible that patients might not understand that they can take different medications at the same time, especially when the instructions are not identical.

Our study has certain limitations. First, we investigated older adults' dosing of a hypothetical medication regimen and not their actual medication. Therefore, the context and task of demonstrating use via the medication box might not directly reflect the way that participants would self-administer prescribed drugs in their daily life. Further research is needed to investigate in-depth patient dosing strategies and beliefs about their own regimens. Second, our study was limited to the outcome of demonstration of medication use for a multidrug regimen, and not adherence. While prior studies support the premise that taking medication more times daily could negatively affect long-term regimen adherence, our findings do not directly offer evidence for that association. Third, our analysis of root causes of overcomplicating regimens was post hoc and exploratory, and other aspects of the instruction for sets 2 and 3, such as different doses (1 vs 2 tablets), could have contributed to patient confusion. Fourth, our sample was representative of older adults of higher socioeconomic strata, as indicated by education attainment and household income. However, our findings should be viewed as the best case scenario, as more socioeconomically disadvantaged patients are more likely to have limited health literacy and face even greater difficulty in organizing and dosing complex medication regimens.[20,21] Finally, we provided participants only with the task of demonstrating how and when they would take a 7-drug regimen; a large proportion of chronically ill and elderly patients take far more medications daily. Therefore, our findings may provide a conservative estimate of the potential confusion older adults face when attempting to consolidate and manage all of their prescribed medications.

Table 3. Older Adults' Dosing of Medications to Be Taken 2 or 3 Times a Day

Medication to Be Taken 2 Times a Day	Medication to Be Taken 3 Times a Day	
Hours Between Doses (%)	Hours Between Doses 1 and 2 (%)	Hours Between Doses 2 and 3 (%)
≤8 (20.4)	≤4 (52.4)	≤4 (7.7)
9-11 (29.2)	5-6 (18.2)	5-6 (61.4)
12 (37.9)	7-8 (16.2)	7-8 (18.1)
13-18 (12.5)	9-13 (3.2)	9-13 (12.8)

The UMS was not directly evaluated, but our study highlights patient confusion surrounding medication use. Standardized instructions could be one of many remedies to aid patients and families. Of note, an efficacy trial of the UMS to improve patient comprehension was also conducted recently; findings show that patients are better able to dose medications safely with UMS vs current standard instructions.[22] With these findings and the Institute of Medicine report, legislation has already been approved and passed by the State Board of Pharmacy in California requiring pharmacies to use these UMS in-

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structions when applicable.[23] Further study of the possible benefits, as well as risks, of the UMS strategy is warranted, and evidence will soon be available from ongoing National Institutes of Health and Agency for Healthcare Research and Quality (AHRQ) studies that are currently testing the UMS in actual use (AHRQ grants R01 HS017687 and R01 HS019435).[24]

If standardizing prescription instructions does aid patients in consolidating and taking their medication regimens, the UMS could further unite medical and pharmacological practice. Beyond pharmacy labeling, physicians could write the instructions with the more explicit UMS times to help patients have an adequate understanding of when to take not only their newly prescribed medications but also their entire regimen at the point of prescribing. Opportunities now exist with medical practices increasingly adopting electronic health record systems to leverage these tools and to standardize prescribing practices following the UMS concept (National Institutes of Health grant R21 CA132771 and AHRQ grant R18 HS017220). By working across the medication prescribing and dispensing continuum, the previously noted variability within and between physician prescription writing and pharmacist transcribing can be reduced, and patient understanding and adherence to medication regimens can be improved.[14-16]

We offer compelling, preliminary evidence of the need to help all patients more clearly understand, organize, and simplify their medication regimens. While providing standard, explicit instructions is one possible response, other interventions will likely be necessary. For instance, drug labeling is meant to support, not replace, prescriber and pharmacist spoken communication with patients. Educational and health system strategies are needed to target provider communication skills and screening methods for identifying those at risk for complicating regimens and poor adherence. Similarly, prescribing 1-a-day regimens and bundling medications by times per day at the pharmacy might also be possible solutions. Ultimately, public health initiatives should help patients acquire a fundamental understanding of prescription medication use and when it would be safe and appropriate to take medications together.

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Correction

Error in Wording. In the Research Letter titled "Persistence of Cardiovascular Risk After Rofecoxib Discontinuation" by Ross et al, published in the December 13/27 issue of the *Archives* (2010;170[22]:2035-2036), an error occurred in the "Results" section on page 2035, where the last sentence should have read "Overall, an investigator-reported cardiovascular thromboembolic adverse event or death occurred during off-drug follow-up for 45 subjects, 32 in 287 patient-years among rofecoxib users and 13 in 234 patient-years among placebo users (RR, 2.01; 95% CI, 1.05-3.82; $P = .03$) (**Figure**)."

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