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Health Care Reform

Influence of Therapeutic Complexity on Medication Adherence in the Netherlands

In their study on the implications of therapeutic complexity on adherence to cardiovascular medications, Choudhry et al[1] describe predictors that are associated with poor adherence. They suggest that a number of these predictors could also be aimed at improving adherence, including reducing copayments, reducing the frequency with which prescriptions need to be filled, and creating a "pharmacy home" or a single pharmacy at which a patient refills his or her prescriptions.[1,2] In the Netherlands, virtually all of these recommendations are implemented. In the Dutch health care system, larger supplies with a maximum of 90 days may be prescribed; no copayment with long-term medication exists; virtually all patients use a single pharmacy; all prescription medication is captured by the database; and hardly any mail-order pharmacies are present.[3]

We investigated whether in the Dutch situation adherence would be better, and whether a similar association with therapeutic complexity as found by Choudhry et al[1] would be seen. From the PHARMO database we selected a sample of patients who initiated statin therapy between January 1 and December 31, 2004, and investigated whether therapeutic complexity predicted nonpersistence and poor drug-taking compliance after 12 months of follow-up.[4] A patient was considered nonpersistent if a continuous gap of 60 days or more was present, and a patient had poor compliance if the Continuous Measure of Medication Acquisition (CMA) was lower than 80%.[5] We used binary logistic regression to calculate the odds ratios for either nonpersistence or poor compliance. We investigated the following variables, calculated in the year previous to new statin use: (1) number of pharmacy visits, (2) number of medications filled, (3)

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number of long-term medication classes, (4) number of single medication dispensings (ie, single pharmacy pickups like an antibiotic course), (5) refill consolidation, (6) number of dose changes within each drug class, (7) number of prescribing physicians, and (8) number of switches within each drug class (eg, enalapril to ramipril). We included 6614 new statin users and identified 4189 statin users (63%) with a 60-day continuous gap during follow-up. Of the remaining 2425 continuous statin users, 111 (5%) had a CMA lower than 80%. The odds ratios and mean values for each investigated variable are presented in the **Table** for both persistence and compliance.

We observed a statistical significant correlation between therapeutic complexity and nonpersistence for the number of visits, number of fills, number of single dispensings, number of prescribing physicians, and total number of switches within each drug class. However, odds ratios approached 1, indicating a low predictive value. For compliance, only the number of single dispensings

Table. The Association Between Therapeutic Complexity and Adherence to Statin Therapy

Variable[a]	Persistent vs Nonpersistent, OR (95% CI)	Mean (SD)		Good vs Poor Drug-Taking Compliance, OR (95% CI)	Mean (SD)	
		Persistent (n = 2425)	Nonpersistent (n = 4189)		Good Drug-Taking Compliance (n = 2314)	Poor Drug-Taking Compliance (n = 111)
No. of visits	1.010 (1.004-1.015)	14 (10)	15 (9)	1.004 (0.985-1.023)	14 (9)	14 (14)
No. of fills	1.003 (1.001-1.005)	25 (24)	27 (22)	1.001 (0.994-1.009)	25 (22)	26 (46)
No. of long-term medication classes	1.020 (1.000-1.041)	4 (3)	4 (3)	0.972 (0.895-1.055)	4 (3)	4 (3)
No. of single dispensings	1.035 (1.011-1.060)	3 (2)	3 (2)	1.088 (1.005-1.178)	3 (2)	4 (3)
Refill, consolidation	1.228 (0.985-1.537)	0.36 (0.20)	0.37 (0.20)	0.631 (0.250-1.595)	0.36 (0.21)	0.34 (0.19)
No. of dose changes within drug class	1.015 (0.999-1.032)	2 (3)	2 (3)	1.032 (0.998-1.067)	2 (3)	2 (9)
No. of prescribing physicians	1.092 (1.040-1.146)	2 (1)	2 (1)	1.019 (0.848-1.224)	2 (1)	2 (1)
Total No. of switches within each drug class	1.020 (1.011-1.030)	8 (6)	9 (6)	1.022 (0.999-1.046)	8 (6)	9 (12)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Calculated 12 months before statin initiation.

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reached statistical significance, again with a very poor predictive value.

We were able to also link therapeutic complexity to both nonpersistence and poor compliance in the Dutch health care system, but odds ratios were too low to be clinically meaningful. We agree with Choudhry and coworkers[1] that therapeutic complexity should be reduced, but we believe differences in health care systems have a much larger impact on both (non)persistence and (poor) compliance because we could not identify any clinical meaningful relation between therapeutic complexity and adherence. Predicting medication adherence remains an important challenge.[6]

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In reply

Geers et al applied our measures of therapeutic complexity to statin adherence in the Dutch health care system and found less strong correlations between complexity and adherence than we recently reported.[1] Their analysis highlights the importance of context in evaluating research results. Like all studies, our findings are primarily generalizable to settings similar to that of the population evaluated. The US health care system is unique in the extent to which coverage and care are fragmented: patients may receive coverage from private or public sources; drug coverage is often "carved out" and administered separately from medical benefits; patients can receive care from numerous different physicians or other health care providers; and prescriptions may be written by multiple prescribers and filled at many pharmacies on numerous visits. We evaluated this last set of factors and found them to be strongly associated with nonadherence. In contrast, Geers and colleagues' analysis based on a health care system with very little complexity for patients to receive and fill prescriptions found the influence of these factors to be smaller. Rather than contradictory, the results of Geers et al amplify the importance of complexity and the potential role of a "pharmacy home" in the US health care system.

Methodological differences may have also contributed to the apparent discrepancy between analyses. We restricted our measures of complexity because of their overlapping nature (eg, number of fills and long-term medication classes) or collinearity with adherence (eg, patients with more fills are by definition more adherent). Geers et al entered many variables into 1 model; this may have spread the predictive ability among multiple measures of the same construct. We evaluated a linear outcome in contrast to the binary measures used by Geers et al. While these models produce different outputs, the nonsignificant 23% increase in the odds of nonpersistence from poor refill consolidation in the much smaller study by Geers et al generates inferences very similar to those from ours. We assessed complexity during the 90-day period after the first statin fill, whereas Geers et al evaluated complexity during the year prior to the first fill. The burden of medication access and filling may be particularly high after, rather than before, starting therapy, and thus the evaluation by Geers et al may have measured exposure variables that would be expected to have less relationship to adherence.

Notwithstanding these differences, the research letter by Geers et al highlights the difficulties evaluating nonadherence in all health care systems and the need to identify modifiable factors unique to each setting.

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