Suboptimal Medication Use and Mortality in an Older Adult Community-Based Cohort: Results From the Hispanic EPESE Study

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Background. Numerous methods have been used to evaluate medication management quality in older adults; however, their predictive validities are unknown. Major medication quality indicators include polypharmacy, drug–drug interactions, and inappropriate medication use. To date, no study has attempted to evaluate the three approaches systematically or the effect of each approach on mortality in a Hispanic population. Our objective was to evaluate the relationship between polypharmacy, drug–drug interactions, and inappropriate medication use on the mortality of a community-based population of Mexican American older adults.

Methods. We used a life table survival analysis of a longitudinal survey of a representative sample of 3050 older Mexican Americans of whom 1823 were taking prescription and over-the-counter medications.

Results. After adjustment for relevant covariates, use of more than four different medications (polypharmacy) was independently associated with mortality. The presence of major drug interactions and the use of inappropriate medications were not significantly associated with mortality in our study sample.

Conclusion. Polypharmacy (>4 medications) is significantly associated with mortality in Mexican American older adults. This community-based study is the first to demonstrate a direct association between polypharmacy and mortality in this population.
a community-based older adult population. This article describes the impact of polypharmacy, drug–drug interactions, and inappropriate medication use on the mortality of a selected population of community-based Mexican American older adults living in the southwestern United States.

**METHODS**

**Participants**

The Hispanic Established Populations for Epidemiologic Studies of the Elderly (EPESE) is an ongoing longitudinal study of Mexican American older adults between the ages of 65 and 99. The study design and sampling have been described previously (14). In brief, the sample was drawn using area probability sampling procedures to represent the Mexican American older adult population residing in Texas, New Mexico, Colorado, Arizona, and California. In 1993, the study team completed in-home contacts with the participants that included medication information. There were 3050 participants interviewed and evaluated in their own homes by trained interviewers. Follow-up in-home evaluations were done approximately 2 years apart with the most recent contact being approximately 8 years after the original contact. Of the 3050 baseline interviewees, 1823 reported using medication and 1227 did not. Eight-year mortality data were used in the present study. There were 940 deaths (30.8%) since baseline. For deceased persons, a brief proxy interview was obtained that included information on the time and place of death, causes of death, and any hospitalizations or nursing home admissions. Validation of death was confirmed by a National Death Index search. Research protocol was approved by the UTHSCSA and UTMB institutional review boards, and all participants gave informed oral consent.

**Medication Definitions**

We define suboptimal medication use as any of the following:

**Polypharmacy.**—Polypharmacy is defined as the use of more than four medications. This number was chosen for clarity of presentation and to be consistent with prior definitions of polypharmacy (15–18). The total number of prescription and over-the-counter medications taken by each participant were counted, and participants were categorized into groups taking 1, 2, 3, 4, or >4 medications. Combination products were counted as more than one medication by the total number of active ingredients.

**Drug–drug interactions.**—Potential adverse drug–drug interactions were determined for each participant by use of the Micromedex Intranet Knowledge Base System (19). This system was selected because it is comprehensive, widely available, and interactive. The Micromedex system, part of the mobile Physicians Desk Reference, is designed to assist the clinician in interpreting interaction data. The Micromedex system used an expert panel to identify drug interactions and classify them into three groups. Each participant’s medications were entered from the Hispanic EPESE database into the Micromedex system: Drug interactions were then categorized into major, moderate, or minor

**Other Variables**

**Age-adjusted mortality.**—Mortality was evaluated at follow-up visits every 2 years for a total of 8 years, and was validated by using the National Death Index. Mortality rates for those participants who met criteria for suboptimal medication use, compared to those who did not, were age-adjusted using the direct method of adjustment. The 1990 U.S. Census data, as the Census time closest to the EPESE medication data collection, was used as the standard population for age distribution of Mexican Americans age 65 years or older.

**Sociodemographic variables.**—Sociodemographic variables collected included age, gender, date of birth, current household income, current employment status, and acculturation. Acculturation was measured using Hazuda’s algorithm (20).

**Illness severity.**—Instrumental Activities of Daily Living (IADL) and self-reported health status were used to estimate illness severity. IADLs were assessed using the modified Older American Resource Scale (OARS) (21). For self-reported health status, participants were asked to rate their current health status as excellent, good, fair, or poor.

**Disease states.**—We assessed the presence of chronic illnesses with a self-reported condition checklist used previously in the EPESE studies. The major disease states listed were those defined by the National Center for Health Statistics as the leading causes of death in the United States (22). In order, these are: cardiovascular disease, neoplasms, cerebrovascular disease, chronic obstructive pulmonary disease, and diabetes mellitus. Hypertension was also included due to its major impact on morbidity and medication use in the Mexican American population. We examined each disease separately, as individual diseases have differential impact on medication use and on mortality.
Chronic obstructive pulmonary disease was not included in the EPESE baseline evaluation and was therefore excluded from the analyses.

Statistical Analysis
Life table survival estimates were obtained using SAS software (23). The survival function $S(t)$ was calculated as $S(t) = 1 - f(t)$, where $f(t)$ indicates the death rate as a function of time. Homogeneity of the estimated survival curves between the various medication usage groups were tested using the Wilcoxon signed rank and log-rank test statistics (24). These statistics test the null hypothesis that the rates of decline in each group are not statistically different. Survival distribution plots were drawn for visual inspection. In addition, Cox proportional hazards regression models (25) were used to control for gender, age, educational level, illness severity, and six chronic comorbid disease states.

RESULTS

Sample Characteristics
The demographic characteristics (Table 1) show that 40.2% ($n = 1227$) of participants used no medications. Those participants who used medications were more likely to be female, have poor self-reported health, have ADL limitations, and suffer differentially from the five chronic diseases examined.

Unadjusted Survival Models
The unadjusted proportional hazards models for drug–drug interactions, polypharmacy, and inappropriate medication use are shown in Table 2. Participants who had the potential of major drug–drug interactions relative to those with no interactions had significantly poorer survival (43% increased mortality risk). Also, those participants with a moderate drug interaction potential had a marginally significant poorer survival. Participants who used more than four medications relative to those using one medication showed a 54% decreased survival rate. Inappropriate medication use was not significantly associated with increased mortality risk.

Drug–Drug Interactions
Figure 1A depicts survival by medication interaction group. Significant differences in mortality were found over time in those participants who had the potential for a major drug–drug interaction only ($p < .05$). Table 3 shows the results of the adjusted and unadjusted proportional hazards model where a dichotomous drug interaction variable (major or moderate = 1; other = 0) was used to predict mortality. Relative to those with no drug interactions, those participants with a major or moderate drug interaction demonstrated a 27% increase in mortality risk (Model 1 in top part of Table 3). After adjusting for age and gender (Model 2), the increased risk remained significant. However, after adjustment for comorbid disease (Model 3) and functional status (Model 4), the increased risk for participants with a major or moderate drug interaction was no longer significant. This finding indicates that the association between drug interaction and mortality is explained by the significant comorbid factors.

Polypharmacy
Figure 1B depicts survival in the cohort by five polypharmacy groups (use of 1, 2, 3, 4, or >4 medications). Those participants taking more than four medications had significantly higher mortality rates ($p < .0002$).

Table 1. Sample Characteristics Predictive of Medication Use in the Hispanic EPESE Study ($N = 3050$)

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Medication Use $N = 1823$</th>
<th>No Medication Use $N = 1227$</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>72.98 (6.46)</td>
<td>73.03 (7.17)</td>
<td>.840</td>
</tr>
<tr>
<td>Mean educational level (completed)</td>
<td>4.97 (3.96)</td>
<td>4.66 (3.80)</td>
<td>.030</td>
</tr>
<tr>
<td>% Female</td>
<td>64.51</td>
<td>47.43</td>
<td>.001</td>
</tr>
<tr>
<td>% Poor/fair health</td>
<td>72.03</td>
<td>39.13</td>
<td>.001</td>
</tr>
<tr>
<td>Annual income</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;$10,000</td>
<td>56.62</td>
<td>58.60</td>
<td></td>
</tr>
<tr>
<td>$10,000 &lt;$20,000</td>
<td>35.38</td>
<td>34.03</td>
<td></td>
</tr>
<tr>
<td>$20,000</td>
<td>8.00</td>
<td>7.37</td>
<td>.570</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>12.46</td>
<td>4.72</td>
<td>.001</td>
</tr>
<tr>
<td>% Neoplasms</td>
<td>6.28</td>
<td>3.92</td>
<td>.005</td>
</tr>
<tr>
<td>% Stroke</td>
<td>7.13</td>
<td>5.00</td>
<td>.017</td>
</tr>
<tr>
<td>% Diabetes</td>
<td>32.90</td>
<td>10.06</td>
<td>.001</td>
</tr>
<tr>
<td>% Hypertension</td>
<td>56.79</td>
<td>19.80</td>
<td>.001</td>
</tr>
<tr>
<td>% ADL limitation</td>
<td>14.49</td>
<td>12.63</td>
<td>.001</td>
</tr>
<tr>
<td>% IADL limitation</td>
<td>41.49</td>
<td>54.54</td>
<td>.001</td>
</tr>
</tbody>
</table>

Note: EPESE = Established Populations for Epidemiologic Study of the Elderly; SD = standard deviation; ADL = Activities of Daily Living; IADL = Instrumental Activities of Daily Living.

Table 2. Coefficients of the Proportional Hazards Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate (SE)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No meds ($n = 1227$)</td>
<td>$-0.01$ (.08)</td>
<td>0.99 (0.86–1.15)</td>
</tr>
<tr>
<td>No interaction ($n = 1136$)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Minor interaction ($n = 147$)</td>
<td>$-0.06$ (.17)</td>
<td>0.94 (0.68–1.31)</td>
</tr>
<tr>
<td>Moderate interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>($n = 412$)</td>
<td>.19 (.10)*</td>
<td>1.21 (0.99–1.47)</td>
</tr>
<tr>
<td>Major interaction ($n = 128$)</td>
<td>.36 (.15)**</td>
<td>1.43 (1.07–1.92)</td>
</tr>
<tr>
<td>Polypharmacy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No meds ($n = 1227$)</td>
<td>.03 (.10)</td>
<td>1.03 (0.85–1.25)</td>
</tr>
<tr>
<td>1 med ($n = 475$)</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>2 meds ($n = 398$)</td>
<td>$-0.08$ (.13)</td>
<td>0.92 (0.72–1.19)</td>
</tr>
<tr>
<td>3 meds ($n = 306$)</td>
<td>.04 (.14)</td>
<td>1.04 (0.80–1.36)</td>
</tr>
<tr>
<td>4 meds ($n = 260$)</td>
<td>.10 (.14)</td>
<td>1.11 (0.84–1.46)</td>
</tr>
<tr>
<td>$&gt;4$ meds ($n = 384$)</td>
<td>.43 (.12)*</td>
<td>1.54 (1.22–1.94)</td>
</tr>
<tr>
<td>Inappropriate medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No meds ($n = 1227$)</td>
<td>$-0.06$ (.07)</td>
<td>0.94 (0.82–1.08)</td>
</tr>
<tr>
<td>Inappropriate med use ($n = 414$)</td>
<td>.06 (.10)</td>
<td>1.05 (0.87–1.28)</td>
</tr>
<tr>
<td>No inappropriate med use ($n = 1410$)</td>
<td>Reference</td>
<td></td>
</tr>
</tbody>
</table>

Note: *$p < .10$; **$p < .05$; *$p < .01$; **$p < .001$. SE = standard error; CI = confidence interval.
Figure 1. Adjusted Kaplan–Meyer survival curves exploring the association between (A) potential drug–drug interactions, (B) polypharmacy, and risk of all-cause mortality during the follow-up period.
A regimen will cause a potentially adverse reaction in that addition of any single medication to a frail older adult’s regimen will cause a potentially adverse reaction in that individual patient. Our results are of particular importance given the mounting pressure for “recommended” polypharmacy—that is, current disease-specific treatment guidelines that are uniformly being recommended as indications of “quality” care. The preponderance of evidence supporting guidelines was primarily developed in younger participant populations without multiple comorbidities. Whether the risk of “recommended polypharmacy” outweighs the benefit is not known. This study helps to provide some understanding about the potential risk of polypharmacy. Finally, the polypharmacy rate in Mexican Americans may be lower than that expected for non-Hispanic whites because Mexican Americans use fewer over-the-counter medications (7).

The interaction between time and the aforementioned suboptimal medication use was not statistically significant ($p = .40$), demonstrating that the assumptions of proportional hazards were not violated.

### Discussion
To our knowledge, this is the first study to examine the relationship of polypharmacy, drug–drug interactions, and inappropriate medication use with mortality in a community-based cohort of Hispanic older adults in the United States. Polypharmacy was a predictor of mortality, independent of age, socioeconomic status, or chronic disease status and/or severity. It has been thought that polypharmacy is potentially harmful because, in large part, it increases the probability of adverse drug–drug interactions (26,27). Our results do not appear to support this conclusion because polypharmacy alone (not potential adverse drug–drug interactions) was associated with mortality. It has been reported that adverse drug events seem to be most commonly due to failure in proper dosing (28). Rather than a direct toxicity due to adverse drug–drug interactions, polypharmacy might have a direct effect through the cumulative effects of multiple medications on the renal or hepatic systems of older adults, and cause the initiation of a “cascade of interactions” in these older adults, who already suffer from multiple comorbidities (29). Alternatively, polypharmacy increases the odds that the addition of any single medication to a frail older adult’s regimen will cause a potentially adverse reaction in that individual patient. It has been thought that polypharmacy is potentially harmful because it increases the probability of adverse drug–drug interactions (26,27). Our results do not appear to support this conclusion because polypharmacy alone (not potential adverse drug–drug interactions) was associated with mortality. It has been reported that adverse drug events seem to be most commonly due to failure in proper dosing (28). Rather than a direct toxicity due to adverse drug–drug interactions, polypharmacy might have a direct effect through the cumulative effects of multiple medications on the renal or hepatic systems of older adults, and cause the initiation of a “cascade of interactions” in these older adults, who already suffer from multiple comorbidities (29). Alternatively, polypharmacy increases the odds that the addition of any single medication to a frail older adult’s regimen will cause a potentially adverse reaction in that individual patient. Our results are of particular importance given the mounting pressure for “recommended” polypharmacy—that is, current disease-specific treatment guidelines that are uniformly being recommended as indications of “quality” care. The preponderance of evidence supporting guidelines was primarily developed in younger participant populations without multiple comorbidities. Whether the risk of “recommended polypharmacy” outweighs the benefit is not known. This study helps to provide some understanding about the potential risk of polypharmacy. Finally, the polypharmacy rate in Mexican Americans may be lower than that expected for non-Hispanic whites because Mexican Americans use fewer over-the-counter medications (7).

Potential “inappropriate” medication use did not appear to have a mortality effect. Beer’s criteria clearly state that many of the medications that fit the criteria for inappropriateness may, in fact, be indicated in certain situations. Higashi and colleagues (30) found that, among an ambulatory older adult population, pharmacologic management problems other than inappropriate medication prescribing were more common and potentially more important. Our results would seem to support the argument that medication monitoring, documentation, and continuity may be more important parameters to monitor in older populations than reduction of inappropriate medication use alone would be. More research is clearly needed to more fully delineate these issues.

Interestingly, potential major or moderate drug–drug interactions did not independently predict mortality in our participant population. Perhaps significant drug–drug interactions increase morbidity and subsequent detection leading to discontinuation of the offending medications before the drug combinations become lethal. An alternative explanation may be that the potential for a drug–drug interaction does...
not equal an actual interaction, and actual events may not occur frequently enough to establish a relationship between potential drug–drug interaction and mortality. Further study is needed to better understand the role of adverse drug–drug interactions in morbidity and mortality of older adults.

It is also possible that increasing comorbidity and/or disease severity leads to polypharmacy and adverse drug interactions and that the primary mortality risk might be the severity of illness and not polypharmacy or increased medication use. However, polypharmacy remained a significant independent predictor of mortality even when ADL dependency and poor self-reported health, standard proxies for illness severity, were added to our model. A limitation of this study is the self-reported nature of the interviews. We did not determine medication compliance. Furthermore, it is possible that Mexican American elders might be differentially predisposed to polypharmacy-related mortality when compared to the general population, but this predisposition would have to be an effect exclusive of demographic factors. We have previously found that Mexican American older adults taking inappropriate medications tended to fit the criteria for high vulnerability: unmarried, high physician utilization, depressed, and Medicare/Medicaid recipients (31). Another limitation was that underutilization was not examined, which may in itself be an independent predictor of mortality. Finally, although the Micromedex system is a widely used drug–drug interaction clinical tool, to our knowledge, it has not been tested for the validity or reliability of the drug–drug interaction information provided.

Despite these limitations, polypharmacy was the key suboptimal medication independent predictor for mortality in the cohort of Mexican American older adults studied. Our results indicate that increasing the number of medications alone may pose a long-term mortality risk, at least in the older Mexican American population. Further research is needed to confirm our findings.

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