Medication burden attributable to chronic co-morbid conditions in the very old and vulnerable

Kelly L. Moore¹, Kanan Patel¹,², W. John Boscardin,²,³, Michael A. Steinman,²,⁴, & Christine Ritchie,¹,², & Janice B. Schwartz¹,²,⁵, *

¹Center for Research on Aging of the Jewish Home, San Francisco, CA
²Department of Medicine, University of California, San Francisco
³Department of Epidemiology and Biostatistics, University of California San Francisco
⁴San Francisco Veterans Affairs Medical Center, San Francisco, California
⁵Department of Bioengineering and Therapeutic Sciences, University of California San Francisco

*Corresponding Author:

Janice B. Schwartz, MD, Email: Janice.schwartz@ucsf.edu.

¶ These authors contributed equally to this work.

& These authors also contributed equally to this work.
ABSTRACT

OBJECTIVES:
Polypharmacy is common in older patients but relationships between polypharmacy and common co-morbid conditions have not been elucidated. Our goal was to determine relationships between daily oral medication use and common co-morbid disease dyads and triads using comprehensive medication and diagnostic data from a national sample of nursing homes (NH).

DESIGN: Retrospective, cross-sectional study

SETTING: Nationally representative sample of U.S. Nursing Homes

PARTICIPANTS: Nationally representative sample of long-term stay residents (n= 11734, 75% women) aged 65 years or older.

MEASUREMENTS: Diagnosis and medication data were analyzed. Proportion of daily oral medication intake attributed to treatment of common two-(dyads) and three-disease (triad) combinations and “health maintenance” agents (vitamins, dietary supplements, stool softeners without related diagnoses) was determined.

RESULTS: Older NH residents received slightly >8 oral medications/day with the number related to number of medical diagnoses (p<.0001). One third of chronic oral medication intake/day (excluding health maintenance agents) could be attributed to dyad combinations and about half to triad combinations despite an average of 5 other diagnoses. Triads were comprised of hypertension +/- arthritis +/- vascular disease, +/-depression, +/- osteoporosis +/- gastroesophageal reflux disease and +/- diabetes. Health maintenance agents accounted for 15-17% of daily oral medication intake (1.4 medications) such that almost two-thirds of daily oral medications were attributable to disease triads plus health maintenance. Fewer medications were prescribed for NH residents over age 85 (decreased ACE inhibitor and HMG CoA reductase inhibitor USE (p<.001)) while use of Alzheimer medications was higher (p<.01).

CONCLUSIONS: A large fraction of daily oral medications were attributed to management of common co-morbid disease dyads and triads. Efforts to reduce polypharmacy and unwanted medication interactions could focus on regimens for common co-morbid dyads and triads in varying populations.
INTRODUCTION
Aging is often accompanied by increasing numbers of health-related diagnoses (multi-morbidity) and use of multiple medications (polypharmacy). (1, 2) Surveys estimate that slightly over sixty percent of people over 65 years of age are prescribed three or more medications on a daily basis, and about 39 percent have more than five prescribed. (3-5) The number is even higher in nursing home residents, averaging 6-8 medications per day. (6-14) While the risk of adverse drug events and interactions is directly related to the number of medications consumed (8, 15-23), recommendations to use fewer drugs are often difficult to implement in the face of clinical practice guidelines for multiple medications for each medical condition.
Currently, there are no universally accepted approaches to optimizing medication strategies in patients with multiple co-morbid conditions. Our goal was to investigate use of daily oral medications and daily health maintenance agents in older nursing home residents and determine the relationship between agents administered and the most common co-morbid diseases and comorbid disease combinations. If medication burden could be largely attributed to treatment of a relatively small number of common co-morbid conditions in these complex patients, efforts to improve therapeutic regimens could focus on selection of medications that treat more than one of the underlying conditions to decrease the number of medications and the selection of combinations of medications without predictable adverse interactions.

MATERIALS and METHODS
The National Nursing Home Survey (NNHS) methodology has been published elsewhere. (12) In brief, it was a weighted sample from 1,174 facilities and 13,507 residents representing the 1.49 million residents in U.S. nursing homes between August 2004 and January 2005. (24) Our analyses were limited to long-term stay residents older than 65 years. Medication data were from on-site review of medication records -- up to 25 medications taken the day before data collection, and up to 15 medications taken regularly but not the day before data collection. (9) Data collection differentiated between as needed medications and those that were prescribed to be taken “regularly” as defined by not having an end-date for administration or on an as needed designation and we considered these as the chronic medications and limited our analyses to those administered orally. Dosage and frequency data and duration of regular or chronic therapy were not provided. Medications were matched to the “Drug Estimates and Characteristics”(25) to obtain drug names and also organized by 2005 National Drug Code (NDC). Administration route was determined by drug labeling information. Data were reduced and coded to reflect active pharmacologic agents/medications in each formulation using standard references (Lexicomp®, Physicians Desk Reference®). Multivitamins, vitamins, nutraceuticals, stool softeners, and bowel stimulants given by mouth daily were considered “daily health maintenance regimen” agents in the absence of a related diagnosis (see below). Non-oral agents, those given for a short course (antibiotics, chemotherapeutic agents) or “as needed” were excluded from analyses.

Diagnoses Data
A maximum of 16 current diagnoses based on ICD-9-CM (International Classification of Disease, 9th Revision, and Clinical Modification) were collected for each resident, with over 99% of residents sampled having fewer than 16. For the primary diagnosis, error estimates were calculated and S.E. ranged from 0.1-0.6.(26) The most frequent chronic medical conditions were identified with Clinical Classifications Software (CCS) for ICD-9-CM developed as part of the Healthcare Cost and Utilization Project (http://www.hcup-us.ahrq.gov/toolsoftware/ccs/ccsfactsheet.jsp). Single level CCS rankings (http://www.hcup-us.ahrq.gov/toolsoftware/ccs/ccs.jsp) were used for
initial aggregations of chronic medical conditions identified in over 5% of residents, with additional grouping into single medical conditions based on probable common physiologic basis as previously described. (13) Example: for “Hypertension”, any ICD-9 code that contained “Hypertension complications” resulted in the resident classified as having hypertension. Gastroesophageal reflux disease heartburn and peptic ulcer disease were combined into a single chronic condition related to acid/peptic acid disease (GERD); and, diabetes with and without complications were combined into a single “diabetes” chronic medical condition. For combined ICD-9 diagnoses of delirium and dementia, delirium diagnoses were excluded to leave only dementia diagnoses. The complete list of ICD-9 codes appearing in the NNHS dataset and corresponding grouped chronic medical conditions are available upon request from the authors (13). The resulting twenty-one most common chronic medical conditions of atrial fibrillation, anemia, arthritis, atherosclerosis, congestive heart failure, constipation, chronic obstructive pulmonary disease, cerebrovascular disease, dementia, depression, diabetes, GERD /heartburn /ulcer disease, hypertension, lipid disorder, osteoporosis, Parkinson’s disease, peripheral vascular disease, renal failure, thyroid disorders, benign prostatic hyperplasia, and an “all vascular disease” composite diagnosis (including all codes for atherosclerosis, coronary artery disease, cerebrovascular disease, and peripheral vascular disease with these codes not considered individually) were examined in relation to medication usage.

**Medication Data**

The NNHS dataset does not include medication indications as collected data failed to meet data quality standards for delineating reason for medication use (12). We took the following approach to assigning potential indications for administration. For formulations with multiple active therapeutic agents (combination products), each active ingredient was considered an individual entity. For individual pharmacologic entities, clinical indications for use were identified by review of 2004 FDA-approved prescribing information and practice guidelines for the 21 chronic medical conditions of interest published up to and including 2005. Multiple indications for an individual agent could exist. For example, indications for metoprolol included hypertension, atherosclerosis or coronary artery disease (including post myocardial infarction), atrial fibrillation, and the composite vascular disease category. Use of vitamins, nutritional supplements, or bowel agents (including laxatives) termed “daily health maintenance agents” were considered therapeutic agents if a diagnosis/clinical indication for use was present. For example, calcium or vitamin D with a diagnosis of osteoporosis or bone fracture, iron or vitamin B12 if a diagnosis of anemia was present, and stool softeners or bowel motility agents with a constipation diagnosis were considered as therapeutic agents. Assignments were reviewed and refined with an expert panel of consultants using a modified Delphi consensus process. Then, each unique medication identified was classified as a) indicated for at least one of the 21 chronic medical conditions, b) indicated for a diagnosis other than the 21 chronic medical conditions considered, or c) a daily health regimen agent. Number of daily oral medications were computed as 1) A+B, and 2) A+B+C. Estimates of numbers of daily medications for management of co-morbid conditions are presented as the sum of medications potentially indicated for each condition. Estimates of the proportion of daily oral “medication” intake due to daily health regimens were the sum of the number of agents that could not be identified as potentially indicated for a medical condition (as described above). To estimate total daily oral medication intake, health regimen agents were combined with the medications for each disease combination and counted in the total.

**Statistical Analysis**
Due to the complex probability survey design of the data, SAS survey procedures in SAS version 9.2 (SURVEYMEANS, SURVEYFREQ, SURVEYLOGISTIC) for analyzing survey data were used to account for design effects of stratification and clustering to generate nationally representative estimates. Percentages represent weight- and cluster-adjusted results. Comparisons of characteristics were made between women and men using t-tests for continuous variables using Taylor series method to estimate sampling errors and Rao-Scott Chi-square tests for categorical variables. Standard errors of the prevalence estimates displayed were estimated with the Taylor series linearization method. Corrections for multiple comparisons were made by the Bonferroni method. Linear regression for survey data was used to estimate the relationship between the number of medications and number of diagnoses; and the relationship between age and number of medications administered. Logistic regression was used to estimate odds ratios for age effects as a continuous variable for each sex.

The work was approved for performance as protocol number 12-08640 by the UCSF Committee on Human Research (UCSF Institutional Review Board).

RESULTS
Data were collected for 11,788 long-term care residents aged ≥ 65 years. Residents without ICD9 data were excluded (n=54), yielding data on 11,734 residents: 2989 men and 8745 women, representative of 325,919 men and 960,282 women. Table 1 provides demographic and clinical characteristics. The mean age was 84 years with 52% over age 85 years with women on average older than men. (Table 1).
Table 1. Characteristics of Long-Stay Nursing Home Residents Aged 65 and Older

| Characteristic      | All Participants | Women (n= 8745, nw=960,282) | Men (n=2989, nw=325,919) | Sex Effect |
|---------------------|------------------|-----------------------------|--------------------------|------------|
| Age (y)             |                  |                             |                          | p<.001     |
| 65–69               | 84±0.11          | 85±0.11                     | 81±0.19                  |            |
| 70–74               | 5.1%             | 37594 (3.9%)                | 43276                    |            |
| 75–79               | 8.0%             | 59062 (6.2%)                | 65356                    |            |
| 80–84               | 14.3%            | (12.3%)                     | 201316                   | 39898(12.2%)|
| 85–89               | 21.3%            | (21.1%)                     | 242786                   | 66036      |
| ≥95                 | 8.6%             | (10.3%)                     | 99245                    | 11435 (3.5%)|

Number of Diagnoses p=0.6
| Age     | 65-74 | 75-84 | 85+   |
|---------|-------|-------|-------|
| 6.3±0.12| 6.3±0.14| 6.3±0.16|       |
| 6.5±0.09| 6.4±0.09| 6.5±0.14|       |
| 6.4±0.08| 6.4±0.08| 6.5±0.14|       |

Number of daily oral medications (including health maintenance agents)* p<0.001
| Age     | 65-74 | 75-84 | 85+   |
|---------|-------|-------|-------|
| 8.6±0.13| 9.0±0.18| 8.1±0.17|       |
| 8.3±0.09| 8.5±0.10| 7.9±0.13|       |
| 7.7±0.07| 7.8±0.07| 7.3±0.14|       |

Number of daily oral medications (excluding health maintenance agents) p<.001
health maintenance agents defined as vitamins, nutritional supplements, or bowel agents without a diagnosis as clinical indication for use.

Women received slightly more medications than men and mean number of daily oral medications decreased as resident age increased (Table 1, Figure 1) although the number of diagnoses did not differ between women and men or across the agespan of nursing home residents. Figure 1. The distribution of the number of chronic daily oral medications for older long-stay nursing homes residents including (solid bars) and excluding (striped bars) daily health maintenance agents (MA) is shown in the larger panel on the left and the mean number of chronic oral daily medications (excluding health maintenance agents) for men (blue) and women (pink) by age group is shown in the smaller inset panel on the right.

Table 2 lists individual medications taken daily in >5% of men or women and effects of age or sex. In men and women, the three most commonly administered medications were aspirin, acetaminophen and furosemide. Age*sex interactions were only detected for atorvastatin (p<.01), carbidopa (p=.007), and L-dopa(p=.004).
| Medication      | ATC Code#  | ATC System/major category       | Women (% receiving) | Men (% receiving) | Sex Effect (p) | Age Effect (p) | Odds ratio^ Age Women | Odds ratio^ Age Men |
|-----------------|------------|---------------------------------|---------------------|-------------------|----------------|-----------------|------------------------|---------------------|
| ACETAMINOPHEN   | N02BE01    | Nervous/analgesic               | 33.8                | 26.4              | 0.001          | 0.006          | ns                     | ns                  |
| ASPIRIN         | B01AC06    | Blood/antithrombotic            | 32.7                | 36.3              | 0.01           | 0.87           | ns                     | ns                  |
| FUROSEMIDE      | C03CA01    | Cardiovascular/diuretic         | 29.9                | 28.0              | ns             | <.001          | 1.06*                  | 1.09*               |
| POTASSIUM       | A12BA      | Alimentary/mineral supplements  | 24.2                | 18.7              | <0.001         | 0.03           | ns                     | ns                  |
| L-THYROXINE     | H03AA01    | Hormonal/thyroid                | 23.7                | 11.5              | <0.001         | <.001          | ns                     | 1.13*               |
| LISISNORPRIL    | C09AA03    | Cardiovascular/renin-angiotensin system | 14.2              | 14.1              | ns             | <.001          | 0.94*                  | 0.88**              |
| METOPROLOL      | C07AB02    | Cardiovascular/beta blocking    | 14.2                | 17.7              | <0.001         | <.001          | ns                     | 0.90*               |
| DONEPEZIL       | N06DA02    | Nervous-dementia                | 13.2                | 13.9              | ns             | 0.71           | ns                     | ns                  |
| CITALOPRAM      | N06AB04    | Nervous/antidepressant          | 13.1                | 12.7              | ns             | <.001          | 0.91**                 | ns                  |
| Medicine   | ATC Code   | Medical Category                          | Baseline | After | p-value  | p-value  | p-value  |
|------------|------------|-------------------------------------------|----------|-------|----------|----------|----------|
| DIGOXIN    | C01AA05    | Cardiovascular/cardiac therapy            | 11.3     | 10.9  | ns       | <.001    | 1.14**   | 1.13*    |
| MIRTAZAPINE| N06AX11    | Nervous/antidepressant                     | 10.9     | 8.7   | <0.01    | 0.001    | ns       | ns       |
| AMLODIPINE | C08CA01    | Cardiovascular/calcium channel blocker    | 10.3     | 8.9   | ns       | 0.06     | ns       | 0.88*    |
| WARFARIN   | B01AA03    | Blood/antithrombotic                      | 9.7      | 11.3  | ns       | 0.003    | 0.92*    | ns       |
| CLOPIDOGREL| B01AC04    | Blood/antithrombotic                      | 9.7      | 10.8  | ns       | 0.001    | 0.92*    | ns       |
| SERTRALINE | N06AB06    | Nervous/antidepressant                     | 9.6      | 9.7   | ns       | 0.12     | ns       | ns       |
| RANITIDINE | A02BA02    | Alimentary/acid-related disorders          | 9.6      | 10.3  | ns       | 0.64     | ns       | ns       |
| PANTOPRAZOLE| A02BC02   | Alimentary/acid-related disorders          | 9.6      | 8.6   | ns       | 0.02     | 0.93*    | ns       |
| LANSOPRAZOLE| A02BC03  | Alimentary/acid-related disorders          | 8.9      | 10.3  | <.001    | 0.89**   | ns       |
| Drug                          | ATC Code | Therapeutic Class                  | Mean | Control | p-value | t-value | p-value | ns | ns |
|------------------------------|----------|------------------------------------|------|---------|---------|----------|---------|----|----|
| Hydrochlorothiazide          | C03AA03  | Cardiovascular-diuretic            | 8.8  | 6.9     | <0.01   | 0.22     | ns      | ns | ns |
| Olanzapine                   | N05AH03  | Nervous/psycholeptic               | 8.3  | 8.6     | ns      | <.001    | 0.88**  | ns | ns |
| Quetiapine                   | N05AH04  | Nervous/psycholeptic               | 6.1  | 8.2     | <0.01   | <.001    | 0.91*   | ns | ns |
| Risperidone                  | N05AX08  | Nervous/psycholeptic               | 7.9  | 8.1     | ns      | 0.004    | 0.91*   | ns | ns |
| Celecoxib                    | MO1AH    | Musculoskeletal/anti-inflammatory  | 7.8  | 5.9     | <0.01   | 0.39     | ns      | ns | ns |
| Atenolol                     | C07FB03  | Cardiovascular/beta-blocking       | 7.7  | 6.9     | ns      | 0.89     | ns      | ns | ns |
| Omeprazole                   | A02BC01  | Alimentary/acid-related disorders  | 7.3  | 7.3     | ns      | 0.93     | ns      | ns | ns |
| Isosorbide                   | C01DA08  | Cardiovascular/cardiac therapy     | 7.2  | 6.6     | ns      | 0.39     | ns      | ns | ns |
| Lorazepam                    | N05CD06  | Nervous/psycholeptic               | 6.9  | 5.7     | ns      | <.001    | 0.87**  | ns | ns |
| Hydrocodone                  | N02AA08  | Nervous/analgesic                  | 6.9  | 5.3     | <0.01   | <.001    | 0.86**  | ns | ns |
| Atorvastatin                 | C10AA05  | Cardiovascular/lipid-              | 6.8  | 8.4     | ns      | <.001    | 0.71**  | 0.81** | ns | ns |
| Drug          | Code      | Category                          | Lowering | Change | p-value  | Ratio  | p-value  |
|--------------|-----------|-----------------------------------|----------|--------|----------|--------|----------|
| CALCITONIN   | H05BA01   | Hormone/calcium homeostatis       | 5.9      | 1.8    | <0.001   | 1.08   | <0.001   |
| GABAPENTIN   | N03AX12   | Nervous/anti-seizure              | 5.7      | 5.7    | ns       | 0.80** | 0.91     |
| DILTIAZEM    | C08DB01   | Cardiovascular/calcium channel blocker | 5.6      | 4.6    | ns       | 0.94   | 1.01     |
| PAROXETINE   | N06AB05   | Nervous/antidepressant            | 5.6      | 4.9    | ns       | 0.99   | 0.96     |
| CARBIDOPA    | N04BA02   | Nervous/antiparkinson             | 5.1      | 8.4    | <0.001   | 0.81** | 0.94     |
| L-DOPA       | N04BA01   | Nervous/antiparkinson             | 4.5      | 6.9    | <0.001   | 0.82** | 0.96     |
| RISEDRONATE  | M05BA07   | Musculoskeletal/bone              | 4.8      | 1.0    | <0.001   | 0.98   | 0.95     |
| TRAZODONE    | N06AX05   | Nervous/antidepressant            | 4.5      | 4.8    | ns       | 0.93   | 1.01     |
| PHENYTOIN    | N03AB02   | Nervous/anti-seizure              | 4.0      | 6.4    | <0.001   | 0.76** | 0.76**   |
| MEMANTINE    | N06DX01   | Nervous-dementia                  | 4.0      | 5.0    | ns       | 0.93   | 1.01     |
| DIVALPROEX   | N03AG01   | Nervous/anti-seizure              | 3.7      | 5.8    | <0.001   | 0.73** | 0.83**   |
| GLIPIZIDE | A10BB07 | Alimentary-diabetes | 3.6 | 5.4 | <0.001 | <.001 | 0.8** | 0.95 |
|-----------|---------|---------------------|-----|-----|---------|-------|-------|------|

* ^ Odds ratio for age considered as a continuous variable. * p-value ≤0.01. ** p-value ≤0.001

The number of daily oral medications was positively related to number of diagnoses (p<.0001) without any single chronic disease diagnosis associated with the highest number of daily oral medications. In contrast, residents with dementia were prescribed the lowest average number of daily oral medications (6.1 per day).

We next examined medication use in long stay residents with two co-morbid conditions that were present in at least 10 percent of men or women (Table 3). The dyads included combinations of hypertension, dementia, vascular disease, depression, arthritis, diabetes, GERD, heart failure, anemia, thyroid disease, osteoporosis and chronic obstructive pulmonary disease. Treatment of these dyads explained from 6-30% of daily oral medication intake (excluding the use of daily health maintenance agents) in both men and women. The overall prevalence of the dyads ranged from 7.9-27% and these older residents had an average of more than five additional medical diagnoses.
Table 3. Medication Usage Attributable to Common Chronic Disease Dyads

| DYAD              | Proportion (%) Daily Oral Medication Use Attributed to Dyad | Total Number of Daily Oral Medications* | Additional Diagnoses (n) | Overall Prevalence of Dyad (%) |
|-------------------|-------------------------------------------------------------|----------------------------------------|-------------------------|--------------------------------|
| ARTH+HTN          | 41                                                          | 7.68 ±0.09                             | 5.5                     | 20                             |
| Vasc+HTN          | 39                                                          | 7.54 ±0.08                             | 5.3                     | 26.3                           |
| Vasc+CHF          | 36                                                          | 8.43 ±0.12                             | 5.6                     | 10.4                           |
| DEP+HTN           | 35                                                          | 7.90 ±0.09                             | 5.5                     | 21                             |
| GERD+HTN          | 35                                                          | 8.21 ±0.11                             | 5.6                     | 14.2                           |
| Vasc+GERD         | 35                                                          | 8.18 ±0.13                             | 5.6                     | 11.4                           |
| Vasc+DEP          | 34                                                          | 8.01 ±0.11                             | 5.5                     | 16.1                           |
| Vasc+ARTH         | 34                                                          | 7.69 ±0.11                             | 5.5                     | 15                             |
| HTN+THYR          | 34                                                          | 8.04 ±0.12                             | 5.7                     | 9.7                            |
| DIA+HTN           | 33                                                          | 8.03 ±0.11                             | 5.6                     | 15.1                           |
| ARTH+DEP          | 33                                                          | 7.87 ±0.11                             | 5.7                     | 13.5                           |
| HTN+OSTEO         | 32                                                          | 8.25 ±0.13                             | 5.7                     | 9.6                            |
| Vasc+DIA          | 31                                                          | 8.14 ±0.13                             | 5.6                     | 12.1                           |
| ANEMIA+HTN        | 31                                                          | 7.53 ±0.12                             | 5.7                     | 11.5                           |
| HTN+DEM           | 30                                                          | 6.73 ±0.08                             | 5.3                     | 27.4                           |
| Vasc+DEM          | 28                                                          | 6.66 ±0.09                             | 5.3                     | 21.1                           |
| CHF+HTN           | 27                                                          | 8.23 ±0.11                             | 5.7                     | 12.2                           |
| ARTH+DEM          | 26                                                          | 6.54 ±0.08                             | 5.5                     | 17.4                           |
| DEP+GERD          | 26                                                          | 8.64 ±0.15                             | 5.8                     | 10.2                           |
| COPD+HTN          | 25                                                          | 7.76 ±0.14                             | 5.7                     | 7.9                            |
| DEM+THYR          | 23                                                          | 6.83 ±0.13                             | 5.7                     | 9.2                            |
| DEM+DEP           | 22                                                          | 6.79 ±0.10                             | 5.5                     | 19.4                           |
| DEM+GERD          | 21                                                          | 7.23 ±0.13                             | 5.6                     | 10.7                           |
| DEM+OSTEO         | 20                                                          | 7.08 ±0.13                             | 5.7                     | 9.4                            |
| ANEMIA+DEM        | 15                                                          | 6.61 ±0.13                             | 5.7                     | 10.3                           |
| DEM+DIA           | 15                                                          | 7.16 ±0.12                             | 5.6                     | 10.1                           |

Data represent co-morbid 2-disease combinations present in over 5% of either men or women. 
HTN=hypertension, DEM=dementia, DEP=depression, ARTH=Arthritis, DIA=diabetes mellitus, GERD=gastroesophageal reflux and acid peptic disorders, CHF=congestive heart failure, THYR=thyroid disease, OSTEO=osteoarthritis, COPD=chronic obstructive pulmonary disease, Vasc=composite of vascular diseases (atherosclerosis, cerebrovascular disease, coronary artery disease, peripheral artery disease).*mean ±SEM.

Increasing the number of co-morbid conditions to three increased the proportion of medication use attributable to the three co-morbid conditions to 31-51% of daily oral medication intake (excluding the use of daily health maintenance agents, Table 4).
Table 4. Medication Usage Attributable to Common Chronic Disease Triads

| TRIAD | Proportion of Medication Use Attributed to Triad (%) | Number of daily oral medications* | Additional Diagnoses (n) | Overall Prevalence of Triad |
|-------|-----------------------------------------------------|----------------------------------|-------------------------|---------------------------|
| HTN+ARTH+DEP | 51 | 8.36 ±0.14 | 5.2 | 8.3 |
| HTN+ARTH+OSTEO | 50 | 8.73 ±0.19 | 5.3 | 4.0 |
| HTN+ARTH+GERD | 50 | 8.79 ±0.16 | 5.3 | 6.2 |
| HTN+Vasc+ARTH | 49 | 8.13 ±0.12 | 5 | 9.7 |
| HTN+Vasc+GERD | 49 | 8.51 ±0.15 | 5.2 | 7.4 |
| HTN+Vasc+DIA | 48 | 8.36 ±0.15 | 5 | 7.9 |
| HTN+Vasc+DEP | 48 | 8.29 ±0.13 | 5 | 10.1 |
| HTN+Vasc+THY | 47 | 8.61 ±0.17 | 5.1 | 4.8 |
| HTN+ARTH+DEM | 46 | 7.18 ±0.11 | 5 | 10.2 |
| Vasc+DEP+GERD | 46 | 9.03 ±0.20 | 5.2 | 5.3 |
| Vasc+ARTH+DEP | 46 | 8.47 ±0.17 | 5.1 | 6.4 |
| Vasc+ARTH+GERD | 45 | 8.98 ±0.19 | 5.2 | 4.7 |
| HTN+ARTH+ANEMIA | 45 | 8.19 ±0.18 | 5.3 | 4.7 |
| A | | | | |
| HTN+DEP+GERD | 45 | 9.08 ±0.20 | 5.3 | 6.5 |
| HTN+Vasc+ANEMIA | 44 | 8.10 ±0.16 | 5.1 | 5.6 |
| HTN+Vasc+DEM | 44 | 7.06 ±0.11 | 4.7 | 12.6 |
| HTN+ARTH+CHF | 42 | 8.61 ±0.16 | 5.3 | 4.7 |
| HTN+DEP+DIA | 42 | 9.01 ±0.18 | 5.3 | 5.4 |
| HTN+DEM+DEP | 41 | 7.32 ±0.12 | 5 | 11.2 |
| HTN+GERD+DEM | 41 | 7.74 ±0.16 | 5.1 | 6.4 |
| HTN+DEP+OSTEO | 41 | 9.06 ±0.20 | 5.3 | 4.3 |
| HTN+Vasc+CHF | 41 | 8.66 ±0.15 | 5.1 | 6.6 |
| Vasc+DEM+DEP | 40 | 7.32 ±0.14 | 4.9 | 8.3 |
| HTN+Vasc+COPD | 40 | 8.16 ±0.20 | 5.1 | 4.0 |
| Vasc+DEM+GERD | 39 | 7.57 ±0.17 | 5 | 5.2 |
| HTN+DEP+ANEMIA | 39 | 8.32 ±0.19 | 5.3 | 4.7 |
| Vasc+ARTH+DEM | 39 | 7.05 ±0.13 | 4.9 | 7.5 |
| ARTH+DEM+DEP | 38 | 7.24 ±0.13 | 5 | 7.4 |
| HTN+DEM+DIA | 38 | 7.58 ±0.15 | 5.1 | 6.4 |
| HTN+DEM+OSTEO | 37 | 7.81 ±0.17 | 5.1 | 5.1 |
| HTN+DEM+ANEMIA | 37 | 7.20 ±0.16 | 5.1 | 6.1 |
| Vasc+DEM+DIA | 36 | 7.35 ±0.17 | 5.1 | 5.0 |
| DEM+DEP+GERD | 32 | 7.94 ±0.19 | 5.3 | 5.2 |
| DEM+DEP+OSTEO | 31 | 7.84 ±0.21 | 5.3 | 4.2 |
| HTN+DEM+CHF | 31 | 7.94 ±0.15 | 5.1 | 5.2 |

Data represent co-morbid 3-disease combinations (Triads) present in over 5% of either men or women.

HTN=hypertension, DEM=dementia, DEP=depression, ARTH=Arthritis, DIA=diabetes mellitus, GERD=gastroesophageal reflux and acid peptic disorders, CHF=congestive heart failure, THYR=thyroid disease, OSTEO=osteoporosis, COPD=chronic obstructive pulmonary disease, Vasc=composite of vascular diseases (atherosclerosis, cerebrovascular
disease, coronary artery disease, peripheral artery disease). HTN=hypertension, DEM=dementia, DEP=depression, ARTH=Arthritis, DIA=diabetes mellitus, GERD=gastroesophageal reflux and acid peptic disorders, CHF=congestive heart failure, THYR=thyroid disease, OSTEO=osteoporosis, COPD=chronic obstructive pulmonary disease, Vasc=composite of vascular diseases (atherosclerosis, cerebrovascular disease, coronary artery disease, peripheral artery disease).*mean ±SEM.

Triads were slightly less prevalent than the dyads and were present in 4-13% of the older long-stay nursing home residents. Residents with these triads also had an average of five other diagnoses. Triads explaining the highest proportion of daily medications included hypertension in all, vascular disease or arthritis in half, and depression or GERD in one quarter (Table 4). No sex differences in the proportions of medications attributed to treatment of combinations of the three co-morbid conditions were detected. Health maintenance agents accounted for 15-17% of daily oral medication intake in all residents. Considering the medications attributed to the treatment of the triads combined with oral agents attributable to health maintenance agents thus explained from half to almost two-thirds of daily oral medication intake in patients with the most common three co-morbid conditions studied.

DISCUSSION
There is current dialogue on how the understanding of multi-morbidity should inform health system design, care guidelines, and quality measures (2, 27). The impetus for our work was to understand therapeutic regimens in older people with multimorbidity to both simplify regimens and decrease the number of medications prescribed, since polypharmacy is the major risk factor for adverse drug reactions that has been consistently identified. (15, 28-30) We analyzed data from the only survey to date that comprehensively collected individual U.S. nursing home resident medication and diagnostic data from on-site medical record review by trained researchers with methodology procedures to assure accuracy and quality standards. (12) Similar to reports from other countries, polypharmacy was present with about half of the older nursing home residents receiving more than six daily oral medications (excluding health maintenance agents). (31) Thirty-five percent of residents received nine or more oral medications daily. While the number of medications was related to the number of diagnoses, from one-third to half of the oral prescription medication burden of long-term care residents of nursing homes with three co-morbid conditions could be attributed to management of the triad despite the presence of an additional five diagnoses.

Efforts to improve medication usage in older patients and nursing home residents have largely focused on individual high risk medications considered “inappropriate for use in the elderly”(32, 33) or as high-risk in older adults and not based on the prevalence of single or co-morbid conditions. With the exception of off-label use of antipsychotics, medications considered “inappropriate for use in the elderly” during the time of the survey (32, 33) were used infrequently (lorazepam in 6-7%) or not at all (<1%). Subsequent to collection of the data we reported, efforts have reduced use of antipsychotics by 15%, (34) but the challenge of how to optimize medication regimens and minimize adverse events for patients with multiple co-morbid conditions has not been solved. (35, 36) Hypertension, vascular disease (coronary, cerebral, or peripheral), dementia, arthritis, depression, and GERD were diagnoses within the most common disease dyads and triads followed by diabetes, heart failure, osteoporosis, and anemia. These data suggest potential starting points for considering drug combinations in relation to common co-morbid diseases with likelihood for polypharmacy.

Some progress has been made in considering medication choices for hypertension in older adults with co-morbid conditions such as coronary artery disease, heart failure, diabetes, and renal insufficiency but not for hypertension in combination with other highly prevalent diagnoses in older adults or those in nursing homes. (37, 38) Specifically, antihypertensive treatment guidelines do not consider arthritis, GERD, dementia, depression, osteoporosis or anemia, though these commonly co-exist with hypertension. Nor, do guidelines
often consider the duration of therapy needed to see benefits that may be greater than the estimated lifespan of older patients with multiple medical conditions. With a wide range of effective antihypertensive medications from which to choose, consideration of effects on common co-morbid conditions, time to benefit, and the medications to treat co-morbid conditions should be considered if medication therapy is to be optimized. (39) In the NHHS dataset, vascular disease or arthritis were commonly part of three co-morbid conditions that included hypertension followed by depression or GERD. An approach to therapeutic choices to minimize medications could be as follows. For (Hypertension + Vascular Disease), a beta-blocker or calcium channel blocker could treat both conditions and would be preferred to diuretics, ACE, ARB, or renin inhibitors that do not treat atherosclerotic, coronary or cerebrovascular disease. In the presence of arthritis with (Hypertension + Vascular disease), the preferences of agents remain the same. However, if GERD is added to (Hypertension + Vascular Disease), beta-blockers are preferred to calcium channel blockers that may cause or exacerbate GERD. When depression is present, many would avoid beta-blocker use. As the need for medications to treat multiple medical conditions and the choices and potential interactions increase complexity, minimization and deprescribing approaches are less obvious. There is a need for development and testing of approaches, algorithms, and automated real time decision support tools to address the challenge. (5)

Some comments are warranted regarding other patterns of medication use observed. The decrease in number of medications prescribed to the oldest nursing home residents likely represented appropriate attempts to reduce medication burden or side effects near the end of life. Reduced ACE inhibitor use could reflect risks of postural hypotension, hyperkalemia in combination with non-steroidal anti-inflammatory arthritis medications, less stringent blood pressure targets for the elderly with functional impairments, or avoidance of cough side effects. Decreased prescription of HMG CoA-reductase inhibitors likely reflects lesser importance of cholesterol lowering in the very old and mirrors recent international data.(40) Frequency of prescribing did not match frequency of related ICD-9 diagnoses for several medications. Furosemide use was highly prevalent (49%) in residents with a diagnosis of hypertension in the absence of diagnoses of heart failure, edema, or renal disease and thiazide diuretic use was infrequent (<10 % of residents). This likely contributed to the use of potassium supplements. Celecoxib was prescribed for 10% or more of patients with triads that included hypertension and may have contributed to the use of multiple medications for treatment of hypertension. Gabapentin use was higher than seizure diagnosis prevalence and was likely used for pain that was not a frequent ICD-9 diagnosis. A high prevalence of use of health maintaining agents in the absence of a specific diagnosis related to their use was observed and accounted for an average of 1.4 oral medications per day across all age groups. In fact, the number one most frequently prescribed agents were multivitamins in 36% of nursing home residents.

Constipation was diagnosed in 10% of residents yet docusate was the fourth most commonly prescribed individual agents in 25% and senna was the ninth most common medication prescribed for 14%. Vitamin C ranked twenty-fourth in daily prescribed medications in 9% of residents. These agents clearly contribute to the polypharmacy and pill burden and may represent classes and categories that should be considered in efforts to reduce polypharmacy.

Our work has limitations. Although 2004 data, the number and demographics of the nursing home population remained unchanged (41) and the diseases and medication prescribing by class have remained stable (42). Furthermore, prescribing patterns are also very similar to 2013 Medicare Part D claims data, which reports that nine of the top ten medication claims were for treatment of hypertension, cardiovascular disease, GERD, thyroid disorders, and pain suggests that the patterns noted and opportunities for medication prescribing improvement remain. (42) In both 2004 NNHS and 2013 Medicare claims, lisinopril, L-thyroxine, amlodipine, furosemide and metoprolol were among the ten most commonly prescribed medications. In addition, a distinct pattern of polypharmacy due to vascular disease has also been identified in older outpatients. (43) Data were from clinical care records and billing and diagnostic criteria were not standardized. Medication doses were not reported limiting assessment of inappropriate medication use and only chronic oral medications were considered (e.g. antibiotics, chemotherapeutic agents, “as needed ” agents excluded).

In summary, at least half of the medications burden of long-term care residents of nursing homes were attributed to management of three co-morbid diseases. Hypertension, vascular disease, dementia, arthritis, depression, and GERD were diagnoses within the most common three co-morbid conditions. Vascular disease, arthritis, or GERD have not been the focus of efforts to improve medication prescribing in nursing homes. A focus on improving combinations of medications to treat combinations of common co-morbid conditions would be a logical starting point for optimizing care of the elderly nursing home resident with multimorbidity and for those
at high risk for adverse drug events but could also be applied to common co-morbid conditions in other settings and patient groups.

ACKNOWLEDGMENTS

This study was funded in part by NIA grants RC1 AG 036377 and K24AG049057, and with funds from the Jewish Home of San Francisco. The authors report no conflicts of interest in relation to this work.
REFERENCES

1. Boyd C, Darer J, Boult C, Fried L, Boult L, Wu A. Clinical practice guidelines and quality of care for older patients with multiple comorbid diseases. Implications for pay for performance. JAMA. 2005;294(6):716-24.

2. Boyd C, Fortin M. Future of multimorbidity research: how should understanding of multimorbidity inform health system design? Public Health Reviews. 2011;32:451-74.

3. Sharma M, Cornelius VR, Patel JP, Davies JG, Molokhia M. Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism. Systematic Review and Meta-Analysis. Circulation. 2015;132:194-204.

4. Kantor ED RC, Haas JS, Chan AT, Giovannucci EL. Trends in Prescription Drug Use Among Adults in the United States From 1999-2012. JAMA Intern Med. 2015;314(17):1918-30. doi:10.001/jama.2015.13766.

5. Scott IA HS, Reeve E, Potter K, Le Couteur D, Rigby D, Gnijdic D, Del Mar CB, Roughhead EE, Page A, Jansen J, Martin JH Reducing Inappropriate Polypharmacy The Process of Deprescribing. JAMA Intern Med. 2015;175(5):827-34. doi:10.1001/jamainternmed.2015.0324.

6. Gurwitz J, Field T, Judge J, Rochold L, Cadoret C, et al. The incidence of adverse drug events in two large academic long-term care facilities. Am J Med. 2005;118(3):251-8.

7. Gurwitz J, Rochon P. Improving the quality of medication use in elderly patients. A not-so-simple prescription. Arch Intern Med. 2002;162(15):1670-2.

8. Gurwitz JH FT, Harrold LR, Rothschild J, Debellis K, Seger AC, Cadoret C, Fish LS, Garber L, Kelleher M, Bates DW. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. JAMA. 2003;289(9):1107-16.

9. Dwyer L. Collecting medication data in the 2004 National Nursing Home Survey. Vital Health Stat. National Center for Health Statistics. 2009;47(1):1-25.

10. Field TS GJ, Avorn J, McCormick D, Jain S, Eckler M, Benser M, Bates DW. Risk factors for adverse drug events among nursing home residents. Arch Intern Med. 2001;161:1629-34.

11. Kharkare S, Bhattacharjee S, Kamble P, Aparasu R. Prevalence and predictors of antidepressant prescribing in nursing home residents in the United States. Am J Geriatr Pharmacother. 2011 2:109-19.

12. The National Nursing Home Survey: 2004 overview. National Center for Health Statistics [Internet]. 2009.

13. Moore K, Boscardin WJ, Steinman MA, Schwartz JB. Age and sex variation in prevalence of chronic medical conditions in older residents of U.S. Nursing Homes. J Am Geriatr Soc 2012;60:756-64.

14. Jokanovic N, Tan, E. C., Dooley, M. J., Kirkpatrick, C. M., & Bell, J. S.. Prevalence and factors associated with polypharmacy in long-term care facilities: a systematic review. Journal of the American Medical Directors Association. 2015;16(6):535.e1-.e.12.

15. Steinman MA, Miao Y, Boscardin W, Komaiko KDR, Schwartz JB. Prescribing quality in older veterans: A multifocal approach. J Gen Int Med. 2014;29 (10):1379-86.

16. Budnitz DS, Shehab N, Kegler SR, Richards CL. Medication use leading to emergency visits for adverse drug events in older adults. Ann Intern Med. 2007;147:755-65

17. Gurwitz J, Rochon P. Improving the quality of medication use in elderly patients. A not-so-simple prescription. Arch Intern Med. 2002;162(15):1670-2.

18. Helling DK, Lemke JH, Sema TP, Wallace RB, Lipson DP, Curnoni-Huntley J. Medication use characteristics in the elderly: The Iowa 65+ rural health study. J Am Geriatr Soc. 1987;35:4-12.

19. Kaufman D KJ, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States. The Slone Survey. JAMA. 2002;287:337-44.

20. Carbonin P, Pahor M, Bernabei R, Sgadari A. Is age an independent risk factor of adverse drug reactions in hospitalized medical patients? J Am Geriatr Soc. 1991;39:1093-9.

21. Gurwitz JH, Avorn J. The ambiguous relation between aging and adverse drug reactions. Ann Intern Med. 1991;114:956-66.

22. Nolan L, O’Malley K. Prescribing for the elderly: Part I: Sensitivity of the elderly to adverse drug reactions. J Am Geriatr Soc. 1988;36:142-9.

23. Nolan L, O’Malley K. The need for a more rational approach to drug prescribing for elderly people in nursing homes. Age Ageing. 1989;18:52-6.

24. National Nursing Home Survey [Internet]. [cited August 7, 2012].
25. National Nursing Home Survey Data. Drug estimates and characteristics. p.
file(http://www.cdc.gov/nchs/data/nnhsd/Drugestimatesandcharacteristics.pdf).
26. (http://www.cdc.gov/nchs/data/series/sr_13/sr13_167.pdf).
27. American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity. Guiding Principles for the Care of Older Adults with Multimorbidity: An Approach for Clinicians. J Am Geriatr Soc. 2012; 60(10):E1-E25.
28. Maher R, Hanlon J, Hajjar E. Clinical consequences of polypharmacy in elderly. Expert Opinion on Drug Safety. 2014;13:57-65.
29. U.S. Department of Health and Human Services Office, of Disease Prevention and Health Promotion. National action plan for adverse drug event prevention. Washington, DC. 2014;available at: http://www.health.gov/hai/pdfs/ADE-Action-Plan-508C.pdf. Accessed September 3, 2015.
30. Budnitz D, Lovegrove M, Shehab N, Richards C. Emergency hospitalizations for adverse drug events in older Americans. New England Journal of Medicine. 2011;365:2002-12.
31. Onder G, Liperoti R, Fialova D, opinkova E, Tosato M, Danese P, Gallo P, et al. for the SHELTER Project. Polypharmacy in Nursing Home in Europe: Results From the SHELTER Study. J Gerontol A Biol Sci Med Sci 2012;67A (6):698-704.
32. Beers M. Explicit criteria for determining potentially inappropriate medication by the elderly. Arch Intern Med. 1997;157:1531-6.
33. Fick D, Cooper J, Wade W, Waller J, Maclean J, Beers M. Updating the Beers Criteria for Potentially Inappropriate Medication Use in Older Adults Results of a US Consensus Panel of Experts . Arch Intern Med. 2003;163:2716-24
34. CMS. Data show National Partnership to Improve Dementia Care exceeds goals to reduce unnecessary antipsychotic medications in nursing homes. https://www.cms.gov/Newsroom/MediaReleaseDatabase/Fact-sheets/2014-Fact-sheets-items/2014-09-19.html. Washington, DC: cms.gov; 2014 [ ]
35. Schwartz J. Potential impact of substituting estimated Glomerular Filtration Rate for estimated Creatinine Clearance for dosing of Direct Oral Anticoagulants. J Am Geriatr Soc. 2016;64:1996-2002. doi: 10.1111/jgs.14288.
36. Calderón-Larrañaga A, Poblador-Plou B, González-Rubio F, Gimeno-Feliu LA, Abad-Díez JM, .. Prados-Torres A. Multimorbidity, polypharmacy, referrals, and adverse drug events: are we doing things well? Br J Gen Pract. 2012;62(605):e821-6.
37. Aronow WS, Fleg JL, Pepine CJ, Artinian NT, Bakris G, Brown AS, et al. ACCF/AHA 2011 Expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on. JACC [Internet]. 2011; 57:[2037-114 pp.].
38. Arnett D, Goodman R, Halperin J, Anderson J, Anderson J, Parekh A, et al. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and U.S. Deopartment of Health and Human Services. J Am Coll Cardiol. 2014;64:1851-6.
39. Moore K, Boccardin W, Steinman M, Schwartz J. Patterns of chronic co-morbid medical conditions in older residents of U.S. Nursing Homes: differences between the sexes and across the agespan. J Nutrition, Health, and Aging. 2014;18:429-36.
40. Bach P, McClellan M. The first months of the prescription-drug benefit-- a CMS update. N Engl J Med. 2006;354(22):2312-4.
41. CMS. Nursing Home Data Compendium 2015 EditionJune 23, 2016. Available from: https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=0ahUKEwjxxMmSz8vNAhUN7mMKHe4RDD0QFggkMAEurl=https%3A%2F%2Fwww.cms.gov%2FMedicare%2FProvider-Enrollment-and Certification%2FCertificationComplianc%2FDownloads%2Fnursinghomedatacompendium_508-2015.pdf&usg=AFQjCNHmKJElhw7IKqlIMbk7jrAfDr5Ng&sig2=WtHh200c9I6RTK5Zb-iiWbgw.
42. CMS. 2015. CMS releases prescriber-level Medicare data for first time. wwwcmsgov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Medicare-Provider-Charge-Data/Part-D-Prescriber.html.Accessed June 23, 2016.
43. Calderón-Larrañaga A, Gimeno-Feliu L, González-Rubio F, Poblador-Plou B, Lairla-San José M, José M. Abad-Díez, Antonio Poncel-Falcó, & Alexandra Prados-Torres. Polypharmacy Patterns: Unravelling
Systematic Associations between Prescribed Medications. PLoS ONE 2013;8(12):e84967. doi:10.1371/journal.pone.0084967.
