Associations Between Chronic Disease, Polypharmacy, and Medication-Related Problems Among Medicare Beneficiaries

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ABSTRACT

BACKGROUND: Mismanaged polypharmacy among older adults costs the health care system approximately $2 billion each year. Medication therapy management (MTM), a service designed to optimize medication use, improve health outcomes, and reduce associated costs, is available to eligible Medicare beneficiaries. Yet, it remains unclear which beneficiaries benefit most from this service.

OBJECTIVE: To assess associations between patient characteristics, chronic disease, polypharmacy, and medication-related problems (MRPs) in a sample population of Medicare beneficiaries.

METHODS: This study was a retrospective cross-sectional analysis of 1 Medicare Part D plan provider for the year 2015. Medicare beneficiaries were included if they were eligible to receive MTM services and excluded if they were aged under 65 years or the dataset had no count of MRPs for the beneficiary. A negative binomial regression assessed the relationship between age, sex, and chronic health conditions with MRPs. Second and third negative binomial regressions assessed the relationship between age, sex, and polypharmacy with MRPs.

RESULTS: A sample of 27,765 Medicare beneficiaries had a mean (SD) age of 76 (±7) years, were predominantly female (59%), and used a mean (SD) of 11 (±4) chronic medications. Beneficiaries with certain conditions were more likely to incur an MRP than those without, including depression (OR = 1.58; 95% CI = 1.51-1.64), congestive heart failure (OR = 1.26; 95% CI = 1.20-1.31), diabetes (OR = 1.24; 95% CI = 1.18-1.29), end-stage renal disease (OR = 1.38; 95% CI = 1.25-1.52), respiratory conditions (OR = 1.25; 95% CI = 1.19-1.31), and hypertension (OR = 1.09; 95% CI = 1.01-1.18). Medicare beneficiaries with polypharmacy (11 or more medications) were 1.86 (95% CI = 1.80-1.93) times more likely to experience an MRP than those taking fewer medications. For every additional medication, the odds of incurring an MRP increased by 10% (OR = 1.11; 95% CI = 1.10-1.1.11).

CONCLUSIONS: The diagnosis of depression presented with the strongest association with MRPs. Diabetes, congestive heart failure, end-stage renal disease, respiratory conditions, and hypertension also presented with significant associations with MRPs. Beneficiaries with polypharmacy (11 or more medications) were almost 2 times more likely to experience an MRP than those taking fewer medications. Addition of a chronic medication resulted in a 10% increase in the odds of incurring an MRP. MTM programs may find a greater number of MRPs among those diagnosed with depression in their MTM-eligible patient populations.

J Manag Care Spec Pharm. 2019;25(5):573-77

What is already known about this subject

- Mismanagement of complex medication regimens among older adults may lead to approximately $2 billion in avoidable health care costs each year.
- Previous research found medication-related problems (MRPs) to be associated with multiple medications (polypharmacy), number of chronic diseases, annual drug spend, age, gender, region, race, household income, and health care utilization.

What this study adds

- Medicare beneficiaries eligible for medication therapy management with the diagnosis of depression or with significant polypharmacy had the strongest associations of incurring an MRP.
- MRPs were also significantly associated with individuals who had certain chronic conditions (e.g., diabetes, congestive heart failure, end-stage renal disease, respiratory conditions, and hypertension).

It is estimated that the mismanagement of complex medication regimens among older adults has directly led to approximately $2 billion in avoidable health care costs such as hospitalizations and ER visits each year.[1] Incorrect use of medications, drug interactions, adverse drug events, and suboptimal medication regimens are partly responsible for the avoidable costs associated with chronic medication use.[2] To address this issue, in 2003, the Centers for Medicare & Medicaid Services (CMS) required Medicare Part D plan providers to offer medication therapy management (MTM) services to eligible beneficiaries.[3] MTM services include comprehensive medication reviews (CMRs) and targeted medication reviews (TMRs), which are expected to optimize medication use, improve health outcomes, and reduce health care costs.[4]

To receive these services, Medicare beneficiaries must meet specific thresholds based on chronic conditions, polypharmacy, and medication costs.[4] MTM providers then deliver respective services (CMRs and TMRs) to address a beneficiary's medication-related problems (MRPs). However, it is unknown which of these beneficiaries benefit more from these services. In 2015, Medicare providers completed CMRs with roughly 60% of the eligible population.[5] Key differences may exist among eligible Medicare beneficiaries, resulting in an uneven distribution of the benefits gained from MTM services. These differences in the beneficial effects of MTM may help explain the conflicting evidence regarding its efficacy on health outcomes and health care utilization.[6,7]

Previous research found that CMRs may reduce use of high-risk medications among older adults.[8,9] A randomized controlled pragmatic trial by Zillich et al. (2014) reported that patients assigned to home health centers with the lowest CMS risk score for hospitalization were less likely to visit an emergency department within 30 days or be hospitalized within 60 days after receiving CMRs in comparison to usual care.[10] Moore et al. (2013) found medication adherence significantly increased with provision of MTM services for medications used for treating hypertension and hypercholesterolemia,[11] which are known to significantly reduce ischemic and acute cardiovascular events.[12] In contrast, a review and meta-analysis by Viswanathan et al. (2014) concluded there was insufficient evidence to adequately assess the benefits of MTM on health outcomes.[7]

Beginning in 2017, CMS launched an enhanced MTM (eMTM) program, based on MTM's effectiveness in reducing overall health care costs for patients with diabetes and congestive heart failure (CHF) and significantly improving medication adherence for those with CHF, diabetes, and chronic obstructive pulmonary disease (COPD).[13] Additionally, the eMTM program allowed Medicare insurance plan providers greater autonomy in determining who received MTM and what services were provided.[13]

Although diabetes, CHF, and COPD were highlighted as targeted disease states in establishing eMTM, it is unknown which chronic conditions are most associated with MRPs among MTM-eligible Medicare beneficiaries. A study by Lee et al. (2016) found that polypharmacy (having more than 3 chronic diseases), an annual drug spend exceeding $3,144, age, gender, race, and increased health care utilization were significantly associated with MRPs.[14]

The objective of this study was to elucidate the associations among patient characteristics, chronic disease, polypharmacy, and MRPs to identify and prioritize patients with significant disease burden who may benefit most (e.g., improved outcomes and reduced costs) from MTM.

Methods

Study Design and Sample Population

This was a retrospective cross-sectional analysis of a national telehealth MTM provider. Medicare beneficiaries were included in the study if they were eligible to receive MTM services. Beneficiaries were excluded if they were aged under 65 years or did not have an MRP count recorded. For this study, polypharmacy was defined as having claims for 11 or more unique chronic medications covered by Medicare Part D.[15] The institutional review board determined this study was exempt from human subject's research.

Data Source

Proprietary software analyzed data provided by insurance plan providers to evaluate whether a Medicare beneficiary was qualified to receive a CMR. This process assessed (a) the number of unique chronic medications in a 4-month span before the date of qualification; (b) if the beneficiary had qualifying chronic conditions; and (c) the overall cost of medications paid by the plan and the beneficiary in the previous 3 months. Further, the software, using proprietary algorithms, identified MRPs that may be assessed via CMRs and TMRs. MRPs that generate a facsimile (fax) are automatically tracked. This MTM service is described in greater detail elsewhere in the literature.[16]

Medication-Related Problems

In MTM, MRPs are traditionally identified and assessed by a pharmacist and resolved according to clinical decision making.[17] The teleheath MTM provider facilitates this process by using proprietary software that automatically identifies specific MRPs that generate and send a fax to the prescribing practitioner. Pharmacists have the choice of resolving MRPs that they identified through CMRs by communicating directly with patients or prescribers or by generating a fax of their own. Automatic faxes include serious drug-drug interactions; unsafe medications used in older adults with dementia or chronic kidney disease; a need for additional therapy in patients with diabetes, asthma, COPD, CHF, and hypertension; cost-savings opportunities such as switches to generic formulations; additional disease monitoring for patients using specific medications; and nonadherence identified by a measured proportion of days covered that dropped below a prespecified threshold. These automatic interventions were designed using Medicare star and display measures to improve medication use among insurance plan providers.[18,19] MRPs included in this study were only those that generated a fax. MRPs that did not generate a fax are not tracked and are thus unreportable.

Data Collection

The researchers obtained a deidentified dataset that included age, sex, number of chronically used medications, which chronic conditions a beneficiary had, and a list of MRPs reported to CMS. MRPs were converted to count data for analysis. The chronic conditions were limited to those that the Medicare insurance plan provider used as qualification criteria for the receipt of MTM services (Table 1).

Data Analysis

Data were coded and organized using IBM SPSS software version 25.0 (IBM, Armonk, NY). Descriptive statistics (counts and percentages and means and standard deviations) were calculated as appropriate. Three negative binomial models were used to determine associations between subject characteristics and MRPs (count data).[14] Independent variables in the first model included age, sex, and chronic conditions. The second model included the independent variables of age, sex, and polypharmacy, and the third model included age, sex, and number of medications. A 2-tailed a priori alpha level of 0.05 was used.

Results

The initial sample consisted of 28,948 Medicare beneficiaries. Of those, 995 were excluded based on age (under 65 years), and another 188 were excluded for unreported MRPs, resulting in a final sample of 27,765 beneficiaries. The beneficiaries in this study had a mean (SD) age of 76 (±7) years, were

TABLE 1 Characteristics of MTM-Eligible Beneficiaries from 1 Medicare Part D Provider (N = 27,765)

Characteristics	n (%)
Age, years, mean (±SD)	76 (±7)
Sex (male)	11,418 (41)
Chronic disease	
Polypharmacy (using 11 or more medications)	14,091 (51)
CHF	7,477 (27)
Depression	10,463 (38)
Diabetes	15,861 (57)
Dyslipidemia	21,299 (77)
ESRD	797 (3)
Hypertension	26,065 (94)
Osteoporosis	2,947 (11)
Respiratory conditions	6,507 (23)
MPR count	
0	16,720 (60)
1	7,169 (26)
2	2,512 (9)
3	915 (3)
≥4	449 (2)

CHF = congestive heart failure; ESRD = end-stage renal disease; MRP = medication-related problem; MTM = medication therapy management; SD = standard deviation.

TABLE 2 Results from Negative Binomial Regression Models Assessing the Relationship Between Medicare Beneficiary Characteristics and MRPs (N = 27,765)

Characteristics	*P* Value	Adjusted OR (95% CI)
Model 1[a]		
Age	0.080	1.00 (1.00-1.00)
Female sex	<0.001	1.19 (1.14-1.23)
Chronic condition		
CHF	<0.001	1.26 (1.20-1.31)
Depression	<0.001	1.58 (1.51-1.64)
Diabetes	<0.001	1.24 (1.18-1.29)
Dyslipidemia	0.510	0.99 (0.94-1.03)
ESRD	<0.001	1.38 (1.25-1.52)
Hypertension	0.040	1.09 (1.01-1.18)
Osteoporosis	0.360	0.97 (0.91-1.04)
Respiratory conditions	<0.001	1.25 (1.19-1.31)
Model 2[b]		
Age	0.003	0.996 (0.994-1.00)
Female sex	<0.001	1.23 (1.18-1.27)
Polypharmacy (using 11 or more medications)	<0.001	1.86 (1.80-1.93)
Model 3[c]		
Age	0.004	0.996 (0.994-0.999)
Female sex	<0.001	1.21 (1.17-1.26)
Number of medications	<0.001	1.11 (1.10-1.11)

[a]*Deviance = 25,642.769; df = 27,753; Value/df = 0.924; AIC = 58,625.563.*
[b]*Deviance = 25,647.921; df = 27,760; Value/df = 0.924; AIC = 58,130.716.*
[c]*Deviance = 25,826.990; df = 27,760; Value/df = 0.930; AIC = 57,397.564.*
AIC = Akaikes's Information Criterion; CHF = congestive heart failure; CI = confidence interval; df = degrees of freedom; ESRD = end-stage renal disease; OR = odds ratio.

predominantly female (59.0%), used a mean (standard deviation [SD]) of 11 (±4) chronic medications, and had 17,006 MRPs in the assessed population. The prevalence of chronic health conditions is reported in Table 1. In the overall population, there were 10,280 (59.0%) MRPs, suggesting unsafe medication use; 2,684 (15.0%) MRPs identified potential problems with adherence; 1,727 (10.0%) MRPs recommended additional medication therapy; 1,843 (11.0%) MRPs identified serious drug-drug interactions; 593 (3.0%) MRPs recommended additional chronic disease screenings or monitoring; 321 (2.0%) MRPs reflected cost savings recommendations; and 27 (0.2%) MRPs could not be categorized.

The findings from the negative binomial regressions are presented in Table 2. In the first model, female sex, CHF, depression, diabetes, end-stage renal disease (ESRD), hypertension, and respiratory conditions were significantly associated with the presence of MRPs ($P \leq 0.04$). Female sex was significantly associated with incurring an MRP (odds ratio [OR] = 1.19, 95% confidence interval [CI] = 1.14-1.23). Among the chronic health conditions, depression had the strongest relationship with MRPs (OR = 1.58, 95% CI = 1.51-1.64), and other chronic conditions with significant associations included CHF (OR = 1.26, 95% CI = 1.20-1.31), diabetes (OR = 1.24, 95% CI = 1.18-1.29), ESRD (OR = 1.38, 95% CI = 1.25-1.52), hypertension (OR = 1.09, 95% CI = 1.01-1.18), and respiratory conditions (OR = 1.25, 95% CI = 1.19-1.31).

In the second model, increasing age, male sex, and number of medications were significantly associated with MRPs ($P \leq 0.003$). Females presented with greater odds of incurring an MRP (OR = 1.23, 95% CI = 1.18-1.27). Medicare beneficiaries with 11 or more medications were approximately 2 times more likely to experience an MRP than those taking fewer medications (OR = 1.86, 95% CI = 1.80-1.93).

The third model showed that the number of medications had an OR of 1.11 (95% CI = 1.10-1.11). A Medicare beneficiary's odds of incurring an MRP increased by 10% with the addition of a chronic medication.

Discussion

This retrospective database review revealed significant associations between age, sex, polypharmacy, specific chronic diseases (e.g., depression, ESRD, CHF, respiratory conditions, diabetes, and hypertension), and MRPs. Previous research found that MRPs were significantly associated with polypharmacy, having more than 3 chronic diseases, an annual drug spend exceeding $3,144, age, gender, race, region, and increased health care utilization.[14] MTM services are valuable for patients with multiple chronic conditions, since they identify and address MRPs to reduce unnecessary hospitalizations and emergency visits.[20] However, because of the current differences in chronic health conditions among eligible Medicare beneficiaries, the benefits

of MTM may be unevenly distributed. This study adds to this body of knowledge by identifying chronic diseases and characteristics that are strongly associated with MRPs.

Among the chronic diseases evaluated in this study, beneficiaries with depression had the highest odds (nearly 1.6 times) of incurring MRPs. In the United States, roughly 11% of adults aged over 71 years experience depression,[21] and adding to the complexity, is that older adults may be less likely to recognize or admit to experiencing depressive symptoms.[22] Further, multiple chronic health conditions may influence the severity and prevalence of depression.[23] A previous meta-analysis highlighted the strong relationship between depression and MRPs in relation to nonadherence.[24] Moreover, older adults with depressive symptoms commonly use high-risk medications.[25] The findings from previous research and this study suggest MTM sponsors may find a greater number of MRPs among eligible beneficiaries with depression than those without.

This study also revealed that MTM-eligible Medicare beneficiaries with CHF, diabetes, ESRD, respiratory conditions, or hypertension also had significantly higher odds of incurring MRPs. These conditions are complex, requiring continued and consistent medication use to mitigate disease progression. While depression had the strongest risk for MRPs, the associations observed with these chronic conditions, along with the overwhelming burden that these conditions represent to patients and the health care system, suggest that these are worthy targets for medication optimization programs, as well.[26-31]

More than one half (51%) of this study's Medicare population used 11 or more medications chronically and were roughly 2 times more likely to experience an MRP than those taking fewer medications. Furthermore, this study found that the odds of incurring an MRP increased by 10% with the addition of a chronic medication. These results are similar to a previous study where patients with more than 8 medications were 2 times more likely to incur an MRP.[14] It is important to note that the analysis in the study included all Medicare patients in a plan, not just an MTM-eligible population.[14]

Polypharmacy remains a significant challenge in geriatric medicine, given the prevalence of multiple chronic conditions among older adults, leading to a greater risk of drug-drug and drug-disease interactions.[32] A recent review highlighted 6 of 9 investigations that found positive associations between polypharmacy and medication nonadherence.[33] Weng et al. (2013) found polypharmacy to be positively associated with the presence of potentially inappropriate medications among older adults (e.g., Screening Tool of Older Person's potentially inappropriate Prescriptions (STOPP) criteria).[34] Moreover, Guthrie et al. (2015) reported that the number of drugs was positively associated with the prevalence of drug-drug interactions.[35] CMRs and TMRs, as part of the MTM service, may identify and address MRPs among Medicare beneficiaries.[16]

It is also important to highlight the sex differences identified in this study. Women were approximately 1.2 times more likely to incur an MRP. Women are twice as likely to experience depression in their lifetime when compared with men.[36] This fact, coupled with underreported depression among older adults and consequently its treatment,[23] may have affected the results of this study. This finding may also have been influenced by chronic conditions more prevalent among women, prescribing of medications unique to women, and medication use behaviors that were unassessed in the current study. Further research is needed to elucidate the type of MRPs that are more prevalent in woman and in men.

Services such as MTM that are designed to optimize medication regimens through the identification and resolution of MRPs serve to mitigate costs associated with medication-related morbidity and mortality.[2] However, identification of patients more likely to benefit from these services is imperative to maximize their effect and optimize use of finite resources. This study's findings suggest that MTM sponsors should consider prioritizing their Medicare beneficiaries who have depression, as well as consider those with diabetes, CHF, respiratory conditions, and ESRD as a priority for receipt of MTM services. Further, these MTM providers should consider targeting polypharmacy (beneficiaries taking 11 or more medications), since these patients were nearly 2 times more likely to incur an MRP than those taking fewer medications. Thus, highlighting and targeting these high priority areas may increase the effect of MTM programs and contribute to the optimization of health outcomes given the finite resources of the Medicare program.

Limitations

Our study had several limitations. First, the study included data from only 1 Medicare Part D provider, limiting the generalizability of our findings. Furthermore, the data were limited to only MRPs that resulted in a fax to a beneficiary's primary care provider, since interventions that do not result in a fax are unable to be tracked. MRPs resolved directly with patients or physicians via phone were not included in this retrospective study, potentially underestimating the relationship between certain chronic diseases and MRPs. The relationship between MRPs with region, race, household income, health care utilization, annual drug spend, and number of prescribers was not assessed.[14,37] Future research is needed to assess the types of MRPs and their associations with specific chronic disease states.

Conclusions

In this study of Medicare Part D beneficiaries from 1 provider, individuals with a diagnosis of depression or presence of polypharmacy had the greatest chance of incurring MRPs. Additionally, diagnoses of diabetes, CHF, ESRD, respiratory conditions, and hypertension were significantly associated with higher odds of incurring an MRP. Prioritizing Medicare patients with these characteristics may enhance the effect of MTM programs, while simultaneously optimizing health outcomes and using health care resources more effectively.

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DISCLOSURES

No outside funding supported this research. Silva Almodóvar reports fees from SinfoniaRx, outside the submitted work. Nahata has nothing to disclose.

ACKNOWLEDGMENTS

The authors acknowledge the editorial contributions of Ann M. Taylor, MPH, MCHES; David Rhys Axon, MPharm, MS; and Terri Warholak, PhD, RPh, CPHQ, FAPhA. The authors also acknowledge the efforts of Shepin Werner, PharmD, in producing the deidentified dataset.

REFERENCES

1. Aitken M, Valkova S. Avoidable costs in U.S. healthcare: the $200 billion opportunity from using medicines more responsibly. IMS Institute for Healthcare Informatics. June 2013. Available at: http://offers.premierinc.com/rs/381-NBB-525/images/Avoidable_Costs_in%20_US_Healthcare-IHII_AvoidableCosts_2013%5B1%5D.pdf. Accessed March 5, 2019.

2. Watanabe JH, McInnis T, Hirsch JD. Cost of prescription drug-related morbidity and mortality. *Ann Pharmacother.* 2018;52(9):829-37.

3. Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Pub L. No. 108-173, 117 Stat 2066 (December 8, 2003).

4. Centers for Medicare & Medicaid Services. Fact sheet. Summary of 2017 MTM programs. August 16, 2017. Available at: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/CY2017-MTM-Fact-Sheet.pdf. Accessed March 5, 2019.

5. Centers for Medicare & Medicaid Services. 2017 Report card master table. October 26, 2016. In: 2017 Star ratings and display Measures. Zip file. 2017 Star ratings fall release. Retrieved June 6, 2018. Available at: https://www.cms.gov/medicare/prescription-drug-coverage/prescriptiondrugcovgenin/performancedata.html. Accessed March 5, 2019.

6. DeZeeuw EA, Coleman AM, Nahata MC. Impact of telephonic comprehensive medication reviews on patient outcomes. *Am J Manag Care.* 2018;24(2):e54-58.

7. Viswanathan M, Kahwati LC, Golin CE, et al. Medication therapy management interventions in outpatient settings. Comparative Effectiveness Reviews, no. 138. November 2014. Agency for Healthcare Research and Quality. Baltimore, MD. Available at: https://www.ncbi.nlm.nih.gov/books/NBK294489/. Accessed March 5, 2019.

8. Silva Almodovar A, Axon DR, Coleman AM, Warholak T, Nahata MC. The effect of plan type and comprehensive medication reviews on high-risk medication use. *J Manag Care Spec Pharm.* 2018;24(5):416-22. Available at: https://www.jmcp.org/doi/10.18553/jmcp.2018.24.5.416.

9. Kiel WJ, Phillips SW. Impact of pharmacist-conducted comprehensive medication reviews for older adult patients to reduce medication related problems. *Pharmacy (Basel).* 2017;6(1):2. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5874541/. Accessed March 5, 2019.

10. Zillich AJ, Snyder ME, Frail CK, et al. A randomized, controlled pragmatic trial of telephonic medication therapy management to reduce hospitalization in home health patients. *Health Serv Res.* 2014;49(5):1537-54.

11. Moore JM, Shartle D, Faudskar L, Matlin OS, Brennan TA. Impact of a patient-centered pharmacy program and intervention in a high-risk group. *J Manag Care Pharm.* 2013;19(3):228-36. Available at: https://www.jmcp.org/doi/10.18553/jmcp.2013.19.3.228.

12. Brown MT, Bussell JK. Medication adherence: WHO cares? *Mayo Clin Proc.* 2011;86(4):304-14.

13. Barlas S. CMS to test enhanced medication therapy management model: aims for greater use of pharmacists, cost savings, and better outcomes. *P T.* 2016;41(7):423-41.

14. Lee JS, Yang J, Stockl KM, Lew H, Solow BK. Evaluation of eligibility criteria used to identify patients for medication therapy management services: a retrospective cohort study in a Medicare Advantage Part D population. *J Manag Care Spec Pharm.* 2016;22(1):22-30. Available at: https://www.jmcp.org/doi/10.18553/jmcp.2016.22.1.22.

15. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatrics.* 2017;17(1):230.

16. Buhl A, Augustine J, Taylor AM, Martin R, Warholak TL. Positive medication changes resulting from comprehensive and noncomprehensive medication reviews in a Medicare Part D population. *J Manag Care Spec Pharm.* 2017;23(3):388-94. Available at: https://www.jmcp.org/doi/10.18553/jmcp.2017.23.3.388.

17. American Pharmacist Association, National Association of Chain Drug Stores Foundation. Medication therapy management in pharmacy practice: core elements of an MTM service model. Version 2.0. March 2008. Available at: https://www.pharmacist.com/sites/default/files/files/core_elements_of_an_mtm_practice.pdf. Accessed March 5, 2019.

18. Centers for Medicare & Medicaid Services. 2015 Display tech notes 11-20-14. In: 2015 Star ratings and display measures. Zip file. Available at: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/PerformanceData.html. Accessed March 5, 2019.

19. Centers for Medicare & Medicaid Services. 2015 Star ratings technical notes 4-10-2015. In: 2015 star ratings and display measures. Zip file. Available at: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovGenIn/PerformanceData.html. Accessed March 5, 2019.

20. Brummel A, Lustig A, Westrich K, et al. Best practices: improving patient outcomes and costs in an ACO through comprehensive medication therapy management. *J Manag Care Spec Pharm.* 2014;20(12):1152-58. Available at: https://www.jmcp.org/doi/abs/10.18553/jmcp.2014.20.12.1152.

21. Steffens DC, Fisher GG, Langa KM, Potter GG, Plassman BL. Prevalence of depression among older Americans: the Aging, Demographics and Memory Study. *Int Psychogeriatr.* 2009;21(5):879-88.

22. National Institute of Mental Health. Depression basics. Revised 2016. Available at: https://www.nimh.nih.gov/health/publications/depression/depressionbasics-508-01112017_150043.pdf. Accessed March 5, 2019.

23. Voinov B, Richie WD, Bailey RK. Depression and chronic diseases: it is time for a synergistic mental health and primary care approach. *Prim Care Companion CNS Disord.* 2013;15(2):PCC.12r01468. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3733529/. Accessed March 5, 2019.

24. Grenard JL, Munjas BA, Adams JL, et al. Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. *J Gen Intern Med.* 2011;26(10):1175-82.

25. Lee D, Martini N, Moyes S, Hayman K, Zolezzi M, Kerse N. Potentially inappropriate medication use: the Beers' Criteria used among older adults with depressive symptoms. *J Prim Health Care.* 2013;5(3):182-90.

26. Guarascio AJ, Ray SM, Finch CK, Self TH. The clinical and economic burden of chronic obstructive pulmonary disease in the USA. *Clinicoecon Outcomes Res.* 2013;5:235-45.

27. Voigt J, Sasha JM, Taylor A, Krucoff M, Reynolds MR, Michael Gibson C. A reevaluation of the costs of heart failure and its implications for allocation of health resources in the United States. *Clin Cardiol.* 2014;37(5):312-21.

28. Nunes C, Pereira AM, Morais-Almeida M. Asthma costs and social impact. *Asthma Res Pract.* 2017;3:1.

29. American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care.* 2018;41(5):917-28.

30. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2017 annual data report: epidemiology of kidney disease in the United States. *Am J Kidney Dis.* 2018;71(3 Suppl 1):A7.

31. Constant AF, Geladari EV, Geladari CV. The economic burden of hypertension. In: Andreadis EA, ed. *Hypertension and Cardiovascular Disease.* Cham, Switzerland: Springer International Publishing; 2016.

32. Mortazavi SS, Shati M, Keshtkar A, Malakouti SK, Bazargan M, Assari S. Defining polypharmacy in the elderly: a systematic review protocol. *BMJ Open.* 2016;6(3):e010989.

33. Marcum ZA, Gellad WF. Medication adherence to multidrug regimens. *Clin Geriatr Med.* 2012;28(2):287-300.

34. Weng MC, Tsai CF, Sheu KL, et al. The impact of number of drugs prescribed on the risk of potentially inappropriate medication among outpatient older adults with chronic diseases. *QJM.* 2013;106(11):1009-15.

35. Guthrie B, Makubate B, Hernandez-Santiago V, Dreischulte T. The rising tide of polypharmacy and drug-drug interactions: population database analysis 1995-2010. *BMC Med.* 2015;13:74.

36. Fiske A, Wetherell JL, Gatz M. Depression in older adults. *Annu Rev Clin Psychol.* 2009;5:363-89.

37. Gray CL, Gardner C. Adverse drug events in the elderly: an ongoing problem. *J Manag Care Pharm.* 2009;15(7):568-71. Available at: https://www.jmcp.org/doi/10.18553/jmcp.2009.15.7.568.