COMPARATIVE EFFECTIVENESS OF SECOND GENERATION ANTIDEPRESSANTS ON COGNITION AND DEMENTIA IN THE ELDERLY

DISSERTATION

By

VISHAL BALI, MS

A dissertation submitted in partial fulfillment of
the requirement for the degree of

DOCTOR OF PHILOSOPHY

IN

PHARMACEUTICAL HEALTH OUTCOMES AND POLICY

University of Houston

College of Pharmacy

December, 2014

COMPARATIVE EFFECTIVENESS OF SECOND GENERATION ANTIDEPRESSANTS ON COGNITION AND DEMENTIA IN THE ELDERLY

To the Faculty of the University of Houston, College of Pharmacy:

The members of the committee appointed to examine the dissertation of **VISHAL BALI** find it satisfactory and recommend that it be accepted on December 22, 2014.

_____

Committee Chair, (Rajender R. Aparasu, Ph.D., FAPhA)

_____

Committee Member, (Hua Chen, M.D., Ph.D.)

_____

Committee Member, (Michael L. Johnson, Ph.D.)

_____

Committee Member, (Holly M. Holmes, M.D.)

_____

Committee Member, (Marc L. Fleming, Ph.D.)

_____

Dean, (F. Lamar Pritchard, Ph.D.)

ACKNOWLEDGEMENT

I would like to take this opportunity to express my gratitude to everyone who supported me throughout my tenure in the Ph.D. program in Pharmaceutical Health Outcomes and Policy at the University of Houston. I would like to express my deepest gratitude to my advisor, Dr. Rajender R. Aparasu, for his excellent guidance, continuous support and motivation throughout the doctoral program. I feel really fortunate for having the opportunity to work with such an experienced researcher and knowledgeable professor. He involved me in diverse research projects and was always there to guide me with any problems that I faced during the course of my studies. His commitment to the highest standards inspired and motivated me work harder and deliver work of high quality. He has been a good friend and an excellent mentor. I am sincerely thankful to him for my doctoral studies such an enriching and memorable experience.

I would also like to thank my committee members Dr. Chen, Dr. Johnson, Dr. Holmes and Dr. Fleming for their constructive feedback and suggestions that helped me improve the quality of my dissertation. I am thankful to them for giving me their time to have an in-depth discussion about the issues related to the dissertation and for their worthy recommendations. I would also like to express my gratitude to all other faculty members at College of Pharmacy who shared their knowledge with me: Dr. James Essein, Dr. Sujit Sansgiry and Dr. Abughosh. I want to sincerely thank them for the teaching all those exciting courses.

I want to express my thanks the staff at the College of Pharmacy, Christen Gould, Steve Boss, Golda Hallette, Olga Zamora-Loa and Ashley N. Adams. I am thankful to them for the enormous amount of help throughout these years. I owe special thanks to Steve Boss for his selfless help with any technology related issues, be it college desktop or my laptop.

I would take this opportunity to also thank my classmates Yasser, Ayush, Shivani and I-Hsuan. Thanks for making my time at the University of Houston, memorable and splendid. I will always miss our get together parties. I also owe gratitude to my senior doctoral students especially Pravin, Debajyoti, and Satabdi for sharing their knowledge, experiences and giving me suggestions whenever I needed any advice. I must not forget my close friends Farid and Nitin They were also there to help me and cheer me up during tough times. I would always cherish the memories of the time that I spent with them, and wish them good luck in all their future endeavors.

My earnest respect and gratitude goes to my parents for their unconditional love and support. Thanks for always believing in me and motivating me to work hard and achieve my goals in life. I must acknowledge my brother Vikas, whose love, encouragement and support made me to pursue my doctoral studies. It was a great comfort and relief when he took responsibilities of our household activities while I completed my doctoral studies. I am also thankful to my sister in law for her patient listening and emotional support. My heartfelt thanks to my loving and caring sister and brother in law, for all their encouragement and profound understanding. Last but not the least, my thanks go to my naughty nephew and niece for their undying love for me and being a continuous source of enormous joy and happiness in my life. There are no words to convey how much I love you all!

I dedicate this dissertation work to my family, especially my parents…..

Vidya Wanti and Pritam Bali

TABLE OF CONTENTS

DISSERTATION SUMMARY

Objectives

The two primary objectives of this study were: 1) to evaluate the comparative effectiveness of second generation antidepressants classes on cognition in elderly nursing home residents with depression, and 2) to evaluate the comparative effectiveness of second generation antidepressants classes on dementia in elderly nursing home residents with depression.

Methods

This study involved retrospective cohort study design conducted using data from Medicare Part D claims and Minimum Data Set (MDS) from 2007-2010. The study population included elderly nursing home residents with depression who initiated treatment with second generation antidepressant classes namely selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) or tetracyclics. These patients were followed for one year to examine cognition; and two years to evaluate the risk of dementia. Cognition was identified using the MDS Cognition Scale. Time to diagnosis of dementia was ascertained using the chronic condition flag for dementia in Medicare Beneficiary Summary File. The differences in covariate distributions between the antidepressant users and non-users were evaluated using chi-squared (χ^2) tests for categorical variables and t-tests for continuous variables. A multiple propensity score adjusted repeated measures mixed model was used to evaluate the comparative effectiveness of SSRIs, SNRIs and Tetracyclics with respect to cognition. A multiple propensity score adjusted Cox proportional hazards model was used to examine comparative effectiveness of SSRIs, SNRIs and Tetracyclics on dementia.

Results

For the first objective, the study cohort consisted of 1,518 elderly nursing home residents. Of these, 1,081 received SSRIs (71.21%), 320 received Tetracyclics (21.08%) and 117 received SNRIs (7.71%). After adjusting for multiple propensity scores, the repeated measures mixed model did not find any statistically significant difference in cognition with the use of SSRIs (β = -0.23; 95% Confidence Interval (95% CI), -0.67, 0.22) or Tetracyclics (β = -0.45; 95% CI, -0.96, 0.05) when compared to SNRIs (reference group). Results of multiple sensitivity analyses were consistent with the main findings. For the second objective, the study cohort constituted 13,354 elderly nursing home residents with depression. Of these, 19,952 received SSRIs (79.77%), 2,381 received SNRIs (9.48%) and the rest 2,775 received Tetracyclics (11.05%). The unadjusted incidence of dementia was 8.20% for SSRIs users, 6.01% for the SNRIs users and 7.21% for Tetracyclics users. The propensity score adjusted Cox proportional hazard model did not find any significant difference in the comparative effectiveness of SNRIs [Hazards Ratio, HR, 0.99; 95% CI, 0.84, 1.19] or Tetracyclics [HR, 1.01; 95% CI, 0.87, 1.17] when compared to the SSRIs for the risk of dementia in elderly nursing home residents with depression. Results from the two sensitivity analyses supported the main findings.

Conclusions

This multiple propensity score adjusted retrospective cohort study did not find any statistically significant difference in the comparative effectiveness of three commonly used second generation antidepressant classes on cognition and risk of dementia. Future studies are required to examine the long-term effectiveness of these antidepressants classes on cognition and dementia.

SPECIFIC AIMS

One of the most critical public health concerns in the United States is dementia, a general term for a group of disorders that causes progressive deterioration in cognitive functioning. Alzheimer's disease accounts for 50-60% of dementia cases.[1] Other types of dementia include Lewy body dementia, vascular dementia, mixed dementia, and frontotemporal dementia. Neurobiological factors in dementia interfere with activities of daily living including the inability to follow simple directions, language and memory disturbances, failure to identify objects, and delusions.[2,3] About 5.3 million people in the United States have Alzheimer's dementia, the seventh leading cause of death.[4,5] Available drugs for dementia such as cholinesterase inhibitors (ChEIs) and memantine have small effect sizes and do not alter the disease progression.[6] Consequently, prevention of dementia through risk factor identification and modification is the key to reduce the disease burden.[6] It is estimated that the prevalence of dementia could be reduced by 50% if risk reduction strategies were successful in delaying its onset by 5 years.[7]

Depression is a major risk factor for cognitive decline and dementia. Ownby et al. (2006) found odds ratios of 2.03 for case-control and 1.90 for cohort studies for the risk of Alzheimer's Dementia due to depression.[8] Meta-analysis by Jorm et al. (1998) found that depression was consistently associated with an increased relative risk of dementia in both case control studies (95% CI, 1.16-3.50) and prospective studies (95% CI, 1.08-3.2).[9] In addition, meta-analysis by Christensen et al. revealed that depressive patients had low performance on almost all cognitive tests.[10] A recent Agency for Healthcare Research and Quality (AHRQ) report found increased risk of cognitive decline in depressed patients based on thirteen studies with a follow-up of 1.5 to 5.6 years.[11] Although the effects of antidepressants can vary due to underlying

pharmacodynamics, antidepressants can play an important role in preventing or delaying dementia in patients with depression.

Second generation antidepressants like selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are considered as the first line therapy in treating depression.[12,13] Others such as tetracyclics like mirtazapine are frequently used in elderly patients with depression. Our previous investigations have found that, the most frequently prescribed antidepressants in nursing homes were SSRIs, tetracyclics, and SNRIs.[14,15] Pharmacotherapy to manage depression can not only have short-term effects on depression symptomatology, but also render cognitive benefits. Two recent systematic reviews have found that SSRIs and SNRIs may offer a protective effect on cognitive impairment.[16,17]

Antidepressants can improve cognition in short-term and reduce the risk of dementia in long-term in two primary ways. First, antidepressants can reduce depression symptomatology and associated neurobiological abnormalities, and thereby improve cognition in patients with depression.[18] Previous studies have found strong evidence of improvement in cognition with decreased depression symptomatology.[3,16,17,19] Second, positive effects of neural progenitors, reduction of pro-inflammatory mediators, and stimulation of neurotrophic factors attributed to the use of antidepressants can improve cognition and exert neuroprotective effects against dementia.[20-22] Various second generation antidepressant classes improve depression symptomology by different mechanisms of action leading to differences in direct and indirect effects.[23,24] However, very little is known about the comparative effectiveness of second generation antidepressants in improving cognition and reducing the risk of dementia in the elderly, and none have examined the short and long-term beneficial effects of antidepressants in nursing homes, a setting with a significant disease burden. Given the high prevalence of

depression in nursing homes and its associated risks of cognitive impairment and dementia, it is important to examine the comparative effectiveness of antidepressants on cognition and dementia. The specific aims of this research were:

Specific Aim 1: To examine the comparative effectiveness of 3 commonly used second generation antidepressants classes on cognition in elderly nursing home residents with depression.

Hypothesis 1: Due to differences in pharmacology, there are differences among second generation antidepressants classes on cognition in elderly nursing home residents with depression after adjusting for other confounding factors.

Specific Aim 2: To evaluate the comparative effectiveness of 3 commonly used second generation antidepressants classes on dementia in elderly nursing home residents with depression.

Hypothesis 2: Due to differences in pharmacology, there are differences among second generation antidepressants classes on the risk of dementia in elderly nursing home residents with depression after controlling for selection bias.

BACKGROUND AND SIGNIFICANCE

Depression and Cognition

Depression is one of the most common mental disorders in the elderly population in long-term care.[25] Characterized by several physical, psychological, and behavioral symptoms, it can include depressed mood, irritability, anxiety, social withdrawal and fatigue. Depression is a major public health concern because it affects a large number of elderly people and has a significant impact on quality of life.[26] Prevalence rates vary by setting and definitions used; depression affects up to 10% of the community-dwelling elderly and up to 35% of the institutionalized elderly.[27-29] In general, prevalence rates of depression in nursing homes are up to 5 times that of community settings.[30] Residents with depression require more staff services and healthcare utilization, and are at significant risk for one-year mortality.[31,32] Consequently, the Omnibus Budget Reconciliation Act of 1987 incorporated regulations to improve care for residents with depression.[33]

Depression and Dementia

Depression is a major risk factor for cognitive decline and dementia.[8-11] Nursing home residents with depression often present with significant cognitive complaints or deficits including impairment in executive function, attention, memory, and processing of information.[34] Neuronal studies have found greater reduction in white and grey matter volumes consistent with small vessel vascular changes in depression patients.[35] Structural and functional imaging evidence shows significant disruption in prefrontal-striatal pathways that could affect executive functioning, information processing, and other cognitive functions in the above population. Studies have consistently found that depression is a major risk factor for dementia.[8,9,36] The possible hypotheses include (i) depression as a prodromal phase of dementia, (ii) depression as a

disease that unmasks impending dementia, and (iii) depression can damage the hippocampus via glucocorticoid cascade.[36]

Antidepressants use and Cognition

The treatment guidelines recommend second generation antidepressants as first line of therapy for depression.[12] The first generation antidepressants like tricyclic antidepressants and monoamine oxidase inhibitors are not preferred in the elderly due to their safety profiles.[37,38] The second generation antidepressants like SSRIs and SNRIs are drugs of choice in older patients. Other classes such as tetracyclics and serotonin modulators are alternatives to first line agents.[12,13] Meta-analytical studies have found that, second generation classes like SSRIs and SNRIs are effective in the elderly, with response and remission rates of 1.40 and (95% CI 1.24 – 1.57) and 1.27 (95% CI 1.12–1.44), respectively.[39] A previous study has found that in 2007, up to 90% of elderly nursing home residents with depression in the US used antidepressants, mostly SSRIs.[15]

A few studies have evaluated the effects of selected antidepressants on cognition in elderly. These studies suggest that SSRIs have little or no anticholinergic activity and therefore, may not cause any harmful effect on cognition in depressed elderly patients.[18,40,41] A pooled analysis of two double-blind 12-week studies conducted in elderly patients indicated that antidepressant use was associated with improvement in cognitive function that was highest for sertraline followed by nortriptyline and fluoxetine.[18]

Antidepressants use and Dementia

Previous studies have indicated that antidepressants exert neuroprotective effects due to their response on neural progenitors in hippocampus and improved survival of newborn neurons.[21,22,42] Others have suggested that antidepressants can suppress serum and plasma levels

of pro-inflammatory mediators, which can lead to chronic inflammation and thus dementia.[43] Antidepressants can also stimulate brain derived neurotrophic factor (BDNF), transforming growth factor beta 1 (TGF-β1) synthesis and can thus exert neuroprotective effects against dementia.[20]

Two observational studies conducted in Danish population examined the effect of antidepressant use on dementia. The authors concluded that long-term use of antidepressants was associated with reduced dementia risk. However, the researchers observed some unanticipated findings such as decreased rate of dementia among non-users and older antidepressants (e.g. Tricyclic antidepressants (TCAs)) when compared to the newer antidepressants (SSRIs, newer non-SSRI antidepressants.[44,45] However, there were severe methodological limitations in these studies such as the inclusion of prevalent users of antidepressants, and weak study design.

Significance

Depression and dementia are common disorders in nursing homes as they are considered major precipitants of long-term care admission. Recent national estimates suggest that over one-third of nursing home residents have depression,[29] and over 50% have dementia.[46] The total cost of dementia was estimated between $157 billion to $215 billion in 2010; nursing home care accounts for nearly 66% of dementia care.[47] Prevention of dementia can be valuable in reducing this healthcare burden. Since depression is a major risk factor for dementia, there is a significant need to manage these at-risk patients to reduce dementia burden.

Antidepressants can improve cognition in short-term and reduce risk of dementia in long-term in two primary ways.[18,20-22] First, antidepressants can reduce depression symptomatology and associated neurobiological abnormalities, and thereby improve cognition in patients with depression.[18] Previous studies have found strong evidence of improvement in cognition with

decreased depression symptomatology.[3,16,17,19] However, antidepressants improve symptomology by different mechanisms of action.[23,24] Second, positive effects of neural progenitors, reduction of pro-inflammatory mediators, and stimulation of neurotrophic factors attributed to the use of antidepressants can improve cognition and exert neuroprotective effects against dementia.[20-22]

Two recent meta-analyses found that SSRIs, SNRIs, and Tetracyclics are similar in their efficacy but they have different onsets of action and safety profiles due to different receptor binding properties and sites of action.[48,49] For example, paroxetine is highly anticholinergic among the SSRIs. Mirtazapine has faster onset of action than other second generation antidepressants.[48] These differences can lead to differential short- and long-term cognitive effects which may be clinically relevant.[48,49] However, none of the studies have examined comparative effectiveness of SSRIs, SNRIs and Tetracyclics on cognition and dementia. Therefore, there is a strong need to conduct head to head comparison of second generation antidepressant classes in the elderly using a strong study design and analytical approach. The primary goal of this study was to evaluate comparative effectiveness of different second generation antidepressant classes on cognition and dementia in a real world setting. The findings from this observational study will provide empirical knowledge regarding the beneficial effects of antidepressants and strong evidence base for the comparative effectiveness of frequently prescribed antidepressant classes in reducing the risk of cognitive impairment and dementia in elderly patients with depression.

REFERENCES

1. Kamat SM, Kamat AS, Grossberg GT. Dementia risk prediction: are we there yet? *Clinics in geriatric medicine.* Feb 2010;26(1):113-123.

2. Sherrod RA, Collins A, Wynn S, Gragg M. Dissecting dementia, depression, and drug effects in older adults. *Journal of psychosocial nursing and mental health services.* Jan 2010;48(1):39-47.

3. Steffens DC, Potter GG. Geriatric depression and cognitive impairment. *Psychological medicine.* Feb 2008;38(2):163-175.

4. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Jul 2007;3(3):186-191.

5. Thies W, Bleiler L. 2011 Alzheimer's disease facts and figures. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Mar 2011;7(2):208-244.

6. Middleton LE, Yaffe K. Promising strategies for the prevention of dementia. *Archives of neurology.* Oct 2009;66(10):1210-1215.

7. Jorm AF, Korten AE, Henderson AS. The prevalence of dementia: a quantitative integration of the literature. *Acta psychiatrica Scandinavica.* Nov 1987;76(5):465-479.

8. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Archives of general psychiatry.* May 2006;63(5):530-538.

9. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology.* Sep 1998;51(3):728-733.

10. Christensen H, Griffiths K, Mackinnon A, Jacomb P. A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *Journal of the International Neuropsychological Society : JINS.* Nov 1997;3(6):631-651.

11. Williams JW, Plassman BL, Burke J, Benjamin S. Preventing Alzheimer's disease and cognitive decline. *Evid Rep Technol Assess.* Apr 2010;(193):1-727.

12. Alexopoulos GS, Katz IR, Reynolds CF, 3rd, Carpenter D, Docherty JP. The expert consensus guideline series. Pharmacotherapy of depressive disorders in older patients. *Postgraduate medicine.* Oct 2001;Spec No Pharmacotherapy:1-86.

13. Salzman C, Small GW. Treatment of depression with new antidepressants. In: Salzman C, ed. *Clinical geriatric psychopharmacology*. Philadelphia: Lippincott, Williams and Wilkins; 2005:305-333.

14. Karkare SU, Bhattacharjee S, Kamble P, Aparasu R. Prevalence and predictors of antidepressant prescribing in nursing home residents in the United States. *The American journal of geriatric pharmacotherapy.* Apr 2011;9(2):109-119.

15. Aparasu RR, Bali V. Antidepressant use among elderly nursing home residents with depression in the United States. *65th Annual Indian Pharmaceutical Congress*. New Delhi, India. 2013.

16. Biringer E, Rongve A, Lund A. A Review of Modern Antidepressants Effects on Neurocognitive Function. *Current Psychiatry Reviews.* 2009;5(3):164-174.

17. Francomano A, Bonanno B, Fucà L, La Placa M, La Barbera D. The role of antidepressant treatments on cognitive deficits a review of recent literature. *Clin Neuropsychiatry.* 2011;8:354-366.

18. Doraiswamy PM, Krishnan KRR, Oxman T, et al. Does antidepressant therapy improve cognition in elderly depressed patients? *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2003;58(12):M1137-M1144.

19. Culang ME, Sneed JR, Keilp JG, et al. Change in cognitive functioning following acute antidepressant treatment in late-life depression. *American Journal of Geriatric Psych.* 2009;17(10):881-888.

20. Caraci F, Copani A, Nicoletti F, Drago F. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. *European journal of pharmacology.* 2010;626(1):64-71.

21. Banasr M, Duman RS. Regulation of neurogenesis and gliogenesis by stress and antidepressant treatment. *CNS & neurological disorders drug targets.* Oct 2007;6(5):311-320.

22. Dranovsky A, Hen R. Hippocampal neurogenesis: regulation by stress and antidepressants. *Biological psychiatry.* Jun 15 2006;59(12):1136-1143.

23. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. *Primary care companion to the Journal of clinical psychiatry.* 2001;3(1):22-27.

24. Moller HJ, Volz HP. Drug treatment of depression in the 1990s. An overview of achievements and future possibilities. *Drugs.* Nov 1996;52(5):625-638.

25. Consensus statement on improving the quality of mental health care in U.S. nursing homes: management of depression and behavioral symptoms associated with dementia. *Journal of the American Geriatrics Society.* Sep 2003;51(9):1287-1298.

26. Alexopoulos GS, Buckwalter K, Olin J, Martinez R, Wainscott C, Krishnan KR. Comorbidity of late life depression: an opportunity for research on mechanisms and treatment. *Biological psychiatry.* Sep 15 2002;52(6):543-558.

27. Gallo JJ, Lebowitz BD. The epidemiology of common late-life mental disorders in the community: themes for the new century. *Psychiatr Serv.* Sep 1999;50(9):1158-1166.

28. Lebowitz BD, Pearson JL, Schneider LS, et al. Diagnosis and treatment of depression in late life. Consensus statement update. *JAMA : the journal of the American Medical Association.* Oct 8 1997;278(14):1186-1190.

29. Thakur M, Blazer DG. Depression in long-term care. *Journal of the American Medical Directors Association.* 2008;9(2):82-87.

30. Blazer DG. Depression in late life: review and commentary. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2003;58(3):M249-M265.

31. Fries BE, Mehr DR, Schneider D, Foley WJ, Burke R. Mental dysfunction and resource use in nursing homes. *Med Care.* Oct 1993;31(10):898-920.

32. Kane KD, Yochim BP, Lichtenberg PA. Depressive symptoms and cognitive impairment predict all-cause mortality in long-term care residents. *Psychology and aging.* Jun 2010;25(2):446-452.

33. Act OBR. Public Law 100-203. *Nursing Home Reform, Part C.* 1987.

34. Wilkins CH, Mathews J, Sheline YI. Late life depression with cognitive impairment: evaluation and treatment. *Clinical interventions in aging.* 2009;4:51-57.

35. Crocco EA, Castro K, Loewenstein DA. How late-life depression affects cognition: neural mechanisms. *Current psychiatry reports.* 2010;12(1):34-38.

36. Jorm AF. Is depression a risk factor for dementia or cognitive decline? A review. *Gerontology.* 2000;46(4):219-227.

37. Anderson IM. SSRIS versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety.* 1998;7 Suppl 1:11-17.

38. Yamada M, Yasuhara H. Clinical pharmacology of MAO inhibitors: safety and future. *Neurotoxicology.* Jan 2004;25(1-2):215-221.

39. Nelson JC, Delucchi K, Schneider LS. Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* Jul 2008;16(7):558-567.

40. Knegtering H, Eijck M, Huijsman A. Effects of antidepressants on cognitive functioning of elderly patients. A review. *Drugs & aging.* Sep 1994;5(3):192-199.

41. Oxman TE. Antidepressants and cognitive impairment in the elderly. *The Journal of clinical psychiatry.* 1996;57 Suppl 5:38-44.

42. Hunsberger J, Austin DR, Henter ID, Chen G. The neurotrophic and neuroprotective effects of psychotropic agents. *Dialogues in clinical neuroscience.* 2009;11(3):333.

43. Hashioka S, McGeer PL, Monji A, Kanba S. Anti-inflammatory effects of antidepressants: possibilities for preventives against Alzheimers disease. *Central Nervous System Agents in Medicinal Chemistry.* 2009;9(1):12-19.

44. Kessing LV, Forman JL, Andersen PK. Do continued antidepressants protect against dementia in patients with severe depressive disorder? *International clinical psychopharmacology.* Nov 2011;26(6):316-322.

45. Kessing LV, Sondergard L, Forman JL, Andersen PK. Antidepressants and dementia. *Journal of affective disorders.* Sep 2009;117(1-2):24-29.

46. Chatterjee S, Mehta S, Sherer JT, Aparasu RR. Prevalence and predictors of anticholinergic medication use in elderly nursing home residents with dementia: analysis of data from the 2004 National Nursing Home Survey. *Drugs & aging.* Dec 1 2010;27(12):987-997.

47. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *The New England journal of medicine.* Apr 4 2013;368(14):1326-1334.

48. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive DisorderAn Updated Meta-analysis. *Annals of internal medicine.* 2011;155(11):772-785.

49. Gartlehner G, Thieda P, Hansen RA, et al. Comparative risk for harms of second-generation antidepressants : a systematic review and meta-analysis. *Drug Saf.* 2008;31(10):851-865.

The next two sections provide study design details, results, conclusions in the form of manuscript drafts for each of the specific aims

Manuscript 1: Specific Aim 1

Manuscript 2: Specific Aim 2

MANUSCRIPT 1

Comparative Effectiveness of Second Generation Antidepressants on Cognition in the Elderly Nursing Home Residents with Depression

ABSTRACT

Background: Second generation antidepressants like selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and tetracyclics are commonly used for the treatment of depression in elderly nursing home residents. Past literature suggests differential effects of these antidepressants on cognition. However, none of the studies assessed the comparative safety of second generation antidepressants with respect to cognition.

Objective: The aim of this study was to evaluate the association between cognition and use of SSRIs, SNRIs and tetracyclics in elderly nursing home residents with depression with age ≥ 65 years.

Methods: A multiple propensity score adjusted retrospective cohort study was conducted using data from Medicare Part D claims and Minimum Data Set (MDS) from 2007-2010. New users of SSRIs, SNRIs and tetracyclics were followed until they reached the end of the follow up period (1 year), switched to a different antidepressant class, used psychotherapy, had a gap of more than 15 days in the use of the index antidepressant class, whichever occurred earlier. The repeated measures mixed model was used to evaluate the comparative effectiveness of SSRIs, SNRIs and tetracyclics with respect to cognition. The covariates in the final model included propensity scores and their interaction terms.

Results: The study cohort comprised of 1,518 elderly nursing home residents. Of these, 1,081 received SSRIs (71.21%), 320 received tetracyclics (21.08%) and 117 received SNRIs (7.71%).

After adjusting for propensity scores, the repeated measure mixed model did not find any statistically significant difference in cognition with the use of SSRIs (β = -0.23 [95% CI, -0.67, 0.22) or tetracyclics (β = -0.45 [95% CI, -0.96, 0.05]) when compared to SNRIs (reference group).

Conclusions: This study found no significant difference in the comparative effectiveness of SSRIs, SNRIs and tetracyclics with respect to cognition in elderly nursing home residents with depression. Further studies are needed to evaluate the overall safety profiles of the second generation antidepressants in this vulnerable population.

INTRODUCTION

Depression is one of the most common diseases among the elderly population in long-term care.[29] It is characterized by several physical, psychological and behavioral symptoms which include depressed mood, irritability, anxiety, social withdrawal and fatigue, among others.[50] Depression in later life is a major public health concern because it affects a large number of elderly people and has a significant impact on quality of life due to impaired physical and cognitive function.[51,30] Late-life depression refers to depressive syndromes defined as a mood disorder with symptoms of sadness, negative self-regard, loss of interest in life, and disruptions of sleep, appetite, thinking, and energy level that interfere with daily life. Depression in the elderly includes major depressive disorder, dysthymic disorder, and minor depression. Prevalence rates vary by setting and definitions used; depression affects up to 10% of community-dwelling elderly and up to 35% of institutionalized elderly.[30] In general, prevalence rates of depression in nursing homes are up to 5 times that of community settings.[52] Several biological, physiological, and social factors contribute to a high prevalence of depression in nursing homes.[53] These factors are intrinsic and extrinsic in nature and commonly include psychosocial stressors, medical conditions, and medications. Residents with depression require more staff services and healthcare utilization, and are at significant risk for one-year mortality. Consequently, the Omnibus Budget Reconciliation Act of 1987 incorporated regulations to improve care for residents with depression.[33]

Nursing home residents with depression often present with significant cognitive complaints or deficits including impairment in executive function, attention, memory, and processing of information.[54,55] Neuronal studies have found greater reduction in white and grey matter volumes consistent with small vessel vascular changes in depression patients.[56] Structural

and functional imaging evidence shows significant evidence of disruption in prefrontal-striatal pathways that could affect executive functioning, information processing, and other cognitive deficits in the above population.[57,58] A meta-analysis by Christensen et al. (1997) revealed that depressive patients had lower performance on almost all cognitive tests.[10] A recently published Agency for Healthcare Quality and Research (AHRQ) report found probable increased risks of cognitive decline based on thirteen studies with a follow-up of 1.5 to 5.6 years in later life. This report summarized results qualitatively and did not provide an estimate of the effect size owing to variability in the measurement of depressive symptoms.[11]

As shown in **figure 1**, several molecular and neurobiological mechanisms establish the link between depression and cognitive impairment in elderly patients. Various animal and human studies have shown that depression activates the hypothalamic-pituitary-adrenal (HPA) axis that in turn damages the hippocampus and increases adrenal glucocorticoid levels, ultimately resulting in hippocampal atrophy and cognitive deficits.[20,59-61] Depression-induced alteration in the serotonergic system along with the HPA axis can lead to Alzheimer's disease related neurodegeneration like the formation of neurofibrillary tangles and amyloid plaques.[20,59-61] Several studies have also shown that chronic inflammation plays a central role in the pathophysiology of depression, cognitive impairment and dementia.[20] Chronic inflammation leads to increased levels of proinflammatory cytokines, which in turn decreases anti-inflammatory regulation and hippocampal neurogenesis thereby leading to decrease in cognition and ultimately dementia.[20,59-61] Another proposed link between depression, cognitive impairment and dementia is a decrease in the levels of neurotophic factors such as brain-derived neurotrophic factor (BDNF) and transforming growth factor (TGF-β_1) that impairs neuronal protection and signaling. The ‘vascular depression hypothesis’ which states that cerebrovascular diseases

predispose to, precipitates or perpetuates geriatric depressive syndromes also supports the link between depression, cognitive impairment and dementia. A number of studies have reported that cortical white matter lesions as well as structural brain changes may contribute to late-life depression or vice versa. Ischemic changes in frontostriatal brain regions may lead to substantial cognitive deficits.[20,59-61]

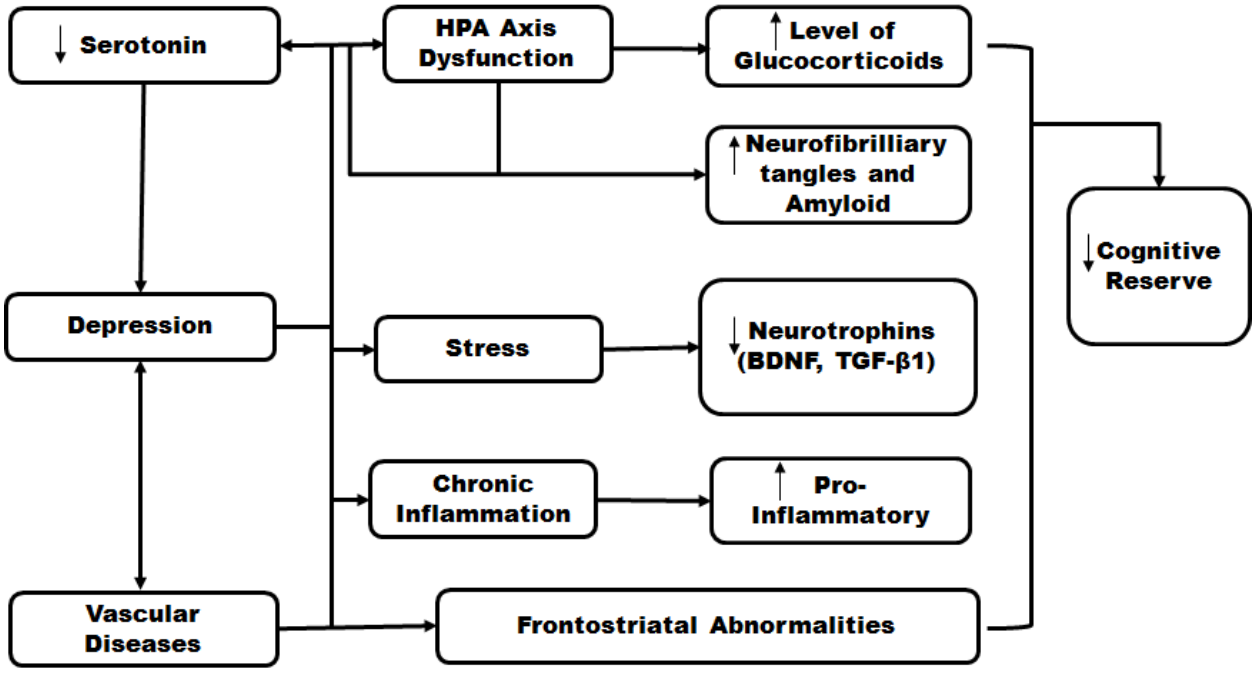

Figure 1: Relationship between depression and risk of cognitive impairment

In 1993, the Agency for Healthcare Research and Quality (AHRQ) developed guidelines for the treatment of depression.[62] The American Medical Director's Association (AMDA) updated the AHRQ guidelines and adapted them to nursing homes.[63] The treatment guidelines recommended psychotherapy and antidepressants in treatment plans based on the type and severity of depression. The psychotherapy preferred in the elderly includes cognitive behavioral therapy, supportive psychotherapy and interpersonal psychotherapy. Among the antidepressants, selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, escitalopram, fluoxetine, and

sertraline are drugs of choice in older patients. Serotonin-norepinephrine reuptake inhibitor (SNRIs) such as duloxetine, venlafaxine are also considered as the first line agents. Other classes such as dopamine norepinephrine reuptake inhibitor (bupropion), tetracyclics (mirtazapine), serotonin modulator (trazodone) are alternatives if the first lines are not tolerated or effective. Tri-cyclic antidepressants (TCAs) such as amitriptyline and doxepin are often considered inappropriate as they are associated with anticholinergic effects. Previous studies have reported that 65-74% of depressed elderly nursing home patients received an antidepressant, mainly SSRIs.[14,64]

As shown in **figure 2**, antidepressants can improve cognitive impairment in two primary ways. Firstly, antidepressants can reduce depression severity and thereby improve cognition in patients with depression. Previous studies have found strong evidence of improvement in cognition with decreased depression symptomatology.[3,16,17,19] Secondly, antidepressants can suppress serum and plasma levels of pro-inflammatory mediators, which can lead to chronic inflammation and decrease in cognitive reserve.[43] Antidepressants also stimulate BDNF and TGF- β_1) synthesis and thus can exert neuroprotective effects against Alzheimer disease.[20] Antidepressant agents increase monoaminergic activity and thereby play a crucial role in modulation of cognition. However, SSRIs, SNRIs, and tetracyclics improve depression symptomology by different mechanisms of action.[23,24] SSRIs block the reuptake of 5-hydroxytryptamine receptors (5HT) and increase synaptic 5HT transmission. Although most SSRIs lack any muscarinic and histaminergic receptors activity, some SSRIs like paroxetine act on muscarinic receptors and can worsen cognitive impairment due to its anticholinergic activity. SNRIs improve depression symptomology by blocking the reuptake of both norepinephrine (NE) and serotonin (5HT). Additionally, they do not cause any anticholinergic, sedative, or

hypotensive side effects. Tetracyclics such as mirtazapine act on both adrenergic (α2 antagonist) and serotonergic (5-HT2 antagonist) receptors.[23,24]

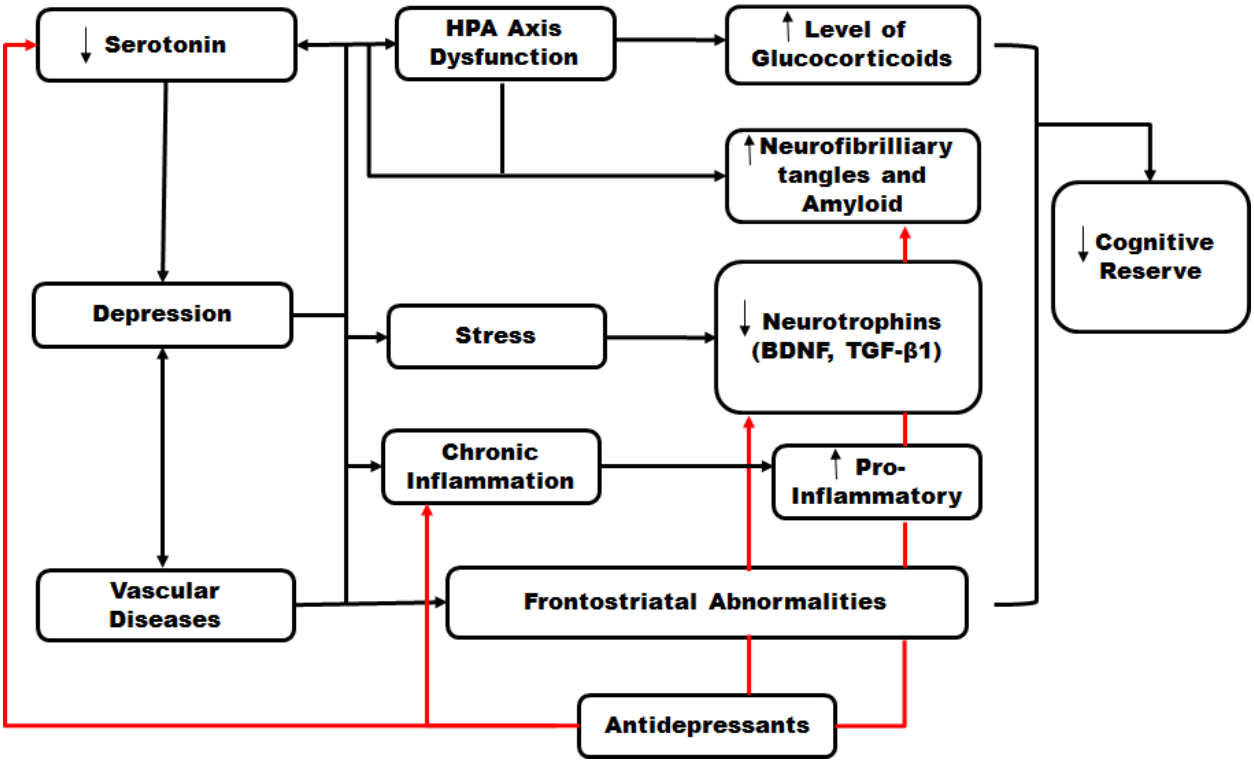

Figure 2: Relationship between antidepressant, depression and risk of cognitive impairment

Evidence from previous literature suggests differential effect of antidepressants on cognition. Biringer et al. (2009) reviewed the effects of modern antidepressants on neurocognitive function and found that paroxetine is associated with a lower performance on neurocognitive tests than other SSRIs; and that sertraline has a better performance on neurocognitive function than the other SSRIs. Additionally, SNRIs may be more beneficial with regard to cognitive function than other antidepressants.[16] A recent literature review conducted by Francomano and colleagues (2011) summarized the impact of antidepressants on cognition. They concluded that an early treatment with antidepressants, especially SSRIs and SNRIs may offer a

protective effect on cognitive impairment. They also suggest that SNRIs appear to have a stronger effect on cognitive functions which persists even after cessation of the treatment during recovery.[17] Two meta-analyses that looked at the benefits and harms of second generation antidepressants for treating major depressive disorder found that SSRIs, SNRIs, and tetracyclics were similar in their efficacy and side-effects despite having different onsets of action and adverse event profiles due to different receptor binding properties and sites of action.[48,49] For example, mirtazapine has a statistically significantly faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline.[48] Paroxetine and mirtazapine led to higher weight gain than other second generation antidepressants. As per the American Geriatrics Society 2012 Beers Criteria, paroxetine has strong anticholinergic properties and can lead to cognitive problems in the elderly.[65] These differences can lead to differential cognitive effects which may be clinically relevant and influence the choice of a medication for a particular patient.[48,49]

Little is known about the cognitive effects of antidepressants in depressed elderly patients. Available literature suggests that SSRIs have little or no anticholinergic activity and therefore, may not cause any harmful effect on cognition in depressed elderly patients.[18,40,41] Doraiswamy et al. (2003) examined the effects of antidepressants on cognitive functioning in elderly patients with depression by pooling data from two double-blind 12-week studies. Their study found that improvements in depression and improvement in tested cognitive function were highest for patients receiving sertraline followed by nortriptyline and fluoxetine.[18] Mainly, it is unclear if pharmacological differences in second generation antidepressant classes translate into differential effects on cognition, particularly in elderly nursing home, a setting with high prevalence of depression and risk of cognitive impairment. This ambiguity needs to be resolved quickly as second generation antidepressants, specifically; SSRIs, tetracyclics, and SNRIs are the

most commonly prescribed classes of antidepressants in depressed nursing home residents.[14,15] Consequently, this study tested the hypothesis that the short-term effectiveness of different antidepressant classes, mainly SSRIs, SNRIs and tetracyclics varies due to differences in direct and indirect effects on cognitive performance. The primary goal of this study was to evaluate comparative effectiveness of different antidepressant classes in reducing the risk of cognitive impairment in elderly nursing home residents with depression. The findings from this observational study will generate empirical knowledge regarding beneficial effects of antidepressants and provide a strong evidence base for the comparative effectiveness of antidepressant classes in reducing the risk of cognitive impairment. This information will be valuable to clinicians in the management of depression and reducing cognitive impairment in elderly nursing home residents with depression.

METHODS

Data Source

The present study used four years (2007-2010) of Medicare data obtained from the Centers for Medicare and Medicaid Services Chronic Condition Data Warehouse (CCW) to achieve the research objective.[66] Medicare Part D, launched in 2006, provides prescription benefits for Medicare beneficiaries but its structure differs from Part A and B benefits. For Part D, Medicare enrollees sign up for prescription drug plans administered by a private third party payer such as a pharmaceutical benefit management company or health insurer.[67] The MDS is a national standardized assessment tool which forms the foundation of a comprehensive assessment of all residents in federally certified nursing home facilities.[68,69] The MDS contains over 350 variables designed to provide extensive clinical and assessment data for individual residents.[70] Most of these data elements reflect the resident's condition during the seven days

prior to the assessments. They are documented by the nursing staff trained in MDS standardized assessments and are then electronically captured. Previous studies reported strong inter-rater reliability and internal consistency of scales used for the assessment of nursing home residents.[71,72] This study used 2007-2010 MDS linked Medicare claims including Part D data to address the research objective.

All Centers for Medicaid & Medicare Services (CMS) certified nursing homes are required to complete comprehensive MDS annual assessments on each resident admission and when the resident shows "significant change in status". A subset of the full MDS assessment is conducted quarterly. The admission assessment in MDS is completed within 14 calendar days of admission to the facility and the annual assessment is completed within 366 days of the admission assessment but not more than 92 days of a quarterly assessment. Quarterly assessments are brief in nature and are captured quarterly or following any adverse events.[72-77] This study was approved by the University of Houston Committee for the Protection of Human Subjects under the exempt category.

Study Design and Cohort

A retrospective cohort design involving propensity score adjustment was used in this study to examine the comparative risk of cognitive impairment in elderly long-term care patients diagnosed with depression and using SSRIs, SNRIs and tetracyclics. **Figure 3** outlines the definitions used to construct the study and comparison groups. Patients were classified as long-term residents if they had an admission assessment matched with an annual assessment. Use of the index antidepressant was defined as having a first prescription of an antidepressant after at least six months without any prescription fill date for any of the above medications. Patients were identified as elderly new users of antidepressants if they were: (i) 65 years and older; (ii)

diagnosed with depression, (iii) initiated SSRIs, SNRIs or tetracyclics antidepressant after 6 months washout period; (iii) continuously eligible for Medicare Part D in the six months baseline and during one year of follow up; (iv) non-comatose and (v) not diagnosed with dementia in the baseline period. MDS assessments are not conducted for subjects, who are comatose, thus these patients were excluded in the present study. [78]

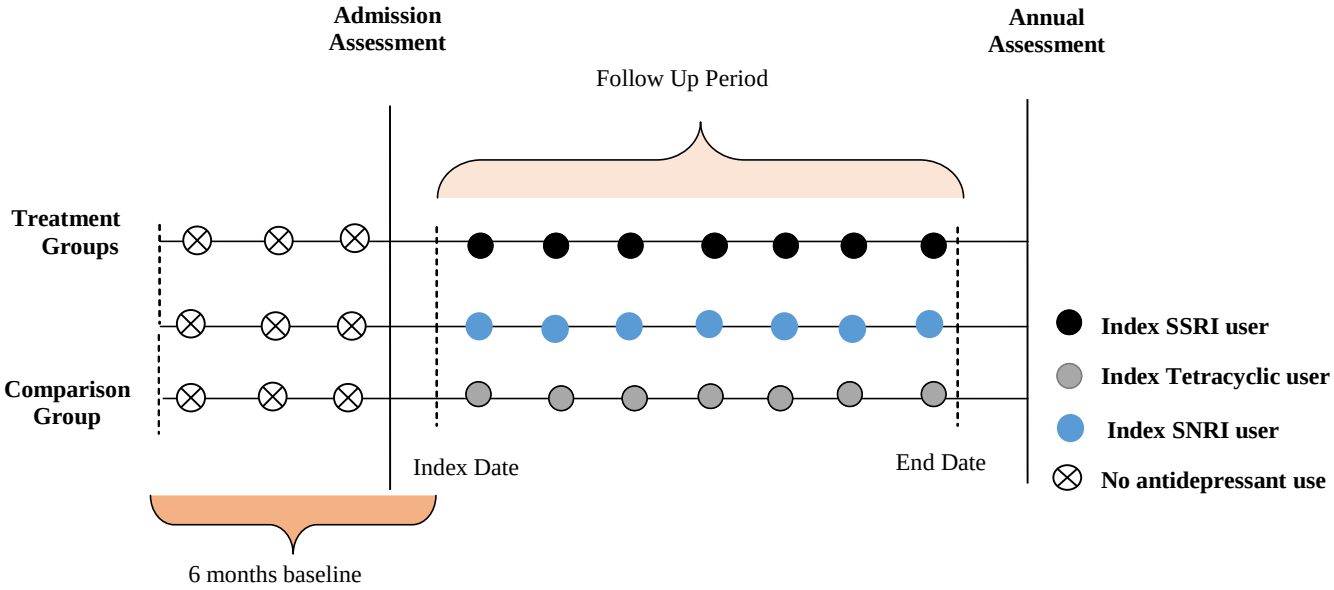

Figure 3: Development of study and comparison groups

Exposures and Outcome Definitions

The index antidepressant exposure was measured using Part D claims data. Antidepressant agents were grouped into SSRIs, SNRIs and tetracyclics. These three classes were selected given their high prevalence of use in nursing home residents with depression.[15] SSRIs included sertraline, escitalopram, fluoxetine, fluvoxamine, citalopram and paroxetine; SNRIs included venlafaxine, desvenlafaxine, milnacipran and duloxetine; tetracyclics included mirtazapine and maprotiline. The Multum drug classification codes and National Drug Codes

(NDC) in the Medicare Part D prescription claims were used to identify new antidepressant users with six months of washout period without antidepressant use.

The primary outcome measured was cognitive improvement, identified using MDS Cognition Scale. MDS Cognition Scale is a 11-point scale that ranges from 0 (intact cognition) to 10 (very severe impairment), and evaluates short- and long-term memory, orientation, communication, and dressing.[79] MDS Cognition Scale is highly correlated with the Mini-Mental State Examination (MMSE) in nursing home residents,[80] and has been proposed as more continuous, more intuitive, easier to compute, and better at discriminating among the severely impaired than the Cognitive Performance Scale.[79,80] It has also been found to be valid for measuring cognition in nursing home residents.[71,81] Cognition was measured as a continuous variable using MDS Cognition Scale. Quarterly assessments after antidepressants initiation were used to assess cognition. The maximum follow up period for the study was one year. Study subjects were censored if they reached the end of the follow up period; switched to a different antidepressant; had a gap of more than 15 days in the use of the index antidepressant;[82-84] used psychotherapy; whichever occurred earlier.

Multiple Propensity Score Adjustment

The strength of observational studies lies in their ability to estimate treatment effects in real world settings. However, selection bias due to non-randomization is a key concern in observational studies.[85] This bias occurs because selection of a medication is based on both observable and non-observable factors that are considered non-random.[86] Propensity scores are frequently applied in observational studies to reduce overt selection bias.[87,88] Overt bias occurs as a result of existing pretreatment differences rather than treatment effects due to lack of randomization in observational studies.[86] The propensity score method was proposed by

Rosenbaum and Rubin in 1983,[89] and is the conditional probability of assignment to a particular treatment given a vector of observed covariates. There are four commonly used propensity score methods.[87,90] Studies comparing the ability of various propensity score models to balance the measured variables between the treated and control subjects found that covariate adjustment using the propensity score had the best performance in estimating relative risks.[91,92] Moreover, in clinical practice, the use of matching and stratification based on propensity scores becomes difficult when there are multiple treatment groups. Since this investigation involves three groups, the multiple propensity score adjustment method was used to achieve the study objective.

The present study employed the 7-step approach for the calculation of multiple propensity score as recommended by Spreeuwenberg et al. (2010).[93] The steps include estimating the treatment effects before propensity score adjustment, checking the distribution of the baseline covariates, selection of pretreatment characteristics to estimate the propensity scores, estimation of the propensity scores, checking distribution after propensity score adjustment and estimating the treatment effect after propensity score adjustment. The baseline confounders and risk factors for the outcome were identified using the conceptual framework of the Andersen Behavioral Model (ABM). According to the ABM, an individual's health service use including medication use is a function of predisposing, enabling and need factors.[94] The critical step is the calculation of propensity scores using multinomial logistic regression with treatment allocation as the dependent variable and baseline covariates as the explanatory variables. Predisposing, enabling, and need factors for this study were selected from past literature and availability of variables in the MDS and Medicare datasets.[6,11,95-97]

Demographic characteristics such as age, gender, and race were grouped under predisposing factors. Enabling factors included type of prescription insurance. Need factors

included cognitive characteristics, behavioural characteristics, comorbidities and use of medications captured at the baseline period. Depression severity was captured using Minimum Data Set Depression Rating Scale (MDSDRS).[98] Cognitive characteristics were captured using baseline MDS Cognition Scale. Behavioural characteristics were evaluated using Index of Social Engagement and Aggressive Behavior Scale and Pain Scale. Medical conditions included were arthritis, cancer, asthma, chronic obstructive pulmonary disease (COPD), Parkinson's disease, diabetes, hypertension, stroke, congestive heart failure (CHF), other cardiac disorders, schizophrenia, anxiety disorder, manic depression. Use of medications such as antipsychotics, antianxiety, hypnotics, diuretics and utilization of psychotherapy were classified as need factors.

Multinomial logistic regression was used to estimate the multiple propensity scores. This study compared three treatment groups, hence three propensity scores (calculated as the estimated predicted probabilities of assignment to one of the three treatment groups) were obtained for each subject as per Spreeuwenberg et al. (2010).[93] However, only two propensity scores were needed for the purpose of covariate adjustment as the three calculated propensity scores add up to one. In the adjusted analysis, two propensity scores along with their interaction terms were included to obtain robust estimates.[93] The use of multinomial logistic regression for calculation of propensity scores also required testing for the assumption of independence of irrelevant alternatives.[99] This assumption was checked using the Hausman test, and it was found that omitting SNRIs did not significantly change the parameter estimates (χ^2 test, 30.20; P = 0.99) of the full model versus the reduced model.

Statistical analysis

An appropriately calculated multiple propensity score should achieve balance in the distribution of all the observed covariates between the three treatment groups. Similarities among

the three treatment groups before and after correction on the multiple propensity score were assessed using logistic regression analysis for the dichotomous variables, ANCOVA for the continuous variables and multinomial logistic regression analysis for the nominal variables. Antidepressant treatment was used as a fixed factor along with two out of three propensity scores and their interactions terms as covariates.[93]

The primary outcome measured was cognition which was measured using MDS Cognition Scale. Quarterly assessments after the index antidepressant initiation were used to assess cognition. Residents who are in a nursing home for long-term would have their cognition measured at every 90-day period between admission and annual assessment. As a result, the outcome measure is repeated for each resident and outcome measurements made on the same resident are correlated with each other. In the final step, the repeated measures mixed model analysis was used to examine the association between cognition and use of SSRIs, SNRIs and tetracyclics in elderly nursing home residents with depression. This regression model accounts for correlation among outcome measurements collected on the same resident, allows for missing data and uses all available data for the analysis.[100] Results were presented as beta (β) estimates along with 95% confidence intervals using SNRIs use as the reference category. Statistical significance was set at an a priori α level of 0.05.

Sensitivity analysis

Additional sensitivity analysis was conducted to evaluate the robustness of the study findings. In the sensitivity analysis, generalized linear regression model was used. In this model, baseline covariates were measured at admission assessment and outcomes was measured at first quarterly assessment after the index antidepressant use.

RESULTS

Figure 4 presents the process of development of study cohort and sample selection. Nursing home residents might have several admission and annual assessments. To keep uniformity, only the last admission and first annual assessment conducted during the nursing home stay were used to capture long-term care residents. There were 44,475 nursing home residents with a gap ≥ 365 days between last admission and first annual assessment during 2007-2010. Of these, 33,371 residents had continuous Part D coverage 6 months before and one year after admission assessment date. Among these, 24,137 patients used antidepressants within 1 year of admission assessment. Out of these, 5,670 had not used any antidepressant in the past 6 months and were classified as new users of antidepressants. Among these new users, 3,969 patients had a gap greater than 365 days and less than 568 days between last admission and first annual assessment. Of these nursing home residents, 2,288 residents did not receive diagnosis of dementia at baseline. One patient was in coma and therefore, excluded during cohort development. There were 2,287 patients who were diagnosed with depression and were age ≥ 65 years. Of these, 1,518 patients had at least 1 quarterly assessment during the follow up and constituted the study cohort. Of these, 1,081 received SSRIs (71.21%), 320 received tetracyclics (21.08%) and the rest 117 received SNRIs (7.71%).

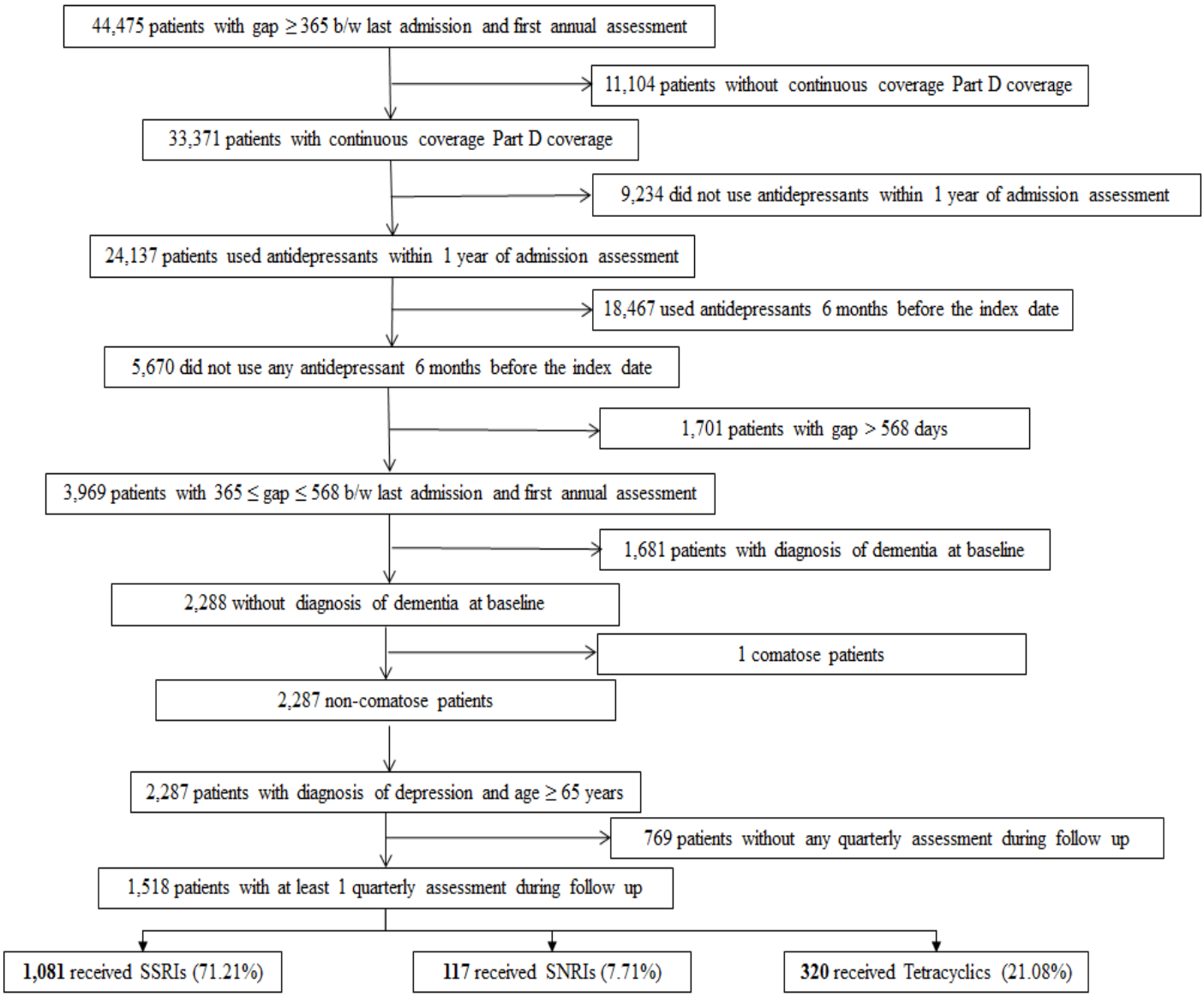

Figure 4: Flowchart of study sample selection and cohort development

Table 1 presents the baseline characteristics of the users of SSRIs, SNRIs and tetracyclics, and their distribution before and after propensity score adjustment. After adjusting for propensity scores, there was no significant difference in any of the baseline characteristics except for age. This meant that the multiple propensity score approach was able to achieve a balance for all the baseline characteristics that could have an effect on the final outcome.

Table 1: Baseline characteristics of elderly nursing home patients with depression using 1) SSRIs, 2) SNRIs and 3) tetracyclics

Characteristics	SSRI Users (n=1,081)	SNRI Users (n=117)	Tetracyclic Users (n=320)	P value before adjustment	P value after adjustment
Gender				0.02*	0.19
Female	761 (70.40)	44 (37.61)	77 (24.06)		
Male	320 (29.60)	73 (62.39)	243 (75.94)		
Age in years ± SD	80.55 ± 9.82	77.64 ± 9.05	82.32 ± 8.73	<.0001*	0.02*
Race				0.15	0.36
White	846 (78.26)	82 (70.09)	239 (74.69)		
Non-White	144 (13.32)	18 (15.38)	46 (14.38)		
Missing	91 (8.42)	17 (14.53)	35 (10.94)		
Behavioral characteristics					
Baseline MDS Cognition Scale	2.47 ± 2.37	2.31 ± 2.23	2.71 ± 2.48	0.18	0.16
Index of Social engagement	2.48 ± 1.50	2.79 ± 1.57	2.40 ± 1.46	0.048*	0.89
Depression Rating Scale	0.85 ± 1.53	0.91 ± 1.60	0.73 ± 1.26	0.35	0.33
Aggressive Behavior Scale	0.29 ± 0.94	0.28 ± 0.90	0.26 ± 0.82	0.87	0.86
Pain scale	0.73 ± 0.75	0.96 ± 0.82	0.68 ± 0.74	0.003*	0.79
Medical characteristics					
Arthritis	314 (29.05)	37 (31.62)	96 (30.00)	0.82	0.91
Diabetes	415 (38.39)	55 (47.01)	102 (31.88)	0.01*	0.12
Hypertension	803 (74.28)	83 (70.94)	242 (75.63)	0.61	0.93
Cancer	65 (6.01)	4 (3.42)	24 (7.50)	0.29	0.90
Stroke	245 (22.66)	23 (19.66)	80 (25.00)	0.47	0.77
CHF	236 (21.83)	34 (29.06)	71 (22.19)	0.21	0.87
COPD	212 (19.61)	34 (29.06)	65 (20.31)	0.06	0.73
Parkinson	39 (3.61)	6 (5.13)	14 (4.38)	0.64	0.78
Other cardiac disorders	243 (22.48)	33 (28.21)	62 (19.38)	0.14	0.60
Schizophrenia	41 (3.79)	7 (5.98)	5 (1.56)	0.06	0.21
Anxiety disorder	160 (14.80)	17 (14.53)	45 (14.06)	0.95	0.94
Asthma	45 (4.16)	2 (1.71)	9 (2.81)	0.28	0.66
Manic depression	25 (2.31)	2 (1.71)	3 (0.94)	0.32	0.42
Medication Characteristics					
Antipsychotics	123 (11.38)	14 (11.97)	30 (9.38)	0.57	0.62
Antianxiety	196 (18.13)	22 (18.80)	44 (13.75)	0.17	0.16
Hypnotics	117 (10.82)	16 (13.68)	37 (11.56)	0.63	0.87
Diuretics	394 (36.45)	43 (36.75)	97 (30.31)	0.12	0.09
Use of psychotherapy	13 (1.20)	1 (0.85)	5 (1.56)	0.81	0.96

***p-value significant at 0.05**

Figure 5 presents the distribution of propensity scores among the three treatment groups. The graph indicates that there is not a common region of overlap across the users of the SSRIs, SNRIs and tetracyclics.

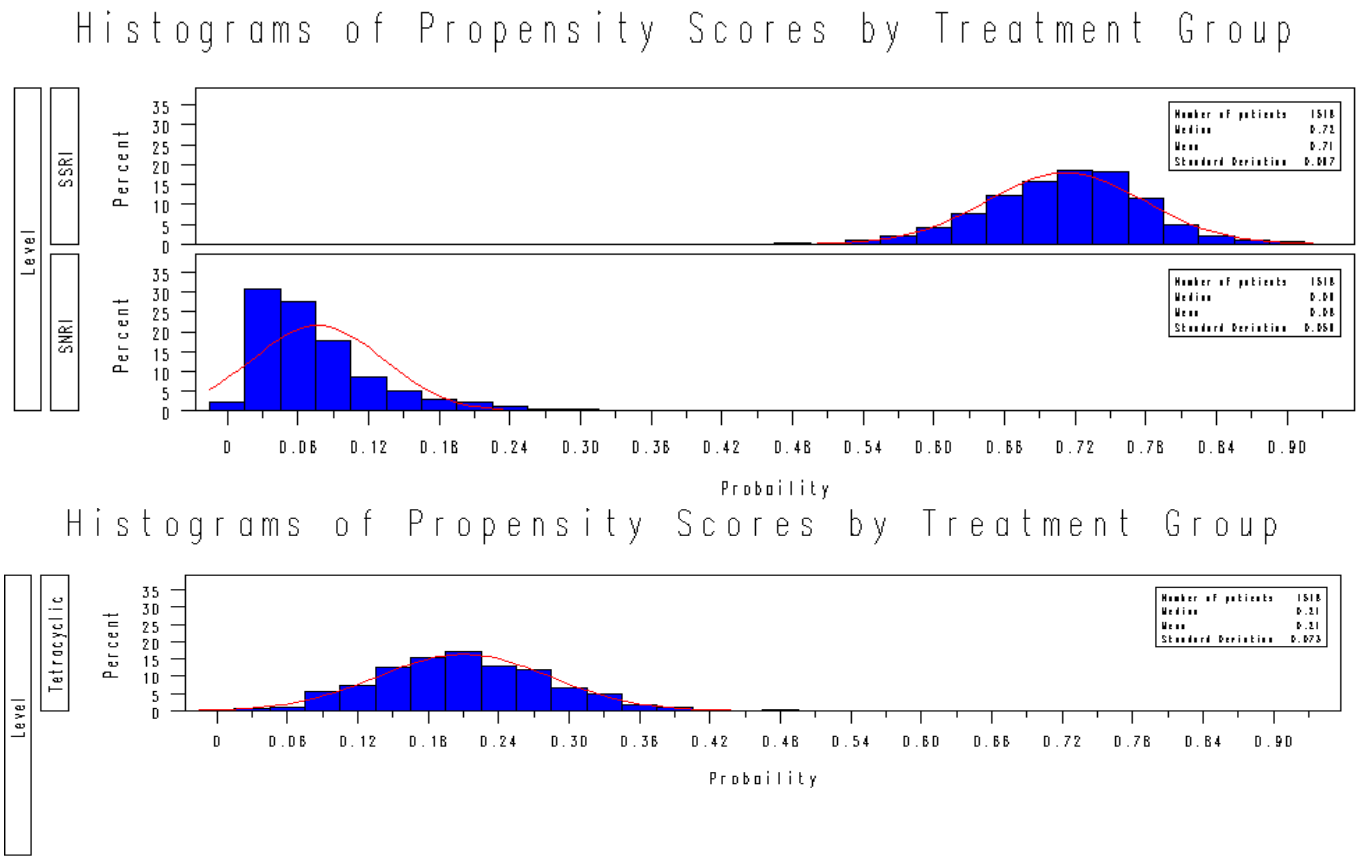

FIGURE 5: Distribution of propensity scores among the users of 1) SSRIs, 2) SNRIs and 3) tetracyclics. Data source: MDS linked CCW Medicare Claims Database, 2007–2010

To compare the three treatment groups, patients in a particular therapy group should also have a certain probability of receiving the other two treatments. As shown in **figure 6**, there was a lack of overlap when the ranges of multiple propensity scores were compared across the three treatment groups using box plots.

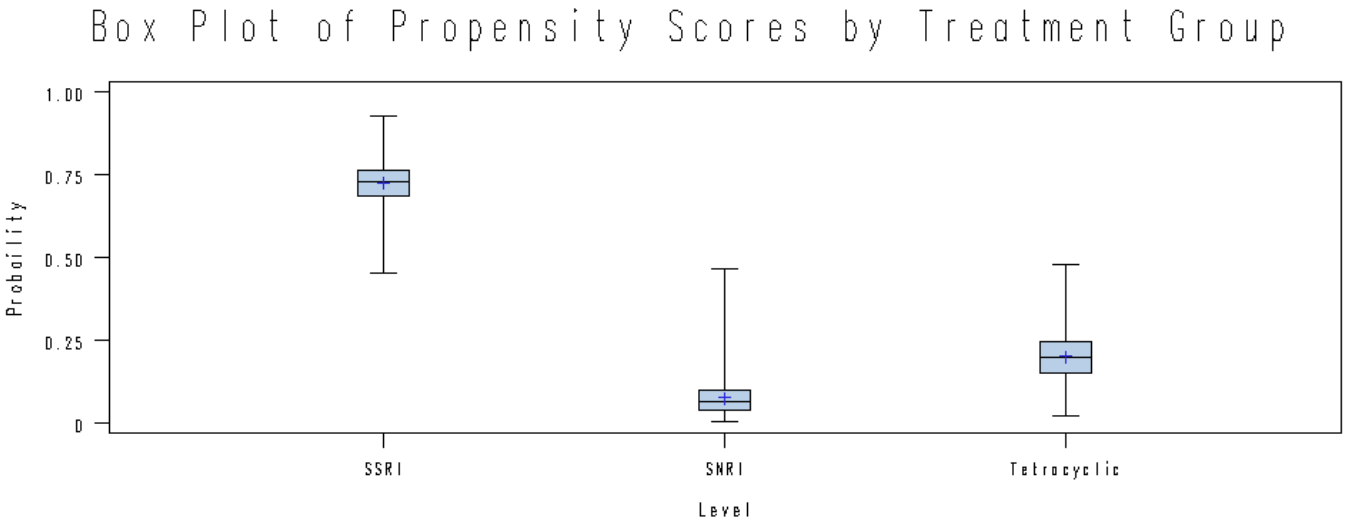

FIGURE 6: Distribution of propensity scores among the users of 1) SSRIs, 2) SNRIs and 3) tetracyclics. Data source: MDS linked CCW Medicare Claims Database, 2007–2010

Although multiple propensity score were able to achieve a balance for all baseline characteristics that could have an effect on the final outcome, there was not enough common region of overlap across the users of the three antidepressants groups; hence, two types of adjusted regression analysis were conducted. 1) Model adjusted for propensity score and their interaction terms, time of quarterly assessment and interaction of time of quarterly assessment, and antidepressant use; 2) Model adjusted for demographic characteristics, behavioral characteristics, common chronic conditions, and co-medications, psychotherapy, time and interaction of time, and antidepressant use.

Table 2 presents the results of repeated measures mixed model analysis after adjusting for propensity scores. This model shows that there is no significant association between cognition and antidepressant use after adjusting for propensity score and their interaction terms, time and interaction of time, and antidepressant use. When compared with SNRI users, there was

no difference with use of SSRIs (β = -0.23 [95% CI, -0.67, 0.22 or tetracyclics (β = -0.45 [95% CI, -0.96, 0.05]) in terms of cognition.

TABLE 2: Repeated measures mixed model for the association between cognition and use of 1) SSRIs, 2) SNRIs and 3) tetracyclics in elderly nursing home residents with depression.

Variables*	Parameter Estimate	95% CI	p-value
Antidepressant Drug Class			
SNRIs	1.00	Reference	
SSRIs	-0.23	-0.67, 0.22	0.32
Tetracyclics	-0.45	-0.96, 0.05	0.08

Data source: MDS linked CCW Medicare Claims Database, 2007–2010
*Model adjusted for propensity score and their interaction terms, time and interaction of time, and antidepressant use

Table 3 presents the results of association between cognition and three classes of antidepressant use after adjusting for all the baseline covariates. This model shows that there is no significant association between cognition and antidepressant use after adjusting for all the baseline covariates. When compared with SNRI users, there was no difference with use of SSRIs (β = -0.21 [95% CI, -0.57, 0.14) or tetracyclics (β = -0.24 [95% CI, -0.63, 0.16]) in terms of cognition.

TABLE 3: Repeated measures mixed model for the association between cognition and use of 1) SSRIs, 2) SNRIs and 3) tetracyclics in elderly nursing home patients with depression.

Variables*	Parameter Estimate	95% CI	p-value
Antidepressant Drug Class			
SNRIs	1.00	Reference	
SSRIs	-0.21	-0.57, 0.14	0.23
Tetracyclics	-0.24	-0.63, 0.16	0.24

Data source: MDS linked CCW Medicare Claims Database, 2007–2010
*Model adjusted for demographic characteristics such as age, gender, race; behavioral characteristics such as baseline MDS Cognition Scale, Index of Social engagement, Depression Rating Scale, Aggressive Behavior Scale, Pain, scale; common chronic conditions such as arthritis, cancer, asthma, COPD, Parkinson, diabetes, hypertension, , stroke, CHF,

other cardiac disorders, schizophrenia, anxiety disorder, manic depression; and use of medications such as antipsychotics, antianxiety, hypnotics, diuretics and use of psychotherapy, time and interaction of time and antidepressant use.

Sensitivity analysis

In the sensitivity analysis, generalized linear regression model was used. In this model, baseline covariates were measured at admission assessment and outcome was measured at the first quarterly assessment after the index antidepressant use. **Table 4** presents the results of association between cognition and three classes of antidepressant use after adjusting for all the baseline covariates. This model shows that there is no significant association between cognition and antidepressant use after adjusting for propensity score and their interaction terms, time and interaction of time, and antidepressant use. When compared with SNRI users, there was no difference with use of SSRIs (β = -0.19 [95% CI, -0.47, 0.10) or tetracyclics (β = -0.18 [95% CI, -0.50, 0.14]) in terms of cognition.

TABLE 4: Generalized linear regression model for association between cognition and use of 1) SSRIs, 2) SNRIs and 3) tetracyclics in elderly nursing home patients with depression

Variables*	Parameter Estimate	95% CI	p-value
Antidepressant Drug Class			
SNRIs	1.00	Reference	
SSRIs	-0.19	-0.47, 0.10	0.20
Tetracyclics	-0.18	-0.50, 0.14	0.28

Data source: MDS linked CCW Medicare Claims Database, 2007–2010

*Model adjusted for demographic characteristics such as age, gender, race; behavioral characteristics such as baseline MDS Cognition Scale, Index of Social engagement, Depression Rating Scale, Aggressive Behavior Scale, Pain, scale; common chronic conditions such as arthritis, cancer, asthma, COPD, Parkinson, diabetes, hypertension, , stroke, CHF, other cardiac disorders, schizophrenia, anxiety disorder, manic depression; and use of medications such as antipsychotics, antianxiety, hypnotics, diuretics and use of psychotherapy.

DISCUSSION

To our knowledge, this is the first population-based study to compare the association between cognition and three most frequently used classes of antidepressants among nursing home residents. The association between cognition and antidepressants use was examined using a multiple propensity score adjusted cohort study design. This study did not find any significant difference in cognition across the three classes of antidepressants. Past literature suggest that use of second generation antidepressants, specifically SSRIs, does not lead to detrimental effects on cognition in elderly patients with depression.[18,40,41] However, all of these studies were conducted in elderly patients, and none of them conducted a head to head comparison of these three antidepressant classes in elderly nursing home residents. The non-significant findings with respect to cognition can be attributed to the fact that these three antidepressant classes are similar in their efficacy.[48,49] Although SSRIs, SNRIs, and tetracyclics may differ in their onset of action and frequency of adverse events due to their different receptor binding properties, the study findings suggest that these pharmacologic differences do not translate into significant clinical differences with respect to cognition. Also, patients in this study had mild-to-moderate cognitive impairment at the baseline, and thus there was very little room for reducing the cognitive impairment at the lower end of the MDS Cognition Scale. Furthermore, it is possible that the MDS Cognition Scale may not be sensitive to the effect of antidepressant classes.

Previous research suggests that antidepressant treatment shows little improvement on cognitive functioning of depressed older adults and thus, cognitive impairment may persist even after adequate treatment with antidepressant use.[101-103] This might also explain the non-significant association between cognition and use of any of the three antidepressant classes. Additionally, the non-significant findings may not imply that there is no association between

cognition and use of any of the three antidepressant classes. Rather, these findings reinforce that safety profile of the three second generation antidepressants agents are similar with respect to cognition. Nursing home patients in this study were followed for one year to evaluate the effect of antidepressants on cognition. Future studies are required to evaluate the long-term effectiveness of these antidepressants classes on cognition in elderly nursing home residents with depression.

Overall, the current study found that the three second generation antidepressant classes do not differ significantly in the pharmacology regarding their association with cognition in elderly nursing home residents after controlling for the observable pretreatment characteristics of patients by using a propensity score adjusted approach. Previous studies have evaluated the safety profiles of individual antidepressants classes. However, it is also important to evaluate the overall safety profiles of the agents in the elderly nursing home population. Although second generation antidepressants have similar safety and efficacy profiles, they cannot be considered alike. Physicians should recommend these second generation antidepressants based on patients' risk factors such as age, sex, physical condition, illness and medication history as well as short and long-term consequence of the treatment. Considering patients' preferences regarding dosing and drug tolerability can help physicians in informed decision making.

The main strength of this study lies in its design and analytical approach. The study used propensity score approach to control for selection bias owing to non-randomization of patients to the three treatment groups. Propensity scores were estimated using various observed pretreatment characteristics from past literature. Histogram of propensity scores indicated that there was not a common region of overlap across the users of the SSRIs, SNRIs and tetracyclics. Also, there was a lack of overlap when the ranges of multiple propensity scores were compared

across the three treatment groups using box plots again suggesting that the use of a propensity score adjusted study design might not be well suited for head to head comparison of safety of SSRIs, SNRIs and tetracyclics regarding cognition. Results from **table 1** show that patients getting SSRIs, SNRIs and tetracyclics are different from each other which leads to lack of overlap in propensity scores distribution across these three groups. However, propensity scores were able to achieve a balance for all the baseline characteristics that could have an effect the final outcome. Thus, estimated propensity scores were included as covariates in the repeated measures mixed model which helped to adjust for any differences that were present among the treatment groups for these pretreatment characteristics. The interaction terms between the two propensity scores were included to achieve robust estimates.[93] Finally, only new users of second generation antidepressants were included in the present study to address the issue of prevalence bias.[104]

The finding of this study should be interpreted in the light of some limitations. Exposure to second generation antidepressants was ascertained using pharmacy claims. The claims capture only dispensing data and not actual use by patients. The present study used Medicare data which is a secondary database and thus has limitations due to miscoding and under coding.[105] All the diseases and outcome measures were based on the diagnostic data available in MDS submitted by the health care providers. Incomplete, erroneous records submitted by the health care providers, availability of little clinical detail in the ICD-9 CM system and incomplete or inaccurate demographic information may limit the accuracy of administrative data.[106] Also, variables used for propensity score calculation were limited to those available in the MDS data and used in previous literature. Due to their unavailability in the dataset, important variables such as smoking, alcohol consumption could not be included as pretreatment characteristics for the

estimation of the propensity score. Thus, it is possible that propensity score model may not completely control for hidden non-observable covariates that may alter the estimation and interpretation of study findings, particularly since there remained two distinct population distributions for propensity scores by antidepressant agents. However, results of sensitivity analysis confirmed the study findings. Also, the study population comprised of elderly nursing home residents, and hence our study findings may not be generalizable to other treatment settings.

CONCLUSIONS

In this propensity score adjusted retrospective study, the three second generation antidepressants classes did not differ significantly regarding their association with cognition in elderly nursing home residents. This can be attributed to their similar efficacy profile. Although SSRIs, SNRIs, and tetracyclics may differ in their onset of action and frequency of adverse events; these pharmacologic differences among second generation antidepressants do not translate into significant clinical differences with respect to cognition. Patient risk factors such as age, sex, physical condition, comorbidities and comedications as well as short and long-term consequence of the treatment should be considered by the physician before prescribing any antidepressant to elderly patients in nursing home setting, a setting where patients are at high risk for depression and cognitive impairment.

REFERENCES

1. Thakur M, Blazer DG. Depression in long-term care. *Journal of the American Medical Directors Association.* 2008;9(2):82-87.

2. Alexopoulos GS. Depression in the elderly. *Lancet.* Jun 4-10 2005;365(9475):1961-1970.

3. Hasche LK, Morrow-Howell N, Proctor EK. Quality of life outcomes for depressed and nondepressed older adults in community long-term care. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* Jun 2010;18(6):544-553.

4. Blazer DG. Depression in late life: review and commentary. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2003;58(3):M249-M265.

5. NIH consensus conference. Diagnosis and treatment of depression in late life. *JAMA : the journal of the American Medical Association.* Aug 26 1992;268(8):1018-1024.

6. Kallenbach LE, Rigler SK. Identification and management of depression in nursing facility residents. *J Am Med Dir Assoc.* Sep 2006;7(7):448-455.

7. Act OBR. Public Law 100-203. *Nursing Home Reform, Part C.* 1987.

8. Rapp MA, Dahlman K, Sano M, Grossman HT, Haroutunian V, Gorman JM. Neuropsychological differences between late-onset and recurrent geriatric major depression. *American Journal of Psychiatry.* 2005;162(4):691-698.

9. Simpson SW, Baldwin R, Burns A, Jackson A. Regional cerebral volume measurements in late-life depression: relationship to clinical correlates, neuropsychological impairment and response to treatment. *International journal of geriatric psychiatry.* 2001;16(5):469-476.

10. Santos M, Kövari E, Hof PR, Gold G, Bouras C, Giannakopoulos P. The impact of vascular burden on late-life depression. *Brain research reviews.* 2009;62(1):19-32.

11. O'Brien J, Barber B. Neuroimaging in dementia and depression. *Advances in Psychiatric Treatment.* 2000;6(2):109-119.

12. Petrella JR, Coleman RE, Doraiswamy PM. Neuroimaging and early diagnosis of alzheimer disease: A look to the future1. *Radiology.* 2003;226(2):315-336.

13. Christensen H, Griffiths K, Mackinnon A, Jacomb P. A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *Journal of the International Neuropsychological Society : JINS.* Nov 1997;3(6):631-651.

14. Williams JW, Plassman BL, Burke J, Benjamin S. Preventing Alzheimer's disease and cognitive decline. *Evid Rep Technol Assess.* Apr 2010;(193):1-727.

15. Butters MA, Young JB, Lopez O, et al. Pathways linking late-life depression to persistent cognitive impairment and dementia. *Dialogues Clin Neurosci.* 2008;10(3):345-357.

16. Sierksma AS, van den Hove DL, Steinbusch HW, Prickaerts J. Major depression, cognitive dysfunction and Alzheimer's disease: is there a link? *Eur J Pharmacol.* Jan 10 2010;626(1):72-82.

17. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nature reviews. Neurology.* Jun 2011;7(6):323-331.

18. Caraci F, Copani A, Nicoletti F, Drago F. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. *European journal of pharmacology.* 2010;626(1):64-71.

19. Panel DG. Depression in Primary Care: Volume 2. Treatment of Major Depression. Clinical Practice Guideline, Number 5.(AHCPR Publication No. 93-0551). Rockville,

MD: US Department of Health and Human Services. *Public Health Service, Agency for Health Care Policy and Research*1993.

20. Kaldyand J, Tarnove L. A Clinical Practice Guideline approach to treating depression in long-term care. *J Am Med Dir Assoc.* Mar-Apr 2003;4(2 Suppl):S60-68.

21. Karkare SU, Bhattacharjee S, Kamble P, Aparasu R. Prevalence and predictors of antidepressant prescribing in nursing home residents in the United States. *The American journal of geriatric pharmacotherapy.* Apr 2011;9(2):109-119.

22. Levin CA, Wei W, Akincigil A, Lucas JA, Bilder S, Crystal S. Prevalence and treatment of diagnosed depression among elderly nursing home residents in Ohio. *J Am Med Dir Assoc.* Nov 2007;8(9):585-594.

23. Biringer E, Rongve A, Lund A. A Review of Modern Antidepressants Effects on Neurocognitive Function. *Current Psychiatry Reviews.* 2009;5(3):164-174.

24. Culang ME, Sneed JR, Keilp JG, et al. Change in cognitive functioning following acute antidepressant treatment in late-life depression. *American Journal of Geriatric Psych.* 2009;17(10):881-888.

25. Francomano A, Bonanno B, Fucà L, La Placa M, La Barbera D. The role of antidepressant treatments on cognitive deficits a review of recent literature. *Clin Neuropsychiatry.* 2011;8:354-366.

26. Steffens DC, Potter GG. Geriatric depression and cognitive impairment. *Psychological medicine.* Feb 2008;38(2):163-175.

27. Hashioka S, McGeer PL, Monji A, Kanba S. Anti-inflammatory effects of antidepressants: possibilities for preventives against Alzheimers disease. *Central Nervous System Agents in Medicinal Chemistry.* 2009;9(1):12-19.

28. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. *Primary care companion to the Journal of clinical psychiatry.* 2001;3(1):22-27.

29. Moller HJ, Volz HP. Drug treatment of depression in the 1990s. An overview of achievements and future possibilities. *Drugs.* Nov 1996;52(5):625-638.

30. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive DisorderAn Updated Meta-analysis. *Annals of internal medicine.* 2011;155(11):772-785.

31. Gartlehner G, Thieda P, Hansen RA, et al. Comparative risk for harms of second-generation antidepressants : a systematic review and meta-analysis. *Drug Saf.* 2008;31(10):851-865.

32. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.

33. Knegtering H, Eijck M, Huijsman A. Effects of antidepressants on cognitive functioning of elderly patients. A review. *Drugs & aging.* Sep 1994;5(3):192-199.

34. Oxman TE. Antidepressants and cognitive impairment in the elderly. *The Journal of clinical psychiatry.* 1996;57 Suppl 5:38-44.

35. Doraiswamy PM, Krishnan KRR, Oxman T, et al. Does antidepressant therapy improve cognition in elderly depressed patients? *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2003;58(12):M1137-M1144.

36. Aparasu RR, Bali V. Antidepressant use among elderly nursing home residents with depression in the United States. *65th Annual Indian Pharmaceutical Congress*. New Delhi, India. 2013.

37. Medicare Standard Analytical Files: Identifiable Data Files. Centers for Medicare & Medicaid Services. http://www.cms.hhs.gov/IdentifiableDataFiles/02_StandardAnalyticalFiles.asp.

38. Hanlon JT, Donohue J. Medicare Part D data: A valuable tool for pharmacoepidemiology and pharmacoeconomic research. *The American journal of geriatric pharmacotherapy.* 2010;8(6):483-484.

39. Avorn J, Gurwitz JH. Drug use in the nursing home. *Annals of internal medicine.* 1995;123(3):195-204.

40. Mor V. A comprehensive clinical assessment tool to inform policy and practice: applications of the minimum data set. *Med Care.* Apr 2004;42(4 Suppl):III50-59.

41. Li Y, Schnelle J, Spector WD, Glance LG, Mukamel DB. The "Nursing Home Compare" measure of urinary/fecal incontinence: cross-sectional variation, stability over time, and the impact of case mix. *Health Serv Res.* 2010;45(1):79-97.

42. Frederiksen K, Tariot P, De Jonghe E. Minimum Data Set Plus (MDS+) scores compared with scores from five rating scales. *Journal of the American Geriatrics Society.* Mar 1996;44(3):305-309.

43. Hawes C, Morris JN, Phillips CD, Mor V, Fries BE, Nonemaker S. Reliability estimates for the Minimum Data Set for nursing home resident assessment and care screening (MDS). *The Gerontologist.* 1995;35(2):172-178.

44. Porock D, Parker-Oliver D, Petroski GF, Rantz M. The MDS Mortality Risk Index: The evolution of a method for predicting 6-month mortality in nursing home residents. *BMC research notes.* 2010;3:200.

45. Morris JN, Murphy K, Nonemaker S. *Long Term Care Facility Resident Assessment Instrument (RAI) User's Manual: For Use with Version 2.0 of the Health Care Financing Administration's Minimum Data Set, Resident Assessment Protocols, and Utilization Guidelines*: Health Care Financing Administration; 1995.

46. Morris JN, Hawes C, Fries BE, et al. Designing the national resident assessment instrument for nursing homes. *The Gerontologist.* 1990;30(3):293-307.

47. Morris JN, Fries BE, Mehr DR, et al. MDS cognitive performance scale©. *Journal of Gerontology.* 1994;49(4):M174-M182.

48. Federal Register.Health Care Financing Administration, Medicare and Medicaid: Resident Assessment in Long Term Care Facilities; Final Rule. Vol 62 23 December 1997:67174.

49. Gruber-Baldini AL, Zimmerman SI, Mortimore E, Magaziner J. The validity of the minimum data set in measuring the cognitive impairment of persons admitted to nursing homes. *Journal of the American Geriatrics Society.* Dec 2000;48(12):1601-1606.

50. Hartmaier SL, Sloane PD, Guess HA, Koch GG. The MDS Cognition Scale: a valid instrument for identifying and staging nursing home residents with dementia using the minimum data set. *Journal of the American Geriatrics Society.* 1994;42(11):1173-1179.

51. Gruber-Baldini AL, Zimmerman SI, Mortimore E, Magaziner J. The validity of the minimum data set in measuring the cognitive impairment of persons admitted to nursing homes. *J Am Geriatr Soc.* 2000;48(12):1601-1606.

52. Cohen-Mansfield J, Taylor L, McConnell D, Horton D. Estimating the cognitive ability of nursing home residents from the minimum data set. *Outcomes management for nursing practice.* Jan-Mar 1999;3(1):43-46.

53. Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. *Medical care.* 2006;44(4):300-303.

54. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value in Health.* 2008;11(1):44-47.

55. Liu X, Chen Y, Faries DE. Adherence and persistence with branded antidepressants and generic SSRIs among managed care patients with major depressive disorder. *ClinicoEconomics and outcomes research: CEOR.* 2011;3:63.

56. Winship C, Mare RD. Models for sample selection bias. *Annual Review of Sociology.* 1992:327-350.

57. Rosenbaum PR. Discussing hidden bias in observational studies. *Annals of internal medicine.* 1991;115(11):901-905.

58. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate behavioral research.* May 2011;46(3):399-424.

59. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *Jama.* 2007;297(3):278-285.

60. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70(1):41-55.

61. Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol.* Feb 1 2006;163(3):262-270.

62. Austin PC. The performance of different propensity-score methods for estimating relative risks. *Journal of clinical epidemiology.* Jun 2008;61(6):537-545.

63. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biometrical journal. Biometrische Zeitschrift.* Feb 2009;51(1):171-184.

64. Spreeuwenberg MD, Bartak A, Croon MA, et al. The multiple propensity score as control for bias in the comparison of more than two treatment arms: an introduction from a case study in mental health. *Medical care.* 2010;48(2):166-174.

65. Andersen R, Newman JF. Societal and individual determinants of medical care utilization in the United States. *The Milbank Memorial Fund Quarterly. Health and Society.* 1973:95-124.

66. Gorelick PB. Risk factors for vascular dementia and Alzheimer disease. *Stroke; a journal of cerebral circulation.* Nov 2004;35(11 Suppl 1):2620-2622.

67. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology.* Aug 23 2005;65(4):545-551.

68. Middleton LE, Yaffe K. Promising strategies for the prevention of dementia. *Archives of neurology.* Oct 2009;66(10):1210-1215.

69. Savica R, Petersen RC. Prevention of dementia. *The Psychiatric clinics of North America.* Mar 2011;34(1):127-145.

70. Burrows AB, Morris JN, Simon SE, Hirdes JP, Phillips C. Development of a minimum data set-based depression rating scale for use in nursing homes. *Age and ageing.* 2000;29(2):165-172.

71. McFadden D, Train K, Tye WB. An application of diagnostic tests for the independence from irrelevant alternatives property of the multinomial logit model. *Transportation Research Record.* 1976(637):39-45.

72. Singer JD. Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. *Journal of Educational and Behavioral Statistics.* 1998;23(4):323-355.

73. Butters MA, Becker JT, Nebes RD, et al. Changes in cognitive functioning following treatment of late-life depression. *The American journal of psychiatry.* Dec 2000;157(12):1949-1954.

74. Portella MJ, Marcos T, Rami L, Navarro V, Gasto C, Salamero M. Residual cognitive impairment in late-life depression after a 12-month period follow-up. *International journal of geriatric psychiatry.* Jul 2003;18(7):571-576.

75. Nebes RD, Pollock BG, Houck PR, et al. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, double-blind clinical trial with nortriptyline and paroxetine. *Journal of psychiatric research.* 2003;37(2):99-108.

76. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *American journal of epidemiology.* 2003;158(9):915-920.

77. Mitchell JB, Bubolz T, Paul JE, et al. Using Medicare claims for outcomes research. *Med Care.* Jul 1994;32(7 Suppl):JS38-51.

78. Valuck RJ, Libby AM, Sills MR, Giese AA, Allen RR. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. *CNS drugs.* 2004;18(15):1119-1132.

MANUSCRIPT 2

Comparative Effectiveness of Second Generation Antidepressants on Dementia in the Elderly Nursing Home Residents with Depression

ABSTRACT

Background: Depression is a common psychiatric illness among elderly nursing home residents. Second generation antidepressants are commonly used for the treatment of depression in elderly nursing home residents. However, little is known about the comparative safety of antidepressants regarding the risk of dementia.

Objective: The aim of this study was to evaluate the comparative safety of selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and tetracyclics with respect to the risk of dementia in elderly nursing home residents with depression with age ≥ 65 years.

Methods: A propensity score adjusted retrospective cohort study was conducted using data from the Medicare Part A, B and D claims and Minimum Data Set (MDS) from 2007-2010. New users of SSRIs, SNRIs and tetracyclics were followed until they reached the end of the follow up period (2 years), switched to different antidepressant class, had a gap of more than 15 days in the use of the index antidepressant class or died, whichever occurred earlier. A Cox proportional hazards regression model was used to evaluate the comparative effectiveness of SSRIs, SNRIs and tetracyclics in reducing the risk of dementia, with SSRIs as the reference category. The covariates in the final model included propensity scores and their interaction terms.

Results: The study cohort constituted 13,354 elderly nursing home residents with depression. Of these, 19,952 received SSRIs (79.77%), 2,381 received SNRIs (9.48%) and 2,775 received

tetracyclics (11.05%). The unadjusted incidence of dementia was 8.20% for SSRI users, 6.01% for SNRI users and 7.21% for tetracyclic users. The propensity score adjusted Cox model did not find any significant difference in the risk of dementia in elderly nursing home residents who used SNRIs [HR, 0.99; 95% CI, 0.84 – 1.19] or tetracyclics [HR, 1.01; 95% CI, 0.87 - 1.17] compared to the SSRI users.

Conclusions: This study finding did not reveal any significant difference in the comparative safety of SSRIs, SNRIs and tetracyclics regarding the risk of dementia in elderly nursing home residents with depression. Further long-term studies are needed to evaluate the profiles of second generation antidepressants in this population.

INTRODUCTION

One of the most critical public health concerns in the United States is dementia, a general term for a group of disorders that causes progressive deterioration in cognitive functioning. Alzheimer's disease accounts for 50-60% of dementia cases.[1] Other types of dementia include Lewy body dementia, vascular dementia, mixed dementia and frontotemporal dementia. Neurobiological factors in dementia interfere with activities of daily living, including the inability to follow simple directions, language and memory disturbances, failure to identify objects, and delusions.[2,3] About 5.3 million people in the United States have Alzheimer's disease, the seventh leading cause of death.[4,5] Available drugs for dementia such as cholinesterase inhibitors (ChEIs) and memantine have small effect sizes and do not alter disease progression.[6] Consequently, prevention of dementia through risk factor identification and modification is the key to reduce the disease burden until new disease-reversing agents are proved efficacious.[6] It is estimated that the prevalence of dementia could be reduced by 50% if risk reduction strategies were successful in delaying its onset by 5 years.[7]

Depression is a major risk factor for cognitive decline and dementia. Ownby et al. (2006) performed a meta-analysis on the relationship between depression and Alzheimer's disease and found that depression may increase the risk of Alzheimer's disease. They obtained odds ratios of 2.03 for case-control and of 1.90 for cohort studies for the risk of Alzheimer's disease due to depression.[8] Another meta-analysis was conducted by Jorm et al. (2000) which looked at the association between depression and risk of dementia. They found that depression was consistently associated with an increased risk of dementia in both case-control studies (95% confidence interval for relative risk, 1.16-3.50) and prospective studies (95% CI for relative risk,

1.08-3.20).[9] However, both of these meta-analyses focused on general population and not on elderly nursing home residents with depression.

Various studies establish the link between depression and dementia in elderly patients. Past research indicates that cognitive impairment can occur due to hippocampal atrophy resulting from depression induced hypothalamic-pituitary-adrenal (HPA) activation.[20,59-61] The HPA activation along with altered serotonin system can also lead to the formation of neurofibrilliary tangles and amyloid plaques.[20,59-61] Cognitive deficits and dementia can also result from the increased levels of proinflammatory cytokines caused by depression induced chronic inflammation in the brain.[20,59-61] Impaired neuronal protection and signaling can be caused by decrease in the levels of neurotrophins i.e. BDNF and TGF-β_1. Lastly, neuronal studies have found greater reduction in white and grey matter volumes consistent with small vessel vascular changes in depression patients.[35]

Although the effects of antidepressants can vary due to underlying pharmacodynamics, antidepressants can play an important role in preventing or delaying dementia in patients with depression. Second generation antidepressants like selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) are considered as the first line therapy in treating depression.[12,13] Others such as tetracyclics like mirtazapine are frequently used in elderly patients with depression when the first line agents are not effective or not tolerated well. A review of the past literature indicates that treatment with SSRIs and SNRIs may offer a protective effect on cognitive impairment.[16,17] Sertraline is found to be better than other SSRIs with regards to cognitive function. Additionally, Reboxetine, bupropion and SNRIs are found to be more beneficial than other antidepressants in terms of cognitive function.[16,17]

Antidepressants can reduce the risk of dementia in two primary ways. Firstly, antidepressants can reduce depression severity and improve cognition in patients with depression which can reduce the risk of dementia. Secondly, various studies have shown that positive effects of neural progenitors, reduction of pro-inflammatory mediators, and stimulation of neurotrophic factors attributed to the use of antidepressants can improve cognition and exert neuroprotective effects against dementia.[20-22] However, SSRIs, SNRIs and tetracyclics improve depression symptomology by different mechanisms of action.[23,24] SSRIs act as 5-hydroxytryptamine (5HT) reuptake inhibitors and increase synaptic 5HT transmission to improve depression. Most SSRIs lack any muscarinic and histaminergic activity. However, some SSRIs like paroxetine act on muscarinic receptors and can worsen cognitive impairment due to their strong anticholinergic activity. SNRIs improve depression symptomology by blocking the reuptake of both norepinephrine (NE) and serotonin (5HT). Additionally, they do not cause any anticholinergic, sedative or hypotensive side effects. Tetracyclics such as mirtazapine act on both adrenergic (α2 antagonist) and serotonergic (5-HT2 antagonist) receptors.[23,24]

Two meta-analyses that looked at the benefits and harms of second generation antidepressants for treating major depressive disorder found that SSRIs, SNRIs, and tetracyclics were similar in their efficacy and side effects. However, these second generation antidepressants are different in terms of their onset of action, frequency of adverse events and anticholinergic properties due to different receptor binding properties and site of action.[48,49] For example, mirtazapine has a statistically significant faster onset of action than citalopram, fluoxetine, paroxetine, and sertraline.[48] Paroxetine and mirtazapine led to higher weight gain than other second generation antidepressants. As per the American Geriatrics Society 2012 Beers Criteria, paroxetine has strong anticholinergic properties and can lead to cognitive problems in the

elderly.[65] These differences in pharmacological properties of second generation antidepressants can lead to different direct and indirect effects which might be clinically relevant and influence the choice of a medication for a particular patient.[23,24]

Depression and dementia are common disorders in nursing homes as they are considered major precipitants of long-term care admission. Recent national estimates suggest that over one-third of nursing home residents have depression[29] and over 50% have dementia.[46] The total cost of dementia was estimated between $157 billion to $215 billion in 2010; nursing home care accounts for nearly 66% of dementia care.[47] Prevention of dementia can be valuable in reducing this healthcare burden. Since depression is a major risk factor for dementia, there is a significant need to manage these at-risk patients to reduce dementia burden.

Two observational studies have examined the effect of antidepressant use on dementia. Both of these studies were conducted by Kessing et al. (2009, 2011) in Danish population.[44,45] The first study looked at antidepressants use and diagnoses of dementia. They found that continued long-term use of antidepressants is associated with a reduced dementia risk. This pattern was observed in all classes of antidepressants (SSRIs, newer non-SSRI antidepressants and older antidepressants).[44,45] The second study examined association between continued antidepressant use and dementia in patients with diagnosis of severe depression. They found that continued long-term use of antidepressants is associated with a 0.66-0.88 reduction in dementia risk. However, there were severe methodological limitations in these studies, such as the selection of populations with prevalent antidepressant use; this led to some unanticipated findings such as a decreased rate of dementia among non-users of antidepressants. Additionally, patients using older antidepressants had decreased rate of dementia than the patients using newer antidepressants. Largely, what remains unclear is whether differences in pharmacological

properties of second generation antidepressants could lead to differential risk of dementia in the long run, specifically, in nursing homes, a setting with a significant dementia burden. A study that answers this question is urgently needed as second generation antidepressants, SSRIs, tetracyclics and SNRIs are the most frequently prescribed classes of antidepressants in depressed patients in nursing homes.[14,15] Consequently, the objective of this study was to evaluate the long-term comparative effectiveness of different antidepressant classes in reducing the risk of dementia in elderly nursing home residents with depression. The underlying hypothesis was that the effectiveness of different antidepressant classes, mainly SSRIs, SNRIs and tetracyclics, varies due to differences in direct and indirect effects on cognitive performance and consequently in reducing the risk of dementia. The findings from this observational study will provide empirical knowledge regarding comparative effectiveness of antidepressants in reducing the risk of dementia. This information will be valuable to clinicians in the management of depression and reducing risk of dementia in elderly nursing home residents with depression.

METHODS

Data Source

The study used multiyear (2007-2010) multistate Minimum Data Set (MDS) linked Medicare data files obtained from the Centers for Medicare and Medicaid Services Chronic Condition Data Warehouse (CCW).[66] Elderly persons aged 65 years or older are usually covered by Medicare. Medicare Part A provides hospital coverage and supplementary medical insurance is offered through Part B. Medicare Part B covers services such as laboratory, ambulance, outpatient mental health, and some preventive and wellness care services including physical exams, wellness care and other medical services that are not included in Part A. Part D, launched in 2006, provides prescription benefits for Medicare beneficiaries but its structure differs from

Part A and B benefits. For Part D, Medicare enrollees sign up for prescription drug plans administered by a private third party payer such as a pharmaceutical benefit management company or health insurer. Each of the prescription plans offers choices that vary in the comprehensiveness of their formulary, the monthly premiums, and patient copayments.[67] The MDS is a national standardized assessment tool which forms the foundation of a comprehensive assessment of all residents in federally certified nursing home facilities.[68,69] It contains over 350 variables designed to provide extensive clinical and assessment data for individual residents.[70] Most of these data elements reflect the resident's condition during the seven days prior to the assessments. They are documented by the nursing staff trained in MDS standardized assessments and are then electronically captured. Previous studies reported strong inter-rater reliability and internal consistency of scales used for the assessment of nursing home residents.[71,72]

All Centers for Medicaid & Medicare Services (CMS) certified nursing homes are required to complete comprehensive MDS annual assessments on each resident admission, and when the resident shows "significant change in status". A subset of the full MDS assessment is conducted quarterly. The admission assessment in MDS is completed within 14 calendar days of admission to the facility and the annual assessment is completed within 366 days of the admission assessment but not more than 92 days of a quarterly assessment. Quarterly assessments are brief in nature and are captured quarterly or following any adverse events.[72-77] This study was approved by the University of Houston Committee for the Protection of Human Subjects under the exempt category.

Study Design and study cohort

A propensity score adjusted retrospective cohort design was used to evaluate the comparative safety of SSRIs, SNRIs and tetracyclics regarding the risk of dementia in elderly

nursing home patients with depression. **Figure 1** outlines the definitions used to construct the study and comparison groups. Patients were classified as nursing home residents if they had a nursing home stay anytime during 2007-2010. Index use of an antidepressant was defined as having a first prescription of an antidepressant after at least 12 months without any prescription fill date for any of the antidepressant medications. Patients were identified as elderly new users of antidepressants if they were: (i) 65 years and older, (ii) diagnosed with depression, (iii) initiated SSRI, SNRI or tetracyclic antidepressants without any antidepressant prescription in the year prior to initiation, (iii) continuously eligible for Medicare Part A, B, and D and no health maintenance organization, (HMO) coverage in the 12 months baseline period, (iv) non-comatose and (v) not diagnosed with dementia in the baseline period. Patients who were enrolled in a HMO during the study period were excluded because chronic condition indicators are only obtained from the claims files of fee-for-service beneficiaries and not from managed care organizations. MDS assessments are not conducted for subjects who are comatose, thus these patients were also excluded in the present study.[78]

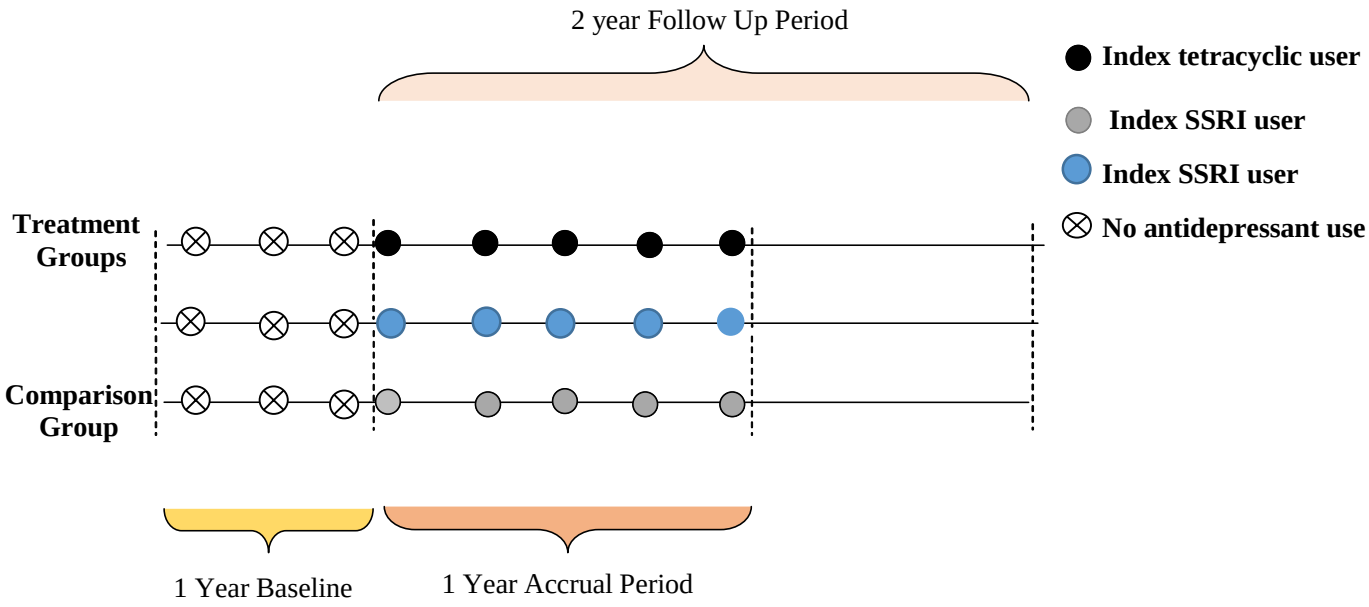

Figure 1: Development of study and comparison groups

Exposure and Outcome Definitions

The index antidepressant exposure was measured using Part D claims data. Antidepressant agents were grouped into SSRIs, SNRIs and tetracyclics. These three classes were selected given their high prevalence of use in nursing home residents with depression.[15] SSRIs included sertraline, escitalopram, fluoxetine, fluvoxamine, citalopram and paroxetine; SNRIs included venlafaxine, desvenlafaxine, milnacipran and duloxetine; tetracyclics included mirtazapine and maprotiline. The Multum drug classification codes and National Drug Codes (NDC) in the Medicare Part D prescription claims were used to identify new antidepressant users without any antidepressant use in the 12 months of baseline period.

The primary outcome measure was diagnosis of dementia, ascertained using the chronic condition indicator from the enrollment file. The maximum follow up period for this study was 2 years. Study subjects were censored if they reached the end of the follow up period, switched to

a different antidepressant, had a gap or more than 15 days in the use of the index antidepressant, or died,[82-84] whichever occurred earlier. To account for the pharmacokinetics and pharmacodynamics of antidepressant medications, a diagnosis of dementia was evaluated after 30 days of antidepressant treatment.[107]

Multiple Propensity Score Adjustment

The strength of observational studies lies in their ability to estimate treatment effects in real world settings. However, selection bias due to non-randomization is a key concern in observational studies.[85] This bias occurs because selection of a medication is based on both observable and non-observable factors that are considered non-random.[86] Propensity scores are frequently applied in observational studies to reduce overt selection bias.[87,88] Overt bias occurs as a result of the existing pretreatment differences rather than treatment effects, due to lack of randomization in observational studies.[86] The propensity score method was proposed by Rosenbaum and Rubin in 1983[89] and is the conditional probability of assignment to a particular treatment given a vector of observed covariates. There are four commonly used propensity score methods: matching, stratification, inverse probability of treatment weighting (IPTW) and adjustment.[87,90] Studies comparing ability of various propensity score models to balance the measured variables between the treated and control subjects found that covariate adjustment using the propensity score had the best performance in estimating relative risks.[91,92] Also, in clinical practice, the use of matching and stratification based on propensity scores becomes difficult when there are multiple treatment groups. Since this study involved three treatment groups, the multiple propensity score adjustment method was used to achieve the study objective.

The present study employed the 7-step approach for the application of multiple propensity score as recommended by Spreeuwenberg et al. (2010).[93] The steps include estimating the treatment effects before propensity score adjustment, checking the distribution of the baseline covariates, selection of pretreatment characteristics to estimate the propensity scores, estimation of the propensity scores, checking distribution after propensity score adjustment and estimating the treatment effect after propensity score adjustment. The baseline confounders and risk factors for the outcome were identified using the conceptual framework of the Andersen Behavioral Model (ABM). According to the ABM, an individual's health service use including medication use is a function of predisposing, enabling and need factors.[94] The critical step is the calculation of propensity scores using multinomial logistic regression with treatment allocation as the dependent variable and baseline covariates as the explanatory variables. Predisposing, enabling, and need factors for this study were selected from past literature and availability of variables in the MDS and Medicare datasets.[6,11,95-97] Demographic characteristics such as age, gender and race were grouped under predisposing factors. Need factors included diagnosis of comorbidities and use of comedications in the baseline period. Propensity score is a non-parsimonious model, thus all possible comorbidities and comedications were used as need factors. Medical conditions included were chronic conditions such as chronic heart failure, endocarditis, ischemic heart disease, acute myocardial infarction, stroke/ transient ischemic attack, cardiac arrhythmia, circulatory disorder, thromboembolic disorder, peripheral arterial disorder, hypertension, diabetes mellitus, hyperlipidemia, renal failure, other renal disease, hip fracture, falls, osteoporosis, rheumatoid arthritis and osteoarthritis, gout and other crystal arthropathies, back pain, Parkinson's disease, extrapyramidal syndrome, fibromyalgia, psychotic disorders such as anxiety, mood disorder, migraine, schizophrenia, bipolar disorder, insomnia, other psychiatric

disorders; other disorders such as liver disorder, gastric disorder, ulcers, cancer, dysphagia, anemia, asthma, chronic obstructive pulmonary disease, pneumonia, benign prostatic hyperplasia, hypothyroidism, cataract, glaucoma, obesity. Use of medications included anti-infective agents, endocrine and metabolic drugs, cardiovascular agents, anti-hyperlipidemic drugs, respiratory agents, antihistamines and other cold remedies, gastrointestinal agents, genitourinary products, antianxiety agents, other antidepressants, antipsychotics, hypnotics, stimulants/anti-obesity/anorexiants, other psychotherapeutic agents, anticonvulsants, antiparkinsonian, analgesics and anti-inflammatories, musculoskeletal agents, nutritional products, hematological agents, topical products, central acetylcholinesterase inhibitors , alcohol and drug dependence agents, antineoplastic agents and other miscellaneous products.

Multinomial logistic regression was used to estimate the multiple propensity scores. This study compared three treatment groups, so three propensity scores (calculated as the estimated predicted probabilities of assignment to one of the three treatment groups) were obtained for each subject.[93] However, only two propensity scores were needed for the purpose of covariate adjustment as the three calculated propensity scores add up to one. In the adjusted analysis, two propensity scores along with their interaction terms were included to obtain robust estimates.[93] The use of multinomial logistic regression for calculation of propensity scores also required testing for the assumption of independence of irrelevant alternatives. This assumption means that adding or deleting alternative outcome categories does not affect the odds among the remaining outcomes.[99] This assumption was checked using the Hausman test and it was found that omitting SNRIs did not significantly change the parameter estimates (χ^2 test, 95.31; P = 0.99) of the full model versus the reduced model.

Statistical Analysis

An appropriately calculated multiple propensity score should achieve balance in the distribution of all the observed covariates between the three treatment groups. Similarities among the three treatment groups before and after correction on the multiple propensity score were assessed using logistic regression analysis for dichotomous variables, ANCOVA for the continuous variables and multinomial logistic regression analysis for the nominal variables. Antidepressant treatment was used as a fixed factor along with two out of three propensity scores and their interactions terms as covariates.[93] Kaplan-Meier survival plots were created to depict the crude (unadjusted) relationships between antidepressant use and time to dementia. Pairwise log-rank tests were used to compare survival curves for statistical difference. Survival analysis was then performed using propensity scores and their interactions terms as covariates to assess the risk of dementia between users of SSRIs, SNRIs and tetracyclics. The Cox proportional-hazard model was used to examine the risk of dementia associated with use of SNRIs and tetracyclics while using SSRIs as the reference category. The Cox regression modeling was conducted using PROC PHREG in SAS 9.1 (SAS Institute, Cary, NC). The proportional hazards assumption for the model was checked by examining log minus-log transformed Kaplan-Meier estimates of the survival functions for the three treatment groups plotted against time to dementia/follow up time. These curves help in identifying non-proportionality patterns in hazard function such as convergent, divergent, or crossing of the curves.[108] In addition, the Schoenfeld test was conducted for evaluation of the proportional hazards assumption. This test assesses the correlation between scaled residuals and time. The proportional-hazard assumptions was met (P = 0.41). Results were presented as adjusted hazard Ratios along with 95% confidence intervals. Statistical significance was set at an a priori level of 0.05.

Sensitivity Analysis

In addition to the main analysis, multiple sensitivity analyses were conducted to evaluate the robustness of the study findings. In the first sensitivity analysis, patients were excluded if they did not have at least one MDS assessment at baseline. This approach assured that patients were nursing home residents when their baseline characteristics were measured. Diagnosis of dementia was ascertained using the MDS assessment as well as the chronic condition indicator. In the second sensitivity analysis, patients were excluded if they had used memantine and cholinesterase inhibitors or had diagnosis of dementia at baseline. Additionally, these anti-dementia medications along with dementia diagnosis were used to identify dementia patients at follow up.

RESULTS

Figure 2 presents the process of development of study cohort and sample selection. There were 1,691,233 patients with a diagnosis of depression in any of the 4 years. Of these, 1,483,145 patients were aged ≥ 65 years. There were 1,458,494 elderly depressed patients who were non-comatose. Of these, 184,678 were new users of antidepressants without any concurrent antidepressant use on the index date. Among these new users, 160,888 were new users of SSRIs, SNRIs or tetracyclics. Patients using concurrent medications are inherently different from patients using single medication. Thus, to avoid selection bias, patients using concurrent antidepressant medications were excluded from the study. Similarly, patients using psychotherapy and antidepressants concurrently are different from patients using antidepressants only. Hence, to avoid selection bias, patients using psychotherapy and antidepressants concurrently were excluded from the study. There were 121,032 new antidepressant users who did not use any psychotherapy at the baseline. Of these, 42,552 patients had continuous coverage

for Parts A, B, D and no HMO at one year prior to baseline. There were 17,444 patients without a diagnosis of dementia at baseline who constituted the study cohort.

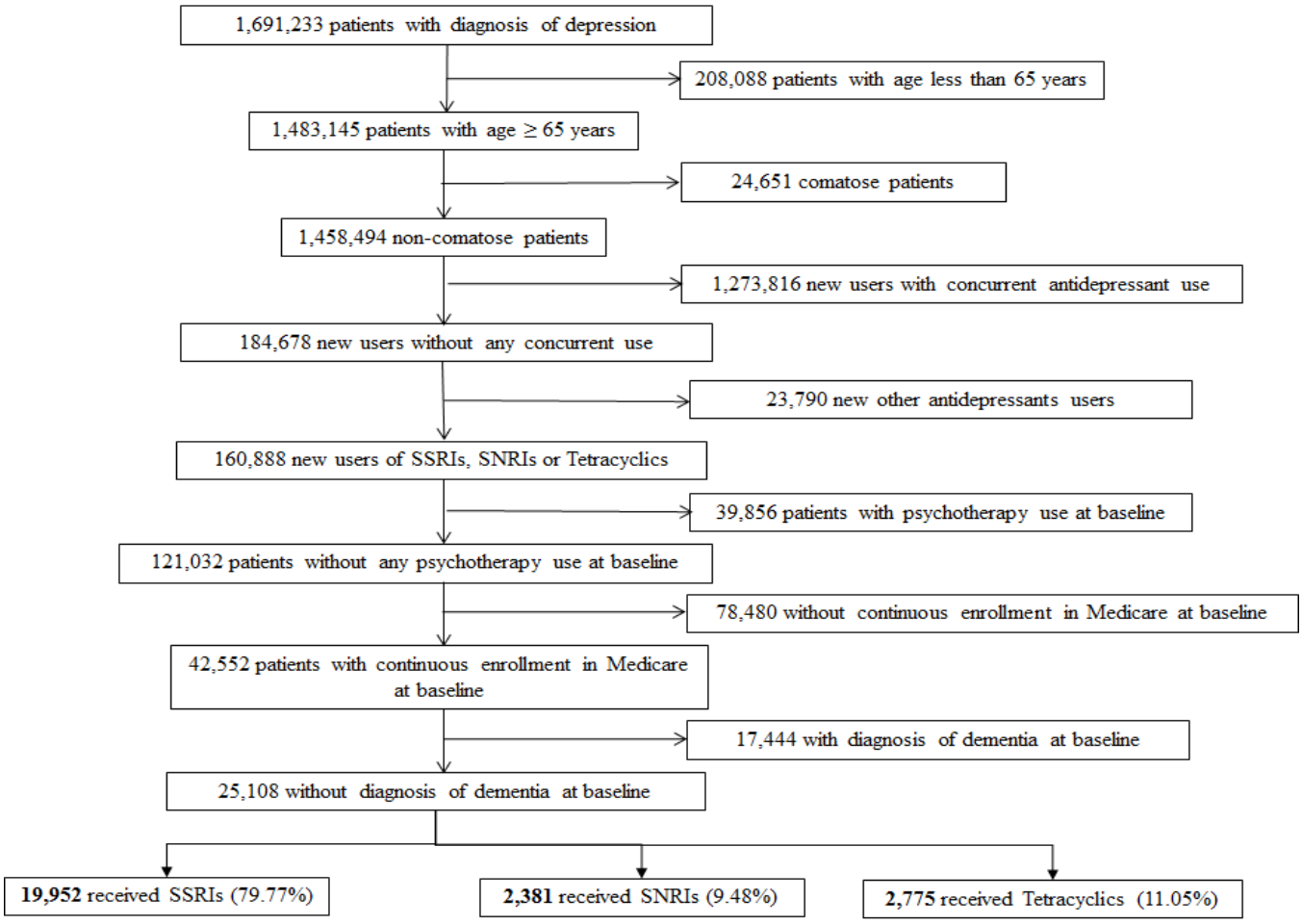

Figure 2: Flowchart of study sample selection and cohort development

Table 1 presents the baseline characteristics of the users of SSRIs, SNRIs and tetracyclics, and their distribution before and after propensity score adjustment. The study cohort constituted 25,108 elderly nursing home residents with depression. Of these, 19,952 received SSRIs (79.77%), 2,381 received SNRIs (9.48%) and the rest 2,775 received tetracyclics (11.05%). The unadjusted incidence of dementia was 8.20% for SSRI users, 6.01% for SNRI users and 7.21% for tetracyclic users. After adjusting for propensity scores, there was no

significant difference in any of the baseline characteristics. This meant that the multiple propensity score approach was able to achieve a balance for all the baseline characteristics that could have an effect on the final outcome.

Table 1: Baseline characteristics of elderly nursing home patients with depression using 1) SSRIs, 2) SNRIs and 3) tetracyclics

Characteristics	SSRI Users (N=19,952)	SNRI Users (N=2,381)	Tetracyclic Users (N=2,775)	P value before Multiple PS correction	P value after Multiple PS Correction
Gender				0.04	0.99
Female	14,129 (70.81)	1,743 (73.20)	1,955 (70.45)		
Male	5,823 (29.19)	638 (26.80)	820 (29.55)		
Age in years [n (%)]				<0.0001*	0.94
65-84	12,615 (63.23)	1,765 (74.13)	1,480 (53.33)		
85 and above	7,337 (36.77)	616 (25.87)	1,295 (46.67)		
Race				0.02*	1.00
White	18,749 (93.97)	2,237 (93.95)	2,561 (92.29)		
Non-White	1,177 (5.90)	142 (5.96)	210 (7.57)		
Missing	26 (0.13)	2 (0.08)	4 (0.14)		
Medical history in past 12 months					
CHF	8,919 (44.70)	1,048 (44.02)	1,280 (46.13)	0.32	0.99
Endocarditis	1,226 (6.14)	140 (5.88)	222 (8.00)	0.46	0.99
Ischemic Heart Disease	12,314 (61.72)	1,478 (62.07)	1,736 (62.56)	0.70	0.99
Acute Myocardial Infarction	1,498 (7.51)	163 (6.85)	212 (7.64)	0.32	0.99
Stroke/ Transient Ischemic Attack	4,586 (22.99)	514 (21.59)	644 (23.21)	0.36	0.99
Cardiac Arrhythmia	6,350 (31.83)	653 (27.43)	1,011 (36.43)	<0.0001*	0.99
Circulatory Disorder	7,352 (36.85)	882 (37.04)	1,141 (41.12)	<0.0001*	0.99
Thromboembolic Disorder	1,611 (8.07)	216 (9.07)	279 (10.05)	0.0009*	0.99
Peripheral Arterial Disorder	2,921 (14.64)	346 (14.53)	474 (17.08)	0.003*	0.99
Hypertension	17,935 (89.89)	2,154 (90.47)	2,498 (90.02)	0.67	0.99
Diabetes Mellitus	7,605 (38.12)	1,015 (42.63)	899 (32.40)	<0.0001*	0.94
Hyperlipidemia	14,441 (72.38)	1,771 (74.38)	1,903 (68.58)	<0.0001*	0.99
Renal Failure	3,984 (19.97)	460 (19.32)	689 (24.83)	<0.0001*	0.99
Other Renal Disease	8,799 (44.10)	1,036 (43.51)	1,049 (50.77)	<0.0001*	0.98

Hip Fracture	1,600 (8.02)	196 (8.23)	302 (10.88)	<0.0001*	0.99
Falls	571 (2.86)	60 (2.52)	94 (3.39)	0.16	1.00
Osteoporosis	6,188 (31.01)	804 (33.77)	1,018 (36.68)	<0.001*	0.99
Rheumatoid Arthritis and Osteoarthritis	13,166 (65.99)	1,761 (73.96)	1,831 (65.98)	<0.001*	0.96
Gout and Other Crystal Arthropathies	852 (4.27)	91 (3.82)	117 (4.22)	0.59	0.99
Back Pain	4,881 (24.46)	875 (36.75)	720 (25.95)	<0.0001*	0.90
Parkinson	480 (2.41)	45 (1.89)	70 (2.52)	0.25	0.99
Extrapyramidal syndrome	482 (2.42)	66 (2.77)	72 (2.59)	0.52	0.99
Fibromyalgia	432 (2.17)	115 (4.83)	68 (2.45)	<0.0001*	0.91
Anxiety	2,138 (10.72)	244 (10.25)	276 (9.95)	0.40	0.99
Mood Disorder	4,252 (21.31)	572 (24.02)	653 (23.53)	0.0007*	0.99
Migraine	103 (0.52)	14 (0.59)	10 (0.36)	0.47	0.99
Schizophrenia	567 (2.84)	67 (2.81)	97 (3.50)	0.15	0.99
Bipolar Disorder	108 (0.54)	26 (1.09)	15 (0.54)	0.005*	0.95
Insomnia	563 (2.82)	55 (2.31)	119 (4.29)	<0.0001*	0.99
Other Psychiatric Disorders	2,709 (13.58)	315 (13.23)	416 (14.99)	0.10	0.99
Liver Disorder	1,834 (9.19)	187 (7.85)	317 (11.42)	<0.0001*	0.99
Gastric Disorder	9,981 (50.03)	1,181 (49.60)	1,635 (58.92)	<0.0001*	0.93
Ulcers	2,121 (10.63)	297 (12.47)	364 (13.12)	<0.0001*	0.99
Cancer	3,849 (19.29)	453 (19.03)	618 (22.27)	0.0008*	0.99
Dysphagia	1,485 (7.44)	144 (6.05)	325 (11.71)	<0.0001*	0.99
Anemia	12,573 (63.02)	1,563 (65.64)	1,896 (68.32)	<0.0001*	0.96
Asthma	3,035 (15.21)	425 (17.85)	357 (12.86)	<0.0001*	0.97
Chronic Obstructive Pulmonary Disease	7,514 (37.66)	925 (38.85)	1,053 (37.95)	0.52	0.99
Pneumonia	2,970 (14.89)	336 (14.11)	568 (20.47)	<0.0001*	0.99
Benign Prostatic Hyperplasia	2,749 (13.78)	304 (12.77)	397 (14.31)	0.23	0.99
Hypothyroidism	5,072 (25.42)	626 (26.29)	688 (24.79)	0.47	0.99
Cataract	1,5077 (75.57)	1,714 (71.99)	2,171 (78.23)	<0.0001*	0.98
Glaucoma	4,661 (23.36)	551 (23.14)	728 (26.23)	0.003*	0.99
Obesity	1,167 (5.85)	179 (7.52)	87 (3.14)	<0.0001*	0.75
Alcohol	615 (3.08)	115 (4.83)	120 (4.32)	<0.0001*	0.97
Medications used in past 12 months					
Anti-Infective Agents	14,757 (73.96)	1,805 (75.81)	2,044 (73.66)	0.30	0.99
Endocrine and Metabolic Drugs	13,161 (65.96)	1,699 (71.36)	1,784 (64.29)	<0.0001*	0.99
Cardiovascular Agents	17,268 (86.55)	2,038 (85.59)	2,420 (87.21)	0.24	0.99
Anti-Hyperlipidemic Drugs	8,725 (43.73)	1,019 (42.80)	1,109 (39.96)	0.0008*	0.99

Respiratory Agents	6,922 (34.69)	881 (37.00)	983 (35.42)	0.07	0.99
Antihistamines and Other Cold Remedies	4,258 (21.34)	579 (24.32)	601 (21.66)	0.004*	0.99
Gastrointestinal Agents	4,675 (24.43)	641 (26.92)	773 (27.86)	<0.0001*	0.99
Genitourinary Products	2,392 (11.99)	319 (13.40)	330 (11.89)	0.13	0.99
Antianxiety Agents	939 (4.71)	136 (5.71)	140 (5.05)	0.08	0.99
Antipsychotics	1,807 (9.06)	263 (11.05)	300 (10.81)	0.0002	0.99
Hypnotics	2,378 (11.92)	349 (14.66)	375 (13.51)	<0.0001*	0.99
Stimulants/Anti-obesity/Anorexiants	528 (2.65)	62 (2.60)	129 (4.65)	<0.0001*	0.98
Other Psychotherapeutic Agents	390 (1.95)	85 (3.57)	68 (2.45)	<0.0001*	0.96
Anticonvulsants	2,903 (14.55)	702 (29.48)	359 (12.94)	<0.0001*	0.60
Antiparkinsonian	1,025(5.14)	150 (6.30)	138 (4.97)	0.045*	0.99
Analgesics and Anti-Inflammatories	12,011 (60.20)	1,747 (73.77)	1,688 (60.83)	<0.0001*	0.86
Musculoskeletal Agents	4,956 (28.84)	742 (31.16)	691 (24.90)	<0.0001*	0.98
Nutritional Products	5,597 (28.05)	677 (28.43)	821 (29.59)	0.24	0.99
Hematological Agents	6,783 (34.00)	764 (32.09)	928 (33.44)	0.16	0.99
Topical Products	9,411 (47.17)	1,185 (49.77)	1,267 (45.66)	0.01*	0.99
Central Acetylcholinesterase Inhibitors	300 (1.50)	32 (1.34)	48 (1.73)	0.51	0.99
Alcohol and Drug Dependence Agents	215 (1.08)	26 (1.09)	18 (0.65)	0.11	0.98
Antineoplastic Agents	1,048 (5.25)	140 (5.88)	160 (5.77)	0.27	0.99
Miscellaneous Products	3,548 (17.78)	464 (19.49)	510 (18.38)	0.11	0.99
Number of dementia cases at follow up	1,637 (8.20)	143 (6.01)	200 (7.21)	-	-

***p-value significant at 0.05**

Figure 3 presents the distribution of propensity scores among the three treatment groups. The graph indicates that there is not a common region of overlap across the users of the SSRIs, SNRIs and tetracyclics.

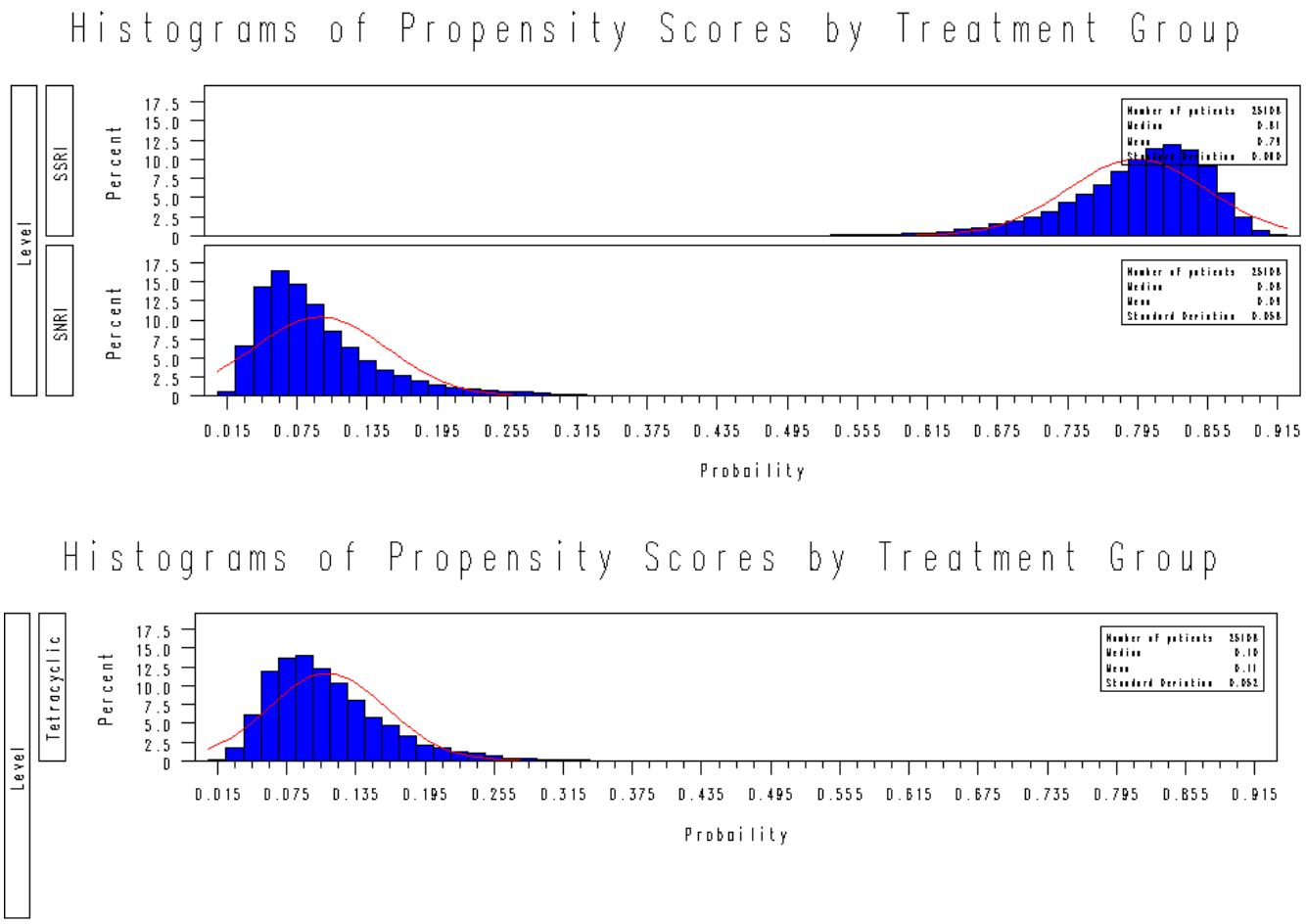

FIGURE 3: Distribution of propensity scores among the users of 1) SSRIs, 2) SNRIs and 3) tetracyclics. Data source: MDS linked CCW Medicare Claims Database, 2007–2010

To compare the three treatment groups, patients in a particular therapy group should also have a certain probability of receiving the other 2 treatments. As shown in **Figure 4**, there was a lack of overlap when the ranges of multiple propensity scores were compared across the three treatment groups using box plots.

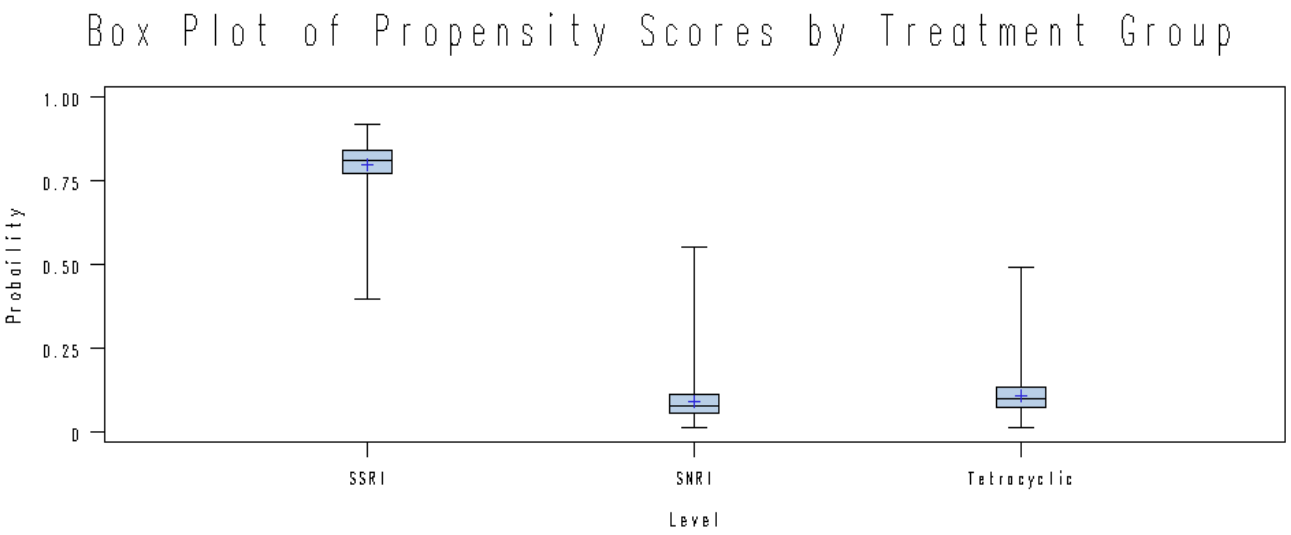

FIGURE 4: Distribution of propensity scores among the users of 1) SSRIs, 2) SNRIs and 3) tetracyclics. Data source: MDS linked CCW Medicare Claims Database, 2007–2010

Although the multiple propensity score approach was able to achieve a balance for all the baseline characteristics that could have an effect on the final outcome, there was not enough common region of overlap across the users of the three antidepressants groups, hence, two types of adjusted regression analysis were conducted. 1) Model that adjusted for propensity score and their interaction terms; 2) Model that adjusted for demographic characteristics, common chronic conditions and use of co-medications.

Table 2 presents the results of association between three classes of antidepressant use and risk of dementia after adjusting for all the baseline covariates. This model shows that there is no significant difference between use of three classes of antidepressant and risk of dementia after adjusting for all the baseline covariates. When compared with SSRI users, there was no difference with use of SNRIs [HR, 0.99; 95% CI, 0.84 – 1.19] or tetracyclics [HR, 1.01; 95% CI, 0.87 - 1.17] in terms of risk of dementia.

TABLE 2: Cox proportional-hazard model for risk of dementia in elderly nursing home patients with depression taking 1) SSRIs, 2) SNRIs and 3) tetracyclics

Variables*	Hazard ratio	95% confidence interval	p-value
Antidepressant Drug Class			
SSRIs	1.00	Reference	
SNRIs	0.99	0.84 - 1.19	0.99
Tetracyclics	1.01	0.87 - 1.17	0.90

Data source: MDS linked CCW Medicare Claims Database, 2007–2010
*Model adjusted for propensity score and their interaction terms

The main analysis was repeated using all the baseline covariates as control variables. As shown in **table 3**, results did not change when analysis was conducted among users of three antidepressant classes after adjusting for all the baseline covariates. There was no difference in the risk of dementia among elderly nursing home residents using SNRIs [HR, 1.02; 95% CI, 0.86 – 1.21] or tetracyclics [HR, 1.01; 95% CI, 0.87 – 1.18] as compared to the SSRI users.

TABLE 3: Cox proportional-hazard model for risk of dementia in elderly nursing home patients with depression taking 1) SSRIs, 2) SNRIs and 3) tetracyclics

Variables*	Hazard ratio	95% confidence interval	p-value
Antidepressant Drug Class			
SSRIs	1.00	Reference	
SNRIs	1.02	0.86 - 1.21	0.84
Tetracyclics	1.01	0.87 - 1.18	0.87

Data source: MDS linked CCW Medicare Claims Database, 2007–2010
*Model adjusted for demographic variables such as gender, age, race; chronic conditions such as chronic heart failure, endocarditis, ischemic heart disease , acute myocardial infarction, stroke/ transient ischemic attack, cardiac arrhythmia, circulatory disorder, thromboembolic disorder, peripheral arterial disorder, hypertension, diabetes mellitus, hyperlipidemia, renal failure, other renal disease, hip fracture, falls, osteoporosis, rheumatoid arthritis and osteoarthritis, gout and other crystal arthropathies, back pain, Parkinson's disease, extrapyramidal syndrome, fibromyalgia; psychotic disorders such as anxiety, mood disorder, migraine, schizophrenia, bipolar disorder, insomnia, other psychiatric disorders; other disorders such as liver disorder, gastric disorder, ulcers, cancer, dysphagia, anemia, asthma, chronic obstructive pulmonary disease, pneumonia, benign prostatic hyperplasia, hypothyroidism, cataract, glaucoma, obesity, alcohol; drugs used in the past 12 months such as anti-infective agents, endocrine and metabolic drugs, cardiovascular agents, anti-hyperlipidemic drugs, respiratory agents, antihistamines and other cold remedies, gastrointestinal agents, genitourinary products, antianxiety agents, other antidepressants,

antipsychotics, hypnotics, stimulants/anti-obesity/anorexiants, other psychotherapeutic agents, anticonvulsants, antiparkinsonian, analgesics and anti-inflammatories, musculoskeletal agents, nutritional products, hematological agents, topical products, central acetylcholinesterase inhibitors , alcohol and drug dependence agents, antineoplastic agents and other miscellaneous products

Sensitivity Analysis

Multiple sensitivity analyses were performed to evaluate the robustness of the study findings. The first sensitivity analysis was performed among patients who were nursing home residents at baseline. Diagnosis of dementia was ascertained using MDS assessment as well as chronic condition indicator. **Table 4** presents the results of association between three classes of antidepressant use and risk of dementia after adjusting for all the baseline covariates. This model shows that there is no significant difference between use of three classes of antidepressants and risk of dementia after adjusting for all the baseline covariates. When compared with SSRI users, there was no difference with use of SNRIs [HR, 1.00; 95% CI, 0.78 – 1.28] or tetracyclics [HR, 1.05; 95% CI, 0.87 – 1.26] in terms of risk of dementia.

TABLE 4: Cox proportional-hazard model for risk of dementia in elderly patients with depression taking 1) SSRIs, 2) SNRIs and 3) tetracyclics

Variables*	Hazard ratio	95% confidence interval	p-value
Antidepressant Drug Class			
SSRIs	1.00	Reference	
SNRIs	1.00	0.78 - 1.28	0.98
Tetracyclics	1.05	0.87 - 1.26	0.61

Data source: MDS linked CCW Medicare Claims Database, 2007–2010
*Model adjusted for propensity score and their interaction terms

The sensitivity analysis was repeated using all the baseline covariates as control variables. As shown in **table 5**, results did not change when the adjusted Cox model was performed for the risk of dementia among users of three antidepressant classes after adjusting for

all the baseline covariates. There was no difference in the risk of dementia among elderly nursing home residents using SNRIs [HR, 1.00; 95% CI, 0.78 – 1.28] or tetracyclics [HR, 1.08; 95% CI, 0.90 – 1.30] when compared to the SSRI users.

TABLE 5: Cox proportional-hazard model for risk of dementia in elderly patients with depression taking 1) SSRIs, 2) SNRIs and 3) tetracyclics

Variables*	Hazard ratio	95% confidence interval	p-value
Antidepressant Drug Class			
SSRIs	1.00	Reference	
SNRIs	1.00	0.78 - 1.28	0.97
Tetracyclics	1.08	0.90 - 1.30	0.41

Data source: MDS linked CCW Medicare Claims Database, 2007–2010

*Model adjusted for demographic variables such as gender, age, race; chronic conditions such as chronic heart failure, endocarditis, ischemic heart disease , acute myocardial infarction, stroke/ transient ischemic attack, cardiac arrhythmia, circulatory disorder, thromboembolic disorder, peripheral arterial disorder, hypertension, diabetes mellitus, hyperlipidemia, renal failure, other renal disease, hip fracture, falls, osteoporosis, rheumatoid arthritis and osteoarthritis, gout and other crystal arthropathies, back pain, Parkinson's disease, extrapyramidal syndrome, fibromyalgia; psychotic disorders such as anxiety, mood disorder, migraine, schizophrenia, bipolar disorder, insomnia, other psychiatric disorders; other disorders such as liver disorder, gastric disorder, ulcers, cancer, dysphagia, anemia, asthma, chronic obstructive pulmonary disease, pneumonia, benign prostatic hyperplasia, hypothyroidism, cataract, glaucoma, obesity, alcohol; drugs used in the past 12 months such as anti-infective agents, endocrine and metabolic drugs, cardiovascular agents, anti-hyperlipidemic drugs, respiratory agents, antihistamines and other cold remedies, gastrointestinal agents, genitourinary products, antianxiety agents, other antidepressants, antipsychotics, hypnotics, stimulants/anti-obesity/anorexiants, other psychotherapeutic agents, anticonvulsants, antiparkinsonian, analgesics and anti-inflammatories, musculoskeletal agents, nutritional products, hematological agents, topical products, central acetylcholinesterase inhibitors , alcohol and drug dependence agents, antineoplastic agents and other miscellaneous products

In the second sensitivity analysis, patients were excluded if they had used memantine and cholinesterase inhibitors at baseline. Additionally, these anti-dementia medications were used to identify dementia patients at follow up. Results from the sensitivity analysis supported the study findings. As shown in **table 6**, there was no significant difference in the risk of dementia among users of SNRIs [HR, 0.96; 95% CI, 0.81 – 1.14] or tetracyclics [HR, 1.03; 95% CI, 0.89 – 1.19] when compared with SSRI users.

TABLE 6: Cox proportional-hazard model for risk of dementia in elderly patients with depression taking 1) SSRIs, 2) SNRIs and 3) tetracyclics

Variables*	Hazard ratio	95% confidence interval	p-value
Antidepressant Drug Class			
SSRIs	1.00	Reference	
SNRIs	0.96	0.81 - 1.14	0.68
Tetracyclics	1.03	0.89 - 1.19	0.72

Data source: MDS linked CCW Medicare Claims Database, 2007–2010

*Model adjusted for demographic variables such as gender, age, race; chronic conditions such as chronic heart failure, endocarditis, ischemic heart disease , acute myocardial infarction, stroke/ transient ischemic attack, cardiac arrhythmia, circulatory disorder, thromboembolic disorder, peripheral arterial disorder, hypertension, diabetes mellitus, hyperlipidemia, renal failure, other renal disease, hip fracture, falls, osteoporosis, rheumatoid arthritis and osteoarthritis, gout and other crystal arthropathies, back pain, Parkinson's disease, extrapyramidal syndrome, fibromyalgia; psychotic disorders such as anxiety, mood disorder, migraine, schizophrenia, bipolar disorder, insomnia, other psychiatric disorders; other disorders such as liver disorder, gastric disorder, ulcers, cancer, dysphagia, anemia, asthma, chronic obstructive pulmonary disease, pneumonia, benign prostatic hyperplasia, hypothyroidism, cataract, glaucoma, obesity, alcohol; drugs used in the past 12 months such as anti-infective agents, endocrine and metabolic drugs, cardiovascular agents, anti-hyperlipidemic drugs, respiratory agents, antihistamines and other cold remedies, gastrointestinal agents, genitourinary products, antianxiety agents, other antidepressants, antipsychotics, hypnotics, stimulants/anti-obesity/anorexiants, other psychotherapeutic agents, anticonvulsants, antiparkinsonian, analgesics and anti-inflammatories, musculoskeletal agents, nutritional products, hematological agents, topical products, central acetylcholinesterase inhibitors , alcohol and drug dependence agents, antineoplastic agents and other miscellaneous products

DISCUSSION

As per our knowledge, this is the first population-based study to compare second-generation antidepressants in nursing home residents with depression. The association between antidepressant use and risk of dementia was examined using a multiple propensity score adjusted cohort study design. This study did not find any significant difference across the three classes of antidepressants in their risk of dementia. This could be due to the fact that despite the pharmacologic differences in these three drug classes; they seem to be clinically similar in terms of efficacy.[48,49] Although second generation antidepressants are similar in safety and efficacy profiles, they have different receptor binding properties and site of action which might lead to

differences in their onset of action, frequency of adverse events and on some measures of health related quality of life.[48,49] However, the present study findings indicate that these pharmacological differences among second generation antidepressants do not translate into clinically significant differences in the risk of dementia.

Only one observational study has been conducted that examined whether continued treatment with different antidepressants was associated with a decreased rate of dementia in patients discharged from a psychiatric hospital with a diagnosis of depression.[44,45] However, the study had some severe methodological limitations due to prevalent user study design and lack of important confounders, which led to some unanticipated findings. Thus, there is a strong need for well-designed long-term studies that would evaluate comparative safety of antidepressants in elderly residents with depression. This population-based study based on strong methodological approach and multiple sensitivity analyses found that here are no differences in the risk of dementia across the three antidepressant classes. These findings may not imply absence of an association between second generation antidepressant use and risk of dementia; rather these findings suggest that safety profiles of second generation antidepressants are similar in terms of the risk of dementia.

In summary, the findings from the current study indicate that SSRIs, SNRIs and tetracyclics do not differ significantly in dementia risk among elderly nursing home residents with depression. Previous studies have evaluated the safety profiles of individual antidepressant classes. However, none of the studies have examined their safety in elderly nursing home residents. Although second generation antidepressants have similar safety and efficacy profiles, they cannot be considered identical drugs. Physicians should consider patients' risk factors such as age, sex, physical condition, comorbidities and comedications, short and long-term

consequence of the treatment, and patients' preferences regarding dosing and drug tolerability for an informed clinical decision making.

One of the major strengths of this study was the use of the propensity score approach to control for potential selection bias owing to non-randomization of patients to the three treatment groups. Propensity scores were estimated using various observed pretreatment characteristics from past literature. Histogram of propensity scores indicated that there was no common region of overlap across the users of the SSRIs, SNRIs and tetracyclics. Also, there was a lack of overlap when the ranges of multiple propensity scores were compared across the three treatment groups using box plots again suggesting that the use of a propensity score adjusted study design might not be well suited for head to head comparison of safety of SSRIs, SNRIs and tetracyclics regarding the risk of dementia. Results from **table 1** show that patients are receiving SSRIs, SNRIs and tetracyclics for different indications. Thus, these three groups are different from each other which lead to the lack of overlap in propensity scores distribution across these three groups. However, propensity scores were able to achieve a balance for all the baseline characteristics that could have an effect the final outcome. Thus, estimated propensity scores and their interaction terms were used as covariates in the adjusted Cox proportional hazards model to examine the risk of dementia across the three treatment groups. The interaction terms between the two propensity scores were included to achieve robust estimates.[93] Additional adjusted Cox proportional hazards regression model was run where all the covariates measured at the one year baseline were used as control variables. Finally, only new users of second generation antidepressants were included in our study to address the issue of prevalence bias.[104]

The finding of this study should be interpreted while considering some of the limitations. Exposure to second generation antidepressants was ascertained using pharmacy claims. The

claims capture only dispensing data and not actual use by patients. The present study used secondary data sources like MDS and Medicare, and thus has limitations due to miscoding and under coding.[105] All the diseases and outcome measurements were based on diagnostic data in the medical claims. Incomplete, erroneous records submitted by the health care providers, availability of little clinical detail in the ICD-9 CM system and incomplete or inaccurate demographic information may limit the accuracy of administrative data.[106] Also, variables used for propensity score calculation were limited to those available in the claims data. Due to their unavailability in the dataset, important variables such as apolipoprotien E, genetic factors, diet, physical activity, stress, smoking, alcohol consumption could not be included as pretreatment characteristics for the estimation of propensity scores. Thus, it is possible that the propensity score model may not completely control for selection bias and other hidden non-observable covariates may alter the estimation and interpretation of the findings, particularly since there remained two distinct population distributions for propensity scores by antidepressant agent. However, sensitivity analysis was conducted and it supported the main findings. Also, the study population comprised of elderly nursing home residents with depression; hence the study findings may not be generalizable to other populations.

CONCLUSIONS

In this propensity score adjusted retrospective study, SSRIs, SNRIs and tetracyclics did not show any clinically significant difference in the risk of dementia in elderly nursing home residents with depression. Further studies are needed to evaluate the long-term safety of second generation antidepressants in nursing homes, a setting with patients at high risk for depression, cognitive impairment and dementia.

REFERENCES

1. Kamat SM, Kamat AS, Grossberg GT. Dementia risk prediction: are we there yet? *Clinics in geriatric medicine.* Feb 2010;26(1):113-123.

2. Sherrod RA, Collins A, Wynn S, Gragg M. Dissecting dementia, depression, and drug effects in older adults. *Journal of psychosocial nursing and mental health services.* Jan 2010;48(1):39-47.

3. Steffens DC, Potter GG. Geriatric depression and cognitive impairment. *Psychological medicine.* Feb 2008;38(2):163-175.

4. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Jul 2007;3(3):186-191.

5. Thies W, Bleiler L. 2011 Alzheimer's disease facts and figures. *Alzheimer's & dementia : the journal of the Alzheimer's Association.* Mar 2011;7(2):208-244.

6. Middleton LE, Yaffe K. Promising strategies for the prevention of dementia. *Archives of neurology.* Oct 2009;66(10):1210-1215.

7. Jorm AF, Korten AE, Henderson AS. The prevalence of dementia: a quantitative integration of the literature. *Acta psychiatrica Scandinavica.* Nov 1987;76(5):465-479.

8. Ownby RL, Crocco E, Acevedo A, John V, Loewenstein D. Depression and risk for Alzheimer disease: systematic review, meta-analysis, and metaregression analysis. *Archives of general psychiatry.* May 2006;63(5):530-538.

9. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology.* Sep 1998;51(3):728-733.

10. Christensen H, Griffiths K, Mackinnon A, Jacomb P. A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *Journal of the International Neuropsychological Society : JINS.* Nov 1997;3(6):631-651.

11. Williams JW, Plassman BL, Burke J, Benjamin S. Preventing Alzheimer's disease and cognitive decline. *Evid Rep Technol Assess.* Apr 2010;(193):1-727.

12. Alexopoulos GS, Katz IR, Reynolds CF, 3rd, Carpenter D, Docherty JP. The expert consensus guideline series. Pharmacotherapy of depressive disorders in older patients. *Postgraduate medicine.* Oct 2001;Spec No Pharmacotherapy:1-86.

13. Salzman C, Small GW. Treatment of depression with new antidepressants. In: Salzman C, ed. *Clinical geriatric psychopharmacology*. Philadelphia: Lippincott, Williams and Wilkins; 2005:305-333.

14. Karkare SU, Bhattacharjee S, Kamble P, Aparasu R. Prevalence and predictors of antidepressant prescribing in nursing home residents in the United States. *The American journal of geriatric pharmacotherapy.* Apr 2011;9(2):109-119.

15. Aparasu RR, Bali V. Antidepressant use among elderly nursing home residents with depression in the United States. *65th Annual Indian Pharmaceutical Congress*. New Delhi, India. 2013.

16. Biringer E, Rongve A, Lund A. A Review of Modern Antidepressants Effects on Neurocognitive Function. *Current Psychiatry Reviews.* 2009;5(3):164-174.

17. Francomano A, Bonanno B, Fucà L, La Placa M, La Barbera D. The role of antidepressant treatments on cognitive deficits a review of recent literature. *Clin Neuropsychiatry.* 2011;8:354-366.

18. Doraiswamy PM, Krishnan KRR, Oxman T, et al. Does antidepressant therapy improve cognition in elderly depressed patients? *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2003;58(12):M1137-M1144.

19. Culang ME, Sneed JR, Keilp JG, et al. Change in cognitive functioning following acute antidepressant treatment in late-life depression. *American Journal of Geriatric Psych.* 2009;17(10):881-888.

20. Caraci F, Copani A, Nicoletti F, Drago F. Depression and Alzheimer's disease: neurobiological links and common pharmacological targets. *European journal of pharmacology.* 2010;626(1):64-71.

21. Banasr M, Duman RS. Regulation of neurogenesis and gliogenesis by stress and antidepressant treatment. *CNS & neurological disorders drug targets.* Oct 2007;6(5):311-320.

22. Dranovsky A, Hen R. Hippocampal neurogenesis: regulation by stress and antidepressants. *Biological psychiatry.* Jun 15 2006;59(12):1136-1143.

23. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. *Primary care companion to the Journal of clinical psychiatry.* 2001;3(1):22-27.

24. Moller HJ, Volz HP. Drug treatment of depression in the 1990s. An overview of achievements and future possibilities. *Drugs.* Nov 1996;52(5):625-638.

25. Consensus statement on improving the quality of mental health care in U.S. nursing homes: management of depression and behavioral symptoms associated with dementia. *Journal of the American Geriatrics Society.* Sep 2003;51(9):1287-1298.

26. Alexopoulos GS, Buckwalter K, Olin J, Martinez R, Wainscott C, Krishnan KR. Comorbidity of late life depression: an opportunity for research on mechanisms and treatment. *Biological psychiatry.* Sep 15 2002;52(6):543-558.

27. Gallo JJ, Lebowitz BD. The epidemiology of common late-life mental disorders in the community: themes for the new century. *Psychiatr Serv.* Sep 1999;50(9):1158-1166.

28. Lebowitz BD, Pearson JL, Schneider LS, et al. Diagnosis and treatment of depression in late life. Consensus statement update. *JAMA : the journal of the American Medical Association.* Oct 8 1997;278(14):1186-1190.

29. Thakur M, Blazer DG. Depression in long-term care. *Journal of the American Medical Directors Association.* 2008;9(2):82-87.

30. Blazer DG. Depression in late life: review and commentary. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences.* 2003;58(3):M249-M265.

31. Fries BE, Mehr DR, Schneider D, Foley WJ, Burke R. Mental dysfunction and resource use in nursing homes. *Med Care.* Oct 1993;31(10):898-920.

32. Kane KD, Yochim BP, Lichtenberg PA. Depressive symptoms and cognitive impairment predict all-cause mortality in long-term care residents. *Psychology and aging.* Jun 2010;25(2):446-452.

33. Act OBR. Public Law 100-203. *Nursing Home Reform, Part C.* 1987.

34. Wilkins CH, Mathews J, Sheline YI. Late life depression with cognitive impairment: evaluation and treatment. *Clinical interventions in aging.* 2009;4:51-57.

35. Crocco EA, Castro K, Loewenstein DA. How late-life depression affects cognition: neural mechanisms. *Current psychiatry reports.* 2010;12(1):34-38.

36. Jorm AF. Is depression a risk factor for dementia or cognitive decline? A review. *Gerontology.* 2000;46(4):219-227.

37. Anderson IM. SSRIS versus tricyclic antidepressants in depressed inpatients: a meta-analysis of efficacy and tolerability. *Depress Anxiety.* 1998;7 Suppl 1:11-17.

38. Yamada M, Yasuhara H. Clinical pharmacology of MAO inhibitors: safety and future. *Neurotoxicology.* Jan 2004;25(1-2):215-221.

39. Nelson JC, Delucchi K, Schneider LS. Efficacy of second generation antidepressants in late-life depression: a meta-analysis of the evidence. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* Jul 2008;16(7):558-567.

40. Knegtering H, Eijck M, Huijsman A. Effects of antidepressants on cognitive functioning of elderly patients. A review. *Drugs & aging.* Sep 1994;5(3):192-199.

41. Oxman TE. Antidepressants and cognitive impairment in the elderly. *The Journal of clinical psychiatry.* 1996;57 Suppl 5:38-44.

42. Hunsberger J, Austin DR, Henter ID, Chen G. The neurotrophic and neuroprotective effects of psychotropic agents. *Dialogues in clinical neuroscience.* 2009;11(3):333.

43. Hashioka S, McGeer PL, Monji A, Kanba S. Anti-inflammatory effects of antidepressants: possibilities for preventives against Alzheimers disease. *Central Nervous System Agents in Medicinal Chemistry.* 2009;9(1):12-19.

44. Kessing LV, Forman JL, Andersen PK. Do continued antidepressants protect against dementia in patients with severe depressive disorder? *International clinical psychopharmacology.* Nov 2011;26(6):316-322.

45. Kessing LV, Sondergard L, Forman JL, Andersen PK. Antidepressants and dementia. *Journal of affective disorders.* Sep 2009;117(1-2):24-29.

46. Chatterjee S, Mehta S, Sherer JT, Aparasu RR. Prevalence and predictors of anticholinergic medication use in elderly nursing home residents with dementia: analysis of data from the 2004 National Nursing Home Survey. *Drugs & aging.* Dec 1 2010;27(12):987-997.

47. Hurd MD, Martorell P, Delavande A, Mullen KJ, Langa KM. Monetary costs of dementia in the United States. *The New England journal of medicine.* Apr 4 2013;368(14):1326-1334.

48. Gartlehner G, Hansen RA, Morgan LC, et al. Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive DisorderAn Updated Meta-analysis. *Annals of internal medicine.* 2011;155(11):772-785.

49. Gartlehner G, Thieda P, Hansen RA, et al. Comparative risk for harms of second-generation antidepressants : a systematic review and meta-analysis. *Drug Saf.* 2008;31(10):851-865.

50. Alexopoulos GS. Depression in the elderly. *Lancet.* Jun 4-10 2005;365(9475):1961-1970.

51. Hasche LK, Morrow-Howell N, Proctor EK. Quality of life outcomes for depressed and nondepressed older adults in community long-term care. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry.* Jun 2010;18(6):544-553.

52. NIH consensus conference. Diagnosis and treatment of depression in late life. *JAMA : the journal of the American Medical Association.* Aug 26 1992;268(8):1018-1024.

53. Kallenbach LE, Rigler SK. Identification and management of depression in nursing facility residents. *J Am Med Dir Assoc.* Sep 2006;7(7):448-455.

54. Rapp MA, Dahlman K, Sano M, Grossman HT, Haroutunian V, Gorman JM. Neuropsychological differences between late-onset and recurrent geriatric major depression. *American Journal of Psychiatry.* 2005;162(4):691-698.

55. Simpson SW, Baldwin R, Burns A, Jackson A. Regional cerebral volume measurements in late-life depression: relationship to clinical correlates, neuropsychological impairment and response to treatment. *International journal of geriatric psychiatry.* 2001;16(5):469-476.

56. Santos M, Kövari E, Hof PR, Gold G, Bouras C, Giannakopoulos P. The impact of vascular burden on late-life depression. *Brain research reviews.* 2009;62(1):19-32.

57. O'Brien J, Barber B. Neuroimaging in dementia and depression. *Advances in Psychiatric Treatment.* 2000;6(2):109-119.

58. Petrella JR, Coleman RE, Doraiswamy PM. Neuroimaging and early diagnosis of alzheimer disease: A look to the future1. *Radiology.* 2003;226(2):315-336.

59. Butters MA, Young JB, Lopez O, et al. Pathways linking late-life depression to persistent cognitive impairment and dementia. *Dialogues Clin Neurosci.* 2008;10(3):345-357.

60. Sierksma AS, van den Hove DL, Steinbusch HW, Prickaerts J. Major depression, cognitive dysfunction and Alzheimer's disease: is there a link? *Eur J Pharmacol.* Jan 10 2010;626(1):72-82.

61. Byers AL, Yaffe K. Depression and risk of developing dementia. *Nature reviews. Neurology.* Jun 2011;7(6):323-331.

62. Panel DG. Depression in Primary Care: Volume 2. Treatment of Major Depression. Clinical Practice Guideline, Number 5.(AHCPR Publication No. 93-0551). Rockville, MD: US Department of Health and Human Services. *Public Health Service, Agency for Health Care Policy and Research*1993.

63. Kaldyand J, Tarnove L. A Clinical Practice Guideline approach to treating depression in long-term care. *J Am Med Dir Assoc.* Mar-Apr 2003;4(2 Suppl):S60-68.

64. Levin CA, Wei W, Akincigil A, Lucas JA, Bilder S, Crystal S. Prevalence and treatment of diagnosed depression among elderly nursing home residents in Ohio. *J Am Med Dir Assoc.* Nov 2007;8(9):585-594.

65. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* 2012;60(4):616-631.

66. Medicare Standard Analytical Files: Identifiable Data Files. Centers for Medicare & Medicaid Services. http://www.cms.hhs.gov/IdentifiableDataFiles/02_StandardAnalyticalFiles.asp.

67. Hanlon JT, Donohue J. Medicare Part D data: A valuable tool for pharmacoepidemiology and pharmacoeconomic research. *The American journal of geriatric pharmacotherapy.* 2010;8(6):483-484.

68. Avorn J, Gurwitz JH. Drug use in the nursing home. *Annals of internal medicine.* 1995;123(3):195-204.

69. Mor V. A comprehensive clinical assessment tool to inform policy and practice: applications of the minimum data set. *Med Care.* Apr 2004;42(4 Suppl):III50-59.

70. Li Y, Schnelle J, Spector WD, Glance LG, Mukamel DB. The "Nursing Home Compare" measure of urinary/fecal incontinence: cross-sectional variation, stability over time, and the impact of case mix. *Health Serv Res.* 2010;45(1):79-97.

71. Frederiksen K, Tariot P, De Jonghe E. Minimum Data Set Plus (MDS+) scores compared with scores from five rating scales. *Journal of the American Geriatrics Society.* Mar 1996;44(3):305-309.

72. Hawes C, Morris JN, Phillips CD, Mor V, Fries BE, Nonemaker S. Reliability estimates for the Minimum Data Set for nursing home resident assessment and care screening (MDS). *The Gerontologist.* 1995;35(2):172-178.

73. Porock D, Parker-Oliver D, Petroski GF, Rantz M. The MDS Mortality Risk Index: The evolution of a method for predicting 6-month mortality in nursing home residents. *BMC research notes.* 2010;3:200.

74. Morris JN, Murphy K, Nonemaker S. *Long Term Care Facility Resident Assessment Instrument (RAI) User's Manual: For Use with Version 2.0 of the Health Care Financing Administration's Minimum Data Set, Resident Assessment Protocols, and Utilization Guidelines*: Health Care Financing Administration; 1995.

75. Morris JN, Hawes C, Fries BE, et al. Designing the national resident assessment instrument for nursing homes. *The Gerontologist.* 1990;30(3):293-307.

76. Morris JN, Fries BE, Mehr DR, et al. MDS cognitive performance scale©. *Journal of Gerontology.* 1994;49(4):M174-M182.

77. Federal Register.Health Care Financing Administration, Medicare and Medicaid: Resident Assessment in Long Term Care Facilities; Final Rule. Vol 62 23 December 1997:67174.

78. Gruber-Baldini AL, Zimmerman SI, Mortimore E, Magaziner J. The validity of the minimum data set in measuring the cognitive impairment of persons admitted to nursing homes. *Journal of the American Geriatrics Society.* Dec 2000;48(12):1601-1606.

79. Hartmaier SL, Sloane PD, Guess HA, Koch GG. The MDS Cognition Scale: a valid instrument for identifying and staging nursing home residents with dementia using the minimum data set. *Journal of the American Geriatrics Society.* 1994;42(11):1173-1179.

80. Gruber-Baldini AL, Zimmerman SI, Mortimore E, Magaziner J. The validity of the minimum data set in measuring the cognitive impairment of persons admitted to nursing homes. *J Am Geriatr Soc.* 2000;48(12):1601-1606.

81. Cohen-Mansfield J, Taylor L, McConnell D, Horton D. Estimating the cognitive ability of nursing home residents from the minimum data set. *Outcomes management for nursing practice.* Jan-Mar 1999;3(1):43-46.

82. Cantrell CR, Eaddy MT, Shah MB, Regan TS, Sokol MC. Methods for evaluating patient adherence to antidepressant therapy: a real-world comparison of adherence and economic outcomes. *Medical care.* 2006;44(4):300-303.

83. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. *Value in Health.* 2008;11(1):44-47.

84. Liu X, Chen Y, Faries DE. Adherence and persistence with branded antidepressants and generic SSRIs among managed care patients with major depressive disorder. *ClinicoEconomics and outcomes research: CEOR.* 2011;3:63.

85. Winship C, Mare RD. Models for sample selection bias. *Annual Review of Sociology.* 1992:327-350.

86. Rosenbaum PR. Discussing hidden bias in observational studies. *Annals of internal medicine.* 1991;115(11):901-905.

87. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate behavioral research.* May 2011;46(3):399-424.

88. Stukel TA, Fisher ES, Wennberg DE, Alter DA, Gottlieb DJ, Vermeulen MJ. Analysis of observational studies in the presence of treatment selection bias: effects of invasive cardiac management on AMI survival using propensity score and instrumental variable methods. *Jama.* 2007;297(3):278-285.

89. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika.* 1983;70(1):41-55.

90. Kurth T, Walker AM, Glynn RJ, et al. Results of multivariable logistic regression, propensity matching, propensity adjustment, and propensity-based weighting under conditions of nonuniform effect. *Am J Epidemiol.* Feb 1 2006;163(3):262-270.

91. Austin PC. The performance of different propensity-score methods for estimating relative risks. *Journal of clinical epidemiology.* Jun 2008;61(6):537-545.

92. Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biometrical journal. Biometrische Zeitschrift.* Feb 2009;51(1):171-184.

93. Spreeuwenberg MD, Bartak A, Croon MA, et al. The multiple propensity score as control for bias in the comparison of more than two treatment arms: an introduction from a case study in mental health. *Medical care.* 2010;48(2):166-174.

94. Andersen R, Newman JF. Societal and individual determinants of medical care utilization in the United States. *The Milbank Memorial Fund Quarterly. Health and Society.* 1973:95-124.

95. Gorelick PB. Risk factors for vascular dementia and Alzheimer disease. *Stroke; a journal of cerebral circulation.* Nov 2004;35(11 Suppl 1):2620-2622.

96. Luchsinger JA, Reitz C, Honig LS, Tang MX, Shea S, Mayeux R. Aggregation of vascular risk factors and risk of incident Alzheimer disease. *Neurology.* Aug 23 2005;65(4):545-551.

97. Savica R, Petersen RC. Prevention of dementia. *The Psychiatric clinics of North America.* Mar 2011;34(1):127-145.

98. Burrows AB, Morris JN, Simon SE, Hirdes JP, Phillips C. Development of a minimum data set-based depression rating scale for use in nursing homes. *Age and ageing.* 2000;29(2):165-172.

99. McFadden D, Train K, Tye WB. An application of diagnostic tests for the independence from irrelevant alternatives property of the multinomial logit model. *Transportation Research Record.* 1976(637):39-45.

100. Singer JD. Using SAS PROC MIXED to fit multilevel models, hierarchical models, and individual growth models. *Journal of Educational and Behavioral Statistics.* 1998;23(4):323-355.

101. Butters MA, Becker JT, Nebes RD, et al. Changes in cognitive functioning following treatment of late-life depression. *The American journal of psychiatry.* Dec 2000;157(12):1949-1954.

102. Portella MJ, Marcos T, Rami L, Navarro V, Gasto C, Salamero M. Residual cognitive impairment in late-life depression after a 12-month period follow-up. *International journal of geriatric psychiatry.* Jul 2003;18(7):571-576.

103. Nebes RD, Pollock BG, Houck PR, et al. Persistence of cognitive impairment in geriatric patients following antidepressant treatment: a randomized, double-blind clinical trial with nortriptyline and paroxetine. *Journal of psychiatric research.* 2003;37(2):99-108.

104. Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. *American journal of epidemiology.* 2003;158(9):915-920.

105. Mitchell JB, Bubolz T, Paul JE, et al. Using Medicare claims for outcomes research. *Med Care.* Jul 1994;32(7 Suppl):JS38-51.

106. Valuck RJ, Libby AM, Sills MR, Giese AA, Allen RR. Antidepressant treatment and risk of suicide attempt by adolescents with major depressive disorder: a propensity-adjusted retrospective cohort study. *CNS drugs.* 2004;18(15):1119-1132.

107. *Choosing Antidepressants for Adults: Clinician's Guide. Comparative Effectiveness Review Summary Guides for Clinicians*. Rockville MD2007.

108. Vittinghoff E, Glidden D, Shiboski S, McCulloch C. Regression methods in biostatistics: linear, logistic, survival, and repeated measures models. 2005: Springer.

CONCLUSIONS AND IMPLICATIONS

This study examined the short-term comparative effectiveness of frequently used second generation antidepressants namely SSRIs, SNRIs and Tetracyclics on cognition in the elderly nursing home residents with depression after controlling for confounding factors. The study cohort constituted 1,518 elderly nursing home residents. Of these, 1,081 received SSRIs (71.21%), 320 received tetracyclics (21.08%) and 117 received SNRIs (7.71%). Mean baseline MDS Cognition Scale value ranged from 2.31-2.71. Results from the propensity score adjusted repeated measures mixed model did not find any statistically significant difference with regards to cognition among elderly nursing home residents who used SSRIs (β = -0.23 [95% CI, -0.67, 0.22) or tetracyclics (β = -0.45 [95% CI, -0.96, 0.05]) when compared to those who used SNRIs during the one year follow up period.

This study also evaluated the long-term comparative effectiveness of SSRIs, SNRIs and tetracyclics on the risk of dementia in depressed elderly nursing home residents with depression after controlling for various confounding factors. There were 25,108 elderly nursing home residents with depression. Of these, 19,952 received SSRIs (79.77%), 2,381 received SNRIs (9.48%) and the rest 2,775 received tetracyclics (11.05%). The incidence of dementia was 8.20% for SSRI users, 6.01% for the SNRI users and 7.21% for tetracyclic users. The propensity score adjusted Cox Proportional Hazard model did not find any statistically significant difference for the risk of dementia among elderly nursing home patients who used SNRIs [HR, 0.99; 95% CI, 0.84 – 1.19] or tetracyclics [HR, 1.01; 95% CI, 0.87 - 1.17] when compared to those who used SSRIs during the 2-year follow up period.

This research found that selected antidepressant classes have no differential effect on cognition and dementia. Several factors could have contributed to these findings. First, these

three antidepressant classes are similar in their efficacy. Although SSRIs, SNRIs, and tetracyclics may differ in their onset of action and frequency of adverse events due to their different receptor binding properties, the study findings suggest that these pharmacologic differences do not translate into significant clinical differences with respect to cognition and dementia. Second, patients in this study had mild-to-moderate cognitive impairment at the baseline, and thus there was very little room for reducing the cognitive impairment or reducing the risk of dementia at the lower end of the MDS Cognition Scale. Furthermore, it is possible that the MDS Cognition Scale may not be sensitive to the effect of antidepressant classes. Finally, the timeframe to evaluate dementia was limited to one year for cognition and two years for dementia. Thus, there is need for studies that evaluate the long term effectiveness of these antidepressant classes on cognition.

Future research using prospective study design is needed to examine the comparative effectiveness of commonly used antidepressant classes on cognition and dementia in elderly nursing home patients with depression. Additionally, there is a need for better evaluation tools besides MDS Cognition Scale for capturing cognition and dementia in elderly nursing homes patients.