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Cost Analysis of Implementing an Exercise Program for Fall and Fracture Prevention in Older Adults on Proton Pump Inhibitor Therapy

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Purpose	Falls have significant financial impact. Proton pump inhibitor (PPI) therapy is associated with an increased risk of falls and fractures. Exercise programs have been shown to decrease risk of falls in the elderly population and are recommended by the U.S. Preventive Services Task Force for patients over age 65 to reduce falls. Our study aimed to explore the potential financial benefit of implementing three different Centers for Disease Control and Prevention-recommended exercise-based interventions for fall prevention (Tai Chi, Stepping On, and Otago Exercise Program) in ≥65-year-old patients on PPI therapy.
Methods	A Markov model was developed to predict the financial implications of fall-related outcomes in the study population. Net cost of the intervention was deducted from the financial savings predicted for fall avoidance relative to the fall reduction conferred by the intervention. Sensitivity analysis was performed on a range of odds ratios between falling and PPI use.
Results	Exercise-based interventions were found to offer financial savings when fall reduction rates exceeded 5%, irrespective of variable odds ratios between PPI use and fall rate. Hypothetical implementation of an exercise-based intervention for PPI users ≥65 years of age was estimated to result in annual fall- and fracture-related savings ranging from \$10,317.35 to \$18,766.28 per individual. Findings suggested an estimated annual reduction in U.S. health care costs of \$18 billion to \$85 billion.
Conclusions	Implementing an exercise-based fall prevention program for elderly PPI users represents a possible strategy to mitigate health care costs in the United States. Future prospective studies are recommended. (<i>J Patient Cent Res Rev.</i> 2022;9:263-271.)
Keywords	proton pump inhibitor; falls; fractures; elderly; exercise; fall prevention; cost analysis

Falls in the elderly have physical, emotional, psychological, and financial ramifications. While quantifying the overall burden of falling is challenging, models to predict the financial impact of falls have been developed. Direct U.S. costs for fall-related injuries in individuals ≥65 years of age are estimated to be over \$31 billion annually.¹ Exercise-based interventions are effective methods for decreasing fall and fracture risk in the elderly.²⁻⁵ The U.S. Preventive Services Task Force (USPSTF) recommends that individuals over age 65 engage in fall prevention exercise programs.^{4,6}

Age, fall history, medications, and overall functionality are cornerstones to fall risk assessment. The American Geriatric Society (AGS) Beers Criteria is a collection of specific recommendations for medications that should be used cautiously in the elderly population.⁷ The 2019 Beers Criteria update recommends cautious extended use (ie. >8 weeks) of proton pump inhibitor (PPI) therapy due to increased risk of fractures.⁷ Recent observational studies have further established and support a link between PPI use and increased rates of falls and fractures, though the exact mechanism remains debated.⁸⁻¹² Lau et al compiled several hypothetical mechanisms for increased fall rates among PPI users including B₁₂ deficiency and visual disturbances.^{11,12} At present, there are no best practice guidelines for prevention of falls and fractures while on PPI therapy despite the perceived elevated risk for PPI users. In 2012, approximately 15 million patients in the United

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States were prescribed a PPI; 7 million were over age 65.¹³⁻¹⁵ Fall prevention in PPI users could result in significant health care savings.

In parallel with USPSTF recommendations, the U.S. Centers for Disease Control and Prevention (CDC) published recommendations on fall-preventing exercise-based interventions, including Tai Chi, Stepping On, and the Otago Exercise Program.¹⁶⁻¹⁸ Tai Chi is an ancient Chinese form of exercise that focuses on balance and strength, utilizing body posturing and precise movements.¹⁷ Stepping On is a mixed individual and group exercise program, based on occupational therapy strategies, that focuses on moving safely.¹⁷ The Otago Exercise Program is physical therapy-based and focuses on strength and balance.¹⁷ All three programs involve easy-to-implement and low-cost strategies that mitigate fall risk in the elderly population.^{2,17}

To determine the financial benefit of these recommended programs for elderly PPI users, we performed a cost-benefit analysis to explore the hypothesis that significant cost savings could result from providing exercise-based interventions in PPI users over 65 years of age.

METHODS

Markov Model

After review, this study was deemed exempt from institutional review board oversight. A 5-state Markov model was developed to evaluate costs of falling-related outcomes in elderly PPI users (Figure 1). Markov models

are used to describe a cohort of “at-risk” patients as they move through different health states in which present and past states are independent.^{19,20} Each state refers to a specific outcome. For example, in a 2-state model, the states could be “alive” and “dead.” Our model combined the incidence, mortality, and costs associated with falling and not falling to simulate all fall-related outcomes of U.S. adults, ≥65 years of age, on PPI therapy. The 5 states in our model were “not falling,” “fall without medical attention,” “fall-related hospitalization,” “fall-related emergency department (ED) visit with treatment and release,” and “fall-related death.” Model assumptions are illustrated in Table 1.

For the initial population, we assumed a 34%–62% “falling” state. Relative risk (RR) was derived by first converting the odds ratio (OR) (lowest and highest possible values) of falling among all PPI users vs non-users obtained via the average OR of several cohort studies cited in a review by Lau et al to RR.^{11,12,21} We used the following formula for conversion:

$$RR = OR / (1 - p_0 + (p_0 \times OR))$$

In the formula, p_0 is the incidence of the outcome of interest in the non-PPI-user group, assumed to be 0.3 based on previously reported fall data.² That study by Carandekulis et al estimated that ≥65-year-olds have approximately a 30% chance of falling annually, with a 33.4% likelihood of seeking medical care after falling.² The probability of falling among PPI users was equal to the multiplication of the RR and incidence of falling among the nonexposed

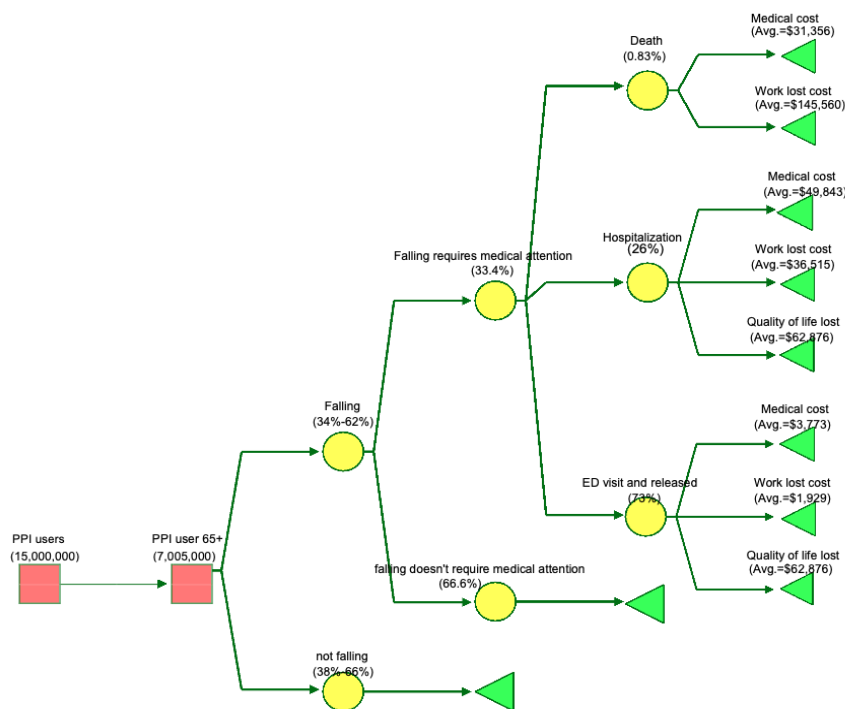


Figure 1. This figure illustrates our financial Markov model of the costs attributable to falling in the U.S. population of proton pump inhibitor (PPI) users ≥65 years of age.

Table 1. Assumptions Made in Financial Markov Model of the Costs Attributable to Falling in U.S. Population of PPI Users ≥65 Years of Age

Financial model assumptions	Reference
Estimated number of prescription PPI users in 2012: 15 million	Kantor et al (2015) ¹³
Estimated number of prescription PPI users age ≥65 years in 2012: 7 million	Maes et al (2017) ¹⁴
Estimated annual falling rate in patients age ≥65 years: 34%–62%	Lau et al (2015) ¹¹
Estimated rate of required medical attention after a fall: 33.4%	Carande-Kulis et al (2015) ²
Estimated rate of falls resulting in death: 0.83%	CDC (2005) ²²
Average medical costs attributable to a death from falling: \$31,356	CDC (2005) ²²
Average work-lost costs attributable to a death from falling: \$145,560	CDC (2005) ²²
Estimated rate of falls resulting in hospitalization: 26%	CDC (2005) ²²
Average medical costs attributable to a hospitalization from falling: \$49,843	CDC (2005) ²²
Average work-lost costs attributable to a hospitalization from falling: \$36,515	CDC (2005) ²²
Average QALY cost attributable to a hospitalization from falling: \$62,876	Zonfrillo et al (2018) ²⁵
Estimated rate of falls resulting in ED visit with discharge home: 73%	CDC (2005) ²²
Average medical costs attributable to an ED visit after falling: \$3773	CDC (2005) ²²
Average work lost costs attributable to an ED visit after falling: \$1929	CDC (2005) ²²
Average QALY cost attributable to an ED visit after falling: \$62,876	Zonfrillo et al (2018) ²⁵
Average fall reduction from Tai Chi program: 55%	Li et al (2005) ²⁷
Average annual cost of participation in Tai Chi program: \$112.70	Carande-Kulis et al (2015) ²
Average fall reduction from the Otago Exercise Program: 35%	Robertson et al (2002) ²⁹
Average annual cost of participation in the Otago Exercise Program: \$336.82	Carande-Kulis et al (2015) ²
Average fall reduction from the Stepping On program: 31%	Clemson et al (2004) ²⁸
Average annual cost of participation in the Stepping On program: \$228.63	Carande-Kulis et al (2015) ²

CDC, Centers for Disease Control and Prevention; ED, emergency department; QALY, quality-adjusted life-year; PPI, proton pump inhibitor.

(ie, non-PPI-user) group. Range of probabilities was used to conduct a sensitivity analysis on the cost-benefit of the three aforementioned fall prevention interventions.

Fall-Related Outcomes Derived From Literature

For demographic data related to falls, we accessed the CDC’s public Web-based Injury Statistics Query and Reporting System (WISQARS) database.²² The WISQARS database provides interactive data for fatal and nonfatal injuries, along with cost of injury, in the United States.²² From WISQARS cost-of-injury reports, we extracted data for the total number of deaths, hospitalizations, and ED visits resulting in discharge caused by unintentional falling among adults age 65 years and older. Average work-lost costs and medical costs for each category were also extracted from this database. All costs were adjusted for inflation to the year 2019.

The probability of each fall-related outcome occurrence was calculated by dividing the number of total cases over the approximated 2019 U.S. population over age 65. The calculated probabilities were then used to build the Markov model decision tree (Figure 1). The total cost for each category was calculated using chain/product rule and combined costs associated with falls, including medical

care cost, work-lost cost, and lost quality-adjusted life-years (QALYs). QALY represents a standardized way to quantitate both survival and health-related quality of life in economic terms for various health outcomes or states.^{23,24} Using data obtained from Zonfrillo et al,²⁵ we included an average inflation-adjusted financial cost for QALY loss representing the potential of a fall imparting lasting impact on the quality of a patient’s life that was derived from data obtained via the Healthcare Cost and Utilization Project’s ED and inpatient datasets.²⁶ QALY costs included medical spending (hospital services, emergency transport, rehabilitation, prescriptions, etc) and lost future work.²⁵ Data compiled by Carande-Kulis et al was used for annual intervention cost information and intervention fall reduction statistics.²

A 55% reduction in falls was found with implementation of the Tai Chi program reported by Li et al (RR: 0.45, 95% CI: 0.30–0.70).^{2,27} Stepping On fall rates were reduced by 31% (RR: 0.69, 95% CI: 0.50–0.96).^{2,28} Otago Exercise Program participant fall rates were reduced by 35% (RR: 0.65, 95% CI: 0.57–0.75).^{2,29} Annual cost to the patient for participation in Tai Chi was estimated at \$112.70 per individual; annual cost to the patient for participation in the Stepping On exercise-based intervention was

estimated at \$228.63 per individual; and annual cost to the patient for participation in the Otago Exercise Program was estimated at \$336.82 per individual.²

Potential annual financial savings for individuals and the United States as a whole were calculated by multiplying the percentage of fall reduction by total fall-related cost. Average cost of each intervention program was then compared to the relative reduction in health care cost associated with fall and fracture reduction from each exercise-based intervention to determine an average possible financial benefit from decreased falls and fractures.^{2,30} National savings were calculated by multiplying the potential individual savings by the approximate 7 million Americans over the age of 65 receiving prescription PPI. In summation, net benefits for individuals and the United States were defined as the financial savings calculated from averting fall-attributable costs after subtracting intervention costs.

Sensitivity Analysis

Assuming the inherent variability in previously published ORs for falling and PPI use, 1-way sensitivity analysis was conducted with variable fall rates and intervention effectiveness (Table 1).^{2,11,12,21,27-29} The threshold effectiveness of the interventions (ie, the fall reduction rate at which the net benefit equaled 0) was then determined for different ORs between PPI use and falling rate.^{2,11,12,21,27-29}

RESULTS

The individual cost of falling and possible fracture experienced by prescription PPI users ≥65 years old was estimated to range from \$10,317.35 to \$18,766.28 annually (Table 2). Extrapolated to the U.S. population, this translated to an average estimated total cost of \$72,057,324,520.74 to \$131,065,398,576.15. Sensitivity

analysis demonstrated a net financial benefit/savings from fall reduction of 5% or greater with fall prevention exercise modalities in PPI users over age 65 despite variable ORs (range: 1.20–3.77) between falling and PPI use (Figure 2).

Tai Chi represented the most cost-beneficial exercise-based intervention, with average expected individual savings of \$8616.35 (95% CI: \$5657.61–\$10,290.65) per person annually in comparison to the \$4997.89 calculated average financial benefit for a non-PPI user over age 65 implementing the same fall prevention program (Figure 3). Average annual financial benefit (averted fall cost savings less the cost of intervention) for PPI users over age 65 ranged from \$5544.91 to \$10,177.95, per ORs of 1.20–3.77 (Table 2). Annual potential U.S. financial savings from implementing Tai Chi in PPI users over age 65 ranged from \$39,720,679,427.00 to \$72,085,969,216.88, per ORs of 1.20–3.77.

Stepping On's individual potential financial savings averaged \$4856.49 (95% CI: \$3188.83–\$5800.18) annually for PPI users in comparison to the \$2816.99 calculated average financial savings for a non-PPI user over age 65 implementing the same fall prevention program (Figures 2 and 3). Average annual financial benefit (averted fall cost savings less the cost of intervention) for PPI users over age 65 ranged from \$2960.23 to \$5571.58, per ORs of 1.20–3.77 (Table 2). Annual potential U.S. financial savings from implementing the Stepping On exercise-based intervention ranged from \$22,337,770,601.43 to \$40,630,273,558.61, per ORs of 1.20–3.77.

The Otago Exercise Program had an average potential individual savings of \$5483.13 (95% CI: \$3600.29–\$6548.59) annually for fall prevention in PPI users, in

Table 2. Data for Individual Annual Program Cost, Expected Annual Savings, and Average Annual Benefit From the Three Studied Exercise-Based Interventions*

Odds ratio for PPI use vs falling rate	Fall-related estimated cost per person	Tai Chi (annual program cost of \$112.70): 5% reduction		Stepping On (annual program cost of \$228.63): 31% reduction		Otago (annual program cost of \$336.82): 35% reduction	
		Expected avg. savings	Avg. annual benefit per person	Expected avg. savings	Avg. annual benefit per person	Expected avg. savings	Avg. annual benefit per person
1.20	\$10,286.56	\$5657.60	\$5544.91	\$3188.83	\$2960.23	\$3600.29	\$3263.49
1.81	\$13,230.76	\$7276.92	\$7164.22	\$4101.54	\$3872.94	\$4630.77	\$4293.97
2.50	\$15,666.10	\$8616.35	\$8503.65	\$4856.49	\$4627.89	\$5483.13	\$5146.33
3.16	\$17,419.90	\$9580.95	\$9468.25	\$5400.17	\$5171.57	\$6096.97	\$5760.17
3.77	\$18,710.26	\$10,290.65	\$10,177.95	\$5800.18	\$5571.58	\$6548.59	\$6211.79

*assuming a 30% annual fall rate for ≥65-year-olds in relation to varying odds ratios between PPI use and fall rate.²

avg., average; PPI, proton pump inhibitor.

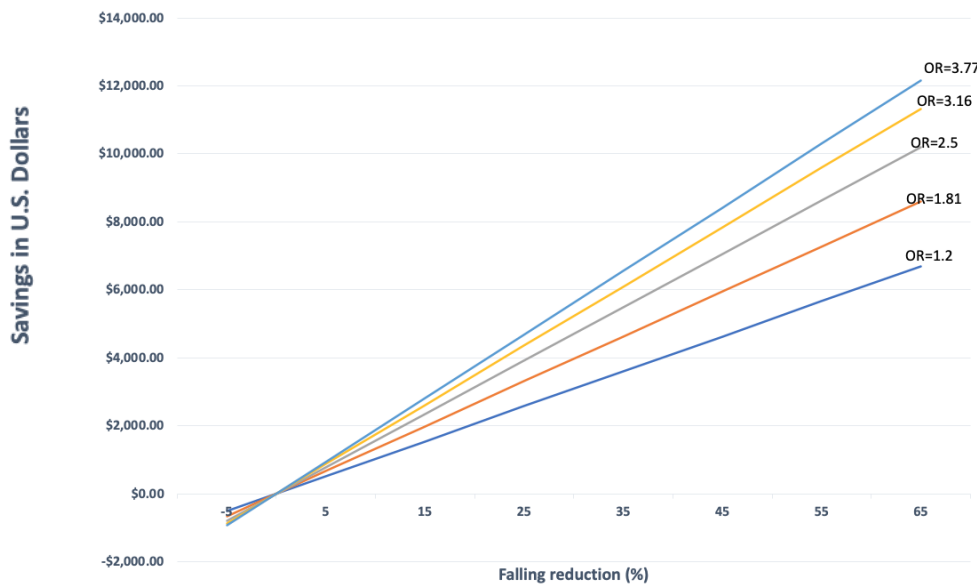


Figure 2. This graph represents the sensitivity analysis model conducted on different odds ratios (OR) between proton pump inhibitor (PPI) therapy and falling rate to determine the variable individual savings and reduction rate needed for potential financial savings. For all ORs, there was an expected annual national benefit when the exercise-based intervention implemented conferred a fall reduction over 5%.

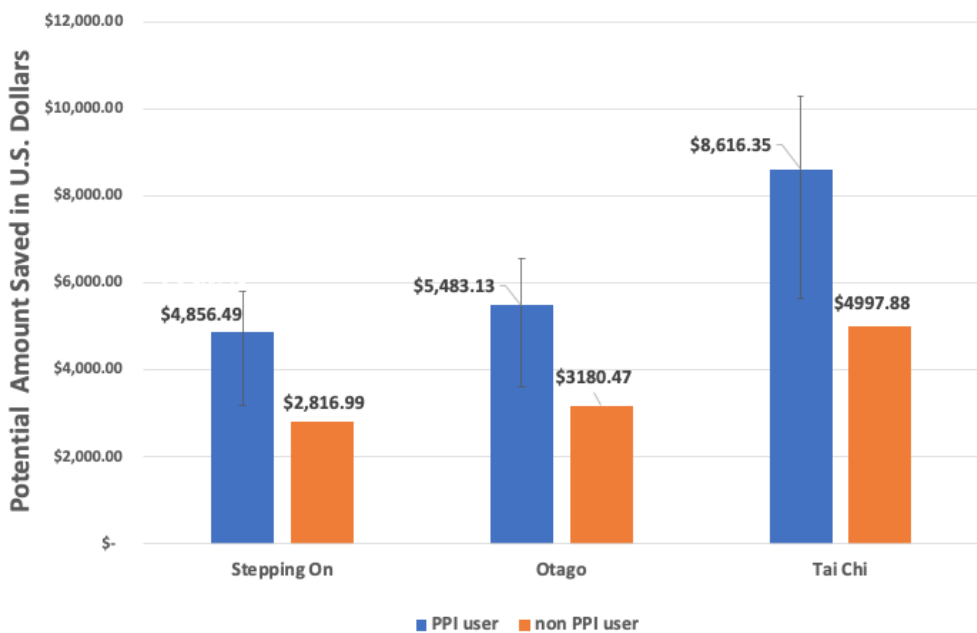


Figure 3. This figure represents the average annual financial benefit of implementing one of three exercise-based interventions to reduce fall and fracture risk in elderly patients (≥ 65 years of age) in comparison between proton pump inhibitor (PPI) and non-PPI users. The 95% CI for Stepping On annual savings was \$3,188.83 to \$5,800.18. The 95% CI for Otago Exercise Program annual savings was \$3,600.29 to \$6,548.59. The 95% CI for Tai Chi annual savings was \$5,657.60 to \$10,290.65.

comparison to the \$3180.47 calculated average financial benefit for a non-PPI user over age 65 implementing the same fall prevention program (Figure 3). Average annual financial benefit (averted fall cost savings less the cost of intervention) ranged from \$3263.49 to \$6211.79, per ORs of 1.20–3.77 (Table 2). Annual potential U.S. financial savings from implementing the Otago Exercise Program in PPI users over age 65 ranged from \$25,220,063,582.26 to \$45,872,889,501.65, per ORs of 1.20–3.77.

DISCUSSION

Falls and fall-related injuries have significant financial implications on both the individual and United States as a whole. Risk of falling and fractures is elevated in PPI users. Our observational study data suggested that these falls result in an average estimated U.S. health care cost of \$72 billion to \$131 billion. It is noteworthy that this figure represents the total impact of prescription PPI use in the United States. Since many patients use over-the-counter PPIs, by definition, our

cost-benefit analysis markedly underestimated the true financial impact of individuals falling while on PPI therapy and the benefits derived from exercise-based interventions.

Using sensitivity analysis, a net potential financial benefit when fall reduction is greater than 5%, despite variable ORs between PPI use and fall/fracture rate, was demonstrated (Figure 2). Given that all three interventions produced fall reduction returns above 30% (far greater than the 5% fall risk reduction needed for financial benefit), our findings suggest that implementing any of the described exercise-based interventions for fall prevention in ≥ 65 -year-old patients taking PPI therapy may offer a hypothetically effective means of reducing the overall financial impact of falls and fractures. With increasing likelihood of falls and fractures with PPI therapy, the financial significance of this recommendation is further emphasized (Figure 2 and Table 2). In comparison to non-PPI users, all three interventions showed significant increases in potential financial savings.

There are several noteworthy differences in the implementation and attrition rates of the three programs that could impact financial benefit. Ory et al implemented Tai Chi: Moving for Better Balance program in Colorado, New York, and Oregon.³¹ The 12-week program consisted of 1-hour sessions twice per week; 421 participants ≥ 60 years of age enrolled (approximately 80% female). Approximately half of participants completed the program, and the average attendance was only 57% of the 24 classes.³¹ Authors hypothesized that older adults may have considered the course a “drop-in” activity instead of an ongoing program or that health issues may have contributed to participants not finishing the program.³¹ They noted that Tai Chi is most effective when practiced for 50 hours or more, cumulatively. This equates to biweekly 1-hour sessions for 6 months with the recommendation of continued self-practice afterward.³¹

Additionally, Ory et al implemented the Stepping On program in Colorado, New York, and Oregon. In total, 336 participants ≥ 60 years of age were enrolled in the program (96% Caucasian, 83% female).³² The 7-week program consisted of weekly 2-hour sessions. Of the 336 participants, 274 (81.5%) attended 5 or more sessions (70% of sessions) and 138 (41.1%) completed all 7 sessions.³² Performance testing showed statistically significant improvements in functionality and decreased fall risk in all participants who completed postprogram evaluations.³² Attrition rates were lower than other studied exercise-based interventions. Authors hypothesized that two factors could have contributed to better adherence.

First, the program included a socialization component that promoted participation.³² Second, testing was considered a positive aspect by participants, with specific goals and affirmation of improvement sought by participants.³²

The Otago Exercise Program consists of strength and balance exercises lasting 30 minutes per day 3 days per week, along with a 30-minute walking program 3 days per week. Individual sessions with an instructor are completed 5 times over an initial 8-week period, and a 6-month minimum commitment is recommended. In a study completed by Shubert et al, 239 homebound elderly participants were enrolled in Otago.³³ In total, 62 participants completed the program (25.9%) and, while insufficiently powered, approximately 80% of participants had increased confidence in ability to prevent falling and most saw improved functionality.³³ Davis et al delivered the Otago Exercise Program via home DVD series.³⁴ Approximately 50% of postprogram participants were compliant with exercise requirements, and 100% of postprogram survey participants were compliant with walking requirements; however, this represented only one-quarter of enrolled participants.³⁴ The importance of this study is heightened in the post-COVID-19 era in which social distancing remains an important caveat to implementing effective fall prevention programs.

While exercise-based intervention selection should be tailored based on individual preferences and level of fall risk, Tai Chi offered the most robust hypothetical annual financial savings with an average of \$8616.35 for PPI users over age 65. On average, this was \$3618.46 higher than non-PPI users. While this is a significant possible benefit parallel to the projected 55% fall reduction and low implementation costs, previous research indicates relatively high attrition rates in the United States (~50%).³¹ The Stepping On program offered average potential annual financial savings of \$4856.49 per PPI user over age 65, which was \$2039.50 higher than non-PPI users. While this represented more modest savings, attrition rates for the Stepping On program were lower comparative to the other two studied interventions (81.5% of participants completed at least 70% of the program), with social aspects or the multifactorial nature of Stepping On conceivably contributing to participant retention and success. The Otago Exercise Program was shown to be effective (35% fall reduction) in a virtual, socially isolated format.³⁴ With lower possible overhead and staff needed as well as the opportunity to maintain social distancing, this exercise method may prove to have further financial and health benefits.

The previously described studies were performed on a relatively homogeneous group of participants (ie,

Caucasian and female), therefore future data in a variety of populations are required to formalize financial recommendations for shaping national policy on fall prevention strategies. This represents an area for future research. Real-world, prospective studies are required to determine the true efficacy of these programs in reducing fall risk in patients receiving PPI therapy. Further, while the focus of our observational study was financial ramifications of fall and fracture reduction among elderly PPI users, our analysis cannot factor other hypothetical benefits of exercise in the older population, including improved memory, socialization, and overall improvements in quality of life.³⁵ Our study was limited to PPI users over age 65 since data on fall prevalence and effects of fall prevention in younger subjects is quite limited. Nonetheless, prior population-based research indicates PPI therapy has been associated with higher fracture rates in younger patients.³⁶ Though the underlying mechanism is not understood, this does suggest an osteoporotic-independent mechanism of fracture. Additional cost modeling for younger patients on PPI therapy is also anticipated, especially as PPI therapy may be the most significant risk factor for falls and fractures in these patients.

Limitations

Our research represents data analysis that was built on prior assumptions made by Carande-Kulis et al, who demonstrated a financial benefit to fall-preventing exercise-based programs in the elderly; we expanded on their research given the increased risk for falls and fractures in elderly PPI users.^{2,8-12} While our study suggested significant hypothetical financial savings, there are several noteworthy limitations intrinsic to the Markov model developed for our study. First, our model utilized observational data that limit the strength of the recommendations that can be made, further supporting the need for real-world, prospective studies. However, observational data have been used successfully in the context of Markov model development in the past.³⁷ Another limitation to our model is the assumption that risk reduction of a Tai Chi intervention program is maintained after 1 year. Li and colleagues' randomized control trial was conducted over a 6-month period of time and not extrapolated to 1 year; however, additional research from Li et al did support extended benefits up to 3 months following a 24-week Tai Chi program.^{27,38}

Given that our study population age was over 65, the CDC recommendation would be to continue fall-reducing exercise-based therapy indefinitely; however, our literature review turned up limited longitudinal studies.^{4,6} Our study also utilized data on costs related specifically to falls resulting in injury. Subsequently, in

its present form, our model is unable to account for the difference in reduction of injurious falls in comparison to the reduction of overall falls and is an area for potential future research. An additional hypothetical impact to our model stems from the multifactor-based intervention strategy of the Stepping On exercise program. Given its multifactorial nature, this could theoretically impact the assumptions made in our model. Finally, while PPI therapy is associated with falls and fractures, falling risk is often multifactorial and fall/fracture mitigation strategies should be tailored to individual patients. Our study could not take into account patients who might have been receiving chronic PPI therapy for erroneous or unknown reasons. We expect that a subgroup of patients included in our analysis fell into this category, and such patients would likely benefit from simply stopping PPI therapy to help mitigate fall risk. Future cost modeling could consider this facet of PPI therapy.

CONCLUSIONS

Study findings support a trial of Tai Chi, Stepping On, or the Otago Exercise Program for fall prevention in older patients on proton pump inhibitor therapy, as warranted by the significant, if hypothetical, financial benefit to both individual elderly PPI users and the nation. The potential clinical importance of this albeit limited evidence is magnified by an aging U.S. population and a CDC-estimated 52 million falls in the year 2030.¹⁶ Our data analysis may even underestimate the financial impact of falling associated with PPI use, as this study focused on prescription PPI users. Real-world, prospective studies on fall prevention in elderly PPI users are indicated.

Patient-Friendly Recap

- Proton pump inhibitor (PPI) therapy is often prescribed to treat acid reflux in seniors, but it increases one's risk of falling and fractures, which result in costly health care services.
- The CDC recommends 3 exercise programs for fall prevention: Tai Chi, Stepping On, and Otago. Authors assessed the hypothetical cost savings each program might yield based on its reported efficacy in preventing falls.
- To financially benefit PPI users over age 65, exercise programs must reduce fall risk by 5%, a mark all three programs greatly exceeded. Potential annual fall-related savings were estimated to range from \$2960 to \$10,178 per individual.
- Prospectively designed studies are warranted to determine actual health and financial benefit of offering these programs to elderly patients.

Author Contributions

Study design: all authors. Data acquisition or analysis: all authors. Manuscript drafting: Wichelmann, Ehrenpreis. Critical revision: all authors.

Conflicts of Interest

E.D.E. serves as the chief executive officer of E2Bio Life Sciences, LLC, a company that is developing Bocaliner, a medical device to improve the treatment of oral mucositis, a complication of chemotherapy (patent pending). E.D.E. has no additional competing interests to disclose, and the remaining authors of this work have no competing interests to disclose.

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