

## An Early Development Budget Impact Model for the Use of Melatonin in the Treatment and Prevention of Osteoporosis

Corry D Bondi<sup>1</sup>, Rahul Khairnar<sup>1</sup>, Khalid M. Kamal<sup>1</sup>, Paula Witt-Enderby<sup>2</sup>.

<sup>1</sup>Division of Clinical, Social and Administrative Sciences, School of Pharmacy, Duquesne University, Pittsburgh, PA, USA

<sup>2</sup>Division of Pharmaceutical Sciences, School of Pharmacy, Duquesne University, Pittsburgh, PA, USA

### Abstract

In the U.S., there are approximately 9 million adults with osteoporosis (OP) and an additional 43 million at-risk. By 2030, this number is expected to increase to 68 million adults. The economic impact is estimated to be \$23 billion by 2025. Current drug therapies either decrease bone resorption (e.g., bisphosphonates) or stimulate bone formation (e.g., teriparatide). Melatonin may be a potential treatment option because research has shown it impacts bone metabolism by promoting osteoblast differentiation and activity and by suppressing osteoclast differentiation and activity. As shown in the Melatonin Osteoporosis Prevention Study (MOPS; NCT01152580), melatonin improved bone health in perimenopausal women by renormalizing bone marker turnover. Also, it is well-tolerated and has a high safety profile. Given the chronic nature of OP, coupled with high treatment costs, economic evaluation of melatonin with existing treatments could be very useful for those who manage and plan healthcare budgets. The objective of this work was to determine the budgetary impact of the addition of melatonin to treat and prevent OP from a payer perspective. A 1-year budget impact model with a hypothetical plan population of 1 million was utilized. Whole sale acquisition costs of melatonin and comparators were taken from Red Book; market share and prevalence data were obtained from the literature. Sensitivity analysis was performed to assess if changes in market share and drug costs affected the results. All costs are in 2013 U.S. dollars. The introduction of melatonin produced as Per Member Per Month (PMPM) change of -\$0.11 for OP and a PMPM of -\$0.20 for osteopenia. In conclusion, the addition of melatonin to a formulary will provide substantial cost offsets to the payer in the treatment and prevention of OP under the assumption that the effectiveness of melatonin is equal to its comparators.

**Keywords:** Budget impact analysis; Melatonin; Osteoporosis; Pharmacoeconomic evaluation; Osteopenia

**Abbreviations:** OP: Osteoporosis; BIA: Budget Impact Analysis; PMPM: Per Member Per Month; WAC: Wholesale Acquisition Cost; U.S.: United States

### Introduction

In the United States (U.S.), there are approximately 9 million adults with Osteoporosis (OP) and an additional 43 million are at-risk. By 2030, the number of adults with OP and at-risk is expected to increase to 68 million [1]. OP is the most common disease of the bone characterized by a reduction in bone density resulting from an imbalance between the highly orchestrated activity of osteoblasts (bone-forming cells) and osteoclasts (bone-breakdown cells) leading to either an increase in bone loss or a decrease in bone formation [2,3]. Because of the reduced density, the bone has a weakened structure which contributes to its increased potential for fracture.

OP-related bone fractures occur in over 1.5 million people with areas commonly affected being the hip, spine, and wrists. OP is more common in women than men (>90%), and it is the leading cause of fractures in older individuals [4]. Estimates predict that about 8 million women have OP of which 4.5 million women, over the age of 50, have osteoporosis of the hip [5,6]. OP is a serious health concern in postmenopausal women. Bone loss in women increases in the five to seven years post-menopause and can result in a loss of up to 20% or more of bone density [7]. Over 200,000 hospital discharges are attributed to hip fractures among women with half of these occurring in women over 85 years of age. Moreover, about 20% of all individuals who have experienced a hip fracture will need nursing home care [8]. The annual economic impact of OP due to bone fractures is substantial with related costs of \$19 billion per year that is projected to increase to \$25.3 billion by 2025 [9].

Current drug therapies either decrease bone resorption (e.g., bisphosphonates) or stimulate bone formation (e.g., teriparatide: the parathyroid hormone analog). Bisphosphonates include alendronate (Fosamax<sup>®</sup>), ibandronate (Boniva<sup>®</sup>), risedronate (Actonel<sup>®</sup>), and zoledronate (Reclast<sup>®</sup>). These drugs decrease bone resorption by affecting various mechanisms involving osteoclast function, activation/formation, and apoptosis. Although these drugs have represented a critical advance in treatment and prevention of OP, they are associated with infrequent adverse effects such as osteonecrosis or degradation of the jaw [10,11] as well as potentially increasing the risk of low-energy subtrochanteric or diaphyseal femur fractures [12]. Conversely, teriparatide (Forteo<sup>®</sup>), an injectable drug, administered once daily subcutaneously, stimulates bone formation resulting in increased bone mass and bone density; bone microarchitecture also improved but usage is limited by its two-year duration [13,14] and high cost to the payer and consumer.

Given the relative low cost of melatonin along with literature suggesting that melatonin deficits are implicated with the etiology of OP [15], the use of melatonin to treat and prevent OP is appealing.

**\*Corresponding author:** Khalid M Kamal, Ph.D., Division of Clinical, Social and Administrative Sciences, School of Pharmacy, Duquesne University, 600 Forbes Avenue, Pittsburgh, PA 15282, USA, Tel: 412 396 1926; Fax: 412 396 5130; E-mail: [kamalk@duq.edu](mailto:kamalk@duq.edu)

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With age, bone marrow cell differentiation shifts towards an adipocyte lineage, reducing the formation of osteoblasts, increasing fat cell accumulation in the marrow, and contributing to overall osteoporosis risk [16]. These events coincide with the decline in melatonin levels with age implying an association between bone homeostasis and melatonin production. In support of this association, the Melatonin Osteoporosis Prevention Study (MOPS; NCT01152580) revealed that melatonin improved bone health in perimenopausal women by renormalizing bone marker turnover [17]. Previous work also from the Witt-Enderby group has shown a role for MT<sub>2</sub> melatonin receptors in melatonin-induced mesenchymal stem cell differentiation into osteoblasts [18,19]. Exposure to artificial light at night affects melatonin production but may also affect bone physiology possibly through reduction in melatonin levels. To demonstrate this association, a recent study has shown that female nightshift workers exposed to artificial light at night, a known suppressor of melatonin production, had an increased risk of hip and wrist fractures over the eight years of follow-up compared to cohorts that worked the day shift [20]. Moreover, melatonin may be a potential treatment option because pre-clinical research has shown it impacts bone metabolism by promoting osteoblast differentiation and activity [15,18,19,21,22] and by suppressing osteoclast activity via increasing osteoprotegerin and actions on receptor activator NF- $\kappa$ B ligand (RANKL) [15,23]. Also, when taken orally, melatonin is well-tolerated and has a high safety profile. Given the chronic nature of OP, coupled with high costs of existing treatments, economic evaluation of melatonin with existing treatments could be very useful for those who manage and plan healthcare budgets. Due to budget constraints, decision makers (e.g., payers) need to estimate the impact of a new drug on the annual and total healthcare expenditures for resource allocation and financial planning. In the absence of any studies evaluating the economic implications of introducing melatonin to adults with OP or those at-risk, there is a need to estimate the annual costs and per member per month (PMPM) changes through a Budget Impact Analysis (BIA). The information contained in the BIA will assist the payer in decision making regarding the inclusion of melatonin in the drug formulary. Therefore, the objective of this work was to determine from a payer perspective the budgetary impact of the addition of melatonin in the treatment and prevention of OP.

## Materials and Methods

A BIA is used by the budget holder to evaluate the economic impact either positively or negatively of a new drug on their short- or long-term budgets [24]. A conceptual BIA model, as proposed by Smith and Tierce, utilizes inputs such as target population, resource utilization and costs, adoption rates, and health plan specific elements to assess the budget impact of the new drug [25]. The study model was developed using Microsoft Excel, which offers flexibility thereby allowing for customization of inputs especially with regards to the model assumptions [26]. A 1-year budget impact model with a hypothetical health plan population of 1 million adults was utilized. The target population was determined from prevalence data provided by the National Osteoporosis Foundation [1], and it was assumed the target population remained constant during the 1-year time horizon. U.S. census data were used to estimate the population over the age of 18 years [27]. Reference comparators to melatonin in the treatment of OP were ibandronate and teriparatide while reference comparators to melatonin in the prevention of OP were alendronate, ibandronate, risedronate, teriparatide, and zoledronate. Wholesale acquisition cost (WAC) of melatonin and reference comparators were taken from Red Book, and the least expensive 1-month supply of drug was selected independent of manufacturer [28]. Patient cost sharing was based on

information from a local payer. Melatonin was considered a Tier 1 drug eligible for cost sharing by the patient. Market shares of relevant comparator drugs were estimated from U.S. sales data and adjusted to 2013 U.S. dollars. Sensitivity analysis was performed to assess if changes in market share and drug costs affected the results. Annual costs and PMPM changes were reported in 2013 U.S. dollars.

## Assumptions

As with all BIAs, the final results are based upon a number of assumptions made by the authors. Even though the model allowed the payer to understand the financial relationships between the treatments and the potential budget consequences through cost estimations, the BIA compared the addition of melatonin to a selected set of approved treatments for OP and osteopenia. A static cohort approach was utilized instead of the dynamic cohort approach that would have enabled analysis of changes in members entering or leaving the target population of the plan. The design of the BIA was flexible in order to accommodate estimates for inputs in areas, including but not limited to, the type of treatment involved during the time horizon, WAC for the drugs, and market share alterations. WAC was used because the payer would only be concerned with the expenses of the drugs. Even though the BIA considered the bisphosphonates and teriparatide, the flexibility of the BIA would allow for the addition of selective estrogen receptor modulators as well as any future competitors. The costs associated with adverse effects requiring additional medical services were not considered, but this could be an option for future more extensive BIAs. The BIA neither considered demographics such as race, gender, socioeconomic status, geographic location, and education level nor did it consider disease severity or indirect societal costs. Also, the BIA did not consider risk factors that are controllable (e.g., dietary and nutritional intake, active/inactive lifestyle, smoking, and alcohol use) or uncontrollable (e.g., over 50 years, gender, menopausal status, family history, and body weight and type) [29]. It was assumed that the target population would be administering only one of the drugs during the 1-year time horizon. Drug adherence was assumed to be 100% because we believed that adherence for each drug would potentially change by the same percentage. Drug discounts or rebates were not included, but these factors may be driving market share; thus, these factors may reflect in the market share data. Moreover, market share may be sensitive to clinician preferences that may be driven by their own preference, a payer directive, or a discontinuance of a drug from the formulary by the payer. Even though we estimated market share by compiling the sales reports of the drugs, the acquisition of market share data provided unique challenges with complexities including, but not limited to, numerous producers and non-branded drugs.

Melatonin was assumed to have comparable effectiveness to its reference comparators. We speculate that due to the overall tolerability and low toxicity profile of melatonin especially in comparison to adverse effects reported for the comparators, adherence to melatonin over time may be higher. Because of this, the annual cost savings and PMPM changes of including melatonin may be enhanced. Even though melatonin is a nutritional drug product readily found on store shelves, we considered that melatonin would now be purchased from a wholesaler and dispensed by a pharmacy due to concerns for potential

Drug	Ibandronate	Teriparatide	Melatonin
Dose (Per Month)	150mg (1x)	20mg/day (30x)	5mg (30x)
Unit Cost (WAC)	\$110.98	\$1300.30	\$2.20
Co-pay	\$14.00	\$90.00	\$14.00
Net Cost	\$96.98	\$1,210.30	-\$11.80

Table 1: The pharmacy costs per month for the treatment of osteoporosis.

quality control issues of an unregulated product that the payer may have. Given this assumption, the payer would designate melatonin as a Tier 1 drug eligible for cost sharing.

## Results

The U.S. population was estimated at 314 million, and the population estimate over the age of 18 years was 76.5% or 242 million. The prevalence of adults with OP or at-risk is reported to be 9 million and 43 million, respectively [1]. The calculated prevalence of OP and those at-risk were 3.7% and 17.78%, respectively. Assuming a hypothetical cohort population in the BIA of 1 million adults, the target population was calculated to be 37,200 adults with OP and 177,800 adults at-risk for developing OP. The drug, dose per month, WAC, co-pay, and net cost were reported for their respective target populations (Tables 1 and 2).

The calculated market shares based on U.S. sales data of ibandronate and teriparatide for treatment of OP were 51.2% and 48.8%, respectively while the market shares of the drugs for the prevention of OP were 24.3% (ibandronate), 23.1% (teriparatide), 25.3% (alendronate), 16.3% (zoledronate), and 11% (risedronate) (Table 3). Univariate sensitivity analysis was performed because of the uncertainty of the BIA especially regarding market share and drug costs. Market shares of the reference comparators were adjusted to allow for a 5% market presence of melatonin. Drug costs of the reference comparators were adjusted by ±5%. Because the overall objective of this work was to determine, from a payer perspective, the budgetary impact of the addition of melatonin

in the treatment and prevention of OP, the BIA considered how the annual and PMPM costs changed with the addition. The introduction of melatonin produced an annual cost savings of \$1,279,133.90 and a PMPM change of -\$0.11 for the treatment of osteoporosis (Table 4). When it was compared to more treatment options, the annual cost savings increased to \$2,439,907.62 and had a PMPM change of -\$0.20 (Table 5).

## Discussion

To our knowledge, this is the first pharmacoeconomic evaluation to estimate the budgetary impact of the addition of melatonin in the treatment and prevention of OP. The BIA demonstrated that the introduction of melatonin produced tremendous annual cost and PMPM savings. Therefore, the addition of melatonin to a formulary will provide substantial cost offsets to the payer in the treatment and prevention of OP under the assumption that the effectiveness of melatonin is equal to or better than its comparators. Long-term, longitudinal trials comparing melatonin to gold standard treatments are warranted; however recently published clinical studies [17] or yet-to-be-published studies by Dr. Amstrup et al., assessing the efficacy of melatonin to prevent or treat OP show promise with respect to renormalizing serum bone marker status in perimenopausal women [17] and improving bone density in postmenopausal osteopenic women, respectively. Although studies assessing the impact of melatonin on bone health in humans are in their infancy, they are gaining ground. Budget Impact Analyses can help to provide significance of early stage translational research on a potentially novel therapy for treatment or prevention of a disease even though the

Drug	Alendronate	Alendronate	Ibandronate	Risedronate	Risedronate	Teriparatide	Zoledronate	Melatonin
Dose (per Month)	5 mg (30x)	35 mg (4x)	150 mg (1x)	5 mg (30x)	35 mg (4x)	20 mcg/day (30x)	5 mg/100 mL (1x)	5 mg (30x)
Unit Cost (WAC)	\$9.99	\$7.50	\$110.98	\$154.89	\$144.56	\$1300.30	\$33.55	\$2.20
Co-pay	\$14.00	\$14.00	\$14.00	\$40.00	\$40.00	\$90.00	\$3.75	\$14.00
Net Cost	-\$4.01	-\$6.50	\$96.98	\$114.89	\$104.56	\$1,210.30	\$29.80	-\$11.80

Table 2: The pharmacy costs per month for the prevention of osteoporosis.

Drug	Brand Name	Sales in USD	Annual sales adjusted to 2013	Market Share	
				Osteoporosis	Osteopenia
Ibandronate	Boniva	\$517 million (2011) <sup>1</sup>	\$535 million	51.2%	24.3
Teriparatide	Forteo	\$511 million (2013) <sup>2</sup>	\$511 million	48.8%	23.1
Alendronate	Fosamax	\$421 million (jan- sep 2013) <sup>3</sup>	\$561 million		25.3
Zoledronate	Reclast	\$355 million (March n2012- Feb 2013) <sup>4</sup>	\$360 million		16.3
Risedronate	Actonel	\$61 million (2013 Q2) <sup>5</sup>	\$244 million		11.0
			Total	100%	100%

<sup>1</sup>Available at: <http://www.gabionline.net/index.php/Generics/News/FDA-approves-first-generic-ibandronate-sodium-osteoporosis-drugs>

<sup>2</sup>Available at: <https://investor.lilly.com/releasedetail.cfm?releaseid=822044>

<sup>3</sup>Available at: <http://www.mercknewsroom.com/news-release/corporate-news/merck-announces-third-quarter-2013-financial-results>

<sup>4</sup>Available at: [http://articles.economictimes.indiatimes.com/2013-04-04/news/38278588\\_1\\_us-market-following-approval-recent-twelve-months-dr-reddy](http://articles.economictimes.indiatimes.com/2013-04-04/news/38278588_1_us-market-following-approval-recent-twelve-months-dr-reddy)

<sup>5</sup>Available at: <http://globenewswire.com/news-release/2013/07/24/562160/10041663/en/Warner-Chilcott-Reports-Operating-Results-for-the-Quarter-Ended-June-30-2013.html>

Table 3: Market shares based on U.S sales data of reference comparators.

Osteoporosis	Ibandronate	Teriparatide	Melatonin	Total
Net Cost	\$98.96	\$1,210.30	-\$11.80	
Current Use	51.2%	48.8%	0.0%	100%
Adjusted Use	48.8%	46.2%	5.0%	100%
Current Cost	\$1,847, 119.87	\$21,971, 302.08	\$0.00	\$23,818, 421.95
Current PMPM	\$0.15	\$1.83	\$0.00	\$1.98
Adjusted Cost	\$1,760, 536.13	\$20,800,699.92	-\$21,948	\$22,539, 288.05
Adjusted PMPM	\$0.15	\$1.73	\$0.00	\$1.88
Budget impact				<b>-\$1,279,133.90</b>
PMPM				<b>-\$0.11</b>

Table 4: The budgetary impact of the addition of melatonin for the treatment of osteoporosis.

Osteopenia	Alendronate 5 mg	Alendronate 35 mg	Ibandronate	Risedronate 5 mg	Risedronate 35 mg	Zoledronate	Teriparatide	Melatonin	Total
Net Cost	-\$4.01	-\$6.50	\$96.98	\$114.89	\$104.56	\$29.80	\$1,210.30	-\$11.80	
Current Use	12.65%	12.65%	24.3%	5.5%	5.5%	16.3%	23.1%	0.0%	100.0%
Adjusted Use	12.1%	12.1%	23.4%	5.0%	5.0%	15.2%	22.2%	5.0%	100.0%
Current Cost	-\$90,191.72	-\$146,196.05	\$4,190,059.69	\$1,1223,509.31	\$1,022,492.24	\$863,645.72	49,709,199.54	\$0.00	\$56,672,518.74
Current PMPM	-\$0.01	-\$0.01	\$0.35	\$0.09	\$0.09	\$0.07	\$4.14	\$0.00	\$4.72
Adjusted cost	-\$86,270.34	-\$139,839.70	\$4,034,872.30	\$1,021,372.10	\$929,538.40	\$805,362.88	\$47,772,477.48	-\$104,902	\$54,232,611.12
Adjusted PMPM	-\$0.01	-\$0.01	\$0.34	\$0.09	\$0.08	\$0.07	\$3.98	-\$0.01	\$4.52
<b>Budget impact PMPM</b>									<b>-\$2,439,907.62</b> <b>-\$0.20</b>

**Table 5:** The budgetary impact of the addition of melatonin for the prevention of osteoporosis.

main goal of a BIA is to assess the budgetary impact of the inclusion of a new drug on healthcare expenditures. In conclusion, based on the model, the addition of melatonin in the treatment and prevention of OP produced tremendous annual and PMPM cost savings. Therefore, the addition of melatonin to a formulary will provide substantial cost savings that the payer needs to consider especially if future clinical trials demonstrate that the effectiveness of melatonin is equal to or greater than its current comparators.

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