

**ORIGINAL ARTICLE**

# Savings through Sildenafil use as a coadjuvant in pharmacological treatment adherence in Hypertension and Type 2 Diabetes in Mexico

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**SUMMARY**

**Objective.** *To estimate net savings and cost effectiveness obtained through the use of 50-100 mg/oral of Sildenafil for Erectile Dysfunction (ED) as a coadjuvant in pharmacological treatment adherence in patients with Hypertension and Type 2 Diabetes versus ED treatment options: non-treatment, 10-20 mg/oral Vardenafil and 20 mg/oral Tadalafil, in the Instituto Mexicano de Seguro Social (Mexican Social Security Institute) (IMSS).*

**Methods.** With a decision tree model, a random, retrospective sample of 1,000 hypertensive patients and 1,000 diabetic patients, all presenting with ED, was created from a total of 13,731 IMSS patients hospitalized for hypertension and 65,523 for diabetes in 2005 (SUI-13 IMSS national database) to determine resource use. The study effectiveness measures were ED treatment success, reduced treatment abandonment rate for hypertension and for diabetes, and avoided hospital stay (for diabetes, hypertension and respective chronic complications). These measures were estimated through analysis of the scientific literature on the subject and through prospective research with an

**RESUMEN**

**Objetivo:** *Estimar el ahorro neto y el costo-efectividad obtenido al utilizar Sildenafil a 50-100 mg/dosis v.o. para la disfunción eréctil, como coadyuvante en la adherencia al tratamiento farmacológico en pacientes hipertensos y diabéticos tipo 2, vs. las opciones para manejo de la DE: no tratar, Vardenafil a 10-20 mg/dosis v.o. y Tadalafil a 20 mg/dosis v.o., en el Instituto Mexicano del Seguro Social (IMSS).*

**Métodos:** *Mediante un modelo de árbol de decisión se generó una muestra aleatoria y retrospectiva de 1000 pacientes hipertensos y 1000 pacientes diabéticos con disfunción eréctil, de un total de 13,731 y 65,523 hospitalizaciones por hipertensión y diabetes en el Instituto Mexicano del Seguro Social en el 2005, respectivamente (base de datos nacional del IMSS SUI-13), para determinar el uso de recursos. Las medidas de efectividad para este estudio fueron el éxito del tratamiento de la DE, la reducción en la tasa de abandono del tratamiento farmacológico para la hipertensión y la diabetes, respectivamente; y los días de hospitalización (por diabetes e hipertensión y sus respectivas complicaciones crónicas)*

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instrument developed *ex profeso* and applied by telephone to a representative Mexico City population of 326 hypertensive patients and 146 diabetic patients. The study horizon was 1 year with projections at 5 and 10 years after treatment initiation, from the perspective of the public health service provider (IMSS) as well as from a social perspective. ED pharmacological management was carried out with 50-100 mg/oral of Sildenafil and compared with the options of non-treatment, treatment with 20 mg/oral of Tadalafil and 10-20 mg/oral of Vardenafil. Results were expressed in US dollars from the year 2006. Sensitivity analysis for each base pathology was carried out individually, starting from cost modifications per patient, effectiveness rates and frequency of chronic complications.

**Results.** A 50mg dose of Sildenafil was the treatment alternative with the lowest annual cost: in DM 2,609.11 – 2,932.23 USD (CI 95%;  $P = 0.0001$ ), and in HTN 2,812.13 – 3,032.69 USD (CI 95%;  $P = 0.0001$ ) and represented a cost-saving ED therapy *versus* non-treatment. In DM, a year of ED treatment with 50mg of Sildenafil *versus* ED non-treatment option produced a savings of 753.13 – 829.94 USD (CI 95%;  $P = 0.0001$ ); 3,213.02 – 3,624.21 USD (CI 95%;  $P = 0.0000$ ) at 5 years of treatment; and 12,070.08 – 13,301.39 USD (CI 95%;  $P = 0.0001$ ) at 10 years of treatment. In HTN, a year of ED treatment with 50mg of Sildenafil *versus* ED non-treatment option produced a savings of 1,540.54 – 1,667.10 USD (CI 95%;  $P = 0.0001$ ); 5,475.72 – 7,190.28 USD (CI 95%;  $P = 0.0000$ ) at 5 years; and 24,325.00 – 26,741.22 USD (CI 95%;  $P = 0.0001$ ) at 10 years. In relation to effectiveness, 14 DM and HTN patients with ED avoided hospitalization (CI 95%) when treated with 50mg of Sildenafil, while 18 DM and HTN patients with ED avoided hospitalization (CI 95%) when treated with 100mg of Sildenafil.

100mg of Sildenafil was the alternative with greater incremental effectiveness (4 avoided hospitalization days *vs.* 50mg of Sildenafil, which was the second best alternative and the least expensive in both base pathologies), and the best Incremental Cost Effectiveness (ICE) for DM (0.13 - 0.36 USD CI 95%;  $P = 0.0001$ ) as well as for HTN (1.07 – 1.89 USD CI 95%;  $P = 0.0001$ ) and superior to the other ED treatment alternatives.

**Conclusions.** The results show Sildenafil to be cost-saving *vs.* ED non-treatment and have superior

*evitados, mismas que fueron estimadas mediante análisis conjunto de la literatura científica, y vía investigación prospectiva, a partir de un instrumento desarrollado ex profeso y aplicado telefónicamente a una muestra poblacional representativa para la ciudad de México, de 326 pacientes hipertensos y 146 pacientes con diabetes. El horizonte del estudio es de 5 años, con proyecciones a 5 y 10 años de iniciado el tratamiento. La perspectiva es tanto la del prestador de servicios públicos de salud (IMSS), como la social. El manejo farmacológico de la DE se hizo con Sildenafil a 50-100 mg/dosis v.o., que se comparó con la opción de no tratar, y con Tadalafil 20 mg/dosis v.o. y Vardenafil 10-20 mg/dosis v.o. Los resultados se expresan en dólares (USD) del año 2006. Se realizó análisis de sensibilidad para cada padecimiento de base en forma individual, a partir de modificaciones en el costo por paciente, en las tasas de efectividad encontradas, y en la frecuencia de las complicaciones crónicas.*

**Resultados:** Sildenafil de 50 mg fue la alternativa de tratamiento con el menor costo anual: en DM 2,609.11-2,932.23 USD (IC 95%;  $p = 0.0001$ ) y en HAS 2,812.13-3,032.69 USD (IC 95%;  $p = 0.0001$ ), y representó una terapia costo-ahorradora *vs.* no tratar de la disfunción eréctil. En DM el tratamiento con Sildenafil de 50 mg produjo un ahorro al año del tratamiento *vs.* la opción de no tratar la DE de 753.13-829.94 USD (IC 95%;  $p = 0.0001$ ) de 3,213.02-3,624.21 USD (IC 95%;  $p = 0.0000$ ) a los 5 años de manejo, y de 12,070.08-13,301.39 USD (IC 95%;  $p = 0.0001$ ) a los 10 años. En HAS el tratamiento con Sildenafil de 50 mg produjo un ahorro al año de tratamiento *vs.* la opción de no tratar la DE de 1,540.54-1,667.10 USD (IC 95%;  $p = 0.0001$ ) de 5,475.72-7,190.28 USD (IC 95%;  $p = 0.0000$ ) a los 5 años de manejo, y de 24,325.00-26,741.22 USD (IC 95%;  $p = 0.0001$ ) a los 10 años. En cuanto a efectividad, Sildenafil de 50 mg evitó 14 hospitalizaciones tanto en DM como en HAS con DE (IC 95%), mientras que Sildenafil de 100 mg evitó 18 hospitalizaciones tanto en DM como en HAS con DE (IC 95%).

Sildenafil de 100 mg fue la alternativa con la mayor efectividad incremental (4 días de hospitalización evitados *vs.* Sildenafil de 50 mg que fue la segunda mejor alternativa además de ser la terapia de menor costo en ambas patologías de base), y la mejor RCEI tanto para DM (0.13-0.36 USD IC 95%;  $p = 0.0001$ ) como para HAS (1.07-1.89 USD

cost-effectiveness vs. 20mg of Tadalafil and 10-20mg of Vardenafil in hypertensive and diabetic patients.

**Key words:** Savings, Adherence, Hospitalization, Diabetes, Hypertension, Erectile Dysfunction, Sildenafil.

IC 95%;  $p = 0.0001$ ), resultando dominante frente a las demás alternativas de manejo para DE.

**Conclusiones:** Los resultados obtenidos evidencian que Sildenafil es costo-ahorrador vs. la opción de no tratar la DE, y costo-efectivo dominante frente a tratar la DE con Tadalafil de 20 mg y Vardenafil de 10 y 20 mg en pacientes hipertensos y diabéticos.

**Palabras clave:** ahorro, adherencia, hospitalización, diabetes, hipertensión, disfunción eréctil, Sildenafil.

## INTRODUCTION

Diabetes Mellitus (DM) and Hypertension (HTN) represent two of the biggest public health problems in Mexico<sup>1-8</sup> and utilize large quantities of health resources.<sup>9-16</sup>

In 2005, the reported incidence was 397,387 new cases of type 2 DM,<sup>9</sup> with a general prevalence reported by ENSA 2000 of 7.5% of patients  $\geq 20$  years of age, and a median of 18.1%  $\geq 40$  years of age.<sup>1</sup> It is an illness with a large disease burden manifested by 8 YHL (Years of Healthy Life Lost) estimated for men and 12.4 YHL for women in 2005.<sup>8</sup> Recent estimates place annual DM care cost at around 317.6 million USD (for hospitalized patients per capita/year the cost is 887.14 USD and for ambulatory patients it is 85.83 USD).<sup>12,14,15</sup> In 2005, HTN had a reported incidence of 519 (298 new cases) and a 30.05% prevalence in ENSA 2001, corroborated by RENAHTA 2004.<sup>1,28</sup> Estimated disease burden in 2005 was 2.5 YHL for men and 4.2 YHL for women.<sup>8</sup> Contemporary estimates place annual public sector HTN care cost per capita/year at 622.57 USD for hospitalized patients and 49.76 USD for ambulatory patients.<sup>12</sup>

The close relation among pharmacological treatment adherence, disease control level and the advent of high impact chronic complications in health and financial costs is a relevant fact.<sup>16-32</sup> Alternative therapy studies reporting more than 11 thousand cases have demonstrated the impact of the percentage change in antidiabetic treatment adherence from rates of  $<50\%$  (mortality OR 1.74 [CI 95% 1.17 – 2.59]; hospitalization OR 1.50 [CI 95% 1.22 – 1.86]) to rates of  $\leq 80\%$  (mortality OR

1.39 [CI 95% 1.07 – 1.82]; hospitalization OR 1.38 [CI 95% 1.21 – 1.58]) and in antihypertensive treatment adherence from rates of  $<50\%$  (mortality OR 2.16 [CI 95% 1.46 – 2.80]; hospitalization OR 2.02 [CI 95% 1.46 – 2.80]) to rates of  $\leq 80\%$  (mortality OR 1.58 [CI 95% 1.22 – 2.05]; hospitalization OR 1.44 [CI 95% 1.24 – 1.67]).<sup>17</sup> In Mexico, glycemia control rates in diabetic patients have been reported from acceptable to good in 43.1%,<sup>1,10</sup> as well as treatment adherence in 54.2%<sup>33</sup> and 59%<sup>34</sup> with  $\geq 12$ th month follow-up. It has been estimated that in a 20-year period of disease evolution  $\geq 20\%$  of patients will present with the severe and costly complications of clinical nephropathy, retinopathy or neuropathy, in an isolated or coincidental manner.<sup>2,5,16-19</sup> In relation to HTN, the optimum control rate in Mexico is only 19.2%,<sup>7</sup> and international as well as national treatment adherence is 50% with  $\geq 12$ th month follow-up.<sup>27,32,33</sup> An acute complication risk reduction is reported between 20 and 40%.<sup>7</sup> The lack of treatment adherence in these diseases carries such weight in the U.S. that it generates about 10% of potentially avoidable hospitalizations annually.<sup>32,34</sup>

Specific adverse effects of pharmacological treatments are greatly responsible for lack of adherence to, indifference to or abandonment of treatments. Among them, erectile dysfunction (ED) is relevant both for its frequency and the importance attributed to it by some patients.<sup>35-39</sup>

Presently, HTN as well as DM, and the medications used in their control, are important factors contributing to ED. Various studies have found that the probability of presenting with ED is 3 times

greater in diabetic men receiving DM treatment with the use of diuretics.<sup>38-43</sup> Likewise, ED has been reported in a range of 8 to 17% in non-treated hypertensive men and up to 61% in those receiving antihypertensive treatment.<sup>35-37</sup> In a study of 5,485 treated hypertensive patients with a follow-up at 5 years, 8.3% were reported to have discontinued medication due to some degree of ED as an adverse effect.<sup>37</sup>

The fact that ED is one of the most outstanding secondary effects of many drugs used in HTN and DM treatment has a negative effect on treatment compliance and contributes to inadequate control of these diseases as well as to the existence of costly complications.<sup>36-41</sup>

Sildenafil is a phosphodiesterase type-5 inhibitor (5-PDE) administered orally and approved in Mexico for ED management. It has been shown to improve the condition according to international ED and sexual satisfaction scales<sup>41,47-51</sup> in diabetic and hypertensive patients with different treatment plans and concomitant diseases. Sildenafil has posed no additional risk to patient safety with monotherapy or combined therapy or in combination with antihypertensive and/or antidiabetic regimens.<sup>41,48,49</sup>

Since the impact that specifically treating ED has on DM and HTN adherence and control, as well as on health and medical savings consequences in Mexico is not known, the purpose of the present study is to show the net savings level obtained through the use of Sildenafil for ED *vs.* non-treatment and the relation of cost-effectiveness in ED treatment *vs.* Tadalafil and Vardenafil as drug treatment coadjuvants in hypertensive and type 2 diabetes IMSS patients. The study has a 1 year horizon with projections at 5 and 10 years from treatment commencement and includes both public health service provider (IMSS) and social perspectives.

## MATERIALS AND METHODS

Cost-effectiveness savings analysis was carried out using a tree decision model. The effect of improving antidiabetic and antihypertensive management by treating ED as the apparent cause of poor treatment adherence and/or abandonment with Sildenafil *vs.* Tadalafil, Vardenafil and the option of ED non-treatment was evaluated.

## TREE DECISION

Model structure is expressed in Figure 1. One of each of the following ED treatment alternatives was begun in a separate hypothetical cohort, made up of 1,000 type 2 DM or HTN patients with ED: 1) one 20mg/dose Tadalafil tablet; 2) one 10 or 20mg/dose Vardenafil tablet; 3) one 50 or 100mg/dose Sildenafil tablet; 4) non-treatment of ED.

The *per capita/annual* ingestion of the evaluated ED drug alternatives was 12 doses.

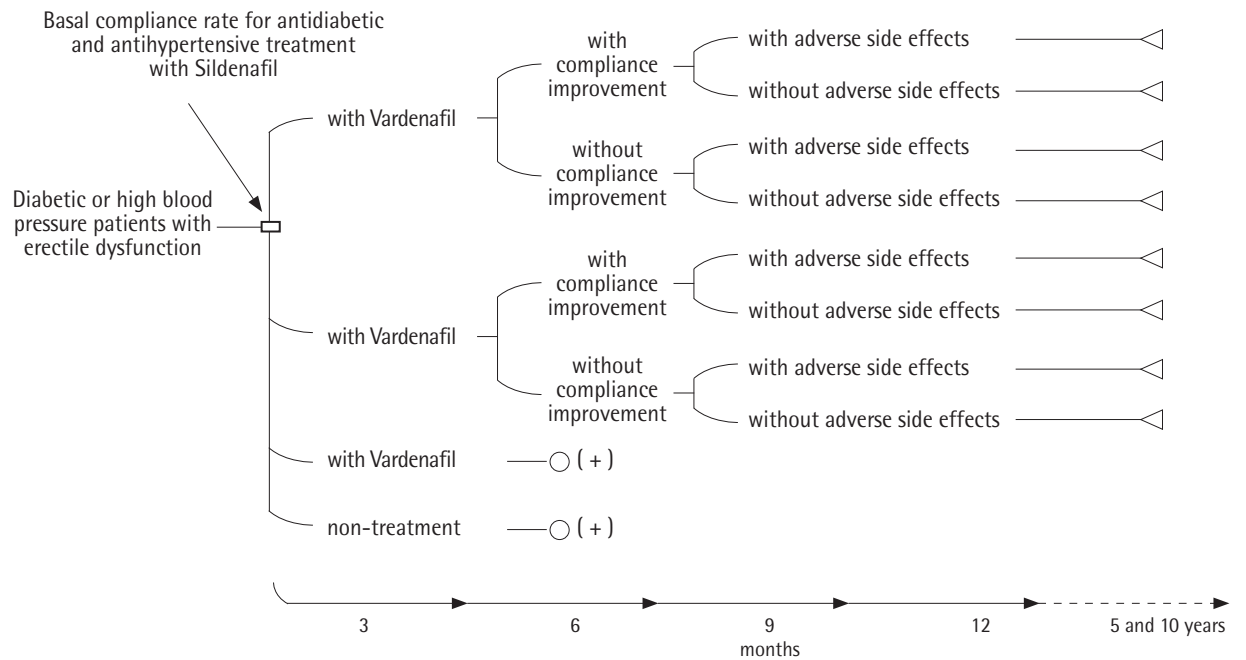
Dichotomic variables were employed: "success" and "failure" as answers to the global efficacy question (GEQ) ("success" was a  $\geq 50\%$  erection improvement; and "failure" was no improvement or  $< 50\%$  erection improvement). The branches of the tree decision model show two possibilities for each of the alternatives: "Compliance Improvement", the result of "success" in ED management (for those patients the definitive abandonment of ED-related antidiabetic or antihypertensive treatment attribution was eliminated) and "No compliance improvement", the result of "failure" in ED management (for those patients the definitive abandonment of ED-related antidiabetic or antihypertensive treatment attribution was not eliminated).

The estimated chronic complication incidence impact was incorporated into the time-line. The study horizon was 1 year and results were presented at 1 year from ED management commencement along with projections at 5 and 10 years. The perspectives taken into account were the public medical service provider (IMSS) perspective and the social perspective. The costs of future events were discounted at an annual 3% rate.<sup>50</sup>

## SUPPOSITIONS OF THE MODEL

The *patient type* for the model were hypertensive or diabetic men  $\geq 50$  years of age, with an 8- to 12-year established diagnosis, receiving drug therapy and presenting with chronic complications within the frequency levels presented in Tables 1 and 2. The baseline hyperglycemia and high blood pressure treatment adherence rate was determined by the one identified in the prospective study (Table 3). The treatment classes were: diuretic, beta blockers, calcium antagonists, converting enzyme inhibitors and angiotensin II inhibitors. It was assumed that all patients within the tree decision model presented

**Figure 1.** Decision tree model of pharmacological therapy management strategy in Diabetic and Hypertensive patients presenting with Erectile Dysfunction.



with ED. One sexual relation every 30 days/year *per capita* and the ingestion of 12 doses of the evaluated ED pharmacological alternative (in other words, one dose per sexual activity) was acknowledged. This signified 12 tablets/year of each drug, corresponding to the frequency average of sexual activity for those patients in relation to the prospective study. Another assumption was that patients maintained the same ED treatment during the entire study.

### EFFICACY AND EFFECTIVENESS MEASURES

Chronic complication rates, evaluated ED alternative clinical efficacy and effectiveness measures were determined by joint analysis of the scientific literature of the last 10 years.<sup>1,10,13-52</sup> The studies were prioritized in the following descending order: controlled, comparative, double-blind and open controlled designs, systematic revision with meta-analysis and natural alternative therapies.

The amount of time with the diagnosis, adherence and abandonment rates, as well as ED abandonment rate and its prevalence were determined through prospective research with an instrument developed from and based on the experience of 2 previous population validated questionnaires from the IMSS<sup>53,54</sup> that were applied by telephone to a population sample representative of HTN and DM prevalence among men in Mexico City. The sample was made up of 326 HTN patients (age  $53.3 \pm 7.3$  years;  $53.7\% \geq 10$  years with the disease), and 146 type 2 DM patients (age  $51.8 \pm 5.9$  years;  $47.3\% \geq 10$  years with the disease), all insured by the IMSS at the Zone No. 32 and No. 8 General Hospitals (Table 3).

The number of days of hospitalization made up the principal effectiveness measure, which in turn, was determined by secondary effectiveness measures of success in ED management and hyperglycemia and high blood pressure treatment adherence improvement.

**Table 1.** Chronic complication frequency in Diabetes Mellitus in relation to disease evolution.

Chronic complication	DM evolution in years		
	<10	≥10-20	>20
Clinical diabetic nephropathy	6.2%	14.5%	22.4%
Diabetic retinopathy	20.1%	35.7%	45.8%
Peripheral diabetic neuropathy	25.7%	47.5%	56.3%
Ischemic cardiopathy	4.9%	10.2%	16.7%
Cerebral vascular disease	2.6%	1.9%	5.2%
Diabetic foot	4.5%	21.4%	16.7%

Source: Joint analysis of the national literature: Vázquez MJL et al. Diabetes mellitus en población adulta del IMSS. Resultados de ENSA 2000. *Revista Mexicana del IMSS*. 2006;44(1):13-26; Rodríguez J et al. Características epidemiológicas de pacientes con diabetes en el Estado de México. *Revista Mexicana del IMSS*. 2003;41(5):383-392; Sabag-Ruiz E et al. Complicaciones crónicas en la diabetes mellitus. Prevalencia en una Unidad de Medicina Familiar. *Revista Mexicana del IMSS*. 2006;44(5):415-421; Ibarra E et al. Años de vida productiva perdidos por complicaciones crónicas de diabetes mellitus en población económicamente activa. *Revista Salud Pública y Nutrición*. 2003;4(2):1-6.

**Table 2.** Chronic complication frequency in High Blood Pressure in relation to disease evolution.

Chronic complication	HTN evolution in years	
	≥ 10	
Acute myocardial infarction	2.4%	
Cerebral vascular disease	1.2%	
Kidney failure	25.2%	
Congestive cardiac insufficiency	12.3%	
Peripheral arterial insufficiency	14.7%	

Source: joint analysis of the international literature: y Rosas M et al. Reencuesta Nacional de Hipertensión Arterial (RENAHTA): Consolidación mexicana de los factores de riesgo cardiovascular. Cohorte Nacional de Seguimiento. *Arch Cardiol Mex*. 2005; 75:96-111.

## COSTS

Costs were evaluated from the point of view of the public health service provider (IMSS) and of the social community. Both direct and indirect (work force productivity loss due to hospitalization) medical costs were considered. Only the IMSS purchase price of Sildenafil could be obtained from the Institute's transparency portal. The purchase price of the other ED treatment drugs was determined from over-the-counter drugstore prices (including that of Sildenafil), creating an estimate factor which

**Table 3.** Prospective research on male diabetic and hypertensive patients presenting with erectile dysfunction treated in the IMSS.

Variables	High blood pressure	Type 2 diabetes mellitus
Number of patients (n)	326	146
AGE Range	(38 to 70 years)	(43 to 78 years)
AGE (Average)	53,3	51,8
Standard deviation (SD)	± 7.3	± 5.9
Hospital to which patients were assigned		
HGZ-IMSS No. 32 (Mexico City)	189	85
%	58,0%	58,0%
HGZ-IMSS No. 8 (Mexico City)	137	61
%	42,0%	42,0%
Evolution in years		
< 10 years	151	77
%	46,3%	52,7%
≥ 10 years	175	69
%	53,7%	47,3%
Treatment	Antihypertensive	Antihyperglycemic
% Of treated patients	100%	100,0%
Treatment compliance	86,0%	52,7%
Treatment non-compliance	14,0%	47,3%
Erectile dysfunction (ED)		
Erectile dysfunction (ED) prevalence	43,0%	76,7%
ED-Related temporary or definitive treatment suspension	19,3%	33,6%
ED-Related definitive treatment suspension	11,3%	25,3%

Source: Prospective research on type 2 DM and SAH patients treated at the IMSS in Mexico City, carried out by telephone from October-November 2006

was the result of the IMSS Sildenafil purchase price quotient divided by the over-the-counter drugstore prices. This factor was multiplied by the public prices of the other drug alternatives (public price x 0.89 for 10mg of Vardenafil; and public price x 1.0 for 20mg of Vardenafil and 20mg of Taladafil), providing the price estimates allocated by the study, under the assumption that the relation between the IMSS price and the over-the-counter drugstore price of the different alternatives was "ceteris paribus" (Table 4). Data for other items were taken from

**Table 4.** Unit Price of alternative ED treatment Public Price Estimate .

ED drug management	Price to the public <sup>1</sup>	Conversion factor <sup>2</sup>	Applied price <sup>3</sup>
Sildenafil bottle with four 50mg tablets	\$39.29	0.89	\$35.10
Sildenafil bottle with four 100mg tablets	\$45.04	1.00	\$45.04
Vardenafil bottle with four 10mg tablets	\$34.88	0.89	\$31.15
Vardenafil bottle with four 20mg tablets	\$41.47	1.00	\$41.47
Tadalafil bottle with four 20mg tablets	\$ 53.37	1.00	\$ 53.37

1 drugstore price to the public.

2 conversion factor used to estimate the price applied in the model.

3 real IMSS purchase prices were used for Sildenafil, estimates were used for the other drugs.

Source: IMSS transparency portal and drugstore public price in Mexico City (October 2006). Costs in USD from 2006

the IMSS Opportune Information Bulletin<sup>49</sup> (Table 5). DM and HTN complication care cost was adjusted based on the studies of Arredondo et al.<sup>11,12</sup> and Villareal,<sup>23</sup> as well as on estimates calculated by FUNSALUD.<sup>24</sup>

Health resource use was obtained from a random, retrospective sample of 1,000 hypertensive and diabetic patients created from the total of IMSS hospitalized type 2 DM and HTN patients also presenting with ED in 2005, taken directly from institutional databases.<sup>9</sup>

Health resource costs corresponded to the year 2004 and were deflated using 2006 Bank of Mexico inflation data.<sup>55,56</sup> Cost per productivity loss was estimated from the daily wage average in the 2004 National Employment Survey (INEGI, 2005).<sup>57</sup> A sensitivity analysis was included by means of bootstrapping. The probability simulation model was developed using Microsoft Excel<sup>®</sup> de SimTools<sup>®</sup>, and the data analysis and the bootstrapping sensitivity analysis by means of STATA<sup>®</sup> version 8.

## RESULTS

In both DM and HTN, there was a 10-year disease evolution in about 10% of patients and all had received specific drug management. In HTN there was an 86% treatment adherence in the month prior to exploratory instrument application. ED prevalence in the sample was 43%, temporary or definitive treatment suspension due to ED was 19.3%, and definitive drug therapy suspension was 11.3%. In DM, treatment adherence was 52.7%, ED prevalence in

the sample was 76.7%, temporary or definitive antihyperglycemic drug suspension was 33.6% and definitive suspension was 25.3% (Table 3).

In reference to the pharmacoeconomic study, the different data analyzed and shown is for yearly periods, with cut-off points the first year of ED treatment and projections at 5 and 10 years. Estimated *per capita* costs for each disease are reported in Tables 6 and 7. Sildenafil 50mg was the treatment alternative with the lowest annual cost: in DM 2,609.11 – 2,932.23 USD (CI 95%) and in HTN 2,812.13 – 3,032.69 USD (CI 95%), Vardenafil 10mg therapy was the alternative with the highest cost/year (in DM 2,889.56 – 3,145.47 USD [CI 95%] and in HTN 2,986.51 – 3,297.72 USD [CI 95%]), despite being the ED therapy with the lowest specific cost. Sildenafil 50mg represented a cost-saving therapy *vs.* non-treatment and the other ED treatment options in those patients. Sildenafil 100mg was cost-saving *vs.* non-treatment, Vardenafil 10 and 20mg and Tadalafil 20 mg.

Tables 8 and 9 show the Incremental Cost-Effectiveness Analysis of avoided hospitalization days (effectiveness measure) due to ED management with the different alternatives in DM and HTN patients, respectively. Sildenafil 100mg was the alternative with greater incremental effectiveness (4 days *vs.* Sildenafil 50mg, which was the second best alternative along with being the lowest cost therapy in both base pathologies), and the best Incremental Cost Effectiveness for both DM (0.13 - 0.36 USD CI 95%) and HTN (1.07 – 1.89 USD CI 95%), superior to the other ED management alternatives.

**Table 5.** Unit cost of erectile dysfunction treatment in type 2 Diabetes Mellitus and High Blood Pressure patients in the IMSS.

Costs	Unit Price USD	Frequency of use/type 2 DM	Frequency of use/HTN	Source
<b>Direct Medical Costs</b>				
Family medicine ambulatory consultation <sup>1</sup>	\$ 27.64	10.19	10.25	Opportune Information Bulletin
Specialty ambulatory consultation	\$ 69.70	4.11	4.11	IMSS and Medical Operative 27 Information Subsystem
Hospitalization <sup>2</sup> (hospital stay)	\$ 248.18	4.90	5.53	Opportune Information Bulletin IMSS and Medical Operative 13 Information Subsystem
<b>Medical treatment for erectile dysfunction</b>				
Sildenafil 50mg	\$ 35.11	3.00	3.00	
Sildenafil 100mg	\$ 45.05	3.00	3.00	Purchase price differential. IMSS transparency portal <sup>3</sup>
Tadalafil 20 mg	\$ 53.39	3.00	3.00	
Vardenafil 10 mg	\$ 31.15	3.00	3.00	
Vardenafil 20 mg	\$ 41.48	3.00	3.00	
Subsequent hospitalizations	\$ 823.58	4.99	5.48	Opportune Information Bulletin IMSS and Medical Operative 13 Information Subsystem
<b>Complications</b>				
<i>Diabetes Mellitus</i>				
Clinical Nephropathy	\$ 7,030.34	2.9%		
Diabetic Retinopathy	\$ 990.93	9.5%		
Diabetic Peripheral Neuropathy	\$ 1,028.09	12.2%		
Ischemic Cardiopathy	\$ 6,579.18	2.3%		Estimated cost of medical attention for main pathologies in the IMSS, FUNSALUD,2004
Cerebral Vascular Disease	\$ 15,613.92	1.2%		
Diabetic Foot	\$ 891.84	2.1%		
<i>Hypertension</i>				
Ischemic Cardiopathy	\$ 6,579.18		0.3%	
Cerebral Vascular Disease	\$ 15,613.92		0.2%	
Kidney Failure	\$ 7,030.34		3.5%	
Congestive Cardiac Insufficiency	\$ 9,444.34		1.7%	
Peripheral Arterial Insufficiency	\$ 6,579.18		2.1%	
<b>Indirect Costs</b>				
Days of work absenteeism of patient	\$ 11.93	9.9	11.0	National Employment Survey and IMSS SUI-13

1 Inflation adjustment to December 2006 prices

2 Daily cost of hospital stay including room and food, medical and nursing attention, medications, treatment material, and laboratory and radiological tests

3 Only information for Sildenafil was found in the IMSS transparency portal. For the other drugs public prices were multiplied by the factor resulting from the IMSS and public price differential for Sildenafil (public price x 0.89 for Vardenafil 10mg, public price x 1.0 for Vardenafil 20mg and Tadalafil 20 mg)

4 Chronic complication frequency for both type 2 DM and HTN corresponds to information on the Mexican population. Costs correspond to the estimate based on the use of institutional resources adjusted according to Arredondo 11,12, Villareal 23 and FUNSALUD 24

Exchange Rate: October 10, 1992 dollar/peso - interbank. Bank of Mexico. December 2006

**Table 6.** Per capita/year treatment cost for type 2 diabetic patients presenting with erectile dysfunction at different disease stages treated in the IMSS.

Costs	Non-treatment	Sildenafil 50mg	Sildenafil 100mg	Tadalafil 20mg	Vardenafil 10mg	Vardenafil 20mg
<b>Direct Medical Costs</b>						
Primary hospitalization	\$620.25	\$397.95	\$392.68	\$405.78	\$431.66	\$405.25
Family medicine ambulatory consultation	\$140.13	\$256.70	\$252.49	\$256.38	\$255.95	\$252.76
Specialty ambulatory consultation	\$146.01	\$267.46	\$263.28	\$267.13	\$266.68	\$263.35
ED medical treatment	\$0.00	\$105.29	\$135.12	\$160.12	\$93.46	\$124.41
Subsequent hospitalizations	\$2,166.63	\$1,471.27	\$1,468.83	\$1,509.51	\$1,587.88	\$1,551.13
<b>Complications</b>	\$413.78	\$241.04	\$220.41	\$259.10	\$260.67	\$249.52
Clinical Nephropathy	\$108.65	\$63.29	\$57.88	\$68.04	\$68.45	\$65.52
Diabetic Retinopathy	\$49.65	\$28.92	\$26.45	\$31.09	\$31.28	\$29.94
Diabetic Peripheral Neuropathy	\$65.86	\$38.37	\$35.08	\$41.24	\$41.49	\$39.72
Ischemic Cardiopathy	\$80.36	\$46.81	\$42.81	\$50.32	\$50.63	\$48.46
Cerebral Vascular Disease	\$99.25	\$57.82	\$52.87	\$62.15	\$62.52	\$59.85
Diabetic Foot	\$10.00	\$5.83	\$5.33	\$6.26	\$6.30	\$6.03
<b>Indirect Costs</b>						
Days of work absenteeism of patient	\$118.03	\$81.76	\$89.69	\$84.03	\$88.88	\$85.17
<b>Total</b>	<b>\$3,604.83</b>	<b>\$2,821.47</b>	<b>\$2,822.49</b>	<b>\$2,942.05</b>	<b>\$2,985.19</b>	<b>\$2,931.60</b>
95% CI of the cost	3,423.62 - 3,842.17	2,609.11-2,932.23	2,633.87-3,082.41	2,724.35-3,145.47	2,889.56-3,145.45	2,719.48-3112.73
P value	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

Costs in USD from 2006

**Table 7.** Per capita/year treatment cost for high blood pressure patients presenting with erectile dysfunction at different disease stages treated in the IMSS.

Costs	Non-treatment	Sildenafil 50mg	Sildenafil 100mg	Tadalafil 20mg	Vardenafil 10mg	Vardenafil 20mg
<b>Direct Medical Costs</b>						
Primary hospitalization	\$811.12	\$448.50	\$442.55	\$457.32	\$486.49	\$456.72
Family medicine ambulatory consultation	\$163.67	\$258.38	\$254.17	\$258.06	\$257.63	\$254.41
Specialty ambulatory consultation	\$238.26	\$267.46	\$263.28	\$267.13	\$266.68	\$263.35
ED medical treatment	\$0.00	\$105.29	\$135.12	\$160.12	\$93.46	\$124.41
Subsequent hospitalizations	\$2,759.63	\$1,614.99	\$1,612.30	\$1,656.96	\$1,742.99	\$1,736.71
<b>Complications</b>	\$462.93	\$182.48	\$166.86	\$196.15	\$197.34	\$188.90
Ischemic Cardiopathy	\$13.52	\$6.79	\$6.21	\$7.29	\$7.34	\$7.03
Cerebral Vascular Disease	\$16.04	\$8.05	\$7.36	\$8.66	\$8.71	\$8.34
Kidney Failure	\$151.67	\$76.15	\$69.63	\$81.85	\$82.35	\$78.82
Congestive Cardiac Insufficiency	\$198.90	\$49.93	\$45.65	\$53.67	\$53.99	\$51.68
Peripheral Arterial Insufficiency	\$82.80	\$41.47	\$38.01	\$44.68	\$44.95	\$43.03
<b>Indirect Costs</b>						
Days of work absenteeism of patient	\$131.28	\$90.93	\$99.76	\$93.46	\$98.85	\$94.73
<b>Total</b>	<b>\$4,566.89</b>	<b>\$2,968.02</b>	<b>\$2974.04</b>	<b>\$3,089.20</b>	<b>\$3,143.44</b>	<b>\$3,119.23</b>
95% CI	(4,429.23-4,673.23)	(2,812.13-3,032.69)	(2,853.24-3,051.48)	(2,878.26-3,187.36)	(2,986.51-3,297.72)	(2,978.18-3,275.84)
P value	0.0001	0.0001	0.0001	0.0001	0.0001	0.0001

Costs in USD from 2006

**Table 8.** Incremental cost-effectiveness ratio estimate of ED treatments in diabetic patients.<sup>1</sup>

Erectile dysfunction management alternative	Cost a	Effectiveness days of hospital stay avoided b	Cost-effectiveness ratio (a/b)	Incremental cost c	Incremental effectiveness days of hospital stay avoided Δb	Incremental cost-effectiveness ratio (c/Δb)	Relation among alternatives
Sildenafil 50mg	\$2,821.47	14	\$195.53	-	-	-	-
Sildenafil 100mg CI 95%	\$2,822.49	18	\$152.82	\$1.02	4	\$0.25	superior
Vardenafil 10mg	\$2,985.19	1	\$1,994.11	\$163.72	-13	-\$12.66	inferior
Vardenafil 20mg	\$2,931.60	1	\$2,050.07	\$110.13	-13	-\$8.47	inferior
Tadalafil 20mg	\$2,942.05	6	\$492.79	\$120.58	-8	-\$14.25	inferior

<sup>1</sup>estimates vs Sildenafil (50mg), which is the least expensive alternative.

**Table 9.** Incremental cost-effectiveness ratio estimate of ED treatments in hypertensive patients.<sup>1</sup>

Erectile dysfunction management alternative	Cost a	Effectiveness days of hospital stay avoided b	Cost-effectiveness ratio (a/b)	Incremental cost c	Incremental effectiveness days of hospital stay avoided b	Incremental cost-effectiveness ratio (c/Δb)	Relation among alternatives
Sildenafil 50mg	\$2,968.02	14	\$205.68	-	-	-	-
Sildenafil 100mg CI 95%	\$2,974.04	18	\$161.02	\$6.02	4	\$1.49	superior
Vardenafil 10mg	\$3,143.44	1	\$2,099.82	\$175.42	-13	-\$13.56	inferior
Vardenafil 20mg	\$3,119.23	1	\$3,119.23	\$151.21	-13	-\$11.26	inferior
Tadalafil 20mg	\$3,089.20	6	\$517.44	\$121.18	-8	-\$14.32	inferior

<sup>1</sup>estimates vs Sildenafil (50mg) which is the least expensive alternative.

The expected net savings estimates are shown in Tables 10 and 11. In DM, 50mg of Sildenafil *vs.* ED non-treatment produced an annual savings of 753.13 – 829.94 USD (CI 95%; *P* = 0.0001); 3,213.02 – 3,624.21 USD (CI 95%; *P* = 0.0000) at 5 years of management; and 12,070.08 – 13,301.39 USD (CI 95%; *P* = 0.0001) at 10 years. The 100mg dose of Sildenafil *vs.* ED non-treatment produced a savings of 748.38 – 821.22 USD (CI 95%; *P* = 0.0002), 3,188.56 – 3,608.23 USD (CI 95%; *P* = 0.0000), and 12,001.01 – 13,110.08 USD (CI 95%; *P* = 0.0001) at 1, 5 and 10 years, respec-

tively. In HTN, 50mg of Sildenafil *vs.* non-treatment produced an annual savings of 1,540.54 – 1,667.10 USD (CI 95%; *P* = 0.0001); 5,475.72 – 7,190.28 USD (CI 95%; *P* = 0.0000) at 5 years of management; and 24,325.00 – 26,741.22 USD (CI 95%; *P* = 0.0001) at 10 years. The 100mg dose of Sildenafil *vs.* ED non-treatment produced a savings of 1,421.75 – 1,625.99 USD (CI 95%; *P* = 0.0002), 6,132.07 – 7,012.97 USD (CI 95%; *P* = 0.0001) and 23,814.18 – 26,091.54 USD (CI 95%; *P* = 0.0001) at 1, 5 and 10 years, respectively.

**Table 10.** Expected Net Savings in different management projection periods of type 2 diabetes mellitus patients presenting with erectile dysfunction in relation to non-treatment.

	Sildenafil 50mg 1 year	Sildenafil 50mg 5 years	Sildenafil 50mg 10 years	Sildenafil 100mg 1 year	Sildenafil 100mg 5 years	Sildenafil 100mg 10 years
<b>Direct Medical Costs</b>						
Primary hospitalization	\$222.30	\$958.77	\$3,567.08	\$227.57	\$981.53	\$3,651.74
Family medicine ambulatory consultation	-\$116.56	-\$502.75	-\$1,870.46	-\$112.35	-\$484.59	-\$1,802.90
Specialty ambulatory consultation	-\$121.45	-\$523.82	-\$1,948.85	-\$117.27	-\$505.80	-\$1,881.82
ED medical treatment	-\$105.29	-\$454.12	-\$1,689.54	-\$135.12	-\$582.77	-\$2,168.19
Subsequent hospitalizations	\$695.36	\$2,999.12	\$11,158.13	\$697.81	\$3,009.67	\$11,197.40
<i>Complications</i>	\$172.73	\$745.01	\$2,771.78	\$193.37	\$834.00	\$3,102.89
<b>Indirect Costs</b>						
Days of work absenteeism of patient	\$36.28	\$156.47	\$582.15	\$28.34	\$122.23	\$454.77
<b>Total</b>	<b>\$783.36</b>	<b>\$3,378.69</b>	<b>\$12,570.30</b>	<b>\$782.34</b>	<b>\$3,374.28</b>	<b>\$12,553.89</b>
95% CI	(753.13-829.94)	(3,213.02-3,624.21)	(12,070.08-13,301.39)	(748.38-821.22)	(3,188.56-3,608.23)	(12,001.01-13,110.08)
<i>P</i> value in relation to non-treatment	0.0001	0.0000	0.0001	0.0002	0.0000	0.0001

Costs in USD from 2006

**Table 11.** Expected Net Savings in different management projection periods of high blood pressure patients presenting with erectile dysfunction in relation to non-treatment.

	Sildenafil 50mg 1 year	Sildenafil 50mg 5 years	Sildenafil 50mg 10 years	Sildenafil 100mg 1 year	Sildenafil 100mg 5 years	Sildenafil 100mg 10 years
<b>Direct Medical Costs</b>						
Primary hospitalization	\$362.62	\$1,564.00	\$5,818.81	\$368.57	\$1,589.64	\$5,914.22
Family medicine ambulatory consultation	-\$94.71	-\$408.49	-\$1,519.77	-\$90.51	-\$390.35	-\$1,452.29
Specialty ambulatory consultation	-\$29.19	-\$125.91	-\$468.43	-\$25.02	-\$107.89	-\$401.40
ED medical treatment	-\$105.29	-\$454.12	-\$1,689.54	-\$135.12	-\$582.77	-\$2,168.19
Subsequent hospitalizations	\$1,144.64	\$4,936.90	\$18,367.58	\$1,147.33	\$4,948.48	\$18,410.69
<i>Complications</i>	\$280.45	\$1,209.58	\$4,500.21	\$296.07	\$1,276.95	\$4,750.87
<b>Indirect Costs</b>						
Days of work absenteeism of patient	\$40.35	\$174.03	\$647.48	\$31.52	\$135.95	\$505.80
<b>Total</b>	<b>\$1,598.87</b>	<b>\$6,895.99</b>	<b>\$25,656.34</b>	<b>\$1,592.85</b>	<b>\$6,870.02</b>	<b>\$25,559.70</b>
95% CI	(1,540.54-1,667.10)	5,475.72-7,190.28	(24,325.00-26,741.22)	(1,421.75-1,625.99)	(6,132.07-7,012.97)	(23,814.18-26,091.54)
<i>P</i> value in relation to non-treatment	0.0001	0.0000	0.0001	0.0002	0.0001	0.0001

Costs in USD from 2006

## SENSITIVITY ANALYSIS

Sensitivity analysis was carried out individually for each base disease, starting from cost modifications in the effectiveness rates per patient and in the frequency of chronic complications, with a standard deviation above and below the mean obtained through *bootstrapping*. Drug treatment cost, the number of adverse effects and hospital stay were all taken into consideration. Discount rate repetition from 0 to 7% was carried out.

In DM, Sildenafil treatment *vs.* ED non-treatment produced an estimated per capita savings at 1 year of treatment of 783 USD, with a  $\geq 95\%$  CI probability that management would be cost-saving in diabetic populations of about 50% of individuals having a  $\geq 10$  year disease evolution. In HTN, Sildenafil treatment *vs.* ED non-treatment produced an estimated per capita savings at 1 year of treatment of approximately 1,599 USD, with a  $\geq 91\%$  CI probability that treatment would be cost-saving in hypertensive populations of about 50% of individuals having a  $\leq 10$  year disease evolution.

## DISCUSSION

These study results show the pertinence of treating type 2 DM and HTN patients, also presenting with ED, given the elevated prevalence of ED and the significant treatment abandonment rate it causes, as demonstrated in the prospective research (Table 3). Sildenafil is seen to be the superior cost-saving and cost-effective strategy for ED treatment in relation to the non-treatment option and treatment with comparative drugs in annual treatment of these cases.

The annual savings obtained with Sildenafil ED management in the IMSS population, in the case of DM, is equivalent to at least 6,035 hemodialysis sessions, 334 breast cancer hospitalizations or 525 asthmatic crisis hospitalizations, respectively, for every 1000 successfully treated patients. In the case of HTN, it is equivalent to 12,119 hemodialysis sessions, 671 breast cancer hospitalizations or 1,053 asthmatic crisis hospitalizations. This, combined with about 200,000 DM patients  $> 40$  years of age, treated at the IMSS, who at a given time abandon antihyperglycemic treatment due to ED incidence (according to the survey of diabetic patients in the IMSS<sup>9</sup> and the prospective study) and 50,000-60,000 hypertensive patients  $> 40$  years of

age who suspend antihypertensive treatment for the same reason (according to the prospective survey and to the patients treated in the IMSS in 2004 in accordance with institutional databases, SUI-27 and SUI-13), attests to the necessity of making the treatment of these patients standard practice in our medical environment.

The study also shows that in relation to the chronic character of both DM and HTN and their significant time-line complication potential, the Sildenafil ED treatment option in its two presentations produces significant net savings at 5 and 10 years of treatment *vs.* non-treatment of ED.

In general, the present study, when added to the available publications on the favorable cost-effective relationship of Sildenafil for ED management,<sup>58-64</sup> is fundamentally different in that it does not focus on ED as a life-style problem<sup>64</sup> or as a health problem of little relevance for the patient, and therefore not a priority, but rather as a health problem with an important impact in both the control and prognosis of such high profile diseases as DM and HTN. This focus, along with the medical and pharmacological study results, identifies Sildenafil ED treatment as a cost-saving strategy in resource consumption related to DM and HTN management in male patients insured by the IMSS.

One research limitation was only having studied patients from an urban nucleus such as Mexico City, given that ED prevalence and its impact on antihyperglycemic and antihypertensive treatment abandonment could be different in other parts of the country for cultural reasons, especially in rural or semi-rural areas. Therefore, care should be taken when making generalizations about results obtained outside of city environments.

It will be interesting in the future to widen the scope of research to include terminal clinical results such as premature death reduction or years of extended life in these patient populations.

This study concludes that ED represents a highly prevalent complication in male DM and HTN populations and that it is frequently the cause of poor adherence to and abandonment of antihyperglycemic and antihypertensive drug treatment. In the same way, Sildenafil ED management in these patients is a cost-saving strategy *vs.* non-treatment of ED and

is a cost-saving and cost-effective strategy superior to treatment with Taladafil and Vardenafil.

## BIBLIOGRAPHY

1. Encuesta Nacional de Salud ENSA 2000. Tomo 2. La Salud de los Adultos. México. Instituto Nacional de Salud Pública. 2003.
2. Vázquez MJL, Vázquez J, Gómez H et al. Diabetes Mellitus en población adulta del IMSS. Resultados de la ENSA 2000. *Rev Inst Mex Seguro Soc.* 2006;44(1):13-26.
3. Otiniano M, Du X, Ottenbacher k, Black SA et al. Lower extremity amputations in diabetic mexican american elders: incidence, prevalence and correlations. *J Diabetes Complications.* 2003;17(2):59-65.
4. Centers of Disease Control and Prevention. Lower extremity amputation episodes among persons with diabetes. New Mexico. 2000. *MMWR. Mortal Wkly Rep.* 2003;52(4):66-68.
5. Escobedo-De la Peña J, Rico B. Incidence and Fatality of the Acute and Chronic Complications of Diabetes Mellitus in Mexico. *Salud Pública Mex.* 1996;38(4):236-42.
6. Barceló A, Rajpathak S. Incidence and Prevalence of Diabetes Mellitus in the Americas. *Pan Am J Public Health.* 2001;10(5):300-308.
7. Secretaría de Salubridad y Asistencia. Reporte de la Encuesta Nacional de Enfermedades Crónicas 1992. México. SSA 1993:19-24.
8. Anuario de Morbilidad. SUIVE. DGE. SSA. [[www.ssa.gob.mx](http://www.ssa.gob.mx)] Consultado el 5 de diciembre de 2006.
9. Secretaría de Salubridad y Asistencia. Reporte de la Encuesta Nacional de Salud II. México. SSA 1994.
10. Estadísticas de morbilidad y mortalidad. SIMO (subsistemas 13 y 27) y SUI. [[www.imss.gob.mx](http://www.imss.gob.mx)]. Consultado el 6 de diciembre de 2006.
11. El IMSS en Cifras. El Censo de Pacientes Diabéticos, 2004. *Rev Med Inst Mex Seguro Soc.* 2006;44(4):375-82.
12. Arredondo A, Zúñiga A. Economic consequences of epidemiological changes in diabetes in middle-income countries: the Mexican case. *Diabetes Care.* 2004;27(1):104-109.
13. Arredondo A. Financial requirements for health services demands for diabetes and hypertension in Mexico. *Rev Invest Clin.* 2001;53(5):422-29.
14. Rascon R, Santillana M, Romero M et al. Sistema de vigilancia epidemiológica para el paciente diabético; el uso de tecnología computacional en la calidad de la atención médica. *Salud Pública Mex.* 2000;42:324-32.
15. Membreño JP, Zonana A. Hospitalización de pacientes con Diabetes Mellitus. Causas, complicaciones y mortalidad. *Rev Inst Mex Seguro Soc.* 2005;43(2):97-101.
16. Rodríguez JR, Murguía C, López JM et al. Egresos de pacientes diabéticos en un Hospital General Regional. Análisis de 7 años. *Rev Inst Mex Seguro Soc.* 2001;39(2):121-26.
17. Ho P M, Rumsfeld JS, Masoudi FA et al. Effect of medication non-adherence on hospitalization and mortality among patients with diabetes mellitus. *Arch Intern Med.* 2006;166:1836-41.
18. Corona HM, Bautista SL. Perfil del paciente diabético en una unidad de Medicina familiar de la ciudad de México. *Arch Med Fam.* 2004;6(2):40-43.
19. Rodríguez JR, López JM, Rodríguez J et al. Características epidemiológicas de pacientes con Diabetes en el Estado de México. *Rev Inst Mex Seguro Soc.* 2003;41(5):383-92.
20. Sabag-Ruiz E, Álvarez A, Celiz S et al. Complicaciones Crónicas en la Diabetes Mellitus. Prevalencia en una Unidad de Medicina Familiar. *Rev Inst Mex Seguro Soc.* 2006;44(5):415-21.
21. Ibarra E, Cantú P. Años de Vida Productiva Perdidos por Complicaciones Crónicas de Diabetes Mellitus en Población Económicamente Activa. *Revista Salud Pública y Nutrición.* 2003;4(2):1-6.
22. Clark C, Lee A. Prevention and treatment of the complications of diabetes mellitus. *N Eng J Med.* 1995;332(18):1210-17.
23. Bloomgarden Z. Glycemic Treatment. *Diabetes Care.* 2004;27(5):1227-34.
24. United Kingdom Prospective Diabetes Study Group (UKPDS). Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *The Lancet.* 1993;328:1675-85.
25. Villarreal E, Mathew A, Garza ME et al. Costo de la Atención de la Hipertensión Arterial y su Impacto en el presupuesto destinado a la Salud en México. *Salud Pública Mex.* 2002;44:7-13.
26. FUNSALUD (2004). Costos estimados de la atención médica por patologías principales en el IMSS (Documento interno).
27. Katsuyuki M, Martha L, Alan R et al. Relationship of blood pressure to 25 year mortality due to Coronary Heart Disease, Cardiovascular Diseases, and all Causes in Young Adult Men. The Chicago Hearth Association Detection Project in Industry. *Arch Intern Med.* 2001;161:1501-1508.

28. Franco O, Peeters A, Bonneux L *et al.* Blood Pressure in Adulthood and Life Expectancy with Cardiovascular Disease in Men and Women Life Course Analysis. *Hypertension*. 2005;46:280-86.
29. Gómez SA. Descontrol del paciente hipertenso e incumplimiento del tratamiento farmacológico. *Rev Inst Mex.Seguro Soc* 2001;39(6):523-29.
30. Prospective Studies Collaboration. Age specific relevant of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *The Lancet*. 2002;360:1903-13.
31. Bramley TJ, Gerbino PP, Nightengale BS *et al.* Relationship of blood pressure control to adherent with antihypertensive monotherapy in 13 Managed Care Organizations. *J Manag Care Pharm*. 2006;12(3): 239-45.
32. Donnan PT, Mac Donald TM, Morris AD *et al.* Adherence to prescribed oral hypoglycemic medication in a population of patients with Type 2 diabetes: a retrospective cohort study. *Diabetes UK. Diabetic Medicine*. 2002;19:279-84.
33. Santana A, Castañeda R. Descontrol del Paciente hipertenso e incumplimiento del tratamiento farmacológico. *Rev Inst Mex Seguro Soc*. 2001;39(6): 523-29.
34. Heart Outcomes Prevention Evaluation (HOPE) Study Investigators. Effects of Ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet*. 2000;355:253-59.
35. Brown JB, Nichols GA, Glauber HS *et al.* Ten year follow-up of antidiabetic drug use, non-adherence and mortality in a defined population with Diabetes Mellitus type 2. *Clinical Therapeutics*. 1999;21(6): 1045-57.
36. Durán B, Rivera B, Franco E. Apego al tratamiento Farmacológico en Pacientes con Diagnóstico de Diabetes Mellitus tipo 2. *Salud Pública Méx*. 2001; 43:233-36.
37. Hernández L, Téllez J, Garduño J *et al.* Factors associated with Therapy Noncompliance in type 2 Diabetes Patients. *Salud Pública Méx*. 2003;45:191-97.
38. Wertheimer A, Santella T. Medication compliance research: still far to go. *The Journal of applied research*. 2003;3(3):2-25.
39. Sabate E. WHO Adherence Meeting Report. Geneva, World Health Organization, 2001.
40. Curb JD, Borhani NO, Blaszkowski TP *et al.* Long term surveillance for adverse effects of antihypertensive drugs. *JAMA*. 1985;253(22).
41. Houston N. Compliance with treatments regimen in chronic asymptomatic Diseases. *Am J Med*. 1997; 102 (2A):43-49.
42. Pickering T, Shepherd A, Puddey I *et al.* Sildenafil Citrate for Erectile Dysfunction in men Receiving Multiple antihypertensive Patients. *AJH*. 2004;17: 1135-42.
43. Grim RH, Grandits GA, Prineas JR *et al.* Long term effects on Sexual Function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. *Hypertension*. 1997;29:8.
44. Kalter LO, Wainstein J, Ziv A *et al.* Clinical, Socioeconomics, and lifestyle parameters associated with erectile Dysfunction among Diabetic Men. *Diabetes Care*. 2005;28:1739-44.
45. Ng KK, HCP Lim, FC Ng *et al.* The use of Sildenafil in patients with erectile Dysfunction in Relation to Diabetes Mellitus- A study of 1,511 patients. *Singapore Med J*. 2002;43(8):387-90.
46. Grant RW, Devita NG, Singer DF *et al.* Polypharmacy and Medication adherence in Patients with type 2 diabetes. *Diabetes Care*. 2003;26(5):1408-12.
47. Lipshultz and Kim. Treatment of erectile dysfunction in men with diabetes. *JAMA*. 1999; 281(5):465-66.
48. El-Sakka A. Efficacy of Sildenafil Citrate in treatment of erectile dysfunction: Effect of type 2 diabetes. *European Urology*. 2004;46: 503-509.
49. Ugarte FR, Aguirre JB. Prevalencia de disfunción eréctil en México y factores de riesgo asociados. *Revista Mexicana de Urología*. 2001;61(2):63-76.
50. Cramer AJ. A systematic Review of adherence with medication for diabetes. *Diabetes Care*. 2004;27:1218-24.
51. Carson CC, Burnet AL, Levine LA *et al.* The efficacy of Sildenafil citrate (Viagra®) in clinical Populations: an update. *Urology*. 2002;60 (Suppl 2B):12-27.
52. ISPOR. Guías de farmacoeconomía en <http://www.ispor.org/PEguidelines/COMP3.asp>. (visitada el 07/12/2006)
53. Kloner AR, Brown M, Prisant ML *et al.* Effect of Sildenafil in Patients with erectile Dysfunction taking antihypertensive Therapy. *AJH*. 2001;14:70-73.
54. Pickering T G, Sheperd A M, Puddey I *et al.* Sildenafil Citrate for Erectile Dysfunction in Men Receiving Multiple Antihypertensive Agents. *AJH*. 2004;17:1135-42.
55. Moore RA, Derry S, McQuay HJ *et al.* Indirect comparison of interventions using public randomized trials: systematic reviews of PDE- 5 inhibitor for erectile dysfunction. *BMC Urology*. 2005;5:18.
56. López JM, Cuauhtémoc R, Rodríguez J *et al.* Construcción y validación inicial de un instrumento para medir

- el estilo de vida en pacientes con diabetes mellitus tipo 2. *Salud Pública Mex.* 2003; 45(4): 259-68.
57. María Rosa RD, Eugenia MF, Belmont JP. Validación de un instrumento para evaluar la adherencia terapéutica en pacientes diabéticas. *Perinatol Reprod Hum.* 2004;18(4):217-24.
58. INEGI (2006) Banco de Información Económica. INEGI. [www.inegi.gob.mx](http://www.inegi.gob.mx). (Actualización al 7 de septiembre de 2006)
59. Banco de México. Reporte de Inflación (histórico hasta diciembre 2006). [www.banxico.gob.mx](http://www.banxico.gob.mx).
60. INEGI, (2005). Encuesta Nacional de Empleo, 2004. INEGI, Aguascalientes, Ags., México.
61. Barroi B, Beatrice C, Bernard M *et al.* Early experience with sildenafil for the treatment of erectile dysfunction in renal transplant recipients. *Nephrol Dial Transplant.* 2003;18:411-17.
62. Ashton-Key M, Sadler M, Walmselyb *et al.* UK Department of Health Guidance on Prescribing for Impotence Following the Introduction of Sildenafil. *Pharmacoeconomics.* 2002;20(12):839-46.
63. Smith KJ, Roberts MS. The Cost-Effectiveness of Sildenafil. *Ann Intern Med.* 2000;132:933-37.
64. Keith Alison. The Economics of Viagra. *Health affairs.* 2000;19(2):147-57.
65. L Tan H. Economic Cost of Male Erection Dysfunction Using a Decision Analytic Model. *Pharmacoeconomics.* 2000;17(1):77-107.
66. Wilson E, McKeen E, Scuffham P *et al.* The Cost to The United Kingdom Health Service of Managing Erectile Dysfunction. *Pharmacoeconomics.* 2000;20(13):879-89.
67. Mitrany Devora. LifeStyle Drugs. *Pharmacoeconomics.* 2001;19(5 pt 1):441-78.