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Are Statins an Effective Treatment in Men With Erectile Dysfunction?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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Abstract

OBJECTIVE: The objective of this selective EBM review is to determine whether or not HMG-CoA Inhibitors (Statins) are an effective treatment for erectile dysfunction (ED).

STUDY DESIGN: Systematic review of three English language randomized controlled trials published between 2011-2013.

DATA SOURCES: Three randomized controlled trials published in peer-reviewed journals comparing the effects of statins on erectile function found using the PubMed database.

OUTCOMES MEASURED: The outcomes measured included erectile function, assessed using the International Index of Erectile Dysfunction Questionnaire (IIEF) in all three studies and Nocturnal Penile Tumescence (NPT) in one study, and male ED-quality of life using the MED-QoL Questionnaire.

RESULTS: Two studies in the review show an insignificant improvement in erectile function of participants taking a statin vs. a placebo. However, one study showed a statistically significant difference in erectile function in participants taking a statin vs. no medication at all. Additionally, one of the studies showed a significant improvement in MED-quality of life in men taking a statin vs. a placebo. Although two of these studies showed no statistically significant improvement in erectile function with use of a statin, they both showed potential in statin use with a larger improvement for men with more severe ED compared to men with a lesser degree of ED.

CONCLUSIONS: Based on these studies, the use of statins for treatment for ED cannot be justified. Trivedi and colleagues, as well as Masttalir and colleagues, both showed no significant difference in erectile function in participants with use of statins. However, Gokce et al showed statin use in men with ED does in fact improve their erectile function compared to men taking no medication at all. Although two studies showed no significant improvement in erectile function they both showed a larger improvement in men with more severe ED and one study showed a significant improvement in male ED-quality of life. Further investigation should continue as this proves there is lead way for the use of statins for their effect in erectile function.

Key Words: Erectile dysfunction, statins

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability for a man to achieve and maintain an erection firm enough for sexual performance[1]. In men without ED, physical and psychological stimulation causes an increase in blood flow to the penis resulting in erection[1]. There are many causes of ED ranging from physical issues to emotional or psychological[1]. One common physical cause of ED is damage to penile arteries resulting in reduced blood flow, often a consequence of other disease processes such as HTN, DM, and atherosclerosis[1]. This paper evaluates three randomized controlled trials comparing the efficacy of a statin as an oral medication for improving erectile function in patients with ED.

This topic is relevant to both patients and the PA practice due to its commonality and because it impacts patients of all races both physically and psychologically[2]. It is believed that ED may be a predictor of future arterial disease of larger vessels such as the coronary arteries, which in turn may lead to fatal consequences[2]. ED is a major cause of male sexual dysfunction and affects many men in the US[1]. It is estimated that 30 million men in the United States have ED[1]. 4% of men in their 50's, 17% of men in their 60's, and 47% of men older than 75 are unable to achieve an erection[1]. Each year, ED results in more than 500,000 visits to physician offices[3]. Incidence in ED increases with age, therefore as life expectancy increases, prevalence of ED will also increase[4].

Treatment for ED is very costly for individuals in the United States. Although the exact number for total healthcare cost of ED has not been identified, according to data from the Defense Health Agency, the Department of Defense spent 41.6 million dollars on Viagra and 84.24 million total drugs on ED in 2014[5]. Viagra is one of the most

common medications used to treat ED and within the first 8 months that it became

available on the market 2.9 million prescriptions were written[3]. In addition, in 2011 an

article published by Clinical Pharmacology and Therapeutics stated that over 1 billion

dollars is spent annually worldwide on the three most popular PDE inhibitor drugs for the

treatment of ED[6].

Contrary to popular belief, erectile dysfunction is not a normal part of aging[7].

Penile erection occurs as an outcome of an increase in NO that leads to vasodilation[7]. ED

is an end result of endothelial dysfunction due to a change in NO, which in turn causes

vasoconstriction of blood vessels and decreased blood flow to the penis[7]. It has been

found that there is an association with vascular disease in about 50% of men older than

50 y/o with ED[7].

Treatment for ED involves decreasing risk factors that may lead to chronic health

issues and consequently ED. This usually begins with lifestyle changes including

smoking cessation, reducing alcohol consumption, losing weight and exercising. If ED is

due to psychological issues, psychotherapy is recommended. Drug therapy such as oral

medications like phosphodiesterase (PDE-5) inhibitors and testosterone or injectable

medications like papaverine hydrocholoride, phentolamine, or alprostadil are often used.

Additional treatment modalities include vacuum devices and surgery such as penile

prosthesis or vascular reconstruction[1].

As stated previously, ED is highly correlated to vascular dysfunction[1]. Some risk

factors for endothelial dysfunction include atherosclerotic disease, obesity, dyslipidemia,

systemic arterial hypertension and diabetes mellitus, which are often found in men with

ED[7]. It is proposed that lowering lipid levels via statins may show improvement in erectile function in men with ED.

OBJECTIVE

The objective of this selective EBM review is to determine weather or not statins are an effective treatment for erectile dysfunction.

SEARCH STRATEGY METHODS

The studies used in this systematic review included two randomized, double blind, placebo controlled clinical trials and one randomized, single blind, controlled trial. The population studied included males diagnosed with erectile dysfunction. The intervention used in each of the studies was an oral statin medication. The population was compared to an experimental group who received either a visually matched placebo or no treatment. The outcomes measured in the studies included erectile function and male ED-specific quality of life.

All articles were published in English language in peer-reviewed journals and searched usimg the PubMed database. All studies were discovered using the keywords "erectile dysfunction" and "statins" and were chosen by relevance to the clinical question and the required standards set forth by the syllabus (POEMS). Inclusion criteria for the sources were randomized, controlled, and double or single blind studies, which used statins as an intervention for ED. Exclusion criteria varied between studies but consisted of history of acute MI or stroke, DM, Peyronie's disease, hypogonadism, hyperprolactinemia, any active inflammatory or infectious disease, previously underwent radical prostatectomy, pelvic surgery or radiation therapy, PDE-5 inhibitor usage 6 months prior to enrollment, neurologic or mental problems, liver or hepatic insufficiency,

use of nitrates, taking antihypertensive or lipid lowering medications, and not a high

cardiovascular risk. Statistics used in this review included p-values, mean change from

baseline, standard deviation, numbers needed to treat (NNT), relative benefit increase

(RBI), and absolute benefit increase (ABI). The specific studies demographics and

characteristics can be found in Table 1.

Table 1: Demographics and Characteristics of included studies

Study	Type	#Pts	Age (yrs)	Inclusion criteria	Exclusion criteria	W/D	Interventions
Gokce[5] (2012)	Single blind RCT	134	31-70	30-70 y/o male pts, normal libido, IEF < 17, No previous use of PDE5 inhibitors, normal serum testosterone levels (>300ng/ml)	History of any pelvic surgery, having any kind of medication for ED, having any neurologic or mental problems, liver or hepatic insufficiency, use of nitrates, use of antiandrogens	14	Atorvastatin 10 mg/day for 3 months
Mastalir[6] (2011)	Double blind RCT	43	35-75	Men aged 35-75 years with ED (IIEF < 22), levels of usCRP $\geq 1.1mgl^{-1}$ and no other medical indication or contraindication	History of acute MI or stroke, DM, Peyronie's disease, hypogonadism, hyperprolactinemia, or any active inflammatory or infectious disease, alcohol abusers, previously underwent radical prostatectomy, pelvic surgery, or radiation therapy, PDE5 inhibitor usage 6 months prior to enrollment	2	Simvastatin 20mg/day for 6 months
Trivedi[7] (2013)	Double blind RCT	173	≥40	Men aged ≥ 40 with untreated ED (score <22	IIEF >21, Diastolic BP > 100, Systolic BP > 170, HDL >	40	Simvastatin 40mg/day for 6 months

				on the IIEF), were not receiving lipid lowering or anti-hypertensive medication, and not at high cardiovascular risk	7.5, Triglycerides > 5, testosterone < 8, ALT > 66, Creatine Kinase > 750, Angina, on BP treatment, Other ED therapy, Other statin therapy, GP exclude, Lactose intolerance		

OUTCOME MEASURES

An outcome measured in all three studies was erectile function. Erectile function was measured via the IIEF questionnaire in all three studies and also using the Nocturnal Penile Tumescence test in Gokce et al. Scores for the IIEF were classified as severe = 5-11 and mild-moderate = 12-21 in Tivedi et al, and normal ≥ 26, mild = 22-25, mild-moderate = 17-21, moderate = 11-16, and severe ≤ 10 in Mastalir et al. Normal NPT was defined as an erectile event of at least 60% rigidity on the tip of the penis with the duration of at least 10 minutes[7]. Male ED – specific quality of life was a secondary outcome measured in Trivedi et al by using the MED-QoL questionnaire.

RESULTS

All three studies that are included in this review are randomized controlled trials that assessed the effectiveness of statin medications for treatment of erectile dysfunction. The population included in all three studies was men over the age of 30. For the comparison group two studies used a visually matched placebo and one study used no treatment at all. All three studies contained dichotomous data that could be used to calculate RBI, ABI, and NNT.

In the study by Mastalir et al, 43 patients with erectile dysfunction and endothelial dysfunction were randomly assigned to either the Simvastatin group (n=21) or the

placebo group (n=20) to determine the effectiveness of statin medication on erectile function. Those with a history of acute MI or stroke, DM, Peyronie's disease, hypogonadism, hyperprolactinemia, any active inflammatory or infectious disease, alcohol abusers, previously underwent radical prostatectomy, pelvic surgery, radiation therapy, or PDE5 inhibitor usage 6 months prior to enrollment were excluded from the study. Patients received a single nightly capsule of either 20 mg of Simvastatin or placebo, which was distributed in a double-blinded manner for 6 months. Erectile function was then assessed using the IIEF questionnaire, which was dispersed at enrollment and repeated every 2 months for 6 months. The severity of erectile function was evaluated by IIEF erection function domain (normal ≥ 26, mild ED = 22-25, mild-to-moderate ED = 17-21, moderate ED = 11-16, and severe ED ≤ 10). Analysis was performed by intention-to-treat.

Of the 43 patients enrolled in the study, 2 patients were lost during follow up for unknown reasons, leaving a total of 41 patients at the end of the trial. No deaths were reported and the only adverse events experienced were insomnia by one patient in each group and dyspepsia by one patient in the placebo group. The results of this study show no statistically significant difference in erectile function after 6 months of treatment with simvastatin compared to placebo (p=.733). However, this study did show improvement in severity of ED by a change in mean baseline although it was not statistically significant (p=.330). At the start of the study 74% of patients of both groups had moderate-to-severe dysfunction. After 6 months, 83% of the placebo group advanced to mild ED compared to 100% of the simvastatin group. The data demonstrated a relative benefit increase (RBI) of 20.5% and an absolute benefit increase (ABI) of 17%. The number needed to

treat (NNT) was 6, therefore 6 patients needed to be treated with simvastatin in order for 1 more patient to experience evolution from severe ED to a more mild form.

In the study by Trivedi et all, 173 patients with ED and no other significant CV risk factors were randomly assigned to two groups in which they received either 40 mg of simvastatin or placebo in a double-blind manner daily for 6 months. Subjects were excluded if they had an IIEF >21, diastolic BP > 100, systolic BP > 170, HDL > 7.5, Triglycerides > 5, testosterone < 8, ALT > 66, Creatine Kinase > 750, angina, were on BP treatment, other ED or statin therapy, GP exclude, or were lactose intolerant. Erectile function was assessed by the IIEF questionnaire that was distributed at baseline and repeated at 3 months and 6 months. The score was then categorized as severe (score 5-11) or mild/moderate (score 12-21). Sexual health-related quality of life was a secondary outcome assessed and was measured at baseline, 3 months, and 6 months using the male ED-specific quality of life questionnaire. Analysis was performed by intention-to-treat.

Of the 173 patients enrolled, 40 patients withdrew, leaving a total of 133 at the end of the study and a total of 128 that completed the IIEF questionnaire. There were a total of 126 adverse events reported and 5 were considered to be serious but not related to the study medication. No deaths were recorded. The results of this study show no statistically significant difference in erectile function with use of Simvastatin compared to placebo by a change in mean from baseline (1.28 vs 0.07, $p = 0.27$) with 95% CI. However, the study did reveal a statistically significant change in individuals that started with severe ED on statins compared to placebo ($p < 0.001$). This data demonstrated an RBI of 39.1%, ABI of 11%, and the NNT was 9. The men in the statin group showed a statistically larger improvement in MED-QoL compared to the placebo group (5% vs 2%,

p = 0.03), which was largest in men with severe ED. The data from the men using a statin with severe ED demonstrated an RBI of 140%, ABI of .07, and the NNT was 15.

Table 2: Analysis of outcomes in men that progressed from a more severe ED to a lesser degree of ED by Mastalir et al and Trivedi et al

Study	Number of patients	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Number needed to treat (NNT)
Mastalir et al	41	20.5%	17%	6
Trivedi et al	128	39.1%	11%	9

Table 3: Results of MED-QOL in men with severe erectile function by Trivedi et al

RBI	ABI	NNT
140%	7%	15

The study done by Gockse et al included 120 participants with moderate to severe ED that were randomly assigned to either a group receiving 10 mg Atorvastatin or placebo daily, or 20 mg tadalafil three time per week for 3 months with treatment being distributed in a single-blind manner. For the purpose of this review the tadalafil group was excluded. Individuals were excluded if they had a history of any pelvic surgery, having any kind of medication for ED, having any neurologic or mental problems, liver or hepatic insufficiency, use of nitrates, or use of antiandrogens. Erectile function was evaluated by the IIEF questionnaire and NPT test at baseline and again at the end of the study. Analysis was performed by intention-to-treat.

Of the 134 patients in the study, 45 were assigned to both the atorvastatin group and to the no treatment group. 1 patient in the atorvastatin group and 2 patients in the no treatment group were lost to follow up. 3 individuals discontinued in the atorvastin group and 4 discontinued in the no treatment group. The total number of patients included at that end of the study from the atorvastatin group (n=41) and no treatment group (n=39) was 80. The results of this study show a statistically significant improvement in erectile function by IIEF scores in the artovastatin group compared to the no treatment group by means +/- SD (7 +/- 2.2 vs 2 +/- 0.6, p = 0.001). It also shows a statistically significant improvement in erectile function by positive NPT test results in the atorvastatin group compared to the no treatment group (39% vs 7.6%, p=0.001). The data for the NPT test demonstrates an RBI of 413%, ABI of 31.4% and the NNT was 3.

Table 4: Results of NPT test for improvement in erectile function by Gockse et al

Number of patients	RBI	ABI	NNT
80	413%	31.4%	3

DISCUSSION

The studies in this review analyze statin medications as a form of treating ED. It is estimated that 40% of presentations of ED are due to vascular damage through hyperlipidemia with the exclusion of effects from DM [4].These studies were performed to evaluate the pleiotropic effects of statin medications on vascular impairment to promote better erectile function. The results of all three studies showed conflicting evidence as two studies found no statistically significant change in erectile function with statin use compared to placebo and the third study found a statistically significant improvement in

erectile function with use of a statin compared to no medication at all. Although the first two studies did not find a significant difference they did find a larger improvement in erectile function in men that had a more severe form of ED compared to a lesser degree of ED, yet only one of the two studies found it to be statistically significant. The Trivedi et al study also found a statistically significant improvement in sexual health related quality of life in the simvastatin group compared to placebo.

The primary use of statin medications is for hyperlipidemia. Statins are the most common drug class used to lower cholesterol levels with 93% of adults on lipid-lowering agents using them[8]. Although used by many, statin medications are known for their side effects of myopathy and, worst-case scenario, rhabdomyolisis[9]. Rhabdomyolisis is a life-threatening condition caused by muscle break down but is rare due to the ability to monitor CK levels if a patient presents with complaints indicating of this condition[9]. Statin medications have also shown to increase LFT's[9]. FDA has recently denied black box warnings for both rhabdomyolisis and serious increase in LFTs because of the rare chance that they will occur[10, 11]. Other possible side effects from statins include GI upset, rash, memory loss, or hyperglycemia. Statins should be avoided in pregnancy and acute/chronic liver disease[9].

Several limitations are found within this review. The population size within two of the studies were fairly small, with a total of 41 patients in Mastalir et al and 80 patients in Gokce. Other limitations found with the Mastalir et al study was the low dose of Simvastatin used and the lack of physiological study of penile vascular function. This limitation was also seen in Trivedi et al, therefore these studies results are based off of subjective matters. All articles are limited in the fact that they do not take into account

the personal relationships of the participants, which could be a major influence in ED. Two other limitations that were found in the Gokce et al study were a lack of placebo and the fact that it was single blind. Gocke et al states within the study that they feel these limitations are made up for by their ability to use the NPT test, which were objective findings.

CONCLUSION

This review shows inconclusive evidence for the use of statin medication as a treatment for ED. Two studies showed no benefit in erectile function and one study showed advantage in statin use for ED. Although no benefit was found in two studies, the authors of these articles did find minor improvement in erectile function when looking at men with more severe ED. In the study by Trivedi et al, the results suggest that simvastatin would also be a cost-effective strategy. According to these results, there may still be potential for statins to be used to treat ED or at least augment therapy. Only one randomized controlled trial in this review used the most potent statin medication, atorvastatin, as its treatment group. Additional research with using higher doses and a more potent statin may prove to be beneficial in men with ED.

REFERENCES

1. Erectile dysfunction. National Institute of Diabetes and Digestive and Kidney Diseases Web site. 2. http://www.niddk.nih.gov/health-information/health-topics/urologic-disease/erectile-dysfunction/Pages/facts.aspx. Published 2009. Updated 2012. Accessed October 9th, 2015.

2. Trivedi D, Kirby M, Wellsted DM, et al. Can simvastatin improve erectile function and health-related quality of life in men aged >/=40 years with erectile dysfunction? results of the erectile dysfunction and statins trial [ISRCTN66772971. *BJU Int*. 2013;111(2):324-333. doi: 10.1111/j.1464-410X.2012.11241.x [doi].

3. Brock G. Issues in the assessment and treatment of erectile dysfunction: Individulizing and optimizing therapy for the "silent majority". Medscape Web site. http://www.medscape.org/viewarticle/432628. Updated 2015. Accessed October 9th, 2015.

4. Gokce MI, Gulpinar O, Ozturk E, Gulec S, Yaman O. Effect of atorvastatin on erectile functions in comparison with regular tadalafil use. A prospective single-blind study. *Int Urol Nephrol*. 2012;44(3):683-687. doi: 10.1007/s11255-012-0126-z [doi].

5. Kime P. DoD spends $84M a year on viagra, similar meds. Military Times Web site. http://www.militarytimes.com/story/military/benefits/health-care/2015/02/13/defense-department-troops-erectile-dysfunction/23350711/. Published 2015. Accessed October 9th, 2015.

6. Polinski J, Kesselheim A. Where cost, medical necessity and mortality meet: Should US government insurance programs pay for erectile dysfunction drugs? . 2011;28(1):17.

7. Mastalir ET, Carvalhal GF, Portal VL. The effect of simvastatin in penile erection: A randomized, double-blind, placebo-controlled clinical trial (simvastatin treatment for erectile dysfunction-STED TRIAL). *Int J Impot Res*. 2011;23(6):242-248. doi: 10.1038/ijir.2011.33 [doi].

8. Reinberg S. Number of americans taking statins keeps rising: CDC. Health Day Web site. http://consumer.healthday.com/general-health-information-16/misc-drugs-news-218/number-of-americans-taking-statins-keeps-rising-cdc-694895.html. Published December 23. Updated 2014. Accessed October, 2015.

9. Mayo Clinic staff. High cholesterol. Mayo Clinic Web site. October 3rd. Published http://www.mayoclinic.org/diseases-conditions/high-blood-cholesterol/in-depth/cholesterol-lowering-supplements/art-20050980. Updated 2015. Accessed October, 2015.

10. FDA drug safety communication: Important safety label changes to cholesterol-lowering statin drugs. U.S. Food and Drug Administration Web site. http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm. Published July 3rd. Updated 2012. Accessed October, 2015.

11. Gibb G. 2014: The year the FDA said no to a black box for statins. Lawyers and Settlements Web site. https://www.lawyersandsettlements.com/articles/crestor-side-

effects/crestor-lawsuit-side-effects-issues-30-20389.html#.VmeP86KPxW1.
Published January 16. Updated 2015. Accessed October, 2015.