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YOHIMBINE FOR ERECTILE DYSFUNCTION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

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ABSTRACT

Purpose: Erectile dysfunction is a common problem, particularly in diabetics. It is associated with a considerable burden of suffering. No generally accepted drug treatment exists. We systematically reviewed and meta-analyzed all randomized, placebo controlled trials of yohimbine monotherapy for erectile dysfunction to determine its therapeutic efficacy. Our secondary aim was to evaluate the safety of yohimbine.

Materials and Methods: We used computerized literature searches and standardized data extraction to rate methodological quality in a meta-analysis using computer statistical software.

Results: Seven trials fit the predefined inclusion criteria. Overall methodological quality of these studies was satisfactory. The meta-analysis demonstrated that yohimbine is superior to placebo in the treatment of erectile dysfunction (odds ratio 3.85, 95% confidence interval 6.67 to 2.22). Serious adverse reactions were infrequent and reversible.

Conclusions: The benefit of yohimbine medication for erectile dysfunction seems to outweigh its risks. Therefore, yohimbine is believed to be a reasonable therapeutic option for erectile dysfunction that should be considered as initial pharmacological intervention.

KEY WORDS: yohimbine, diabetes mellitus, meta-analysis, clinical trials

Erectile dysfunction is a prevalent and often neglected problem. In a survey of men 40 to 70 years old 52% reported some degree of erectile dysfunction.[1] In the general adult population the prevalence of erectile dysfunction ranges from 4 to 9%.[2] Its etiology can be broadly classified as psychogenic and/or organic. In the latter category diabetes mellitus is often the underlying cause. Although considerable advances have been made, "the ideal drug for the treatment of ED has not yet been identified."[3] One traditional plant based therapeutic option is yohimbine.

Yohimbine is an alkaloid derived from the bark of the Central African yohimbine tree. It has α_2-adrenoreceptor blocking activity and produces a rise in sympathetic drive by increasing noradrenaline release and the firing rate of cells located in noradrenergic nuclei of the central nervous system. It is 50 to 100 times more active at presynaptic compared to postsynaptic receptors.[4] It also works at the level of cholinergic, dopaminergic and vaso-intestinal polypeptidic receptors. These mechanisms are believed to work in concert to facilitate penile erection.[5] Yohimbine has no effect on erectility when given intracavernosally, and its action in relation to erectile dysfunction is thought to be almost entirely central.[6]

Traditionally extracts from the yohimbine bark have been used to treat all forms of impotence. Even today the bark is used as the raw material for yohimbine. Animal experiments confirm the action on male potency.[7] Effectiveness in treating erectile dysfunction was further suggested by several case reports and uncontrolled studies.[8–19] Since such studies cannot differentiate among the natural history of the disease, regression toward the mean, placebo effects and specific therapeutic effects,[20] controlled trials are needed to define whether yohimbine has any true therapeutic value in treating erectile dysfunction. Several placebo controlled, nonrandomized trials have suggested the efficacy of yohimbine.[21–24] Since nonrandomization (or inadequate randomization) may lead to a substantial overestimation of the effect in a large number of cases,[25] randomized studies are required for a fair estimation of clinical efficacy. We review systematically randomized, placebo controlled, double-blind trials of yohimbine.

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METHODS

Computerized literature searches were performed to identify all randomized controlled trials of yohimbine for erectile dysfunction. Data bases included MEDLINE (1966 to 1997), Embase (1974 to 1997) and the Cochrane Library (issue 1, 1997). In addition, all manufacturers of pharmaceuticals containing yohimbine were asked to contribute published and unpublished trials, and our own files were searched. Bibliographies of the studies and reviews thus retrieved were scanned for further relevant publications.

Inclusion criteria were randomized, placebo controlled, double-blind clinical trials on men suffering from some form of erectile dysfunction, yohimbine therapy and adequate statistical evaluation. Articles were excluded if they scored less than 3 (maximum 5) points on the Jadad scale assessing methodological quality (table 1).[26] There were no restrictions according to language of publication. All articles were read and evaluated independently by both authors. Data extraction followed a standardized, predefined procedure.

The meta-analysis was performed using computer statistical software. The response rates in the drug and placebo arms were used as a basis for calculating odds ratios that were weighted according to sample size. Odds ratios and 95% confidence interval (CI) were calculated using percentage response rates as basis.

RESULTS

Seven trials meeting these inclusion/exclusion criteria were found.[27–33] Without exception they suggest that yohimbine is clinically more effective than placebo in the treatment of erectile dysfunction. The 2 trials of outstanding quality will be discussed in some detail and all studies are summarized in table 1.

Riley et al conducted a multicenter trial in the United

TABLE 1. *Key data from controlled trials of yohimbine*

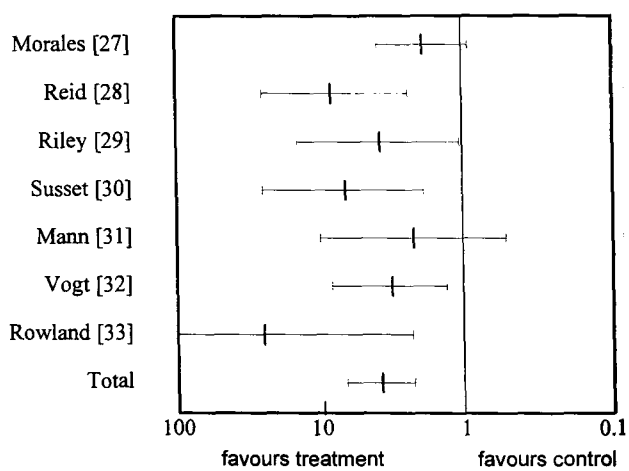
References	Trial Design (Jadad score)	No. Pts. Sample (mean age, yrs.)	Treatment	End Point	Result (%)	Comment
Morales et al[16]	Randomized controlled trial, placebo controlled, double-blind, partial crossover (3)	100 Organic impotence (56)	6 Mg. yohimbine hydrochloride capsules 3/day or identical placebo capsules for 10 wks.	Report of treatment success by pt. and partner	Pos. response drug (43) versus placebo (28)	Difference was not statistically significant
Reid et al[28]	Randomized controlled trial, placebo controlled, double-blind, partial crossover (3)	48 Psychogenic impotence (18 to 70)	6 Mg. yohimbine hydrochloride or placebo 3/day for 10 wks.	Self-reported improvement of sexual function	Improvement drug (62) versus placebo (16)	Effect was unrelated to cause of impotence
Riley et al[29]	Randomized controlled trial, placebo controlled, double-blind, crossover (4)	61 Chronic erectile impotence of mixed etiology (50)	5.4 Mg. yohimbine hydrochloride 3/day for a first/second 8-wk. period or identical placebo	Score on penile erectility and interest in sex	Good stimulated erection drug (37) versus placebo (13) ($p < 0.05$)	No difference between pts. with and without organic etiology
Susset et al[30]	Randomized controlled trial, placebo controlled, double-blind, partial crossover (4)	82 Any kind of erectile impotence (61)	5.4 Mg. yohimbine hydrochloride tablets or identical placebo 4/day increasing to 8/day for 4 wks.	Derogatis sexual functioning inventory, penile brachial index, daytime arousal test	Full or partial response drug (34) versus improvement placebo (3 pts.)	Responders were 4 yrs. younger on average than nonresponders
Mann et al[31]	Randomized controlled trial, placebo controlled, double-blind (3)	31 Erectile dysfunction due to organic or nonorganic etiology (43)	5 Mg. oral yohimbine hydrochloride 3/day or placebo for 7 wks.	Clinical Global Impression Scale pos. penile rigidity	Nonorganic erectile dysfunction improvement was significantly better with drug (60) versus placebo (40)	No significant effect in total group or in organic erectile dysfunction, no correlation between subjective success and objective measurement, small sample size (possibility of type II error)
Vogt et al[32]	Randomized controlled trial, placebo controlled, double-blind (3)	86 Erectile dysfunction without detectable cause (53)	10 Mg. oral yohimbine 3/day or placebo for 8 wks.	Subjective result pos. penile rigidity (by polysonography)	Pos. response drug (71) versus placebo group (45)	Rigorous trial, objective outcome measure, predefined primary end point
Rowland et al[33]	Randomized controlled trial, placebo controlled, double-blind, crossover (3)	11 Erectile dysfunction (49)	5 Mg./10 mg. yohimbine 3/day for a first/second 2-wk. period or identical placebo	Inventory of sexual functioning nocturnal penile tumescence waking erectile assessment	Pos. response drug (73) versus placebo (9)	Objective and subjective outcome measures, comparison of effects in functional group and dysfunctional group possible

Kingdom with 61 men 18 to 70 years old who had been treated for secondary erectile dysfunction for at least 6 months.[29] Patients with psychiatric disease, treated hypertension, or renal or hepatic insufficiency were excluded. Study patients received 5.4 mg. yohimbine hydrochloride or matching placebo 3 times daily for 8 weeks. Subsequently they were crossed over into the other treatment arm for 8 more weeks. At 4-week intervals the quality and frequency of erections were assessed by patient self-report. After the first 8 weeks 36.7% of the drug group and 12.9% of the placebo group ($p < 0.05$) reported good stimulated erections. In the placebo group this figure rose to 41.9% ($p < 0.02$) after crossover to drug. Other parameters (for example morning erection, spontaneous erection) were not affected. The trial rigorously accounts for dropouts (0), withdrawals (1) and adverse events.

Susset et al conducted a partial crossover study on 82 patients between ages 40 and 73 years.[30] Patients were included regardless of the degree, duration or etiology of erectile dysfunction. Patients with cardiac failure or psychiatric disorders were excluded. The study population was divided into 3 groups according to severity of erectile dysfunction (mild, moderate and severe). All patients received tablets of 5.4 mg. yohimbine hydrochloride or indistinguishable placebos. Initially the dose was 1 tablet 4 times daily. This dosage increased at the rate of 1 tablet daily to a maximum of 2 tablets 4 times daily. After 4 weeks placebo treated patients were crossed over to drug and drug patients continued as previously. Therapeutic success was assessed by Derogatis sexual functioning inventory, penile brachial index test and daytime arousal test. Dosage was reduced by 1 tablet per day if adverse effects occurred. After 4 weeks 14% of drug patients had experienced full restoration of erectile function and 20% had partial response. In the placebo group only 3 patients reported a positive response. The effect took 2 to 3 weeks to establish itself fully and patients responded regardless of the etiology of erectile dysfunction.

The meta-analysis of the trials meeting our inclusion criteria is shown in the figure. All trials have odds ratios that favor drug over placebo. For most studies there is no overlap of the 95% CI with the line of zero effect size. The calculated overall odds ratio is 3.85 with a 95% CI of 6.67 to 2.22.

Collectively these results leave little doubt that yohimbine is superior to placebo in treating erectile dysfunction. In 2 trials the results fail to become statistically significant, yet



Meta-analysis of randomized, double-blind trials of yohimbine for erectile dysfunction versus placebo with percentage of responders as end point. Odds ratio (log scale) using random effects model is given with 95% CI. Vertical line (odds ratio = 1) represents absence of difference between yohimbine and placebo.

TABLE 2. *Adverse effects of yohimbine*

References	Type Adverse Effects	Severity Adverse Effects	Frequency Adverse Effects
Morales et al[27]	None	Not reported	Not reported
Reid et al[28]	"No serious undesirable effects were reported"	Not reported	Not reported
Riley et al[29]	Hypertension, loss of antiepileptic action of phenytoin, rash	4 Withdrawals because of adverse effects	10% Drug group, 5% placebo group
Susset et al[30]	Anxiety, dizziness, increased frequency of urination, chills, headache	4 Withdrawals because of adverse effects but all adverse effects disappeared after withdrawal and none was severe	21% Drug group, no mention of nocebo effects
Mann et al[31]	Sweating, agitation, anxiety, headache, tachycardia, gastrointestinal disturbances	Not detailed	19% Drug group, 16% placebo group
Vogt et al[32]	Not detailed	No serious adverse effects	30% Drug group, 10% placebo group
Rowland et al[33]	No effect on blood pressure, 1 case diarrhea, 1 case frequent urination, 1 case lack of energy	Minimal	27% of Drug group

the average size effect is numerically large and clinically relevant.[27,31] Across studies the size effect in terms of positive responders varies from 34 to 73%. This large variability could be due to the differences in patients studied. Some trials investigated erectile dysfunction of mixed etiology,[29,30] while others included only organic[27] or psychogenic erectile dysfunction.[28] Age differences of the studied patients and the methodology in quantifying the end point might also be contributing factors. Generally speaking, younger patients seemed to respond better than older subjects.[29] Dosage and length of treatment were also variable but were not clearly related to clinical outcome.

Adverse effects encountered in the studies included in this analysis are summarized in table 2. In general yohimbine was well tolerated. The adverse effects that did occur were minor and reversible. Across all studies only 8 withdrawals were necessitated by adverse effects.

DISCUSSION

To our knowledge this is the first meta-analysis of randomized placebo controlled, double-blind trials on the effectiveness of yohimbine in erectile dysfunction treatment. This fact in itself seems remarkable since yohimbine has been used extensively for many years and its efficacy is a matter of considerable debate. Our findings suggest that yohimbine is more effective than placebo in treating erectile dysfunction of various etiologies. A meta-analysis of uncontrolled and controlled trials has provided similar conclusions,[34] yet it was incomplete (for example only 4 controlled trials were analyzed) and used weak inclusion/exclusion criteria.

While yohimbine is probably less effective than vasoactive intracavernous injection therapy, it has the considerable advantage of being noninvasive. Compared with other oral drugs used for erectile dysfunction, the evidence for effectiveness is compelling.[3] However, there are caveats. The 2 methodologically best trials, for instance, used unclear etiological definitions for erectile dysfunction.[29,30] Other studies used clearer criteria but lacked etiological definition, limiting the conclusiveness of the overall result. At present it does not seem clear which type of erectile dysfunction responds better to yohimbine therapy.

In most countries yohimbine is not an accepted therapy for erectile dysfunction. The recent American Urological Association (AUA) guidelines on treatment of organic erectile dysfunction, state that "the outcome data for yohimbine clearly indicate a marked placebo efficacy" and point out that "there is a marked placebo effect."[35] In our analysis of placebo controlled trials the latter objection is not relevant. There are several reasons for the difference in judgment about efficacy between the present evaluation and that of the AUA.[35] The AUA results were based on a MEDLINE search only. Trials published after 1994 were not included, and 2 of the 3 more recent studies were strongly positive. AUA guidelines relate to organic erectile dysfunction only, while the data of our analysis relate to less well-defined etiologies of erectile dysfunction.

A further crucial issue is clearly safety. Only a few adverse effects were reported in the studies reviewed (table 2), and in all of the trials analyzed, adverse effects necessitated only 8 withdrawals. This relatively small number may reflect the strict inclusion criteria used for clinical trials rather than true incidence rates. Due to its pharmacological action one might expect an increase in adrenergic tone that may raise blood pressure.[36] The effect was not seen in normotensive subjects during the aforementioned trials.[29] Other adrenergic effects could be anxiety and manic symptoms.[37,38] Susset et al observed such adverse effects in 6 of 82 patients.[30] Sleep disturbances have been observed, yet no patient of the trials analyzed here reported insomnia.[39] Idiosyncratic reactions have also been reported in 1 case of bronchospasm[40] and 1 of a lupus-like syndrome,[41] both after normal doses of yohimbine. In the largest study to date (408 patients) the frequency of adverse effects was 3%,[17] which is similar to adverse effects after placebo administration.[42] Köhler et al emphasize that not a single serious adverse effect has been reported in any clinical study so far.[43] Nevertheless it should be stressed that the drug is not free of adverse effects. In particular those adverse effects relating to cardiovascular conditions are relevant since populations suffering from erectile dysfunction have a high incidence of cardiovascular disease.

A final note of caution relates to publication bias. Positive trials tend to get published more frequently than negative trials, and this phenomenon could distort the overall result of meta-analyses.[44,45] For our analysis we attempted to retrieve unpublished trials but none was located. Thus, in this instance no concrete evidence for publication bias exists but it cannot be excluded with absolute certainty.

CONCLUSIONS

Yohimbine is clinically more effective than placebo. Furthermore, it is relatively safe, its oral administration has obvious advantages and its costs are low. These characteristics render yohimbine an attractive therapeutic option in the treatment of erectile dysfunction that should be considered for initial pharmacological intervention.

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