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Yohimbine treatment of organic erectile dysfunction in a dose-escalation trial

AT Guay[1]*, RF Spark[2], J Jacobson[3], FT Murray[4] and ME Geisser[5]

[1]*Center for Sexual Function, Lahey Clinic Northshore, Peabody, Massachusetts USA;* [2]*Steroid Chemistry Laboratory, Beth Israel Deaconess Hospital, Boston, Massachusetts, USA;* [3]*Section of Biostatistics, Lahey Clinic Medical Center, Burlington, Massachusetts, USA;* [4]*Serono Laboratories, Norwell, Massachusetts, USA; and* [5]*Department of Physical Medicine and Rehabilitation, University of Michigan, Ann Arbor, Michigan, USA*

Yohimbine has had questionable effects in men with organic erectile dysfunction. We conducted this study to better define the population of men responsive to yohimbine, because tobacco was thought to affect a regimen of yohimbine more than other risk factors. We measured nocturnal penile tumescence with the RigiScan™ monitor, hormone profiles, answers to the Florida Sexual Health Questionnaire, and clinical responses at baseline and after two different doses of yohimbine in 18 nonsmoking men with erectile dysfunction. Of the 18 men, nine (50%) were successful in completing intercourse in more than 75% of attempts. The yohimbine responders were men with less severe erectile dysfunction as manifested by improved increased rigidity on RigiScan™ testing, higher Florida Sexual Health Questionnaire scores, and slightly higher levels of serum testosterone. Yohimbine is an effective therapy to treat organic erectile dysfunction in some men with erectile dysfunction.
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Introduction

Yohimbine hydrochloride is the principal alkaloid of the bark of the African yohimbe tree. It is primarily selective for the presynaptic alpha-2 receptor that enhances the central release of norepinephrine[1,2] or even epinephrine,[3] although the latter is controversial.[4] This central action increases sexual arousal[2,5] and appears similar to the central alpha-2 adrenergic mechanism that initiates hot flashes.[6] Peripherally, yohimbine may partially antagonize norepinephrine-induced contraction of corporeal cavernosal smooth muscle.[7,8] The action is that of an antagonist to postjunctional alpha-2 adrenergic receptors, but a direct effect on vascular smooth muscle is also possible.[9]

*Correspondence: AT Guay, Endocrinology/Center for Sexual Function, Lahey Clinic Northshore, One Essex Center Drive, Peabody, MA 01960 USA.
E-mail: Andre.T.Guay@lahey.org
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When given orally, yohimbine reaches peak levels in 10–15 min, and the half-life is 0.6 h. The efficacy of yohimbine in sexual function has been questioned, perhaps because of early questionable multidrug preparations.[10,11] Yohimbine has been shown to have some effect on psychologic erectile dysfunction[12,13] and in reversing fluoxetine-induced sexual dysfunction.[14]

Studies of mixed organic causes for erectile dysfunction showed varied results;[15,16] thus, certain guidelines recommended that it not be used to treat erectile dysfunction.[17] Side effects occurred when a high dose was given.[18] Patients with organic erectile dysfunction had mixed results, with positive effects in 26,[19] 33,[20] 34[21] and 43%,[22] respectively. The results were better when the dose was doubled.[20,21] Several meta-analyses showed a slight positive effect of yohimbine compared with placebo.[23,24]

Guay and Spark observed independently (unpublished data) that yohimbine was associated with a very poor response in cigarette smokers. This is believed to be relevant, because studies several decades ago may have included a large percentage of smokers, which only recently has been recognized as a risk factor for erectile dysfunction. We tested this hypothesis by studying nonsmoking men with documented organic impotence and by judging whether any possible effect might be related to

adrenal or testicular hormones, which, to our knowledge, has not been studied.

Patients and methods

Men, aged 40–80 y, were recruited from new consultations seen for erectile dysfunction at the Lahey Clinic Center for Sexual Function. Patients were screened by history and physical examination and by evaluation of nocturnal penile tumescence and rigidity with the RigiScan™ (Timm Medical Technologies, Inc., Minneapolis, USA). Candidates completed a sexual questionnaire and had morning blood tests for luteinizing hormone (LH), free testosterone, cortisol, dehydroepiandrosterone sulfate and androstenedione. Inclusion criteria included normal initial serum testosterone and prolactin levels and the presence of an organic cause of erectile dysfunction manifested by abnormal nocturnal tumescence and rigidity testing with the RigiScan™ monitor. Active smokers and men with concurrent major psychiatric problems were excluded. No other treatment for erectile dysfunction was permitted during the study. Yohimbine hydrochloride (supplied by Palisades Pharmaceuticals, Palisades, NJ, USA) was started at a dose of 5.4 mg three times a day (tid) for 4 weeks, after which the sex questionnaire was administered again and blood tests, nocturnal penile tumescence and rigidity testing were repeated. The dose of yohimbine then was increased to 10.8 mg tid for 4 additional weeks followed by a third administration of the sex questionnaire and final measurements of hormone levels and nocturnal penile tumescence and rigidity monitoring.

Sexual questionnaire

The Florida Sexual History Questionnaire, a 20-item questionnaire that assesses interest and desire for sexual activity, sexual development, current sexual behaviors, and satisfaction with current sexual activity, was used to assess male sexual dysfunction. Individuals responded to each question by choosing one of six ordinally scaled response categories, with higher scores representing better functioning. Scores on the Florida Sexual History Questionnaire have been shown to significantly discriminate between men with and without impotence[25] and between men with primary organic and primary psychogenic erectile dysfunction.[26] According to Geisser *et al*,[25] the Florida Sexual History Questionnaire has high internal consistency as well as split-half reliability. Chronbach's alpha has been reported to be as high as 0.90, and Spearman Brown's coefficient is reported to be 0.86.

Office evaluation of results

To evaluate the patients' response clinically in the office, a simple grading system was used.[27] The patients were asked about the quality of their erections, which were graded as follows: grade 1, tumescence but no rigidity; grade 2, tumescence with minimal rigidity; grade 3, rigidity sufficient for sexual intercourse; and grade 4, fully rigid erection. At the end of the study, patients were graded as to whether they thought they had improved enough to have satisfactory regular intercourse, which is defined as success in 75% of attempts. The degree of subjective improvement in intercourse was used to classify patients as 'responders' *vs* 'nonresponders' in subsequent analyses. A log was kept by the couple of their sexual activity, and it was taken to the clinic for review by the clinical investigator.

Nocturnal penile tumescence and rigidity testing

The RigiScan™ portable home monitor recorded nocturnal penile tumescence and rigidity testing. The monitor's quantitative analysis software quantitates various parameters of tumescence and rigidity, which includes the area under the curve over time slept, reported as tumescence activity units and rigidity activity units. The reproducibility and accuracy of this technique have been reported.[28] Baseline normal values were used as previously reported,[29] Rigidity had to be at least 60% at the base and 50% at the tip and maintained for at least 10 min. At least half of the episodes had to meet these criteria, with a minimum of three or four episodes per night. Tumescence had to achieve a height of 3 cm at the base and 2 cm at the tip.

Nocturnal monitoring was performed for two nights each session, and the second night's recording was used for calculation unless there was a technical problem with that recording, in which case the first night's recording was used.

Statistical analyses

The paired *t*-test was used to assess differences in responses using various doses of yohimbine in responders and nonresponders. Responder and nonresponder changes in tumescence, rigidity, and other physiologic responses over the entire study period were compared using independent *t*-tests (assuming equal variances). Independent *t*-tests were repeated to determine whether significant differences existed in the mean numbers of risk factors, age, or side effects among groups. Matched pairs *t*-tests were used to compare Florida Sexual

History Questionnaire responses at each dose. Finally, χ^2 analysis (or Fisher's exact test when appropriate) was used to compare the two groups on dichotomous sexual satisfaction ratings at the end of the trial; 95% confidence intervals were consistently examined to determine the magnitudes of differences detected. Two-tailed *P*-levels were used in reporting all results. SPSS 9.0 statistical software (SPSS Inc, Chicago, IL, USA) was used for analysis.

Laboratory determinations

All hormone determinations were performed by radioimmunoassay using kits provided by commercial suppliers. All blood samples were drawn between 8 am and 1 pm, quickly spun down, frozen, and then stored. All determinations were performed at the same time after the end of the study. The serum LH kit was obtained from Nichols Institute (now Quest; Tarzana, CA, USA) (normal male range, 1.4–11.1 mIU/ml). The serum free testosterone kit was obtained from Diagnostic Products Corporation (DPC, Los Angeles, USA) (normal male range, 15–40 pg/ml). The serum cortisol kit was bought from DPC (normal morning range, 10–24 mcg/dl; normal afternoon range, 5–12 mcg/dl). The serum dehydroepiandrosterone sulfate kit was obtained from DPC (normal range, 150–350 mcg/dl from adolescence to the peak at age 50 y, with a progressive decrease with advancing years).

Results

Twenty-one men were screened. Two were rejected because they had normal results on nocturnal penile study, and one man was excluded from the study because of a protocol violation. Eighteen men completed the study. The mean age of the men was 60.2 y (range, 34–69 y). The mean duration of erectile dysfunction was 3.1 y (range, 1–10 y). All men were in stable heterosexual relationships. The listed medical risk factors for erectile dysfunction were hypertension in nine men, atherosclerotic cardiovascular disease in seven, single offending medication in seven (mostly beta-blockers), multiple medications in five, diabetes mellitus in four (one with neuropathy), venous leakage in two, and peripheral vascular insufficiency in one.

Of the 18 men who completed the protocol, nine were responders and nine were nonresponders. The responders were defined as having successful intercourse for at least 75% of attempts.

The side effects of yohimbine therapy were negligible, even in men taking six tablets daily.

Table 1 Cardiovascular responses to yohimbine therapy

	Baseline			*Yohimbine dose change*	
	Yohimbine				
Variable	*Baseline*	*5.4 mg tid*	*5.4 mg tid dose* P-*value*	*Yohimbine 10.8 mg tid*	*from 5.4 to 10.8 mg tid* P-*value*
Systolic BP (mmHg)	135	134	0.57	137	0.14
Diastolic BP (mmHg)	82	81	0.26	82	0.26
Pulse rate (bpm)	69	69	0.82	69	0.80

BP, blood pressure.
No statistically significant changes were noted with either dose of yohimbine.
Paired *t*-tests were used to compare physiologic measures within the entire sample.

Table 2 Hormone responses for various doses of yohimbine three times a day

	Baseline			*Yohimbine dose change*	
Variable	*Baseline*	*5.4 mg tid*	P-*value*	*10.8 mg tid*	P-*value*
Cortisol (μg/ml)	9.6	12.7	0.02*	13.0	0.06[a]
Androstenedione (ng/ml)	1.3	1.4	0.72	1.4	0.72
DHEA-S (μg/ml)	144.8	152.7	0.46	130.7	0.72
LH (mIU/ml)	4.1	4.1	0.97	4.2	0.67
Free testosterone (pg/ml)	14.8	15.4	0.60	16.1	0.23

DHEA-S, dehydroepiandrosterone sulfate; LH, luteinizing hormone.
*Significant where $P \leq 0.05$.
[a]Trend but not statistically significant. Within group differences compared using paired *t*-tests.

One man had mild hot flashes, and another noted mild anxiety. There was no increase in blood pressure or pulse rate while taking yohimbine (Table 1).

Various hormone levels were monitored during therapy, and it did not appear that there were major changes in the group as a whole (Table 2). Cortisol levels rose significantly from baseline to the first dose of yohimbine. When the hormone levels were evaluated in responders *vs* nonresponders (Table 3), slight differences were noted. Free testosterone levels were higher at baseline in the responders but did not increase significantly with the higher doses of yohimbine. Dehydroepiandrosterone sulfate levels were not significantly higher at baseline in the responders, and they did not change with the higher dose of yohimbine. Cortisol levels appeared to increase in both groups with increased doses of yohimbine, significantly more so in responders than in nonresponders ($P = 0.03$).

The response to yohimbine did not vary with patient age; the responders were 60.3 y of age *vs* 60.0 for the nonresponders (Table 4; $P = 0.106$). The number of medical risk factors was slightly higher in the nonresponders (2.3 per person) compared with the responders (1.8 per person), but this difference was not significant ($P = 0.346$). Documenting the quality of the men's erections in the office with a simple grading system showed a significant difference at the end of the study between responders and nonresponders. For the responders, the value was 3.0 compared with 1.9 for the nonresponders ($P < 0.001$). This result correlated with the overall sexual satisfaction of patients who stated whether or not they were able to engage in regular sexual intercourse.

Nocturnal penile tumescence and rigidity monitoring using tumescence and rigidity activity units measure the area under the curve of activity divided by the time slept so that varying sleep times may be compared. All four parameters of base and tip tumescence and rigidity rose more in responders than in nonresponders (Table 5). Most changes showed either a trend toward significance or achieved statistical significance. Baseline tip rigidity activity units and tip tumescence activity unit scores differed significantly between groups ($P = 0.038$ and $P = 0.026$, respectively). In fact, nearly all of the baseline values were higher in the responders compared with the nonresponders. Responder tip tumescence activity unit scores increased steadily, whereas nonresponder scores dropped negligibly with the 10.8 mg tid dose. Responders had a significantly higher final score while taking the 10.8-mg dose ($P = 0.010$). Responder tip rigidity activity unit scores also increased

Table 3 Hormonal responses to yohimbine in responders *vs* nonresponders

	Baseline			*Yohimbine 5.4 mg tid*			*Yohimbine 10.8 mg tid*		
	Resp	*Nonresp*	P-*value*	*Resp*	*Nonresp*	P-*value*	*Resp*	*Nonresp*	P-*value*
Cortisol (μg/dl)	10.8	8.6	0.08	11.6	11.7	0.44	14.2	11.5	0.03*
Androstenedione (ng/ml)	1.4	1.3	0.46	1.5	1.4	0.81	1.5	1.2	0.18
DHEA-S (μg/dl)	153.8	101.8	0.70	159.0	107.4	0.82	145.2	104.3	0.15
LH (mIU/ml)	4.6	3.2	0.25	4.5	3.6	0.43	5.0	3.3	0.09
Free testosterone (pg/ml)	16.1	13.6	0.33	16.3	4.4	0.55	18.2	13.7	0.10

*Significant where $P \leq 0.05$.
DHEA-S, dehydroepiandrosterone sulfate; LH, luteinizing hormone; Nonresp, nonresponders; Resp, responders.
Normal ranges: cortisol, 5-24 μg/dl; androstenedione, 0.8–2.8 ng/ml; DHEA-S, 150–350 μg/dl;
LH, 1.4–11.1 mIU/ml; free testosterone, 10–40 pg/ml.
Note: Mean scores were compared at each time point using independent *t*-tests. The change in cortisol from administration of 5.4 mg tid of yohimbine to administration of 10.8 mg tid of yohimbine was greater for responders than for nonresponders ($P = 0.03$).

Table 4 Office evaluation of patients' sexual response by inquiry of the physician about the home experience with yohimbine

				Erectile response[a]		
	Patient age	*No. risk factors*	*Baseline*	*Yohimbine 5.4 mg tid*	*Yohimbine 10.8 mg tid*	*Satisfactory sexual intercourse*
Responders	60.3	1.8	1.8	2.3	3.0	100% positive
Nonresponders	60.0	2.3	1.6	2.0	1.9	100% negative
P-value	0.11	0.35	0.67	0.77	< 0.001[b]	< 0.001[b]

[a]Grade 1, tumescence but no rigidity; grade 2, tumescence with minimal rigidity; grade 3, rigidity sufficient for sexual intercourse; grade 4, fully rigid erection.
[b]Statistically significant difference where $P \leq 0.001$.
Independent *t*-tests were used to compare mean values between groups. When variables were dichotamous, χ^2 analysis (or Fisher's exact test, where appropriate) was used.

Table 5 Nocturnal penile tumescence and rigidity data recorded during yohimbine therapy in responders and nonresponders

	Baseline	*Yoh 5.4*	*Yoh 10.8*
Tip RAU			
Responders	29.9	36.8	37.0
Nonresponders	13.2	18.9	14.7
P-value	0.04*	0.01*	0.04*
Tip TAU			
Responders	19.2	21.4	25.0
Nonresponders	12.6	10.9	10.8
P-value	0.03*	0.12	0.01*
Base RAU			
Responders	30.3	42.1	42.2
Nonresponders	20.6	27.6	20.7
P-value	0.23	0.06[a]	0.10
Base TAU			
Responders	26.7	24.6	29.5
Nonresponders	14.0	15.7	14.6
P-value	0.23	0.24	0.009**

RAU, Rigidity Activity Units; TAU, Tumescence Activity Units.
*Statistically significant difference where $P \leq 0.05$.
**Statistically significant difference where $P \leq 0.01$.
[a]Trend but not statistically significant.
Independent *t*-tests were used to assess significant differences in mean scores between groups.

steadily, whereas nonresponder scores increased at the second dose, then fell again at the final dose. The mean tip rigidity activity unit score of the responders was significantly higher than that of the nonresponders with the 5.4-mg tid dose ($P = 0.011$). The final scores of the responders were almost twice those of the nonresponders as well (significant where $P = 0.041$). Base rigidity activity unit scores did not differ significantly between the two groups, although the increased responder scores with the initial dose of yohimbine was greater than that of the nonresponders (trend where $P = 0.065$). Finally, base tumescence activity unit scores of the responders who were taking high doses of yohimbine were significantly higher ($P = 0.009$).

Data from the Florida Sexual History Questionnaire collected at each time period (baseline, 5.4 mg tid and 10.8 mg tid) are presented in Table 6. Three patients (two responders and one nonresponder) did not complete the entire questionnaire for each study period and were excluded from the analyses. Thus, data in the table and statistical analyses are based on the responses of seven responders and eight nonresponders.

Responders tended to have consistently higher scores compared with nonresponders. For nonresponders, none of the scores was significantly different when comparing baseline scores with either of the yohimbine doses. However, a trend toward an improved total questionnaire score was noted from baseline to the 5.4 mg tid dose ($P = 0.083$). For responders, a significant increase in the Florida Sexual History Questionnaire total score was observed from baseline to the time the 5.4-mg tid dose was administered ($P = 0.021$). A trend closely approaching statistical significance ($P = 0.055$) was noted from baseline to the administration of the 10.8 mg tid dose of yohimbine. Inspection of changes in the individual items revealed that responders reported significantly greater frequency of vaginal penetration with both the 5.4- and 10.8-mg doses of yohimbine tid compared with baseline ($P = 0.010$ and $P = 0.010$, respectively). Participants also noted less difficulty obtaining an erection for sexual intercourse while taking 10.8 mg of the drug compared with baseline ($P = 0.011$). Responders reported having significantly less difficulty maintaining an erection for sexual intercourse compared with baseline with

Table 6 Florida Sexual History Questionnaire: significant differences in mean item scores for responders and nonresponders with both doses of yohimbine

Florida Sexual History Questionnaire	*Baseline* (P)	*Yohimbine 5.4 mg tid* (P)	*Yohimbine 10.8 mg tid* (P)
Total score			
Responders	84.9 (0.02)*	88.3 (0.11)	100.6 (0.06)[a]
Nonresponders	70.0 (0.16)	66.5 (0.08)[a]	66.8 (1.0)
Frequency of penetration			
Responders	3.3 (1.0)	3.3 (0.01)*	5.1 (0.01)*
Nonresponders	2.8 (0.32)	2.1 (0.86)	2.2 (0.58)
Difficulty obtaining erection before intercourse			
Responders	2.6 (0.06)[a]	3.5 (0.10)	4.5 (0.01)*
Nonresponders	2.1 (0.68)	1.9 (0.59)	1.7 (0.40)
Difficulty maintaining erection during intercourse			
Responders	2.1 (0.05)*	3.4 (0.19)	4.4 (0.001)**
Nonresponders	1.4 (0.40)	1.8 (0.89)	1.9 (0.50)
Rating of firmness pre intercourse/masturbation			
Responders	2.9 (0.02)*	3.8 (0.21)	4.6 (0.01)*
Nonresponders	1.9 (1.0)	1.9 (1.0)	2.0 (0.76)

[a]Trend but not statistically significant.
*Statistically significant difference where $P \leq 0.05$.
**Statistically significant difference where $P \leq 0.01$.
Matched pairs *t*-tests were used to compare differences in mean item scores within groups as Yohimbine dosage increased.

both the 5.4-mg tid dose ($P = 0.049$) and the 10.8-mg tid dose ($P < 0.001$). Responders also reported significantly greater penile firmness and rigidity before intercourse or masturbation in both treatment conditions compared with baseline ($P = 0.02$ for the 5.4-mg tid dose and $P = 0.013$ for the 10.8-mg tid dose).

Discussion

The meta-analysis on the effectiveness of yohimbine by Ernst and Pittler[24] indicated that yohimbine has some measure of effectiveness in men with organic erectile dysfunction. It is important, therefore, to identify the population that might be expected to have a positive response.

Although not direct proof of cause and effect, the positive results that we report in half of the men in the current study may reinforce our clinical observation with objective RigiScan™ data that use of yohimbine might be associated with better effects in nonsmokers. We[30] reported that cessation of smoking may rapidly improve nocturnal erectile activity and found that nicotine was not the noxious agent in our study. We postulated that carbon monoxide might create a hypoxic environment in the penis. This effect probably was mediated through restoration of nitric oxide activity.[31]

Response to yohimbine was not dependent on patient age. Patients who showed a positive response had fewer medical risk factors overall, although the small number of patients was not large enough to provide statistical significance. The positive clinical response was verified subjectively both by the formal questionnaire and by the in-office clinical encounter. The positive response was verified objectively by measuring nocturnal penile tumescence and rigidity with the RigiScan™ home monitor. The trend of the baseline penile erectile response was better in the responders, suggesting that use of yohimbine might be more effective in patients who have less severe erectile dysfunction. Some authors have questioned the effect of yohimbine on penile activity, but either inadequate doses of yohimbine were used or only tumescence was measured,[21,32] often in an office setting where anxiety and embarrassment might affect results.

Even at the higher doses of yohimbine, no changes in blood pressure or pulse were noted. This agent would appear to be safe in men with medically controlled hypertension. There was an increase in the morning cortisol levels in all men; the value was higher but not significantly so in responders. Telöken *et al*[18] reported a high percentage (80%) of adverse events, but these authors administered a large dose (100 mg) of yohimbine. A toxic overdose of 200 mg produced only tachycardia, elevated blood pressure and anxiety of brief duration.[33] Even direct intravenous dosing of yohimbine raised the mean arterial blood pressure by 12%,[34] Goldstein *et al*[35] systematically administered yohimbine and noted large hemodynamic and norepinephrine responses in both normal and hypertensive men; only the men who had a history of anxiety, depression, or other psychopathologic factors had symptoms. Oral administration of yohimbine at standard doses or even four tablets (21.6 mg) at a time has had no effect on blood pressure.[4] Elevated blood pressure and heart rate were recorded when eight tablets (43.2 mg) were given at one time.[3]

Testosterone levels did not differ statistically in the treatment groups and did not change during treatment with yohimbine. The levels of dehydroepiandrosterone and free testosterone tended to be higher in the responder group, but the levels in both groups were well into the age-adjusted normal ranges. Androgens play a part in peripheral erectile activity, but they are not necessary for the central arousal stimulation of yohimbine,[36] in which norepinephrine release acts as an inhibitor antagonist.[2] Peripheral sympathetic stimulation also occurs[37] but less than its adrenergic antagonistic activity. These peripheral effects are prompting the search for new alpha-2 adrenergic antagonists[38]

The positive response in our patients was enhanced with the higher dose of yohimbine, a phenomenon noted previously.[20,21] We agree that several weeks of therapy are needed before clinical effects are seen,[21,22] and that some responders may be able to take yohimbine only on demand before sexual activity.[39] Yohimbine is effective in a subset of men with organic erectile dysfunction, especially nonsmokers, and it deserves a place in our therapeutic armamentarium. When yohimbine is ineffective alone, it may be useful in combination with other treatment modalities, as has been shown with naloxone[39] or trazodone.[40]

We have presented objective evidence that yohimbine has a positive effect in men with organic erectile dysfunction. This is contrary to the blanket statement of the American Urological Association in their clinical guidelines for erectile dysfunction, which states: 'Based on the data to date, yohimbine does not appear to be effective for erectile dysfunction and, thus, it should not be recommended as treatment for the standard patient.'[17] Our data strongly suggest that yohimbine treatment should be revisited. Our study was observational with dose-escalation just to see if there was any rationale to expect any effect in men with organic erectile dysfunction, especially in men who do not have the risk factor of tobacco abuse. The next step would be a double-blind, placebo-controlled study using yohimbine in smokers *vs* non-smokers to verify the current observation. We believe that our data justify such a trial.

Yohimbine will never be a first-line drug for erectile dysfunction, but may be useful in subsets of men with mild disease or few risk factors. Yohimbine might also be useful in combination therapy with other treatment modalities such as sildenafil and intraurethral alprostadil, when they do not produce adequate effects alone, as has already been shown with naloxone[39] or trazedone.[40]

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