International Journal of Impotence Research (2000) 12, Suppl 1, S70–S74
 0955-9930/00 $15.00
www.nature.com/ijir

Yohimbine in erectile dysfunction: the facts

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Yohimbine, a pharmacologically well-characterized α-2-adrenoceptor antagonist with activity in the central and peripheral nervous system, has been used for over a century in the treatment of erectile dysfunction. In-depth, systematic studies in animals have shown that the drug has a remarkable positive effect on sexual performance. Meta-analyses of the few controlled, randomized human studies have consistently shown an advantage of yohimbine over placebo. Despite such a long history and encouraging activity, the drug has not yet been subjected to scientifically rigorous human clinical trials. Although relevant basic pharmacological and animal research information has been available for over 15 y, recent studies were designed with a lack of insight and complete disregard of those fundamental studies. Currently, dose–response investigations are not available, alternative routes of administration (i.e. sublingual) have not been investigated, nor has continuous versus 'on-demand' administration been explored. Synergistic activity with other drugs was last studied nearly four decades ago. Assessment of various populations was carried out in very limited cohorts and only in most general terms. In short, properly designed trials in humans have not been done. Why? Yohimbine is an old drug. As such it does not enjoy patent protection or commercial viability. Until molecular/formulation changes can be brought about (as recently happened with two other agents: phentolamine and apomorphine), serious investigations of yohimbine will remain in limbo. It could be that the nay sayers are right and yohimbine, indeed, lacks clinical activity as a treatment for men with erectile dysfunction. As long as it remains an orphan drug, we will never know. *International Journal of Impotence Research* (2000) **12,** Suppl 1, S70–S74

Keywords: yohimbine; erectile dysfunction

Introduction

Historically, safe and effective oral agents for impotence have not been available. After many years of successful invasive treatments (intracavernosal and intraurethral) for erectile dysfunction (ED), the medical community is now confronted with the availability of oral drugs that, although not quite perfect, are closer to the ideal treatment. These oral agents, which were not predicted just a decade ago, are now appearing at an ever accelerating pace. The effectiveness of oral compounds was initially very limited and only recently, through important developments in basic physiology and pharmacology, could we begin to realize that they represent a viable, safe and useful therapeutic alternative. It is likely that oral medications will never be effective beyond those cases in which the physiological mechanisms of penile erection are either intact or only moderately affected by local or systemic conditions. It is reasonable to assume that, for the foreseeable future, men with severe ED may respond to intracavernosal injections or vacuum devices while the worst cases will find a solution only with prosthetic implants. A few patients will be candidates for vascular surgery.

Among the erectogenic drugs, none has been used longer and assessed more inadequately than yohimbine. Despite claims and counter-claims about its effectiveness, yohimbine today is recognized by many as a drug to be used in first line therapy. Is this claim justified?

Materials and methods

A computerized MEDLINE and PUBMED search of relevant peer reviewed publications on the topics of yohimbine and sexual function was carried out. In addition, manual searches of books and conference proceedings were conducted. The data gathered were scrutinized, collated and the relevant information reviewed and summarized.

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Received 2 September 1999; accepted 15 November 1999

Results

Yohimbine is an alkaloid obtained from the cortex of the *Coryanthe yohimbe* tree and it has been touted as an 'aphrodisiac' in the western world for over a century (Figures 1 and 2). It is currently recognized as a pre-synaptic alpha-2-adrenergic antagonist[1] and considered a 'dirty drug' because, in addition to its effects in the sympathetic system it exhibits other important actions. Thus, independent of the direct effect of yohimbine on alpha-2-adrenoceptors, it also exhibits significant activity in the central serotonergic system.[2] The folkloric use of the drug was wide spread in the first half of the twentieth century[3] but it was not until the 1960s that compounds containing yohimbine underwent extensive clinical testing.[4] Following this, there were a number of anecdotal cases indicating that yohimbine in combination with other drugs such as testosterone, caffeine and vitamin E exhibited significant positive effects in sexual functioning. One of the most remarkable reports included the first heart transplant patients in whom, a 75% response rate was reported.[5] Despite the promise of yohimbine from these and other small studies,[6] the drug did not produce significant interest in the medical research community. It was not until the early 1980s that a

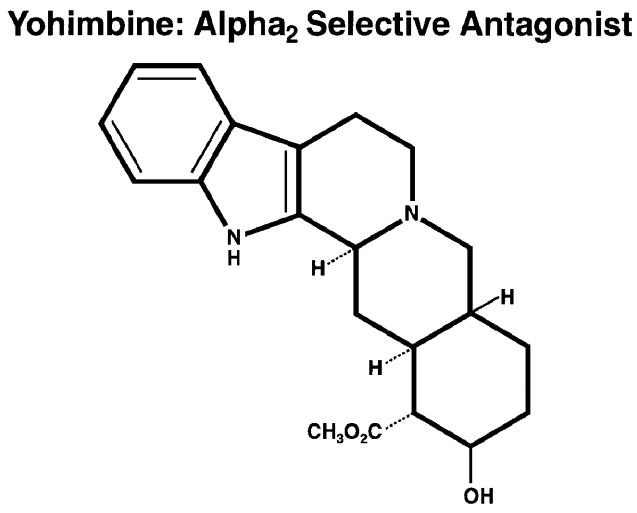
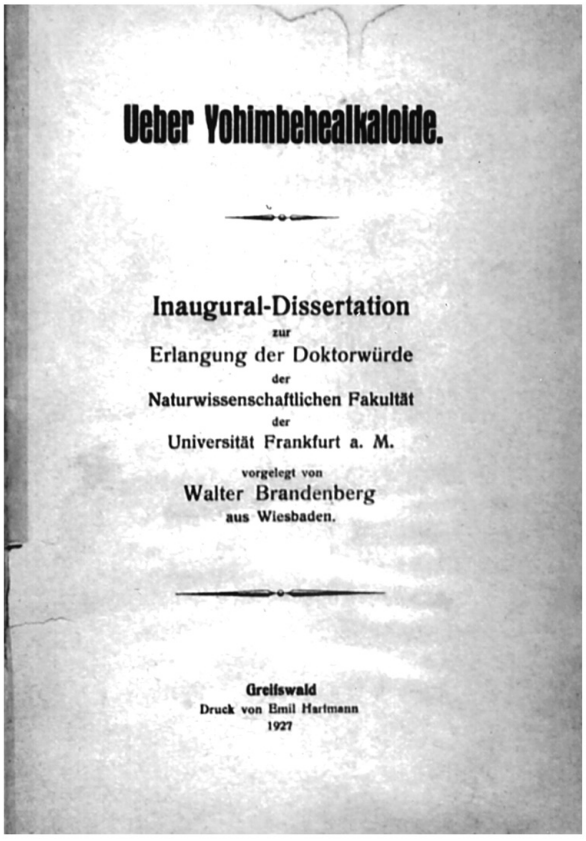


Figure 1 Chemical structure of yohimbine.


Ueber Yohimbehealkaloide.

Inaugural-Dissertation
zur
Erlangung der Doktorwürde
der
Naturwissenschaftlichen Fakultät
der
Universität Frankfurt a. M.
vorgelegt von
Walter Brandenberg
aus Wiesbaden.

Greifswald
Druck von Emil Hartmann
1927

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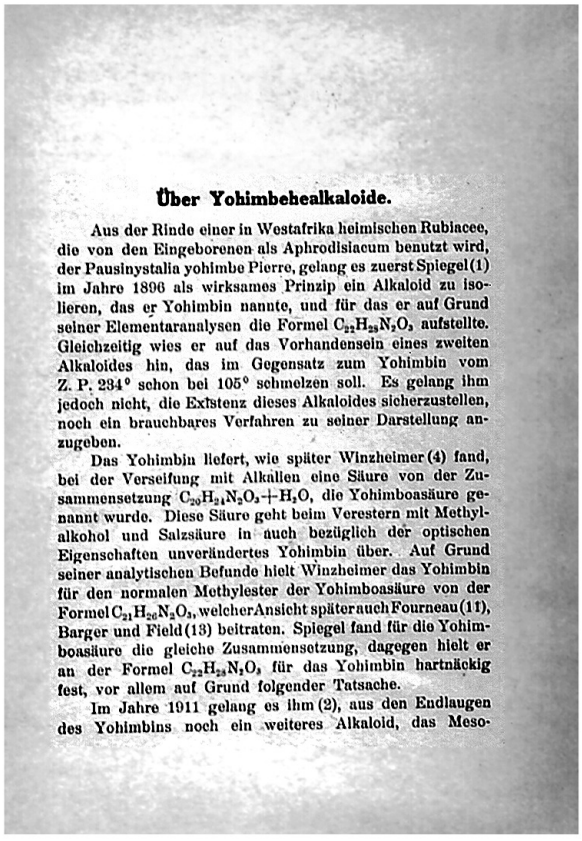
Über Yohimbehealkaloide.

Aus der Rinde einer in Westafrika heimischen Rubiacee, die von den Eingeborenen als Aphrodisiacum benutzt wird, der Pausinystalia yohimbe Pierre, gelang es zuerst Spiegel (1) im Jahre 1896 als wirksames Prinzip ein Alkaloid zu isolieren, das er Yohimbin nannte, und für das er auf Grund seiner Elementaranalysen die Formel $C_{22}H_{28}N_2O_3$ aufstellte. Gleichzeitig wies er auf das Vorhandensein eines zweiten Alkaloides hin, das im Gegensatz zum Yohimbin vom Z. P. 234° schon bei 105° schmelzen soll. Es gelang ihm jedoch nicht, die Existenz dieses Alkaloides sicherzustellen, noch ein brauchbares Verfahren zu seiner Darstellung anzugeben.

Das Yohimbin liefert, wie später Winzheimer (4) fand, bei der Verseifung mit Alkalien eine Säure von der Zusammensetzung $C_{20}H_{24}N_2O_3 + H_2O$, die Yohimboasäure genannt wurde. Diese Säure geht beim Verestern mit Methylalkohol und Salzsäure in auch bezüglich der optischen Eigenschaften unverändertes Yohimbin über. Auf Grund seiner analytischen Befunde hielt Winzheimer das Yohimbin für den normalen Methylester der Yohimboasäure von der Formel $C_{21}H_{26}N_2O_3$, welcher Ansicht später auch Fourneau (11), Barger und Field (13) beitraten. Spiegel fand für die Yohimboasäure die gleiche Zusammensetzung, dagegen hielt er an der Formel $C_{22}H_{28}N_2O_3$ für das Yohimbin hartnäckig fest, vor allem auf Grund folgender Tatsache.

Im Jahre 1911 gelang es ihm (2), aus den Endlaugen des Yohimbins noch ein weiteres Alkaloid, das Meso-

B

Figure 2 (**A**) Front cover of a dissertation on yohimbine by Walter Bandenberg at the University of Frankfurt, Germany in 1927. The document included a detailed biochemical analysis of the alkaloid in a volume of 60 pages. (**B**) First page of the document describing the biochemical analysis of yohimbine. On the second line it is mentioned that the compound has been known as an 'aphrodisiac', in the western world, since before the turn of the century.

systematic clinical evaluation of yohimbine was initiated. The first step was the completion of a non-controlled, non-randomized (phase II) trial in a limited number of patients with ED to determine whether yohimbine alone exhibited any effect on erectile function. This limited study showed some effectiveness of the drug in patients with a variety of conditions associated with an organic etiology. The overall complete response (ability to achieve vaginal penetration) rate was reported as 26%.[7] The first controlled, randomized studies were aimed at populations with either an organic or psychogenic etiology, the classification in vogue at that time. For the organic cohort ($n=100$) the response rate was 40% for yohimbine and 28% for placebo. These results, although showing an advantage for the active compound, failed to reach statistical significance ($P=0.42$).[8] More activity was found for the drug in the group of patients with a primarily emotional etiology: 62% for those men receiving yohimbine while only 18% for those on placebo; this difference was significant ($P<0.05$).[9] It appears that these studies caught the interest of the medical community, perhaps with the help of the usual excitement of the lay press in these matters.[10] Over the ensuing 10 years there were numerous publications on the effect of yohimbine on erectile function. Most of them were small studies with less than 10 patients,[11–13] but few were controlled clinical trials which, however, include only limited number of subjects.[14–18] All these studies employed between 19 and 50 mg in three divided daily doses and demonstrated a better response to yohimbine as compared to placebo. There are two notable exceptions; the study by Teloken *et al*[19] in which a large (100 mg), single dose of the drug was given daily. The authors concluded that, 'yohimbine promotes no improvement in patients with organic erectile dysfunction'. It is evident from the data presented that there was an arithmetic (if not statistical) advantage of the drug over placebo (complete response 13.6% *vs* 4.5%, respectively) in a study with a small number of subjects ($n=22$). Kunelius *et al*,[20] in a similarly small study, treated 29 patients without 'purely psychogenic or organic causes'. In this study no differences were detected between the active drug and the placebo. In fact, there was a tiny arithmetic advantage for the latter.

The value of yohimbine in the treatment of erectile failure has been carefully assessed in two separate, systematic reviews and meta-analyses of randomized clinical trials. The first[21] included four independent but convergent meta-analyses integrating results of trials using yohimbine alone or in combination with other drugs. This extensive and in-depth review, together with a sophisticated statistical evaluation, found a consistent positive effect of yohimbine alone or in combination with other drugs relative to placebo. The authors, however, appropriately pointed to the methodological and reporting shortcomings of most of the studies. The second meta-analytic report focused exclusively on the controlled, randomized studies that used yohimbine alone.[22] In this assessment the superiority of yohimbine was clearly demonstrated (odds ration 3.85, 95% confidence interval 6.67 to 2.22). The study went as far as to recommend yohimbine as 'a reasonable therapeutic option for erectile dysfunction that should be considered as initial pharmacological intervention'.

Shortly before the publication of these two meta-analytic studies, the American Urological Association produced its guidelines on the treatment of organic erectile dysfunction.[23] In this document, the guideline on yohimbine reads: 'Based on the data to date, yohimbine does not appear to be effective for organic erectile dysfunction, and thus should not be recommended as treatment for the standard patient'. Unfortunately the 'standard patient' was not defined. More unfortunate, however, is that as a result of the guideline the medical community and the lay press simply concluded that yohimbine was not effective, period. The document in its analysis of treatment outcomes, and to its credit, indicates that 'efficacy [of yohimbine] has yet to be proven, and demonstrations of efficacy will require larger trials of better design.'

There is extensive pharmacological information on yohimbine. As mentioned before, the drug is classified as an α-2-adrenoceptor antagonist but has other relevant actions on the central nervous system.[2] However, it was not until the demonstration of expression of functional α-2-adrenergic receptors in human corpus cavernosum[24] that a credible mechanism was provided for the improvement in erectile function in patients treated with yohimbine. Post-synaptic α-2-adrenergic receptors localized distally to adrenergic nerve terminals may be activated by circulating catecholamines (epinephrine) and induce contractility of the corporeal tissue. Adrenergic blockade with yohimbine would reverse the process (Figure 3). Systemic administration of yohimbine in rodents has been investigated in depth. It has been conclusively and repeatedly shown to be a powerful enhancer of copulatory behavior.[25]

It is relevant to mention here the phenomenon of drug tolerance that consistently develops when the administration of the drug is increased in frequency or quantity. Clark *et al*,[26] through a series of elegant and detailed experiments showed that daily administration of yohimbine results in an initial enhanced response which, however, declines rapidly with chronic administration. The same phenomenon occurs at higher doses of the drug. These observations, largely ignored by clinicians in recent studies, are of crucial importance for anyone interested in the design of human clinical studies. Furthermore, we reported on the pharmacokinetics of orally administered yohimbine in humans[27] and showed

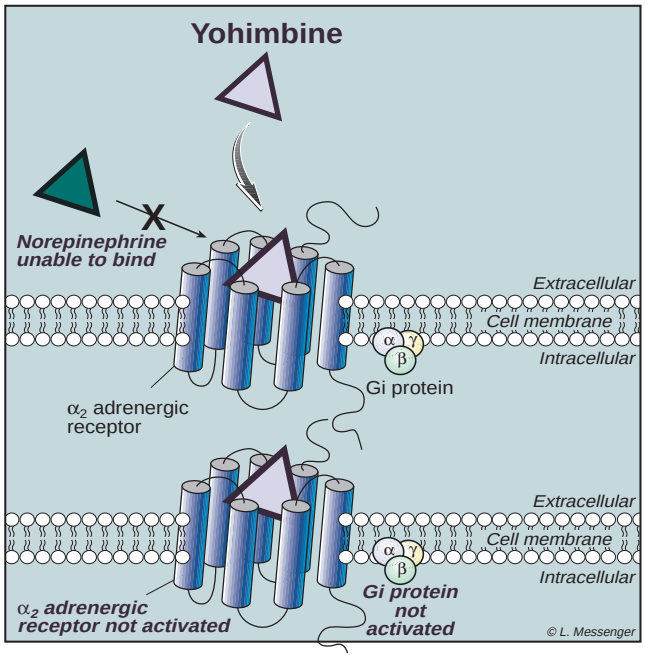

Figure 3 Hypothetical mechanism of action of yohimbine.

that its biological half-life is short (35 min). This, together with the animal data, would suggest that, for clinical studies, its use on an 'on demand' basis is most appropriate. Trials, however, stubbornly persist on the continued daily use of large doses.

It is known that after repeated copulation in rats, there develops a state of sexual exhaustion that lasts from 3 to 6 days.[28] Studies of Rodriguez-Manzo *et al*,[29] show the capacity of yohimbine to restore sexual behaviour in normal, exhausted rats. In addition, yohimbine showed partial restoration in sexually experienced animals that had been administered the neurotoxin DSP_4 to cause lesion of their central noradrenergic system. The importance of this and other studies resides not only on the putative effect of yohimbine, but also in the integrity of the central noradrenergic system which is fundamental for adequate sexual behavior.

Discussion

Yohimbine has been used as an aphrodisiac and an erectogenic drug for a long time. Despite its being pharmacologically well characterized, the mechanism(s) of action in humans are not well understood. It is known to be a post-synaptic alpha-2 adrenoceptor antagonist but it also exhibits central activity not only in the noradrenergic but in the serotonergic systems with profound effect in sexual behavior. This dual activity has gained yohimbine the epithet of a 'dirty drug' since it lacks the specificity of other agents. From a therapeutic point of view, the duality of activity may in fact be beneficial. Its efficacy as a sexual enhancer in animals is unquestioned and, in rodents, the mechanisms and sites of action are well defined. Unfortunately, in humans, the situation is not nearly as clear. Until now there are less than a dozen controlled studies on the effect of yohimbine on sexual function. Most of them lack sufficient power for credible statistical analyses. The populations in these trials have been, for the most part, too vaguely defined and received fixed daily dosing although animal data indicating the inappropriateness of such approach. Different routes of administration (e.g. sublingual) remain unexplored. Despite all this, two separate meta-analytical studies have consistently shown a superiority of yohimbine over placebo in controlled studies. However, yohimbine is an old drug and in its present formulation lacks patentability and commercial appeal. As such, it does not offer the incentives for a proper assessment of its erectogenic value. If a different formulation were to be found, yohimbine may yet enjoy the fame of two other agents such as phentolamine and apomorphine.

There is a great deal of justified optimism for successful and simpler treatments for ED. However, nobody should be misled to believe that oral or topical compounds will solve the problem completely. The emotional causes will still require counselling and support. One foresees a role for all current treatments (from psychotherapy or prosthesis and vacuum constriction devices). Therapeutically, one can easily predict success with combination therapies as a result of well planned strategies based on sound pharmacological principles. It appears that, empirically, our predecessors have perceived the need for synergisms among class compounds.[4] Their vision and experience, astonishing today, will take a long time to reproduce because of current regulations regarding drug combinations.

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