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# Dopamine agonists and their effect on the human penile erectile response

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## Introduction

Almost since the beginning of recorded history, man has searched for substances which might augment his sexual performance. Unfortunately, many patent medicines and folk remedies sold to a gullible public have not been shown to have beneficial effects ( 1 ). At the same time,a considerable research literature has demonstrated that certain pharmacological agents have reproducuble effects on sexual behavior in laboratory animals. It is also well established that many drugs in current usage interfere with human sexual behavior. It is possible that other agents which influence the same neurobiological substrate might enhance sexual behavior in the human. One system of current interest is the dopaminergic system as a considerable number of experiments in laboratory animals have demonstrated that drugs which amplify central dopaminergic activity lower thresholds for erectile and ejaculatory activity ( 2 ). Clinical observation has indicated that drugs with dopamine blocking activity interfere with human erectile capacity ( 3 ). This manuscript will summarize evidence concerning the use of dopamine agonists especially apomorphine to induce erectile responses in the human male.

## Literature Review

There is a growing body of evidence that dopaminergic neurotransmission may also be related to the penile erectile response in the human. Considerable anecdotal evidence suggest that levodopa may be association with increased libido. Numerous clinicians have reported that approximately 20-30% of men taking levodopa have an increase in sexual activity. Other men have noted the occurence of nocturnal erections and emissions, and the return of spontaneous erections while taking this agent. Pergolide, a dopaminergic agonist used in the treatment of Parkinson's Disease has also been reported to cause spontaneous penile erections ( 4, 5, ) . One study by Pierini and Nusimovich ( 6 ) found that 3000mg per day of levodopa had significant improvement in erectile function in male diabetics. It is unclear whether that study was double-blind. A similar study by Benkert and associates (7 ) found that levodopa increased the frequency of spontaneous erections, degree of erections, libido, and sexual dreams but did not restore potency in men with biogenic impotence. It is possible that levodopa had a central nervous system sexual enhancing effect which

was partially obscured by peripheral neuropathy in diabetic patients.

Most of the study of the effect of dopaminergic agents on erectile function involve the use of apomorphine. Apomorphine has mixed D1 and D2 agonist effects. Apomorphine increases growth hormone release and decreases prolactin secretion.It was previously used as an emetic and as a sedative. Its primary current usage is as a drug to investigate dopaminergic mechanisms in neuropsychiatric disorders.

Apomorphine is known to elicit penile erection and yawning in rats. It was first observed to elicit penile erection in humans as an incidental finding in the use of this drug in aversive conditioning of alcoholic patients. In a study of the efficacy of oral apomorphine-induced vomiting in the aversive conditioning treatment of alcoholism, Schlatter and Lal ( 8 ) made the serendipitous observation that approximately 63% of the alcoholic patients complained of spontaneous erections. No erections occurred in the control group. In a subsequent study ( 9 ), 1 mg of apomorphine was given subcutaneously in the arm. Again, approximately 12 out 0f 19 men reported spontaneous erections occurring approximately 10-20 minutes after the injection and lasting 2-5 minutes.

In a series of studies of the effect of apomorphine on growth hormone secretion, Lal and his co-workers provided evidence concerning the probable mechanism of action by which apomorphine induces penile erections. He observed that apomorphine-induced penile erections are not blocked by pretreatment with domperidome, a peripheral dopamine blocker which has a limited ability to cross the blood brain barrier ( 10 ). This suggests that the effect of apomorphine on penile erections occurs at the level of the central nervous system. He also observed that apomorphine does not induce erections in men who have been pretreated with sulpiride or pimozide, both of which are central dopamine blockers ( 11 ).This study combined with the previous study suggests that the mechanism of apomorphine-induced penile erections occurs at the level of the central nervous sytem and involves dopaminergic neurotransmission. In other studies, he found that methysergide , a serotonergic blocker ( 12 ) and naloxone and levallorphan , both opiod antagonists , ( 13 ) did not affect apomorphine-induced penile erections. Unfortunately, most of the studies done by Lal have been single blind.

Subsequently, Lal and his co-workers have published studies ( 14 ) which may have clinical relevance in the treatment of human sexual problems . In a study of the effect of apomorphine on penile erections in normal subjects, Lal and co-workers fould that ,25 to ,75 mg apomorphine given subcutaneously to 9 normal subjects elicited penile erections in 7 out of 9 subjects. Benztropine, a peripheral and central anticholinergic drug. had no effect on apomorphine induced erections. Penile circumference was measured by mercury strain gage attached just below the glans penis. He suggested that apomorphine might be used to identify a subpopulation of impotent men with impaired dopaminergic function. In a susequent study (15) men with idiopathic erectile dysfunction were recruited. All men reported normal libido but erectile failure. A number of disese processes including diabetes mellitus, Peyronie's disese,

abdominal prostatectomy, atropic testes,benign prostatic hypertropy, bladder dilation, and Reiter's syndrome were included. Four doses of subcutaneous apomorphine were employed ( .25mg, .50 mg, .75mg, and 1 mg). Four of the eight men had a full response to the apomorphine-induced erection. three of these responders were subsequently stated on oral bromocriptine ( 2.5 -3.75 mg /day p.o. ). All three reported complete recovery of erectile function within two weeks.

These findings were further extended in a study of normals by Danjou et al ( 16 ). They performed a 4 condition, 2 independent crossover, double-blind study of yohimbine and apomorphine on erections in 19-27 year old men with normal sexual function. Apomorphine was found to induce penile erections without increasing subjective sexual arousal while also potentiating sexual erections induced by exposure to 50 erotic slides.The dose was .0009 mg/ kg.The yohimbine was without effect.

A recent study expanded the study of apomorphine-induced penile erections to men with psychogenic impotence ( 17 ). Each patient reported the absence of full erections in coital activities but the presence of full erection during foreplay , upon awakening, or by masturbation. Prior research had indicated that answers to these questions were highly specfic in distinquishing between psychogenic and organogenic impotence( 18 ), Exclusion criteria also included current use of hypotensive or psychoactive medication, abnormal serum prolactin or testosterone, or abnormal penile blood pressure index. A repeated measures, subject own control, double-blind experiemnetal design was employed. Penile pletysmograph recoreding was done on the Farrell Instrumnets computerized physiological recording system. Barlow strain gages were employed.A highly significant effect on apomorphine-induced erections was found.Maximum erection changes occured after 20 minutes.The average maximum erection was 2 cm and 11 out of 12 demonstrated an erection exceeeding 1 cm. Eight subjects also complained of side effects such as yawning, drowsiness or nausea. Two subjects had extreme nausea and hypotension. Suprisingly, there was a significant association between the use of nicotine and the absence of side effects. Dose ranges included .25mg, .50 mg, ,75mg. and 1 mg. Penile circumference changes were significantly greater to all doses of apomorphine ( except .25 mg ) as compared to placebo at 20, 25, and 30 minutes after injection. Ratings of libido did not differ between placebo and drug conditions.

Discussion

Apomorphine and other dopamine agonists have been shown to have biphasic dose-dependent effects on eliciting penile erection in laboratory animals. Dopamine D-1 antagonist pretreatment increases the erectile response to higher doses of apomorphine whereas pretreatment with D-2 antagonists decreases the penile response to lower doses of apomorphine. These findings have been used to support the hypothesis that D-2 stimulation induces penile erection and that D-1 activation may have opposite effects. If this is true, apomorphine or other mixed dopamine agonist might have differential behavioral effects depending on the D1/D2 receptor

balance ( 19 ) .The effect of dopamine agonists on erection is hypothesized to be central rather than peripheral ( 20 ). Low doses of apomorphine infusions in the medial preoptic area ( 21 ) and paraventricular nucleus ( 22 ) . Whether similar mechanisms apply to the human are unknown. It is of note that D2 receptor agonists have been shown to act centrally to facilitate penile erection in male rhesus monkeys ( 23 ).

There would appear to be at least two possible practical applications of the ability of apomorphine to elicit erections in the human. If apomorphine is eliciting erections by its effect on dopaminergic pathways in the central nervous system, subcutaneous apomorphine injection may be useful as a diagnostic test of neurovascular integrity in patients with idiopathic erectile dysfunction. Such a procedure should be less expensive than nocturnal penile tumescence testing and thus could be more widely available. Currently, many investigators utilize direct injection of vasoactive substances into the corpora cavernosus to investigate integrity of the penile vasculature. Clearly, apomorphine testing has the theoretical advantage of testing both the neurologic and vascular systems. Many patients may find subcutaneous injection less objectionable than intracorporeal injection.

The finding that apomorphine elicits penile erection in the majority of male patients tested suggests a possible therapeutic role for dopaminergic agents in the treatment of erectile dysfunction. Clearly, apomorphine has too many side effects to have therapeutic usefulness.Lal has suggested that bromocriptine may be useful as a therapeutic agent in men who demonstrate an erectile response to apomorphine. Unfortunately, Lal's work with bromocriptine is single-blind. Other investigators have not found bromocriptine to be useful in the treatment of idiopathic erectile problems. If bromocriptine works by way of its effect on brain dopaminergic pathways, the efficacy of bromocriptine in reversing erectile failure would be highly dependent on the patient population studied. For example, one would not expect a man with a severe peripheral neuropathy to demonstrate an erectile response to a drug which works centrally.

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Discussion - DOPAMINE AGONISTS AND THEIR EFFECT ON THE HUMAN PENILE ERECTILE RESPONSE

J.G. Pfaus

In the case where you would actually give your subjects access to an erotic film or some other form of erotic stimulation, what do you think apomorphine might do? Has anybody ever tried it on people with sexual desire disorders?

R.T. Segraves

Concerning your second question, not that I am aware of. With regard to the first question, in one study there were patients with exposure to erotic slides and apomorphine. If I remember correctly, an effect of apomorphine alone on fantasy was not noticed. Lal also reported no effect of apomorphine on libido. We actually systematically studied libido by questionnaires and ratings and post session interviews. So it does not look as if libido is associated with apomorphine. I was surprised to find this.

B.D. Sachs

It is hard to have sexual fantasies when one is very nauseous, maybe even in the presence of erotic sexual stimuli, and I wonder whether any of the men reported incipient fantasies that were disrupted by nausea. Usually there is a kind of feedback effect in the sense that the perception of an erection will create fantasies. And I am wondering what you think might have disrupted that loop, whether it was the pharmacological side effects or whether the loop was simply missing because these were cases of psychogenic impotence.

R.T. Segraves

I do not know, we questioned them fairly thoroughly and no one reported what you are describing. There were, I think, two subjects who went through the whole procedure with minimal side effects and they also did not report any sexual fantasy and Lal has reported the same thing. I think it is an event independent of fantasy or libido change.

J. Bancroft

It is interesting that this does not seem to be linked to sexual desire. The side effects may be the obvious explanation because certainly with hyperprolactinemia it would seem that the primary effect of hyperprolactinemia is on sexual desire rather than on erectile responsiveness. The evidence is not very strong but insofar as there is any evidence it would suggest that. Therefore when you use bromocriptine to lower the prolactin level, for instance in a case of microprolactinoma, then the most convincing effect is on improving sexual desire. Another point I want to make is that I was involved in an early cross-over placebo-controlled study of about 24 men using quinerolane and side effects were disastrous. There was one man where a convincing erection was produced but he was unable to get off the bed because as soon as he lifted his head he would be going around in circles, so that was not terribly satisfactory. But I am not aware of any evidence in our study about any effect on sexual desire induced by this D-2 agonist.

M. Murphy

I do not think it is surprising that there is a dissociation between the erectogenic effect of apomorphine and any effect on desire. The studies with micro-injection into the paraventricular nucleus in the rat seem to demonstrate that there is a specific site of action: Apart from bilateral injections into the hippocampus, there is no other site in the brain at which erections can be induced by apomorphine. It does seem to be quite a specific effect on a central erectile mechanism independent of desire or of arousal.

B.D. Sachs

I think that is true but it still raises the question of why the feedback loop from the erection is interrupted. Morning erections are commonly followed by fantasy or actually engaging in sexual activity. That was not the case in any of these studies, apparently.

R.T. Segraves

In our study laboratory people were heterosexual males in white coats and the study room, the only room we could have, was a room with a lot of chemical bottles on

the shelves and it was not conducive to erotic fantasy.

M. Murphy

If I could comment on that, I think you answered the question yourself. The vast majority of men experience nausea or dizziness or sedation and I think that interrupts the loop. I do have one anecdotal case of a man who did get sexually aroused and that was during a growth hormone study. He was given apomorphine by a female researcher and he did get aroused. In fact she was quite offended because he mentioned the fact that the drug had obviously given him an erection.

R.C. Rosen

Just two follow up questions. One is that I am trying to put your data together with the data on dopamine antagonists, and again the problem I am having is that to my knowledge dopamine antagonists usually are associated in men with loss of libido and/or ejaculatory problems. The second question is if you know of any studies that have looked at dopamine agonists in women. I cannot think of any studies.

R.T. Segraves

Not that I am aware of. I know there have been case reports in the literature of female patients who have had increased libido on L-dopa and on pergolide, which is a dopamine agonist. Concerning your first question, I have again to refer mainly to case reports in literature. The effects on ejaculation are mainly seen with antipsychotics and it may be the alpha-1-antagonism that is causing the ejaculatory side effects.

J. Bancroft

In the benperidol study that we did in the early 70's, we compared it with chlorpromazine and placebo and we measured response to erotic films and slides. We measured erectile responses and we looked at ratings of sexual interest and sexual activity. These were all inmates in Broadmoor Hospital incarcerated there for sexual offenses and there was a definite effect of benperidol over placebo, although it was not huge. It was not apparent, interestingly, in the erectile response to the films but it was apparent in the ratings of sexual interest and frequency of sexual thoughts. And

chlorpromazine in the dosage that we used, I think it was 50 mg three times a day, was no different to placebo.

B.J. Everitt

I just wanted to make a general comment about the efficacy of directly acting postsynaptic dopaminergic agonists in the kind of sexual behaviour situation, or indeed others that we are talking about now. This may not be the best way to stimulate the dopamine system if one wants to get meaningful behavioural effects. I do not think it is an accident, for example, that directly acting dopamine agonists are not abused drugs, while presynaptic acting drugs like amphetamine and cocaine are. This is probably because what the latter drugs do is amplify ongoing activity in those neurons on which they act, which is contingent on what is going on at the time. And that may be particularly true when one is looking at so-called higher functions like those involved with fantasy and self-induced arousal. Directly acting agonists act non-contingently, i.e., independently of on-going neural activity.

S. Erill

I think it would be interesting to know whether anybody has ever tested amantadine. Amantadine is a dopamine releaser and one could get the effects Steve Pomerantz was presenting.

B.D. Sachs

I do not know of any human studies with amantadine, but it was one of the earliest drugs used with rats, and it promoted erections.

S.M. Pomerantz

I want to mention that there is a compound - bupropion - which is a dopamine reuptake inhibitor that also exhibits norepinephrine reuptake properties. That compound has been shown in humans to facilitate some indices of sexual interest and sexual motivation.

R.C. Rosen

Amantadine is being used in a couple of places in the United States to counteract SSRI induced sexual dysfunction. I am involved in one study with it now, and just based on clinical data it seems to be moderately effective. People are looking at cyproheptadine, amantadine and yohimbine as possible pharmacological antidotes to SSRI induced erectile or orgasmic difficulties, and amantadine looks to be moderately effective in that context.