

# High-Dose Ascorbic Acid Increases Intercourse Frequency and Improves Mood: A Randomized Controlled Clinical Trial

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**Background:** *Ascorbic acid (AA) modulates catecholaminergic activity, decreases stress reactivity, approach anxiety and prolactin release, improves vascular function, and increases oxytocin release. These processes are relevant to sexual behavior and mood.*

**Methods:** *In this randomized double-blind, placebo-controlled 14 day trial of sustained-release AA (42 healthy young adults; 3000 mg/day Cetebe) and placebo (39 healthy young adults), subjects with partners recorded penile-vaginal intercourse (FSI), noncoital partner sex, and masturbation in daily diaries, and also completed the Beck Depression Inventory before and after the trial.*

**Results:** *The AA group reported greater FSI (but, as hypothesized, not other sexual behavior) frequency, an effect most prominent in subjects not cohabiting with their sexual partner, and in women. The AA but not placebo group also experienced a decrease in Beck Depression scores.*

**Conclusions:** *AA appears to increase FSI, and the differential benefit to noncohabitants suggests that a central activation or disinhibition, rather than peripheral mechanism may be responsible. Biol Psychiatry 2002;52:371–374 © 2002 Society of Biological Psychiatry*

**Key Words:** Ascorbic acid, coitus, sex behavior, depression, affect, trials

## Introduction

In a recent randomized clinical trial, high-dose ascorbic acid (AA) supplementation reduced physiologic and subjective reactions to a standardized stressor (Brody et al, 2002). Other human studies have shown AA to benefit the cardiovascular system, due at least in part to enhanced endothelium-derived nitric oxide activity (Gokce et al 1999; Wilkinson et al 1999). In animal studies, AA has been shown to reduce behavioral signs of approach anxiety (Satterlee et al 1993), modulate dopaminergic (Girbe et

al 1994, Gulley and Rebec 1999; Nurse et al 1985, Pierce et al 1995, Seitz et al 1998; Sershen et al 1987) and noradrenergic (Kimelberg and Goderie 1993; Paterson and Hertz 1989) activity, potentiate dopamine's inhibitory effect on prolactin release (Shin et al 1990), and increase oxytocin secretion (Luck and Jungclas 1987). All of these phenomena could enhance frequency of penile-vaginal intercourse (FSI; Brody 1997), so the effect of high-dose AA supplementation on FSI was examined in a double-blind clinical trial. There are important differences between FSI and other sexual activities, with only the former being associated with markers of better health (Brody 1997, Brody et al 2000). One possible basis for this association is the evolutionary (sociobiological) preeminence of the only potentially reproductive sexual act. The evolution of human behavior should confer selection advantages, including perhaps enhanced health to this reproductive behavior. Evidence also suggests there is greater dopaminergic activity involved in intercourse than in masturbation, as indexed by women's postorgasmic prolactin rise (presumably reflecting sexual satiety produced by a negative feedback loop; Exton et al 1999, 2001). Therefore it was hypothesized that (for subjects with a current partner, given that absence of a partner could suppress detection of increases in partnered sexual behavior) high dose AA supplementation would increase FSI but not other sexual behavior. Given the effect of AA on central catecholaminergic function as well as anecdotal reports of high-dose AA improving depression (Cocchi et al 1980), it was also hypothesized that high dose AA supplementation would improve mood (decrease depression scores).

## Methods and Materials

Healthy subjects with a current sexual partner (52 female and 29 males, mean age 24.4; 55 cohabited with a sexual partner) were randomized to placebo or sustained release AA (3000 mg/day Cetebe, GlaxoSmithKline; randomized using a random number list prepared by the manufacturer) daily for 14 days (39 subjects were in the placebo group).

Subjects had plasma AA levels determined (details in Brody et al 2002) and completed the Beck Depression Inventory (Hautz-

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inger et al 1994) at baseline and at the end of the trial. At baseline, subjects also completed the "Lie" scale measure of social desirability response bias (Eysenck 1974) and provided a partnership satisfaction rating. During the trial, subjects performed daily diary recording of penile-vaginal intercourse, noncoital partner sex, and masturbation. Other procedures and results are described elsewhere (Brody et al 2002).

For greater ease of interpretation, diary values were transformed to monthly estimates (multiplied by 31/14). Because of small cell size at lower levels, the variable partnership satisfaction was collapsed into "very" satisfied and lesser values, making for a median split: 42 "very," 39 less satisfied. In separate analyses of variance (ANOVAs), the dependent variables of penile-vaginal intercourse days, monthly noncoital partner sexual behavior days and monthly masturbation days were examined in relation to the independent variables medication group, subject's sex, (and to examine the role of factors likely to influence FSI and/or modulate the effect of AA on FSI) cohabitation status, and partnership satisfaction, and the covariate age.

The study was approved by the State Medical Ethics Committee and by the University of Trier Ethics Committee. The study conformed to the Declaration of Helsinki principles. All subjects provided consent, and were informed of their ability to discontinue participation at any time. All data were coded by number for confidentiality and anonymity.

## Results

Plasma AA levels increased significantly [ $F(1,76) = 63.1$ ,  $p < .001$ ] for the AA but not the placebo group, with no sex differences. In ANOVA models, diary monthly (converted from 14 day diaries) intercourse days were significantly [ $F(1,65) = 4.3$ ,  $p = .04$ ] greater in the AA (means: 8.4 vs. 5.0) than placebo group. Women differentially benefited ( $F = 4.7$ ,  $p = .03$ ; means: 10.3 female AA > 3.7 female placebo, 6.3 male placebo, 5.9 male AA), and Figure 1 displays the medication group by cohabitation status interaction [ $F(1,65) = 10.8$ ,  $p = .002$ ] in which noncohabitants in the AA group had greater FSI than did the other three groups. Noncohabitants reporting less than maximum partnership satisfaction had greater FSI than others [ $F(1,65) = 4.2$ ,  $p = .04$ ; means: 10.3 noncohabitant low satisfaction > 4.6-6.2 other combinations]. A zero FSI during the trial was reported by 35.9% of the subjects in the placebo group and 26.2% in the verum group. There was no significant effect of AA on either noncoital partner sex or masturbation (details in Table 1), baseline plasma AA levels were not related to FSI, and the FSI results were not confounded by social desirability response bias. Duration of cohabitation was inversely related to FSI ( $r = -.35$ ,  $p = .01$ ,  $n = 54$ ).

Mean baseline Beck Depression Inventory score was 4.8 (range 0-17). Decreases in depression scores were found in the AA but not placebo group [ $F(1,65) = 4.8$ ,  $p = .03$ ; age-adjusted mean point change:  $-1.56$  AA

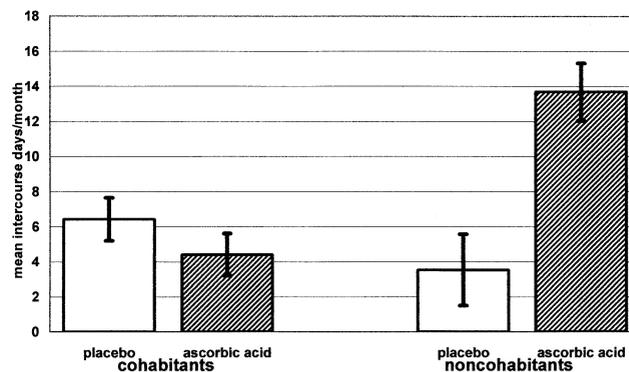


Figure 1. Mean (with SE bars) frequency of penile-vaginal intercourse (converted to days per month from 14 day diaries) as a function of medication group (ascorbic acid [shaded] or placebo [empty]) and cohabitation with a sexual partner.

versus  $-.16$  placebo], with no significant higher level interactions.

There were no differences between groups in the reported frequencies of adverse events (Brody et al, 2002).

## Discussion

As hypothesized, the trial demonstrated that AA supplementation increased FSI but not other sexual behavior (whether with a partner or alone). Once again, it is specifically penile-vaginal intercourse and not other sexual behavior that is associated with a more favorable index of health (in this case, nutritional status; Brody, 1997; Brody et al 2000). This consistent finding speaks to the unique nature of penile-vaginal intercourse, and the importance of not using vague or summary measures of sexual activity in research.

The differential effect for noncohabitants suggests that the mechanism is not a peripheral one (which would be expected to manifest itself more clearly in persons who have potentially daily access to their sexual partner; Brody 1997, Brody et al 2000), but a central one which motivates the person to venture forth to have intercourse. It may be speculated that living separately from one's partner might be a marker for different receptor activity, such that the

Table 1. Mean Frequency of Masturbation and Noncoital Partner Sex and Percentage of Subjects Reporting a Zero Value, As a Function of Medication Group

	M	SE	Zero value (%)
Noncoital partner sex: Placebo group	3.3	.9	56.4
Noncoital partner sex: Verum group	3.6	.7	59.4
Masturbation: Placebo group	2.3	1.0	48.7
Masturbation: Verum group	2.9	.8	54.8

All comparisons are nonsignificant. Mean and standard error (SE) reflect conversion to days per month from 14-day diaries.

noncohabitants experience more effective dopaminergic (or other relevant neurotransmitter) activation from high-dose AA supplementation because of different receptor activity. Indirect support for receptor activity being related to life style comes from the finding that sensation seeking (which, like novelty seeking, has been shown to be related to the dopamine D4 receptor (DRD4) exon III polymorphism; Strobel et al 1999) in married women is associated with greater sexual desire and sexual arousability, but lesser marital satisfaction (Apt and Hurlbert 1992).

The medication group by sex interaction indicated that women were most responsive to AA supplementation. Although it is possible that women differentially benefited as a result of a sex difference in receptor sensitivity (for example, although both sexes exhibit a postorgasmic rise in prolactin [Exton et al 2001], males generally have a substantially longer refractory period than do women), it is probable that sociobiological factors are operative: young women experiencing an increase in sexual motivation may more rapidly fulfill their desires than may young men (Brody, 1997).

The significant interaction of cohabitation status by partnership satisfaction (unhypothesized) favoring noncohabitants reporting less than maximal partnership satisfaction is open to several interpretations: they may be taking action to improve the relationship by increasing FSI, they may have found a new or additional sex partner with whom to augment their FSI, or persons who are more critical (and therefore less superficial) of interpersonal process might also have a greater FSI.

The baseline mean depression scores were in the normal range, and the magnitude of improvement modest. Given that there was only a main effect (and no interaction by cohabitation status or sex), **it does not appear that the depression scores improved as a result of improved FSI.** Rather, a mild antidepressant effect of AA might have benefited a broader range of subjects than just those with a readiness to take action to improve their FSI. Future research might examine to what degree AA reduces depressive affect through a direct catecholaminergic neuromodulatory mechanism (as suggested by the animal research noted in the Introduction) and by lessening the impact of daily stressors (Brody et al 2002).

Although many would consider three grams of AA to be a high dose, it is low on a milligram per kilogram basis when compared to doses used in animal studies. Dose-dependency has been observed in animal research, as have AA effects on other transmitters (notably glutamate; Rebec and Pierce 1994). It is not known whether the obtained benefits would be achieved with a formulation other than the sustained-release preparation used in the instant trial. Future studies might examine the longer term effects of such supplementation, include additional subpopulations

of interest (such as persons with hypoactive sexual desire, or mildly depressed persons).

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