Gender Differences in the Subjective Effects of Cocaine

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Background

The abuse of psychostimulants is an ever-growing problem, as stimulant use has become increasingly prevalent in recreational situations, academic settings, and the work place. Illegal cocaine use, specifically, has continued to increase, in part because users are under the misconception that it is a harmless and nonaddictive stimulant (Iversen, Iversen, Bloom, & Roth, 2009).

Cocaine hydrochloride can be administered intravenously or insufflated and, in the free base form of "crack cocaine," can be smoked. Cocaine hydrochloride produces intoxication in 2 to 3 minutes, while crack, due to its more rapid route of absorption, causes intoxicant effects within 10 seconds. Cocaine inhibits all three monoamine transporters—both catecholamine transporters and the serotonin transporter—increasing the extracellular concentrations of these neurotransmitters and causing stimulating and rewarding effects. Cocaine, like amphetamines, causes an increase in blood pressure and pulse rate in humans, in addition to pupil dilation, urine retention and occasionally increased respiratory rate (Iversen et al., 2009).

The effects of cocaine on mood and performance are what create such its strong dependence among users. In low doses in humans, it produces euphoria, exhilaration and less fatigue when working. As doses increase, the relaxed, alert feeling is replaced by the feeling "driven;" at higher doses, intense euphoria, often compared to an orgasm, is experienced (Iversen et al., 2009).

Research shows that males and females exhibit different responses to abusive drugs. The consensus is that this difference stems from gonadal hormone levels. In order for one to fully comprehend the effects of these hormone levels, however, background

information of the human menstrual cycle is necessary. Females have a 28-day long menstrual cycle that is characterized by two phases, one before and one after ovulation (which occurs around day 14). The first phase, the follicular phase, contains low progesterone levels and rising estradiol levels. Estradiol levels peak just before ovulation. In the second phase, the luteal phase, progesterone levels increase, and peak 3-8 days after ovulation before declining at the end of the cycle. Estradiol levels in this phase are similar to those in the early to mid follicular phase (Campbell & Reece, 2005).

Question of Interest

The literature shows that numerous studies have been done on sex differences in response to drugs of abuse, specifically psychostimulants. Regarding cocaine, significant differences have been found in the initiation of drug use, the development of drug dependence, and treatment-seeking behaviors in men and women. This review strives to summarize these gender-specific differences in cocaine use—including reasons for using, subjective responses while on the drug and the subsequent dependence and treatment—and the role that hormone levels play in this discrepancy. Substantially more studies regarding drug use as a function of sex have been done on rodents. However, differences between the rodent's 4-day estrous cycle and the human menstrual cycle make it difficult to generalize these results to human populations. It is crucial to examine how much research has been done specifically with male and female humans, taking into account the changing hormone levels throughout the female menstrual cycle, in order to draw conclusions of these gender differences and see what more can be studied. This disparity,

and the reasons for it, is extremely important in administering sex-specific treatment in cocaine abuse.

Review of Literature

Gender Differences in Cocaine Effects

In a pilot study performed by Elman, Karlsgodt and Gastfriend (2001), researchers evaluated potential gender differences in cocaine craving among non–treatment-seeking users with cocaine dependence. Participants of this study were 10 female and 11 male individuals that were matched by demographic characteristics and severity of drug use. The study used a multidimensional questionnaire that examined different aspects of craving, including "current intensity, projected intensity, resistance to use cocaine, responsiveness to drug-related conditioned stimuli, and imagined likelihood of use if in a setting with access to drugs." Additionally, the Hamilton Rating Scale for Depression and the Addiction Severity Index were used.

Results suggest that gender potentially influences different aspects of cocaine craving. Female subjects had higher total craving scores, with tests showing "more present desire to use cocaine and responsivity to drug-conditioned stimuli" (Elman et al., 2001). Additionally, females showed lower scores on the desire not to use cocaine. In exploratory analyses, the study found greater depressive symptomatology and severity of family/social problems in females than males.

While this research contributes to our understanding of gender influences on craving, the study had several limitations. The small sample size may not be reflective of a larger population. The study also relied solely on self-reports of subjects. It is possible

that the "craving finding may reflect nonspecific gender effects" given the confounding differences found in the categories of depressive symptomatology and severity of family problems (Elman et al., 2001). Also, while the study discusses the possible role that estrogen plays in cocaine cravings, it did not include estrogen indices to determine phases of menstrual cycles.

Another study, by Najavits and Lester (2008), further explored the gender differences in depressive symptomatolgy and social problems in cocaine-dependent individuals. Participants of this study were 2376 outpatients—1583 males and 783 females—with cocaine dependence on entry into the National Institute of Drug Abuse Collaborative Cocaine Treatment Study, a large randomized clinical trial that explored the efficacy of four different psychological treatments for cocaine dependence. This study compared cocaine-dependent men and women on psychopathology, substance use and treatment variables, such as utilization and attitudes. The findings showed that women had less severe lifetime substance use problems than men (fewer years of use of alcohol, marijuana and hallucinogens), perhaps because of their significantly younger age. However, women and men were comparable in both the number of years and severity of their cocaine use. Researchers found that women had higher patterns of psychiatric, medical, social, family and employment problems than men, results consistent with those of Elman et al. (2001). Women had more physical/sexual traumas, "three times the rate of PTSD and twice the rate of anxiety disorder compared to men" (Najavits and Lester, 2008). Also, the study found that women held more positive attitudes about treatment and had higher expectations for treatment success.

Results of this study led to the conclusion that women, more so than men, may be willing to engage in treatment, but have more complicated psychosocial and/or economic concerns beyond their addiction. However, limitations of the study must be taken into account. The inclusion/exclusion criteria may have biased the study toward a less severe sample of addicts than might be found in the general population. Also, while the sample size was large, as opposed to the small sample in the study by Elman et al. (2001), there were not equal numbers of men and women (there were substantially more men), which could lead to skewed results (Najavits and Lester, 2008). Furthermore, data was collected in the 1990s, and patterns of cocaine use may have changed since then.

A study performed by van der Plas, Crone, van den Wildenberg, Tranel and Bechara (2009) examined the effect of sex on executive function deficits associated with cocaine dependence. The study included 27 cocaine-dependent individuals (14 women and 13 men) that were compared with sex-matched non-dependent counterparts on "decision making, as measured by the Iowa Gambling Task, working memory, cognitive flexibility and response inhibition." All cocaine-dependent individuals were "impaired on complex decision-making, working memory, and cognitive flexibility, but not on response inhibition" (van der Plas et al., 2009). However, decision-making was significantly more impaired in women addicted to cocaine than in men addicted to cocaine.

A major limitation of this study was the discrepancy in age and education between healthy participants and substance-dependent individuals. However, after taking these differences into account using ANCOVA, they observed that while age and education did account for some of the variance, "most group differences were still

significant after age and education effects were partialed out" (van der Plas et al., 2009). Also, the study mentions that they did not address the question whether certain people have a biological predisposition (for example, impulsivity) that may be a potential risk factor for the commencement of substance use. This may be something to address in future studies involving cocaine-dependent individuals.

One study, performed by Adinoff, Williams, Best, Harris, Chandlers and Devous (2006), strove to examine hypoperfusion of the orbitofrontal cortex (OFC) as an explanation for the different clinical trajectories of cocaine-dependent men and women. In this study, 28 cocaine-dependent men, 10 cocaine-dependent women, 18 healthy male controls, and 19 healthy female controls were studied. The study examined regional cerebral blood flow (rCBF) between abstinent cocaine-dependent men and women and sex-matched healthy comparisons. The cocaine-dependent subjects were abstinent from cocaine for 11 to 28 days. rCBF was measured with single photon emission computed tomography following the administration of a placebo saline infusion. Results showed that rCBF was reduced in the bilateral OFC in cocaine dependent-men, but not in cocaine-dependent women, and that rCBF was lower in the medial OFC in cocaine-dependent women, but not in cocaine-dependent men. They proposed that the decrease in the perfusion of the medial OFC may have caused female cocaine-dependent subjects to be less responsive to the rewarding effects of a stimulus, thus producing a decreased response to the rewarding effects of cocaine. The decrease in perfusion in the lateral OFC of dependent males may attenuate their ability to change their behaviors in response to changing contingencies (they would not appropriately respond to the undesirable outcomes of stimuli that are previously associated with reward).

It is important to note that there was an evaluation of relatively few addicted female subjects relative to controls. Also, patient populations meeting the rigorous inclusion/exclusion criteria of neuroimaging studies may not appropriately reflect the greater populations (Adinoff et al., 2006).

The study reveals the interesting finding that male subjects demonstrate greater neurobiological disruption relative to addicted female subjects. The authors note that despite these results, clinical studies imply that women experience a more severe course of substance dependence than men. They propose that it is possible that medial OFC perfusion deficits may result in heightened psychopathology relative to lateral OFC deficits, thus worsening the course of cocaine addiction dependent women relative to men (Adinoff et al., 2006).

Sex Differences in Cocaine Effects With Respect to Menstrual Cycle Fluctuations

Perhaps the results in the study by Adinoff et al. (2006) showing that male subjects experience greater neurobiological disruption correlate to results found in a study performed by Sofuoglu, Dudish-Poulsen, Nelson, Pentel and Hatsukami (1999) that showed that woman may be less sensitive than men in perceiving the physiological changes induced by cocaine. After single deliveries of smoked cocaine (0.4 mg/kg), men rated heart racing/pounding and paranoid/suspicious higher than females. After repeated deliveries of the same dose, men had higher ratings on "feel high, heart racing/pounding, and feel stimulated." Interestingly, these different perceptions of heart rate occurred despite similar heart rate changes in both sexes, emphasizing the notion that women are simply less sensitive to cocaine effects.

This study also examined menstrual cycle effects in response to cocaine administration. Women in the luteal phase showed decreased responses to some of the subjective effects—for example, they reported lower ratings for a measure of "feel high"—of a single delivery of cocaine compared with both women in the follicular phase of their menstrual cycle and men. These results imply that there are significant menstrual phase differences in the subjective effects of cocaine (Sofuoglu et al., 1999).

It should be noted that this research was not primarily done to investigate sex differences in cocaine response. Data acquired "from participants who participated in two different protocols were used for this report" (Sofuoglu et al., 1999). Also, the small number of participants studied for the menstrual phase effect minimized the power to identify differences.

Other studies investigated the responses to doses of cocaine in women during the two different phases of the menstrual cycle. A study done by Evans, Haney and Foltin (2002) examined this in 11 non-treatment seeking female cocaine smokers. Participants were administered smoked cocaine in the follicular and mid-luteal phases of the menstrual cycle (the order of cocaine doses was randomized). There were four cocaine administration sessions during each phase. In "each session, participants could smoke up to six doses of cocaine (either 0, 6, 12, or 25 mg cocaine base, depending on the session) at 14-min intervals" (Evans et al., 2002).

Results showed that the number of cocaine doses administered did not differ between the two phases. However, following cocaine administration, numerous ratings such as good drug effect, high, drug quality and stimulated, as well as heart rate, were elevated more during the follicular phase than the luteal phase. This enhanced subjective

response to cocaine during the follicular phase confirms other studies that have been conducted in humans, such as the study by Sofuoglu et al. (1999).

An interesting finding in this study is that women "reported being more on edge/miserable, depressed, and irritable, and had greater cravings for cocaine during the luteal phase than the follicular phase" (Evans et al., 2002). Dysphoric mood during the luteal phase was improved after cocaine administration. These results suggest that a mild level of dysphoric mood is apparent during the luteal phase among women without significant premenstrual symptoms, and that cocaine can improve these symptoms.

The study concluded that both the cardiovascular and subjective effects of repeated doses of smoked cocaine fluctuate as a function of menstrual cycle phase and cocaine dose. A limitation of this study is that the smoking procedure was not standardized in regard to controlling puff and inhalation duration. Therefore, it is possible that "similar cocaine plasma levels were acquired across the phases of the menstrual cycle due to women titrating the smoked cocaine" (Evans et al., 2002). Furthermore, only a small number of blood samples were collected to determine cocaine plasma levels. Also, since women were allowed to decline cocaine doses, not all doses were administered.

One recent study done by Collins, Evans, Foltin and Haney (2007) on the of sex and menstrual cycle impact on subjective intranasal cocaine effects found results that differ from these other studies. In this study, 8 female cocaine users were admitted to the hospital once during the luteal phase and once during the follicular phase of their menstrual cycle, and during each admission, an intranasal cocaine dose–response curve was determined during four laboratory sessions. Cocaine induced "similar dose-related

increases in ratings of ‘‘positive’’ subjective effects, cardiovascular effects and cocaine plasma levels in women in both menstrual cycle phases” (Collins et al., 2007). This data was compared to published data (Foltin & Haney, 2004) collected in men using an identical procedure in order to examine sex differences in the effects of intranasal cocaine. The study concluded that cocaine produced similar dose-related increases in ratings of positive subjective effects, cardiovascular effects and cocaine plasma levels in men and women. This differs from other studies that examine intravenous or smoked cocaine as routes of administration, for these results show no sex differences or impact of the menstrual cycle on the cardiovascular or subjective response to intranasal cocaine. This suggests that the route of administrations may inform the influence of sex and menstrual cycle on cocaine’s effects (Collins et al., 2007).

Administration of Exogenous Progesterone/Contraceptives

In order to expand on the findings that subjective effects are higher in the follicular phase (when progesterone levels are low) than in the luteal phase (when progesterone levels are high), studies were performed to examine the impact of exogenous progesterone on cocaine effects. Sofuoglu, Mitchell and Kosten (2004) examined the effects of progesterone treatment on cocaine responses in 6 male and 4 female cocaine users. Study participants participated in two experimental sessions. They were given either two oral doses of 200 mg progesterone or placebo before each session. Two hours after the second dose of medication treatment, the participants received a 0.3 mg/kg intravenous dose of cocaine. This began the self-administration period, in which five optional doses of cocaine were offered.

Results showed that progesterone treatment minimized the cocaine-induced diastolic blood pressure increases, and did not affect systolic blood pressure and heart rate increases. Furthermore, progesterone treatment lessened the subjective ratings of "high" and "feel the effect of last dose" in response to cocaine. However, progesterone treatment had no affect self-administration behavior. Based on these results, researchers in this study concluded that progesterone reduces some of the physiological and subjective effects of cocaine in both male and female participants. The study did not find any differences between males and females in subjective response (Sofuoglu et al., 2004).

The study did not examine the dose–effect relationship for progesterone effects on cocaine responses. Also, the duration of treatment was brief, with only two doses of progesterone treatment. It is important to note that most of the participants were mainly crack cocaine users and had no prior experience with intravenous cocaine, so it is possible that crack cocaine users may respond differently than intravenous cocaine users (Sofuoglu et al., 2004). Additionally, the sample was incredibly small, and may not be reflective of the more general population.

These limitations may account for the differences in results between this study and a study performed by Evans and Foltin (2006), in which researchers aimed to determine if exogenously administered progesterone during the follicular phase in females would lessen the response to cocaine compared to the normal follicular phase. This would make the response to cocaine similar to the luteal phase (this expanded upon their previous study (2002) that showed that positive subjective effects of cocaine were higher during the follicular phase). Participants were 11 female and 10 male non-treatment-seeking cocaine smokers. The "females had three inpatient stays: one during a

normal follicular phase, one during a normal luteal phase, and one during a follicular phase when exogenous progesterone was administered" (Evans & Fotlin 2006). Males had two inpatient stays, one in which exogenous progesterone was administered and the second when placebo was administered. As in the previous study, there were four cocaine administration sessions (this time, during inpatient stay) and, during each session, participants could smoke up to six doses of cocaine (either 0, 6, 12, or 25 mg cocaine base, depending on the session) at 14-min intervals. Results were consistent with their previous study and showed that cocaine administration produced dose-related increases in several positive subjective ratings, including the good drug effect cluster, the drug quality cluster, and 'willing to pay' item in both males and females. In females, these ratings were significantly higher in the normal follicular phase compared to the luteal phase.

Furthermore, administration of oral micronized progesterone produced substantial decreases in the positive subjective effects of cocaine in females, but not in males (even though they were administered the same doses of progesterone that resulted in similar progesterone plasma levels). Additionally, oral micronized progesterone decreased the cocaine-induced increases in diastolic pressure and heart rate in both females and males. Thus, the study concluded that progesterone alters the response to cocaine in women and proposes that fluctuations in progesterone levels explain some of the sex differences seen in humans (Evans & Fotlin 2006).

In this study relatively low cocaine doses were tested, and this could not adequately reflect cocaine's effect. Also, participants were administered cocaine, as opposed to being allowed to self-administer, so that they could adequately address

whether or not progesterone would attenuate the subjective effects of cocaine (this would have been confounded if a self-administration procedure had been used).

These results and the findings by Sofuoglu et al. (2004) both showed that progesterone attenuated the subjective effects of cocaine, though the magnitude of attenuation was higher in the Evans and Foltin (2006) study, perhaps because of the increased number of cocaine administrations or the shorter interval between doses. Also, the study by Evans and Foltin (2006) observed significant sex differences regarding progesterone's ability to diminish the subjective effects of cocaine, whereas the study by Sofuoglu et al. (2004) did not find any differences between males and females in subjective response (despite the fact that a higher dose of progesterone was administered that led to higher progesterone levels in that study).

Differences could be attributed to the fact that all participants smoked cocaine in both studies, but in the Sofuoglu et al. (2004) study cocaine was given intravenously. Also, Sofuoglu et al. (2004) used a self-administration procedure and, under those conditions, individuals only self-administered approximately half of the possible five doses of cocaine. Therefore less cocaine was administered over the session compared to the Evans and Foltin (2006) study that administered six 25 mg smoked cocaine doses. Also, as mentioned earlier, the study by Sofuoglu et al (2004) had a smaller sample size (6 males and 4 females) compared to the study by Evans and Foltin (2006) (10 males and 11 females). Also Evans and Foltin (2006) tested multiple doses, while Sofuoglu et al. (2004) tested only one (Evans & Fotlin, 2006).

An interesting study done by Kouri, Lundahl, Boderm, McNeil and Lukas (2002) contributed to the research on the relationship between gonadal hormones and cocaine by

investigating whether oral contraceptives (OCs) mediate the effects of cocaine. Participants consisted of 7 female volunteers who were occasional users of cocaine and were taking triphasic OCs. The study consisted of 4 visits; participants were studied twice during days 6-10 of the menstrual cycle (time of the follicular phase) and twice during days 21-28 of the cycle (time of the luteal phase). They were given either an acute dose of intranasal cocaine or placebo. Results showed no differences in cocaine-induced subjective effects or plasma cocaine and metabolite levels in the two phases.

These results are important because they display that OCs do not pose added risk of cocaine-induced cardiovascular effects. It was concluded that the exogenous administration of estrogen and progesterone at the dose levels in OCs do not change the subjective responses to intranasal cocaine. Despite these findings, it should be noted that all of the women in the study were taking combination OCs, containing both estrogen and progesterone. This might explain why cardiovascular and subjective effects of cocaine were not altered by the OCs, since the possible opposite effects of the two hormones may negate any impact on the response profile (Kouri et al., 2002). The nature of the relationship between progesterone and cocaine response would be clearer if the study investigated the effects of cocaine in women taking progesterone-only contraceptives. Also, this was performed with the administration of intranasal doses of cocaine, as in the study by Collins et al. (2007), which showed no difference in subjective effects on account of menstrual phase. Perhaps studies should be done with OCs and intravenous or smoked cocaine as well, to see if the results differ.

Summary and Conclusion

The majority of the literature shows that there are gender differences in the subjective responses to cocaine. Studies found that cocaine-dependent females have higher total craving scores compared to men, had more depressive symptomatology and higher patterns of social and family problems than men, and were more willing to engage in treatment (Elman et al., 2001, Najavitis & Lester, 2008). This suggests that cocaine use and treatment-seeking behavior may depend on various complicated psychosocial concerns of women. Furthermore, executive function deficits associated with cocaine dependence also appear to be a function of the sex of the user, with cocaine-addicted women having a significantly more impaired decision making ability than cocaine-addicted men (van der Plas et al., 2009).

This disparity between cocaine's effects on different genders tends to be a function of the phase of the menstrual phase and route of administration. Research suggests that women are less sensitive to the subjective effects of cocaine, despite higher cravings and desires to use (Sofuoglu et al., 1999). The decreased responses are most pronounced during the luteal phase of the menstrual cycle, when progesterone levels are high (Sofuoglu et al., 1999, Evans et al., 2002, 2006). However, administration of intranasal cocaine produced comparable increased positive subjective effects in men and women, and in women in both menstrual phases, suggesting that route of administration impacts the influence of menstrual cycle phases or sex on subjective effects of cocaine (Collins et al., 2007). Future studies wishing to examine specific gender differences in cocaine's effects should examine these differences when women are in the luteal phase of

the menstrual cycle (when disparities are the greatest) and when intravenous or smoked cocaine is administered.

A few studies revealed that oral micronized progesterone, at doses that result in similar progesterone levels as the midluteal phase, produces decreases in the subjective response to cocaine. However, it is still unclear whether these effects of progesterone are sex specific, because one study, by Sofuoglu et al. (2004), reported no sex differences and another study, by Evans and Foltin (2006), reported effects in women but not men. More research needs to be done on this sex difference in order for results to be conclusive. Additionally, future studies should examine how estradiol alone affects the response to cocaine in humans. While one study found that oral contraceptives do not alter the effects of cocaine, these contraceptives contained a combination of estrogen and progesterone (Kouri et al., 2002). Future research should examine contraceptives only containing one hormone.

The use of small sample sizes is a major limitation in many of the studies described. Furthermore, in some cases data were combined from previous data sets to address the role of sex differences. In light of the existing research, future clinical trials for stimulant abuse should include larger samples of both men and women and should track the menstrual cycle or hormonal status of women to determine if these hormonal fluctuations affect drug use and treatment outcome. More studies should utilize brain-imaging techniques (like the research done by Adinoff et al., 2006) in order to examine specific regions and receptors involved in the various aspects of cocaine use and dependence. This may help to fully understand these menstrual cycle fluctuations and

gender differences regarding cocaine's effect. Research on this topic is extremely important because it is potentially helpful in providing treatment for cocaine dependence.

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