Indian J. Psychiat., 1996, 38 (3), 182 - 189

EFFECT OF FLUOXETINE AND BROMOCRIPTINE ON CRAVING OCCURRING DURING WITHDRAWAL FROM ALCOHOL

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SUMMARY

Craving is an integral element in the understanding of alcohol dependence. Recent human and animal research implicates the serotonergic and dopaminergic systems in the mediation of excessive alcohol consumption. In this study, a cue-based approach was used to qualify and quantify craving occurring during acute withdrawal from alcohol. Fifty alcoholics were given either placebo, bromocriptine or fluoxetine in a randomised double-blind fashion and craving was sequentially measured over the next 15 days. Both fluoxetine and bromocriptine significantly attenuated total craving scores without similarly affecting withdrawal symptoms. The results suggest the importance of neurotransmitters in mediating craving. The significance of these data in the light of various behavioural and neurochemical models have been discussed.

INTRODUCTION

Most attempts at identifying common defining feature of alcoholism have invoked the concept of 'craving' as a key explanatory parameter. Inspite of the popularity of the term, perhaps due to its intuitive appeal, there is no consensual definition as indeed for'urges' and 'wanting' which have been used interchangeably (Kozlowski & Wilkinson, 1987). Current consensus regards craving as a non-specific vector connected to the subjective desire to take drugs (Tiffany, 1990). It does not by itself define the various states that can potentially activate the desire.

In the search for the determinants of craving, the cue reactivity paradigm has been extensively used. This approach has demonstrated that for a group of alcoholics, various internal and external drug-related cues induce autonomic arousal (Glautier & Drummond, 1994). However, the subjective report of craving is a less consistent finding thus casting doubt on the proposed linear relationship between arousal, craving and drug intake. Conditioning theories have traditionally been used to explain these results. Briefly, negative reinforcement (withdrawal-based) models view craving as a desire of relief from distressing overt or covert withdrawal symptoms (Koob and Bloom, 1988). Postive reinforcement (euphoria-based) theories perceive craving as the desire for the 'high' induced by alcohol (Stewart et al, 1984). Inspite of the limitations (Drummond et al, 1990), these theories have established a framework for the understanding and experimental induction of craving.

A biological basis for craving has been proposed from the observation that certain laboratory animals voluntarily and selectively consume alcohol in a manner similar to that of humans (Murphy et al, 1982). To explain this, all psychoactive drugs, including alcohol, are proposed to act on 'brain-reward systems' (Wise & Bozarth, 1987) altering them in crucial ways to maintain drug use. The ventral tegmental area (VTA) in the ventral midbrain and its projection to the nucleus accumbens (NA) have been identified as the crucial brain area in reward mediation (Robinson & Berridge, 1993). By virtue of being the major neurotransmitter input, the mesocorticolimbic dopamine (DA) system has been implicated in drug reinforcement (Wise and Romprei, 1989) since all abusable drugs share the common property of selectively enhancing DA release in the VTA-NA areas. Alcohol has also been found to increase DA release in these regions following local or systemic application

(Signs et al, 1992). In addition, DA agonists like bromocriptine have been found to attenuate drinking in animals and reduce craving in human subjects (Dongier et al, 1991) suggesting a strong dopaminergic modulation of the need to drink.

The serotonergic (5HT) system has also been implicated in the voluntary consumption of alcohol (Lemarquand et al, 1994). Various pharmacological manipulations increasing brain 5HT have been found to reduce consumption in animal models (Lu et al, 1993). Similarly, the use of specific serotonergic reuptake inhibitors (SSRI) like fluoxetine and zimeldine (Amit et al, 1991) have been observed to reduce craving and subesequent alohol consumption in humans. All this suggests that hypofunctioning of the 5HT system may be relevant to the experience of craving.

The current study, based on the above findings, seeks to examine the effects of DA and 5HT function enhancement during acute withdrawal from alcohol. The hypothesis made was that augmentation of DA and 5HT by appropriate pharamacological tools would reduce craving.

METHOD

Subjects for the study were chosen from males presenting to the outpatient facilities of NIMHANS, Bangalore. After screening, prospective subjects were referred to assess eligibility of participation.

The following inclusion criteria were used to generate a relatively homogeneous population :

1.After a detailed clinical interview with the subject and a key relative, all patients had to unambiguously fulfill diagnostic criteria for alcohol - dependence , as in the DSM - IIIR (APA, 1987).

2.Subjects had to be in the age group of 18 - 45 Years.

3. Only subjects presenting with simple withdrawal were chosen. To facilitate measurement and ensure drug compliance, subjects had to agree to be inpatients during the study period.

4. The manifestations of withdrawal from alchohol are 'time limited'. To acheive uniformity of measurement, all subjects had their last drink within 24 hours of participation in this study.

5. Presence of cognitive deficits was measured by the MMSE (McHugh & Folstein, 1978). Only subjects scoring above the suggested cut - off were selcted.

6. Presence of concurrent depression and anxiety disorders was specifically sought for in the clinical interview. Only subjects without an obvious co - morbid depression anxiety were chosen.

7. Only subjects without serious alcohol - induced medical complications, as assessed by a detailed clinical examination and relevant investigations, were included in the trial.

Information regarding current age, age of onset , duration of drinking and the duration of dependence was also collected since each of these could affect the severity of the withdrawal reaction. The rationale of the study was also explained to the subjects and informed consent for participation obtained.

Measurement of craving

In view of the many limitations inherent in the measurement of craving, 33 alcoholics were asked about common internal and external correlates of the perceived subjective desire to drink during the experience of withdrawal. After content - analysis, the 10 most common responses were identified. These included various internal subjective states as well as cues related to the environment. These items together formed the **Scale for assessment of alcohol withdrawal - related craving** (see Appendix) . To quantify the severity of each item , a ten - point subject - rated visual analogue scale was used.

Measurement of withdrawal

The phenomenology and severity of withdrawal was assessed by the **Scale for alcohol withdrawal.** This is a 22 - item instrument , and each item is graded on a 0-3 scale of severity.

In keeping with the hypothesis, fluoxetine and bromocriptine were chosen to explore the

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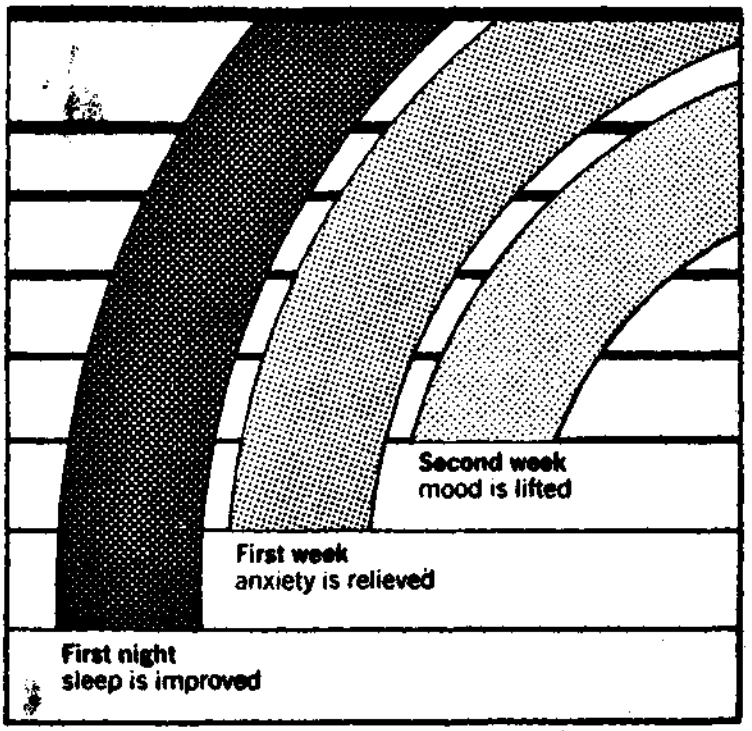

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effects of 5HT and DA system perturbation on experienced craving.

STUDY DESIGN

Subjects were randomly allocated to any one of three groups receiving either fluoxetine, bromocriptine or placebo. Fluoxetine was used at a dose of 40 mg/day, while 5 mg of bromocriptine was administered and glucose powder was the placebo. All groups were given the drugs thrice a day in identical capsules. The active drugs were adminstered in the morning and afternoon with the night dose being a placebo capsule. The allocation of patients and subsequent drug administration was done in a double blind fashion.

On Day 0, both withdrawal and craving - scale items were administered and rated. After this , drugs were started and continued for the next 15 days. Scale items were assessed each day and those found positive were rated for severity.

STATISTICAL TECHNIQUES

1. Descriptive statistical measures like mean and SD were used to describe pre - treatment sample characteristics.

2. Two-way ANOVA (days x drugs) were performed for each item and for the total craving scores between the three groups.

3. The craving - scale items were subjected to principal component analysis with varimax rotation to generate higher - order factors.

4. Two - way ANOVA was also performed for total withdrawal - scores between the three groups.

5. Post - hoc Fisher's 't' - test of significance was carried out for each craving - scale item.

6. Correlation analysis was done between craving and withdrawal items on Day 0.

RESULTS

After initial screening , 50 subjects entered the trial. On opening the blind the group receiving the placebo had 18 subjects, whereas the groups receiving fluoxetine and bromocriptine had 16 subjects each.

Table - 1
Sample description with selected pretreatment variables

Variable	Age	Onset	Duration	Dependence
Bromocriptine				
Sample size	16	16	16	16
Mean	38	29.43	9	3.64
SD	9.42	8.52	5.08	1.15
Placebo				
Sample size	18	18	18	18
Mean	40.42	29	10.43	4.95
SD	8.05	5.37	5.31	2.89
Fluoxetine				
Sample size	16	16	16	16
Mean	38.52	28.63	9.72	4.61
SD	8.61	8.06	4.95	2.22
F Value	0.38	0.09	0.31	1.36
P value *	0.68	0.97	0.73	0.26

* Significance at $P < 0.05$ Degrees of freedom : 2, 49.

Table 1 displays the pretreatment values of variables like age , age of onset of drinking , duration of alcohol use and duration of dependence. There were no significant differences on any of these variables across the guoups.

The principal component analysis of the craving - scale items (Table 2) led to the emergence of three meaningful principal components which together explained 61.2 % of the variance. These were labelled as (1) restoration of bodily comfort, (2) alleviation of negative mood state and (3) responsivity to external cues.

Table II
Principal components analysis of craving-scale items with varimax rotation.

Item	Evals	PC 1: Weights	PC 2: Weights	PC 3: Weights
1. Morning	38.82	0.39	0.16	0.33
2. Thirst	13.32	0.31	0.08	0.08
3. Fatigue	10.71	0.35	0.10	0.27
4. Irritability	9.38	0.17	0.61	0.27
5. Anxiolysis	7.86	0.39	0.61	0.27
6. Insomnia	6.75	0.24	0.16	0.26
7. Wine store	4.76	0.18	0.26	0.32
8. Tremors	3.29	0.37	0.22	0.05
9. Smoking	2.83	0.37	0.25	0.38
10. Food	2.24	0.21	0.02	0.65

The three principal components that emerged were:

1. Restoration of bodily comfort
2. Alleviation of negative mood state
3. Responsiveness to external cues

Table III
Two-way ANOVA for individual craving-scale items

Item	Drug		Days		Interaction	
	f	p*	f	p*	f	p*
1. Morning	115.83	0.001	206.87	0.001	7.28	0.001
2. Thirst	18.93	0.001	51.50	0.001	1.73	0.009
3. Fatigue	80.33	0.001	180.59	0.001	6.07	0.001
4. Irritability	5.35	0.005	22.46	0.001	1.40	0.076
5. Anxiolysis	102.58	0.001	157.72	0.001	6.16	0.001
6. Insomnia	91.76	0.001	107.39	0.001	6.30	0.001
7. Wine store	5.87	0.003	53.89	0.001	2.00	0.001
8. Tremors	104.55	0.001	235.76	0.001	5.75	0.001
9. Smoking	40.97	0.001	36.82	0.001	2.69	0.001
10. Food	3.36	0.035	35.86	0.001	0.67	0.910

* Significance at P < 0.001 Degrees of freedom: 2, 49

The two- way ANOVA scores for individual craving - scale items are displayed in **Table 3** .The items showing statistically significant day x drug interactions tapped craving related to early morning hangovers, fatigue, anxiolysis, insomnia, tremors and in respones to pleasurable external cues like preferred wine store and smoking.

The total craving - scores between the groups are shown in Figure 1. Figure 2. graphically depicts total scores for the withdrawal items.

FIGURE I: TOTAL CRAVING SCORES

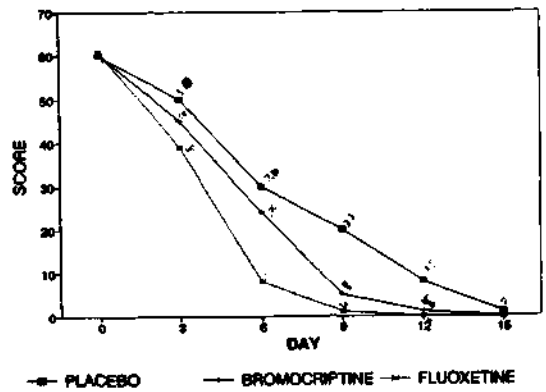
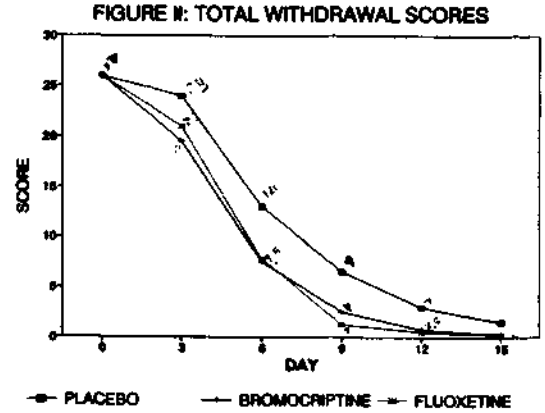


FIGURE II: TOTAL WITHDRAWAL SCORES



The correlation analysis of craving - and withdrawal - scale items was performed for Day 0 to understand the extent of overlap of the constructs (data not shown, available on request). The only meaningful correlations occurred between irritability as a cue and withdrawal symptoms of insomnia, restless sleep, tremors and dehydration.

DISCUSSION

In this study, we chose to investigate craving occurring during withdrawal as it is consistent , vivid and therfore , more amenable to measurement. Secondly , the potential effects of drugs are expected to be more comprehensible since neurotansmitter changes during withdrawal have already been relatively well documented (Nutt and Glue, 1986).

There is a lack of consensus regarding which strategy best identifies craving. In view of this , a 'bottom - up' approach was chosen with alcoholics' self - reports forming the basis for the measurement of craving . This ensures that the dimensions of craving are tapped adequately as demonstrated by adequate face validity and sensitvity of the craving -scale items.

To generate higher - order factors which are closer to the psychological structure of craving, multivariate statistics like principal components analysis were used. To this end three clinically meaningful factors explaining 61.2% of the variance were generated. Factor 1 (restoration of physical comfort) and Factor 2 (alleviation of negative mood) could conceptually be collapsed into a single 'releif from distress' factor. Factor 3, however, was more closely linked to the positive expectancy effects of alcohol.

A large body work sees craving as arising predominantly from the substrate of withdrawal distress (Laberg & Ellertsen, 1987). Alcohol, by removing this distress, has been thought to have a negative reinforcing relationship with craving. In view of the current study being conducted during acute withdrawal, this negative reinforcement relationship was expectedly observed especially with cues tapping the physical symptoms of withdrawal.

Positive expectancy-related cues, as a determinant of craving occurring during a period of distress, is an interesting finding. It suggests that the desire for euphorogenic effects of alcohol are intermingled with, but independent of, the need to relieve distress. The opponent-process theory of alcohol use can explain this observation best (Donovon & Chaney, 1985). This theory suggests that drugs simultaneously elicit mutually inhibitory agonist and antagonist responses. Depending on the context, any one response could assume a greater, but not exclusive, role in determining further drinking. Since withdrawal-related craving was studied, it explains both why drug antagonistic (withdrawal) cues assume greater importance and how agonist (euphoric) responses could coexist.

It is noteworthy that a large part of the variance of the observed results remained unexplained. Conceivably, this could be a function of the study setting, quality of therapeutic alliance, sick-role expectations and personality variables. None of these have been adequately studied and remain an important area for further research.

The double-blind design of the study, use of a placebo group, clear specification of the dependent status, prevention of drop-outs and adequate compliance with experimental drugs are in keeping with the expected methodological standards (Moskowitz, 1983). In addition, the pre-treatment variables were homogeneously distributed across groups thus increasing the robustness of the findings.

The incorporation of the placebo group makes naturalistic observation of the patterns of withdrawal and craving possible. As seen in Diagrams 1 and 2, total scores decline in a fairly similar fashion. However, both active drugs affected craving and withdrawal differentially. Both bromocriptine and fluoxetine produce significantly greater detriment of craving scores as compared to the effects on withdrawal symptoms. Again, between drugs, unlike in withdrawal, fluoxetine produced greater effects between days 3 to 9 on total craving scores. This dissociation of drug effects on craving and withdrawal suggest that the neurobiological substrates of craving are distinct from those mediating withdrawal. Moreover, correlation analysis between craving- and withdrawal- scale items, done on Day O, do not show significant overlap, again suggesting their relative independence.

There is a large body of evidence linking 5HT dysfunction and alcohol consumption. Preclinical studies have mostly shown an inverse relationship betweenralcohol preference and 5HT levels have been demostrated in crucial brain areas like the VTA and NA in alcohol-preferring rats even before exposure to alcohol (Murphy et al, 1982). Interestingly, alcohol increases 5HT in these areas following both acute and chronic exposure, prompting the selfmedication hypothesis of alcohol use (Haleem 1990). Clinical extension of these results with various SSRIs which increase synaptic availabilityof 5HT are found to attenuate craving and alcohol consumption (Gill & Amit, 1989).

This study adds to the growing body of research linking 5HT and craving. It confirms that the postulated inverse relationship holds true even during withdrawal. During acute withdrawal, there is a fall in 5HT levels in the absence of alcohol (Yamamura et al, 1992). This is probably corrected by fluoxetine by producing a specific increase of 5HT in a non-selective manner. The rapid onset of action would suggest that these are independent of fluoxetine's anti-depressant effect. The significantly greater efficacy of fluoxetine would argue against the proposed indirect enhancement of DA in the brain-reward areas as being the primary mode of action (Blandina et al, 1989).

Specific 5HT enhancement thus emerges as the most probable mechanism of fluoxetine's ability to reduce craving. The next logical phase of research would be to identify which speicific 5HT receptor sybtypes mediate this effect. The 5HT3 receptor has emerged as a likely candidate in this regard (Grant & Barrett, 1991). Similarly, the demonstration that m-chlorophenyl papaverine (mCPP), a 5HT agonist with some spicificity for 5HT2a and 5HT2c receptors, could elicit and alcohol-like high in abstinent subjects is a direct demonstration of the link between 5HT and craving (Krystal et al, 1994). This approach would also clarify whether 5HT deficits in alcoholism are unique to the disorder or is a more general marker of psychopathology as has been suggested (Virkkunen et al, 1994).

The other hypothesis made was that bromocriptine by its specific D2 agonism would reduce craving. This has also been substantiated by the results of this study. Neuroleptic-induced dysphoria and related animal work have suggested that DA mediates hedonic properties of cues. This is acheived by attribution of positive salience thus making these cues more attractive and wanted (Robbins & Everitt, 1992). As an extesion of this, drugs are supposed to be reinforcing because of their property of increasing DA in brain-reward areas. During the process of withdrawal, there is a global reduction of DA (Kuriyama & Okhuma, 1991) probably producing distress and therefore craving. Accoriding to this hypodopaminergic theory of craving, bromocriptine probably produces its effects by substituting for the lowered DA.

Direct DA agonism, inspite of its strong theoretical link with drug use, was found to be less effective than fluoxetine at least initially. The reason for this remains unclear. It might be a consequence of the dose of bromocriptine used (5 mg/day) which would cause D2 autoreceptor stimulation, thus lessening the magnitude of postsynaptic agonistic effects (Fuxe et al, 1981).

In conclusion, this study measures craving in relation to withdrawal from alcohol and explores the effect fluoxetine and bromocriptine have on it. It also adds to the evidence linking craving and certain monoamine (DA and 5HT) levels. In addition to discussing the possible mechanisms underlying these findings, this work suggests new approaches for a more comprehensive understanding and probable therapeutic manipulation of the compelling experience of drug craving.

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APPENDIX

1. When you wake up in the morning with a hangover, do you feel like having a drink immediately ?

2. When you are feeling hot and thirsty, does the thought of having a drink come to mind ?

3. When you are tired and exhausted, do you want a drink to feel better ?

4. Whenever you are angry with somebody, do you have the urge to drink at once ?

5. When feeling tense and anxious, do you feel like having a drink?

6. When unable to sleep at night, do you have a strong wish to drink ?

7. When you see your usual wine store, do you feel attracted towards it for a quick drink ?

8. When your hands shake, does the thought of a drink come to mind ?

9. While smoking, do you also experience the desire to drink ?

10. Just before your favourite meal, do you get an urge to drink ?

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