

## Disulfiram-Ethanol Reaction

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### Abstract

**Objective:** To study the nature and severity of ethanol related disulfiram reaction

**Method:** Sixty seven male alcoholics otherwise healthy were randomly allocated into low and high dose Disulfiram group. Patients assigned to high dose group were given a cumulative dose of 5gms spread over 4 days. The low dose groups were given a cumulative dose of 2.5gms spread over 7 days. On fourth day in high and seventh day in low dose patients Ethanol challenge was carried out. Details of DER were recorded on a checklist. Severity of DER was measured on a self devised rating scale.

**Results:** Common DER manifestations were flushing, drowsiness, vomiting, fall in blood pressure and raise in pulse rate, in addition both group had some more additional symptoms. Majority of patients developed severe DER in both groups and most of them recovered in about 6 to 8 hrs. Severity of DER was independent of duration of alcohol use, dose of Disulfiram and BMI.

**Conclusion:** The nature and severity of Disulfiram Ethanol Reaction (DER) determines strength of negative reinforcement in deterrent therapy of alcohol dependence. Knowledge of nature of DER helps in following clinical progress of a patient, planning treatment of a patient ingesting alcohol while on Disulfiram and in determining maintenance dose.

**Key words:** Disulfiram ethanol reaction, Disulfiram Dosage.

### Introduction

Tetramethylthiuram disulfide is an antioxidant used in rubber industry. It was suggested as a potential cure for alcoholism as early as 1937 by Williams<sup>1</sup>. It was rediscovered as an alcohol deterrent in 1945 serendipitously by Hald and Jacobsen<sup>2</sup> when they ingested alcohol in a party during their involvement in experiments on human tolerance of it as an anti-helmenthic drug.

Consumption of alcohol while receiving Disulfiram results in an uncomfortable and unpleasant syndrome known as Disulfiram Ethanol Reaction (DER) or acetaldehydes. Demonstration of

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disulfiram ethanol reaction may be necessary as an educative measure to the patients and their family members. This will help in deterring patients experimenting with large quantity of alcohol while on the drug and ending up with serious consequences. It will also encourage family members to supervise maintenance treatment. Knowledge of nature of DER helps in monitoring clinical progress of a patient who has ingested alcohol while on Disulfiram and plan effective intervention. In addition it acts as a guide in determining maintenance dose of Disulfiram in a particular patient. The Severity of DER determines strength of negative reinforcement in deterrent therapy of Alcohol Dependence. Severity of DER may vary in an individual based on many internal and external factors. Two important external factors are dose of Disulfiram and quantity of alcohol consumed while on the drug.

Hence a study was conducted to evaluate the nature of DER after administration of low and high dose of Disulfiram with a fixed quantity of alcohol.

## Material and Methods

Sixty seven male alcoholics screened out of 150 patients were selected for the study from a Psychiatric service of a general hospital. The inclusion criteria were; patients aged between 18 to 50 years, cases qualifying for Alcohol dependence as per ICD-10<sup>3</sup>, normal general, systemic examination and base line investigations. The exclusion criteria were; patients on any other substance abuse except nicotine, cases with medical illness and psychosis. The selected patients were randomly allocated to low and high dose disulfiram group.

All patients were hospitalized along with a family member. Written informed consent was obtained. Detailed assessment of socio-demographic factors, alcohol use, problems due to alcohol, psychiatric symptoms, and other habits, past, family and personal history were obtained. Physical examination was carried out. Body mass index was calculated by using Quetelet's formula [(weight (Kg)/Height<sup>2</sup> (mt)]<sup>4</sup>. Socio-economic status was assessed using Prasad's classification<sup>5</sup>. Base line investigations were done.

After control of withdrawal symptoms patients were administered Disulfiram in following schedule; patients assigned to high dose group were given two tablets of 250 mg 3 times a day for 3 consecutive days and two tablets of 250 mg on fourth day morning. Patients assigned to low dose group were given one tablet of 250 mg for 3 consecutive days and one tablet twice a day for the next 3 days and one tablet of 250 mg on the seventh day morning. On fourth day in high and seventh day in low dose patients Ethanol challenge was carried out.

On the day of alcohol challenge blood pressure, pulse rate, respiratory rate and other symptoms present were recorded. Patients preferred brand of alcohol equivalent to 34.2gm of absolute alcohol diluted with water to three to four times its volume was given irrespective of disulfiram dose and BMI.

Signs and symptoms of Disulfiram Ethanol Reaction were recorded every 15 minutes during first hour and every 30 minutes later on a checklist till basal parameters returned to normal or patient

got stabilized. When systolic blood pressure dropped below 100 mm Hg and did not show raising trend within 15 to 30 minutes intravenous dextrose saline was infused. Intravenous hydrocortisone was given if BP did not show rising trend within 30 to 45 minutes of administration of dextrose saline depending on need. Injection mephentine was kept ready if there were to be cases in which blood pressure did not improve satisfactorily.

Severity of DER was measured using a self devised severity rating scale (appendix -2). The possible total score was 60. Score 30 and above was considered as severe and score below 30 was considered as not severe.

The details about socio-demographic characteristics, suitability of high dose of disulfiram to bring about DER in comparison to low dose of disulfiram and its relation to duration of dependence, quantity of alcohol consumption, body mass index (Park & Park 1989) of the patient, effect of dose of disulfiram on blood pressure, pulse and hematological parameters and the side effect profile has been communicated elsewhere<sup>6</sup>. The nature and severity of DER are being reported in this paper.

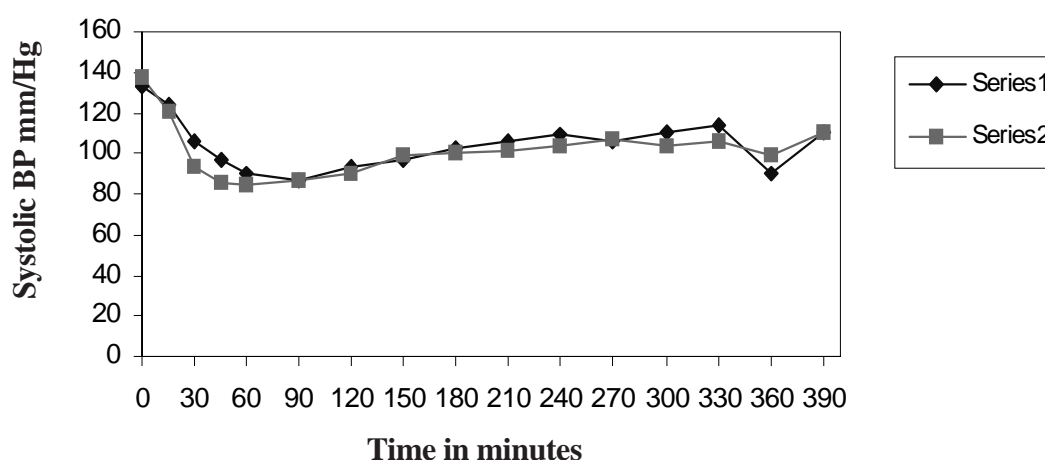
## Results

Common DER manifestations were; 1) Flushing, 2) Drowsiness, 3) Vomiting (Table-1), 4) Fall in Blood Pressure both systolic and diastolic (Fig-1&2), 5) Raise in Pulse rate (Fig-3). Apart

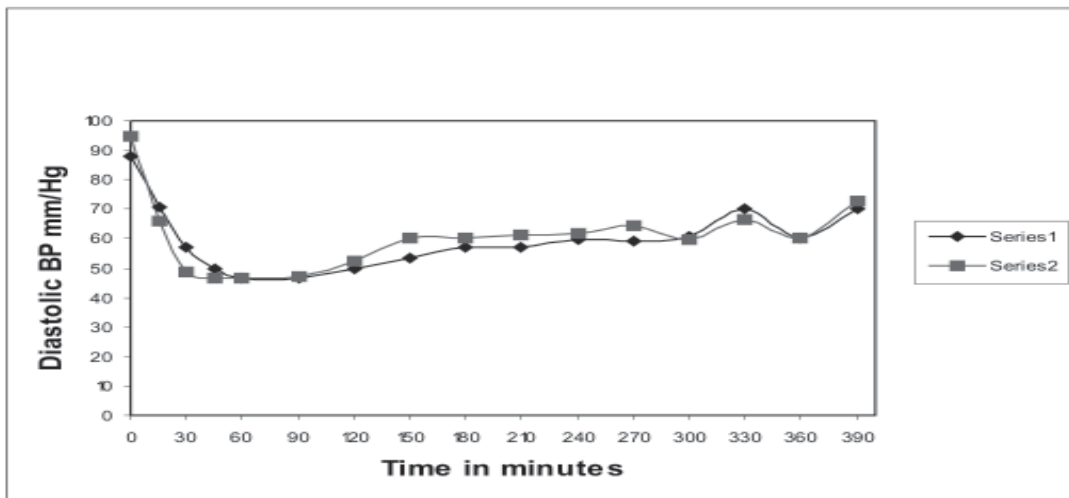
**Table 1: Manifestations of disulfiram ethanol reaction**

(Mean time in minutes)

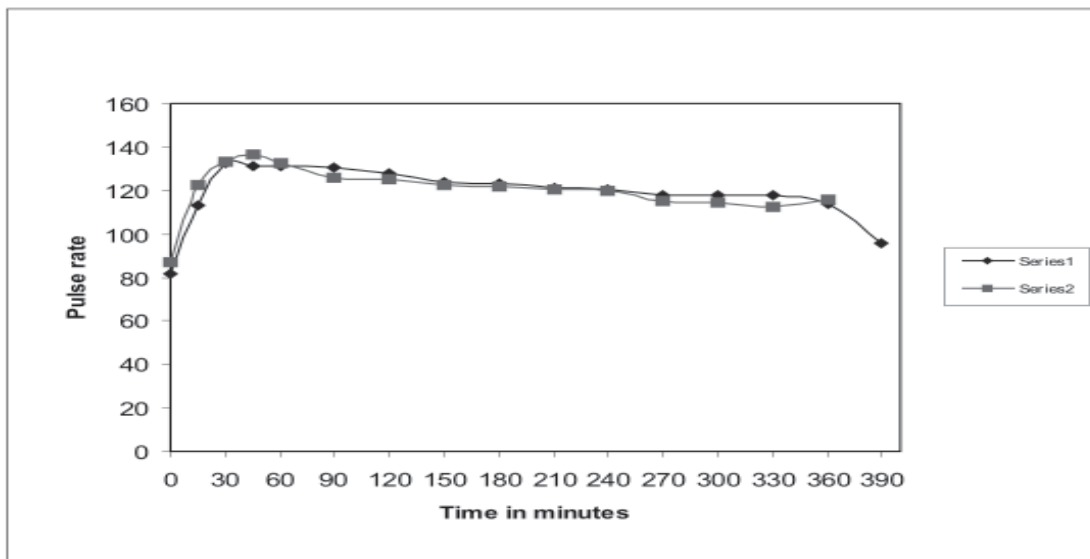
Onset	Termination			
	Low dose	High dose	Low dose	High dose
Flushing	16.8 ± 8.2	13.3± 8.6	114.3± 59.7	100.7 ± 9.5
Drowsiness	64.0± 52.3	70.2± 68.2	266.5 ± 85.5	248.2± 82.8
Vomiting	82.1 ± 93.0	80.5± 84.8	195.6±137.7	180.6±116.2



**Fig. 1. Mean Systolic Blood Pressure in low & high dose Disulfiram**



**Fig. 2. Mean Diastolic Blood Pressure in low & high dose Disulfiram**



**Fig. 3 Mean Pulse rate in low & high dose Disulfiram**

Series-1 = Low Dose; Series-2 = High Dose

from these common manifestations there were additional symptoms in some patients (Table- 2). Majority of patients developed severe DER in both groups and most of them recovered in about 6 to 8 hrs.

Number of cases who developed flushing, vomiting, drowsiness and additional symptoms did not vary statistically between the groups.

The details of each manifestation are as under;

**1) Flushing:** Flushing was the first manifestation to occur. Facial flushing occurred in all patients and flushing of body occurred in some cases. The mean time of appearance of flushing was  $16.8 \text{ min} \pm 8.2$ , (range 10 to 40) minutes in low dose group as against  $13.3 \pm 8.6$ , (range from

**Table 2. Characteristics of disulfiram ethanol reaction**

Particulars	High dose (N=33)	Low dose (N=34)
<b>Onset of flushing</b>		
15-30 minutes	32(96.96%)	33(97%)
31-60 minutes	01(3.04%)	01(03%)
<b>Vomiting</b>		
No	05 ( 15 %)	07( 20.6% ) *
Yes	28 ( 85 %)	27 ( 79.4%)
<b>Drowsy</b>		
Yes	32 ( 97 % )	34 ( 100% )
No	01 ( 03 % )	-
<b>Number of Additional Symptoms</b>		
3 and above	15(45.5%)	08(23.5%)
1-2	16(48.5%)	19 (55.9%)
Nil	02 (06.0%)	07 (20.58%)

\* Chi-square test with Yate's correction - NS.

**Table 3. Number of additional symptoms**

	Low dose (n=34)	High dose (n=33)
Headache	19 (56%)	14 (42%)
Chest pain	06 (18%)	14 (42%)
Palpitation	11 (32%)	09 (27%)
Restlessness	04 (12%)	13 (39%)
Abdominal pain	07 (21%)	05 (15%)
Weakness	05 (15%)	07 (21%)
Giddiness	01 (03%)	03 (09%)
Chills	02 (06%)	02 (06%)
Fear/anxiety	01 (03%)	01 (03%)
Dyspnoea	01 (03%)	01 (03%)

5 to 45) minutes in high dose group. The difference in time of onset of flushing did not vary between the groups ( $t=1.74$ ,  $P=NS$ ). The mean time taken for termination or fading out of flushing was  $114.3\pm 59.7$  (range 30 to 320) minutes in low dose group and  $100.7\pm 69.5$  (range 45 to 360) minutes in high dose group. The difference in time of termination of flushing did not vary between the groups ( $t=1.25$ ,  $P=NS$ ).

**2) Drowsiness:** Occurred in 34 (100 %) patients in low dose group and 32 (96.9 %) patients in high dose group. The mean time taken for onset of drowsiness was  $64.0\pm 52.3$  (range 10 to 260) minutes in low dose group and  $70.2\pm 68.2$  (range 10 to 345) minutes in high dose group. The difference in time of onset of drowsiness did not vary between the groups ( $t=0.43$ ,  $P=NS$ ). The mean time taken for recovery from drowsiness was  $266.5\pm 85.5$  (range 135 to 440) minutes in low dose group and  $248.2\pm 82.8$  (range: 150 to 380) minutes in high dose group. The difference in time of recovery from drowsiness did not vary between the groups ( $t=0.9$ ,  $P=NS$ ).

**3) Vomiting:** - 27(79.4%) patients in low dose group and 28 (84.8%) patients in high dose group had vomiting. The mean time of onset of vomiting in low dose group was  $82.1\pm 93.0$  (range 10 to 300) minutes and  $80.5\pm 84.8$  (range 10 to 300) minutes in high dose group. The bouts of vomiting lasted up to mean duration of  $195.6\pm 137.7$  (range 5 to 440) minutes in low dose group and  $180.6\pm 116.2$  (10 to 330) minutes in high dose group. The mean number of vomiting was  $3.7\pm 3.6$  in low dose and  $2.8\pm 2.2$  in high dose groups ( $t=0.12$ ,  $P=NS$ ).

**4) Blood Pressure:** The mean blood pressure of patients on the day of ethanol challenge prior to administration of ethanol was  $132.4\pm 18.2$  and  $88.0\pm 11.9$  mm Hg in low dose group and  $137.7\pm 15.4$  and  $94.7\pm 12.3$  mm Hg in high dose group in respect of systolic and diastolic blood pressure respectively. After administration of ethanol there was fall of blood pressure in both the groups. In high dose group fall in blood pressure was rapid, systolic pressure falling below a mean of 90 mm Hg in 45 minutes. In low dose group fall was gradual systolic pressure falling below a mean of 90 mm Hg. in 90 minutes. When fluid was infused systolic mean blood pressure reached above 100 mm Hg. in 150 in high and 240 minutes in low dose group. Systolic blood pressure fell below 100 mm Hg. in both groups around 300 minutes after cessation of infusion of fluids but rose again spontaneously to 120 mm Hg. by 330 minutes. The fall of diastolic blood pressure also followed similar trend as that of systolic pressure (Fig-2). However in both the groups values had not returned to basal level up to seven hours. It took 2 to 3 days to return to basal levels in most cases.

**Restoration of Blood Pressure:** Two patients each from low and high dose group did not require IV Dextrose saline as the systolic blood pressure did not fall below 100 mm Hg during the course of DER. The mean time at which systolic blood pressure fell below 100 mm Hg necessitating administration of I V Dextrose saline was  $53.8\pm 32.8$  minutes in low dose group and  $46.8\pm 30.4$  minutes in high dose group. The mean fluid volume administered was 1730 ml in low dose group and 1800 ml in high dose group to stabilize blood pressure to normal levels. Among patients who required I V Hydrocortisone the mean volume of Dextrose saline administered were 1650 ml in low dose group and 2350 ml in high dose group. The high dose group required higher volume of Dextrose saline. I V Hydrocortisone was given in 5 patients in

low and 7 patients in high dose group. All but two cases required single dose of 100 mg of Hydrocortisone. Two cases required 200 mg given in two equal doses at an interval of 40 minutes. Injection Hydrocortisone was given after mean duration of 156 minutes in low dose group and 201 minutes in high dose group, when I.V administration of Dextrose saline did not show satisfactory improvement in systolic blood pressure.

**5) Pulse rate: (Fig 3)** The mean pulse rate on the day of ethanol challenge prior to administration of ethanol was  $81.4 \pm 12.9$  and  $87.1 \pm 14.5$  in low and high dose group respectively. After administration of ethanol there was raise in pulse rate in both the groups. In high dose group there was rapid raise reaching a mean value of  $136.7 \pm 19.9$  beats per minute in 45 minutes. In low dose group the raise was gradual reaching a mean value of  $130.5 \pm 17.3$  beats per minute in 90 minutes. Thereafter infusion of fluids pulse rate declined gradually in high and low dose groups reaching a mean rate of  $112 \pm 11$ ,  $117 \pm 16.9$  beats per minute respectively in 330 minutes. However in both the groups values had not returned to basal level by that time. It took 1 to 2 days to return to normal levels in most cases.

**6) Additional symptoms:** In high dose group common additional symptoms were; headache, chest pain and restlessness followed by palpitation, abdominal pain, weakness and giddiness. One patient each had, anxiety, confusion, tachypnoea and cough. Patients who had tachypnoea and cough had occasional basal crepitations. In low dose group common additional symptoms were headache and palpitation followed by chest pain, restlessness, abdominal pain, and weakness. One patient had anxiety. None had tachypnoea, confusion or cough. Clinically patients had severe additional symptoms in high dose group than in low dose group especially symptoms of headache, restlessness and weakness.

**7) Severity of DER:** Majority of patients developed severe DER in both groups and most of them recovered in about 6 to 8 hrs. Severity of disulfiram ethanol reaction did not vary statistically in relation to dose of disulfiram, BMI and duration of alcohol use<sup>6</sup>. In some individual patients severity was more with low dose regimen and in some severity was less with high dose regimen.

## Discussion

**Flushing:** Confirming with findings of 3 studies in western population as reviewed by Gessner & Kristenson<sup>7</sup> facial flushing was the commonest and earliest symptom in our study too. It was observed in all patients on the face and all over the body in some cases. In contrast to western reports generalized flushing was not seen in our patients, which may be due to dark color of skin. An Indian study<sup>8</sup> has reported facial flushing in only 50% of cases. This study ascribed darkness of skin as the reason for low rate of facial flushing. The flushing appeared faster and lasted for lesser time in high dose group compared to low dose group. Facial flushing being an earliest indicator of DER it could be monitored by family members in patients on maintenance disulfiram if properly instructed.

The drowsiness usually occurred in about one hour and lasted for about four hours. In some cases drowsiness appeared as early as 10 minutes and lasted as long as seven hours. Therefore

it is possible that if a patient while on disulfiram, if gets self induced DER when alone, may have this dangerous adverse effect. However, drowsiness may not be severe enough, in patients on maintenance as the dose will be lesser than the challenge dose.

**Vomiting:** During DER if vomiting occurs family members feel reassured that treatment was effective and patients get warned about the effectiveness of treatment. This conclusion has been born out in a study by Abhyankar<sup>9</sup> which revealed that patients who experienced vomiting and or discomfort as part of DER either therapeutically induced or self induced had better prognosis than those who did not experience these symptoms. However, one study<sup>10</sup> quotes 42% of alcoholics who underwent DER in hospital setting self experimented with further dose of alcohol after discharge. In our experience patients who undergo DER if experiment with further dose of alcohol after discharge from the hospital do so cautiously with low dose of alcohol. Above finding lends support to our view that it is advisable to demonstrate effect of DER in a medical setting to avoid consequences of self experimentation.

**Fall of Blood pressure:** The elevated blood pressure prior to ethanol challenge in both groups after disulfiram is due to increase in level of dopamine despite decrease in noradrenaline synthesis due to inhibition of dopamine β hydroxylase<sup>11</sup>. During DER fall of both systolic and diastolic blood pressure occurred in all cases. Restoration of blood pressure to safe level was achieved by infusing mean volume of 1650ml, 2350ml I.V dextrose saline in low and high dose group. Dangerous fall in blood pressure was recorded in a few patients who responded to intravenous fluids, and in some cases I.V Hydrocortisone. None needed mephentine or dopamine. Raising systolic blood pressure towards normal values after initial fall is a good indicator of satisfactory improvement in patient's clinical condition during the course of management of DER. The changes in pulse rate are in accordance with Marey's law<sup>12</sup> in its inverse relation to blood pressure change.

Severe peripheral vascular failure with collapse has been reported in the literature<sup>13</sup>, we did not encounter any such cases, and this could be due to limited quantity of alcohol for producing DER. This is one of the reason we did not increase alcohol quantity for challenge when DER was not severe. However 2<sup>nd</sup> author (KNR) in his clinical experience has seen 2 cases of recovered hemiplegics (due to cerebral infarction) who were on disulfiram developed dense hemiplegia after alcohol ingestion. Therefore disulfiram is to be avoided in patients with history of any neurological illness where cerebral auto-regulation mechanism is suspected to have failed.

Additional symptoms occurring during DER adds up to severity of DER. Most of the additional symptoms that occurred in the present study could be explained by local gastric irritation and peripheral vasodilatation.

Cough has been reported as a feature of DER by Gessner<sup>7</sup>. In the present study one patient from high dose group developed cough. Presence of basal crepitation in this patient and another patient with tachypnoea may be due to mild pulmonary congestion.

Administration of disulfiram in pure powder form, disulfiram and ethanol dose based on body weight does not seem to have any varying effect in reference to nature and severity of DER as

reflected by results of our study comparing well with that of Hebbar<sup>8</sup>. This may mean that blood acetaldehyde concentration is the important factor in influencing DER. Acetaldehyde concentration itself might be determined by factors other than dose of disulfiram, duration of alcohol ingestion, body weight and BMI.

Some individual patients show very severe reaction with low dose and some individuals with high dose may not show severe reaction. This observation may guide in determining maintenance dose of disulfiram in a particular patient. Therapists may opt for 250 to 750 mg of maintenance dose depending upon the severity of DER in relation to dose in a particular patient.

## Conclusion

Common DER manifestations are; flushing, drowsiness, vomiting, fall in blood pressure and rise in Pulse Rate. Flushing and vomiting appeared earlier and terminated faster in high dose group. Drowsiness occurred earlier and lasted longer in low dose group. Fall of blood pressure was rapid in high dose group than low dose group. Mean blood pressure fell below 90 mm Hg by 45 minutes in high dose group and 90 minutes in low dose group. The blood Pressure could be restored to normal by infusing I.V Dextrose saline mean volume of 1650 ml and 2350 ml in low and high dose group patient respectively. Some cases needed I.V Hydrocortisone in addition to I.V Dextrose saline. The blood Pressure did not recover to baseline even after seven hours in both groups. It took 1 to 3 days to return to normal. The number of additional symptoms was more and clinically severe in high than low dose group. Majority of patients developed severe DER irrespective of low or high dose and most of them recovered in about 6 to 8 hrs. Demonstration of DER in a medical setting helps in avoiding consequences of self experimentation and educates family members to keep watch on the patient after discharge from the hospital and take preventive measures by watching progress of the patient and seeking medical help at the earliest. Severity of DER in relation to dose in a particular patient helps to determine maintenance dose.

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