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# Side Reactions on Meprobamate and Placebo

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## Introduction

Since the recent thalidomide incident, the focus on drug induced side reactions has justifiably been increased. However, as so often occurs in medicine, the pendulum swings to the other extreme, i.e., while drug induced side reactions were neglected before, they often are over-emphasized today. Many well conducted double-blind studies point out that side effects of mild tranquilizers, for example, are relatively minor and infrequent, usually disappearing after a few days[1].

These studies, moreover, demonstrated that a similar percentage of patients on placebo also report side reactions[2,3,4]. Recently, Payne *et al*[5], evaluating diazepam, meprobamate and placebo, reported the percentage of side reactions as being 33% for placebo, 34% for diazepam and 39% for meprobamate. All of these, however, were of a mild nature. Rickels found similar results in double-blind studies with meprobamate and chlordiazepoxide[6,7].

If we consider the number of visits at which side reactions are reported as a percentage of total visits, the incidence of side reactions is smaller than if we report the percentage of patients reporting side reactions at any visit during a given study.

Moreover, different patient populations report different incidence of side reactions depending on such variables as presenting illness and pretreatment complaints, social class, personality make up, previous drug experience, satisfaction with therapy and last but not least, therapeutic milieu (or set), in which the study has been performed[8-11].

We therefore wish to discuss side reactions found in three double-blind studies of meprobamate and placebo, one carried out jointly at three clinics under two different "sets" — therapeutic and experimental, (Drug-Set Interaction (DSI-) Study)[12,13], and the other two studies carried out with private practice patients P-P Studies)[14,15]

## Method

*Part I*: (*Drug-Set Interaction (DSI) Study*):

In this six week double-blind study[13], three psychiatric outpatient clinics, the Henry Phipps Psychiatric Clinic of Johns Hopkins University (JHH), the Neuropsychiatric Clinic at Philadelphia General Hospital (PGH), and the Psychiatric Clinic at the University of Pennsylvania (HUP), participated. Anxious neurotic patients were randomly assigned to one of four treatment combinations: meprobamate or placebo administered either by a "Therapeutic" (T) doctor or by an "Experimental" (E) doctor. At each clinic two psychiatric residents were trained to convey a "therapeutic" attitude and two other residents an "experimental" attitude. The T doctor attempted to convey confidence in the efficacy of the drug and mentioned the possibility of the side effect, "drowsiness", which was interpreted as a favorable sign of the drug's efficacy. In the Experimental role, the doctor attempted to convey uncertainty concerning the efficacy of the drug and the patient was told that he was participating in a research project. No mention was made of possible side effects. In neither role was the physician advised to allow the patient to decrease medication if side effects should occur. Patients received two capsules of meprobamate q.i.d. (1600 mg/d) or placebo.

Patients at JHH were of lower middle to lower socio-economic class, (mean age 34 years, 60% female, 60% white). Modal educational level was 9th — 11th grade and modal income about $3,000. Patients expected relief of psychic symptoms, but

fewer patients expected psychotherapy when compared to HUP patients.

PGH is a city hospital and most patients were from the lower socio-economic class (mean age 35 years, 72% female, 22% white). Modal educational level was 9th grade and modal income not much over $1,000. These patients expected drug therapy.

At HUP, patients were largely drawn from the middle class (mean age 32 years, 64% female, 48% white). Most patients were high school graduates and their modal income was about $3,000. Most patients expected psychotherapy.

*Part II*: (*Private Practice (PP) Studies*):

Two additional double-blind meprobamate - placebo studies carried out in Private Psychiatric[14] and Private General Practice[15] with anxious neurotic patients are discussed in the second part of this paper. Again, patients were randomly assigned and received meprobamate two capsules q.i.d. (1600 mg/d) or placebo.

Patients participating in the private psychiatrist study received psychotherapy along with meprobamate or placebo during a six week study and were evaluated bi-weekly. They were given the medication in a "therapeutic" atmosphere as an adjunct to psychotherapy. They were middle class patients (mean age 33 years, 66% female, 93% white), most having completed high school and 39% with at least some college education. Their modal income level was $8,000.

General practice patients received the medication during a four week study and were evaluated bi-weekly. They expected drug therapy. They were lower middle-middle class patients (mean age 40 years, 81% female, 98% white). Their modal educational level was 11th grade and they had a modal income of $5,000.

In both studies the patient was frequently told by the doctor that if drowsiness should occur he would not have to worry since it was a sign of the drug's efficacy and would gradually disappear. In contrast to the DSI-Study, mentioned in Part I, the patient was allowed to decrease dosage slightly if it became at all necessary.

In all studies, side effects were considered as such only if they were not present at onset, were mentioned spontaneously by the patient, and were attributed by him to the study medication. The physician would inquire into side reactions only in a very general way by asking the patient: "How did the drug make you feel?"

## Results

*Part I*: (*DSI-Study*):

A. *Incidence of side reactions*: Of the total population, (N=217), including those patients who adhered to protocol and those who did not, 36% reported side effects at least once over the six week study period. The percentage of side effects reported by visit over the total study period was lower (20%).

In the 138 adhering patients, 89 side reactions were noted by the doctors over the full treatment period. These 89 side reactions were noted in 52 of the 138 completed patients. Of these 89 side effects, 59 were "drowsiness"/"lethargy" and/or "weakness"/"fatigue" (66.3%). In other words, 2/3 of all side effects noted were in the category which typically is associated with the minor tranquilizers. Thirty (57.7%) patients reported only "drowsiness"/"lethargy" or "weakness"/"fatigue", 28% reported "other" side effects and 15% reported a combination of drowsiness and "other" side reactions.

None of the reported side reactions necessitated discontinuation of the study medication. Most side effects were reported at the initial two week period (N=35), and the number of reports significantly decreased over time (N=22 for the 4 - 6 week periods) (Cochran $Q=7.51$, $df=2$, $p<.05$)[16]. Patients who had side reactions at the two week study period were more likely to also have them at a later study period, as contrasted with patients who did not report side reactions at two weeks ($X^2=6.91$, $df=1$, $p<.01$). Similar results were reported by Letemendia[17].

B. *Incidence of side effects in "adhered" and "deviated" patients*:

An analysis of the data presented in Table I revealed no significant difference in the incidence of side effects reported by adhering and nonadhering patients either (a) over clinics (data combined) or (b) within each clinic separately. Moreover, the pattern of reported side effects was roughly comparable in both patient groups; that is, regardless of deviation or adherence most side reactions were reported at HUP and fewest at JHH. Similarly, more side effects were noted in drug than in placebo patients.

TABLE I

*Incidence of Side Effects by Treatment for the 3 Clinics for Adhered and Deviated Patients at 2 Weeks*

| TREATMENT | J.H.H. | | P.G.H. | | H.U.P. | |
|---|---|---|---|---|---|---|
| *Adhered* | Side Effects | No Side Effects | Side Effects | No Side Effects | Side Effects | No Side Effects |
| T-Meprobamate | 2 | 12 | 3 | 12 | 7 | 7 |
| T-Placebo | 0 | 11 | 1 | 11 | 4 | 5 |
| E-Meprobamate | 3 | 7 | 3 | 7 | 4 | 5 |
| E-Placebo | 2 | 11 | 3 | 6 | 3 | 9 |
| TOTAL | 7 | 41 | 10 | 36 | 18 | 26 |
| *Deviated* | | | | | | |
| T-Meprobamate | 2 | 5 | 0 | 4 | 2 | 2 |
| T-Placebo | 0 | 8 | 1 | 5 | 0 | 4 |
| E-Meprobamate | 1 | 6 | 5 | 5 | 3 | 2 |
| E-Placebo | 0 | 7 | 4 | 6 | 3 | 4 |
| TOTAL | 3 | 26 | 10 | 20 | 8 | 12 |

$X^2 < 1$, df=1, n.s. (Adhered vs. Deviated Patients)
$X^2 = 8.88$, df=2, $p < .02$ (Clinic Difference, Adhered Patients Only)
$X^2 = 6.45$, df=2, $p < .05$ (Clinic Difference, Deviated Patients Only)

C. *Influence of medication*:

Comparing the incidences reported by patients on drug against those on placebo, for each visit separately, no significant differences exist, although more drug than placebo patients report side effects. Only if one divides the number of patients who completed the six week study into the number of patients not reporting side reactions and all other patients irrespective of whether they had side effects only during one two week study period or more frequently, does one detect significant drug-placebo differences in incidences of side effects. (Table II & III). The results reported in Table I are based on a four-fold contingency analysis developed by Rao[18]. Although the magnitude of drug-placebo differences was not reliably different at the three clinics — i.e., the drug x clinic interaction was not significant, it is of some interest to note that the largest difference in report of side reactions on drug as compared with placebo was obtained at HUP (69% drug vs. 33% placebo) with PGH next (44% vs. 28%) and JHH patients showing the smallest difference (29% vs. 21%).

TABLE II

*Incidence of Side Effects by Treatment Condition and Clinic over the 6-week Treatment Period (Completed Patients)*

| TREATMENT | J.H.H. | | P.G.H. | | H.U.P. | |
|---|---|---|---|---|---|---|
| | Side Effects | No Side Effects | Side Effects | No Side Effects | Side Effects | No Side Effects |
| T-Meprobamate | 2 | 12 | 6 | 9 | 11 | 3 |
| T-Placebo | 1 | 10 | 2 | 10 | 4 | 5 |
| E-Meprobamate | 5 | 5 | 5 | 5 | 5 | 4 |
| E-Placebo | 4 | 9 | 4 | 5 | 3 | 9 |

$X^2 = 12.83$, df = 2, $p < .01$ (T-Meprobamate)
$X^2 = 3.93$, df = 2, $.20 > p > .10$ (T-Placebo)
$X^2 < 1$, n.s. (E-Meprobamate)
$X^2 < 1$, n.s. (E-Placebo)

D. *Influence of "clinic" and "role" on reporting of side reactions*:

The analyses reported in Table I and Table III indicate a reliable clinic difference in the incidence of reported side effects. JHH patients reported fewest and HUP patients most (in both "adhered" and "deviated" groups) side reactions. In the more refined side reaction analysis of adhered patients reported in Table III (restricted sample size prevented a comparable analysis of deviated patients), it can be seen that the main clinic effect should,

however, be interpreted in combination with the role variable; that is, a reliable clinic x role interaction was noted. At HUP 65% of patients exposed to the T role reported side effects vs. 38% side reactions for patients in the E role. At JHH by contrast, only 12% of the patients exposed to the T role reported side effects whereas 39% reported side effects under the E role. The pattern at PGH was more similar to JHH than HUP with 29.6% patients and 47.4% patients reporting side effects under T and E roles, respectively. Thus, the influence of the role variable on the report of side effects is most obvious in HUP and JHH patients; the direction of that influence is, however, in opposite directions.

E. *Side reactions and improvement*:

In the analysis of improvement in relation to side effects, the target symptom change scores[19] (Visit I to Visit II and Visit I to Visit IV) were used. Within each clinic the median improvement score was noted. Patients scoring above the median were considered improved, below the median unimproved.

No significant relationship could be detected in the total population between the reporting of side reactions and whether or not a patient improved, although a slight trend pointed toward more improvement in patients with side reactions. Only in the T-placebo group did this relationship reach significance (N=32; $p < .04$, Fisher's Exact Test).

All side reactions were also divided into two main groups, namely dizziness or drowsiness or lethargy and assorted "other" side effects (rash, nausea, blurred vision, fainting, dry mouth, tremor, yawning, euphoria, anger, gastro-intestinal complaints).

Comparing drug and placebo patients, we could observe no relationship of medication to the type of side reaction reported. Comparing frequency of reporting "drowsiness" with "other" side reactions for drug and placebo patients combined, only in the first 2 weeks was significantly more drowsiness reported in the Therapeutic Set than in the Experimental Set, ($X^2 = 5.94$, $N = 43$, $p < .02$). The same trend existed for the 4 and 6 week evaluation periods and may very well have occurred as a result of the fact that drowsiness was mentioned as a possible side effect by the T doctors.

In the total population reporting side effects, a trend existed only in the initial two week period for more improvement to be related to the occurrence of drowsiness instead of "other" side effects, irrespective of whether a patient was receiving drug or placebo ($N=42$, $p<.20$, four-fold table). This was more marked for PGH and JHH than for HUP patients ($p<.10$ four-fold table) (PGH & JHH vs. HUP).

*Part II*: (*PP-Studies*):

To further explore the question of side effects, data from private general practice and private psychiatric practice studies

TABLE III

*Chi-Square Analysis of Side Effect Data*[1]

| Effect | $X^2$ | df | p |
|---|---|---|---|
| Total | 27.05 | 18 | .10 |
| Clinic | 7.29 | 2 | .05 |
| Set | 0.64 | 1 | — |
| Drug | 5.84 | 1 | .02 |
| Clinic x Set | 7.47 | 2 | .05 |
| Clinic x Drug | 1.92 | 2 | — |
| Drug x Set | 0.03 | 1 | — |
| Clinic x Set x Drug | 0.911 | 2 | — |

[1]The following corrections were made for departures from random assignment of patients in treatment conditions:
(a) Clinic x Set = 0.53, (b) Clinic x Drug = 0.18, (c) Drug x Set = 1.75, (d) Clinic x Set x Drug = 0.91.
The unequal patient N's per cell reflect, in part, differential patient "no-shows" in the different treatment conditions.

TABLE IV

*Incidences of "Drowsiness" and "Other" Side Effects Over the Total Study Period*

| | Meprobamate | Placebo |
|---|---|---|
| Drowsiness | 22 | 6 |
| Other | 6 | 19 |

$X^2 = 15.78$, $p < .001$

(N=203) were combined and analyzed together.

For analysis of improvement rate, both the doctor and patient "Global Ratings" were used. These scales measure how the patient felt at the present visit as compared to his last visit and range from (—3) "very much worse", over (0) "no change", to (+3) "very much better". Only results from the patient rating will be discussed but results found in the doctor ratings were similar.

*Incidence of side reactions*:

Patients reported slightly more side reactions on drug (31%) than on placebo (26%). The number of side reactions reported by visit over the total study period was 19%. A trend existed for patients receiving drug to report fewer side reactions at 4 weeks than at 2 weeks ($X^2 = 2.45$, $N = 73$, $p < .20$) and this trend became significant for placebo patients ($X^2 = 4.05$, $N=87$, $p < .05$). This confirms the data of the DSI-Study, reported earlier in Part I.

In an earlier evaluation of chlordiazepoxide and placebo in neurotic medical clinic patients[7] this phenomenon was not observed; no decrease of side reactions over time for either drug or placebo patients occurred and the number of side reactions reported by visit over the total study period was slightly higher (34%) than in the present report. The differences found in these 2 studies, one evaluating meprobamate and one chlordiazepoxide may well be a function of the populations rather than of the drugs, as there existed no significant differences between chlordiazepoxide and placebo patients, i.e., incidence of side reactions did not decrease for the placebo group either. The chlordiazepoxide study was carried out in the medical clinic of a public, city hospital and patients were of the lowest socio-economic class while the meprobamate studies used middle class private psychiatric and lower middle-middle class private General Practice patients.

Dividing side reactions into "drowsiness" and "other", patients receiving meprobamate reported significantly more "drowsiness" than did placebo patients, who reported more "other" side effects ($X^2 = 15.78$, $p<.001$) (Table IV). (The same differential breakdown of side reactions for drug and placebo was also observed in the earlier mentioned chlordiazepoxide study ($p < .02$).)

*Side reactions and improvement*:

Relating total incidence of side reactions to improvement, there existed a trend at the 2 week period only for patients reporting side reactions to improve less as compared to patients with no side reactions. This was the case for drug and placebo patients separately, and almost reached significance for all patients combined ($X^2 = 3.14$, $N=203$, $p < .10$). (The four week data could not be utilized as the N for side reactions became too small, although the direction was the same as in the two week evaluation period.)

However, as reported in Part I, also here a slight trend existed for "drowsy" patients to improve more than patients with "other" side effects, irrespective of the medication received (54% vs. 38%), even if "no side reaction" patients improved the most (66%).

## Discussion and Conclusion

Side reactions observed with meprobamate or placebo were predominantly of the kind often associated with the minor tranquilizers, namely "drowsiness". Some other side effects reported were anger, blurred vision, yawning, diarrhea, headaches, disturbing and vivid dreams, tremor, tension euphoria and fainting.

In all studies discussed, side reactions, when they occurred, were mild in nature, never necessitating discontinuation of study medication; they were of short duration, decreasing over time. This could mean that side reactions can be considered in part an adjustment problem to the (taking of) medication which frequently disappears after a few days. Furthermore, side reactions, particularly if reported while receiving placebo, but also while on drug, may represent an increase or change in symptomatology; and they may also be

psychological in nature, being used by the patient to indicate to the physician his dissatisfaction with therapy, or with the treatment situation. In other words, side reactions may at times be of emotional, rather than of chemical origin.

When side reactions were divided into "drowsiness" and "other", drug patients in the private practice studies reported primarily "drowsiness", and placebo patients primarily "other" side effects, but the same pattern did not hold true for the Drug x Set Interaction (DSI) Study. The more complex design, differences of interpreting "drowsiness" in both studies, and possibly many other factors may have contributed to these observed differences.

No clear-cut relationship could be demonstrated by us between improvement and side effects. In the Drug x Set Interaction Study (Part I), there existed a tendency for side reactions to occur more frequently in improved patients ($X^2 = 1.20$), while the opposite was the case in the two private practice studies ($X^2 = 3.14$). In all studies, however, a small non-significant trend existed for improvement to be related to the reporting of "drowsiness".

These findings again indicate the complexities involved, even if an earlier placebo evaluation also demonstrated that placebo patients improved the least when reporting side reactions.[20] The addition of two roles, three different clinics and a differential explanation of "drowsiness" to the patient according to role may well account for the fact that the relationship between improvement and the reporting of side effects point in the opposite direction in the DSI-Study when compared to the private practice studies.

Comparing the three clinics of the Drug x Set Interaction Study, patients at HUP reported more side reactions, especially in the T role, than patients at PGH and JHH. In the E role PGH and JHH patients reported increased incidences of side reactions, while side reactions for HUP patients decreased.

The clinic x role interaction can perhaps be explained by characteristics of the populations involved. PGH and JHH patients were of lower socio-economic class and were not as psychotherapy oriented as the HUP patients. Expecting psychotherapy, the E role was probably a more appropriate set for the more intelligent, more educated patients at HUP, while the patients treated under the T role may have indicated their dislike for this role, thus the reporting of increased side effects. Furthermore, higher social class patients (HUP), as opposed to lower socio-economic class patients (e.g. PGH and JHH), may view drowsiness as a more disturbing side effect.

The incidence of side effects observed in the Drug x Set Interaction Study illustrates the importance of both pharmacological (main drug effect) and non-pharmacological (clinic x role interaction) factors for study outcome.

## Summary

This paper describes three double-blind studies comprising 420 patients in which meprobamate (1600 mg. daily) was compared with placebo. All side effects reported were of a mild nature and only rarely necessitated a reduction of dosage and never necessitated a discontinuation of study medication. Most side effects were recorded after two weeks of study and tended to decrease significantly over the next four weeks.

There was no significant difference in the incidence of side effects between meprobamate and placebo when the analyses were based on individual visits of patients at intervals during the study. Only if one compares "no side reaction" patients with all other patients who reported at least once side effects, does one detect a significant meprobamate-placebo difference in the DSI-study, a phenomenon contributed primarily by patients at one of three participating clinics. There was no significant relationship between the occurence of side effects and clinical improvement of the patient. Of 203 patients of the two PP-

studies, 31% of patients on drugs reported side effects as compared with 26% on placebo. Patients receiving meprobamate had significantly more drowsiness than did the placebo patients who in turn reported more "other side effects". Since side reactions observed with meprobamate and placebo were mild and transient and tended to decrease as medication continued, it was speculated that they might be considered at least in part as an adjustment problem to medication; many reported side effects were clearly emotional rather than chemical in origin.

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*BIBLIOGRAPHY*

1. Jenner, F.A., Kerry, R. J., Parkin, D.: A Controlled Trial of Methaminodiazepoxide (Chlordiazepoxide, "Librium") in the Treatment of Anxiety in Neurotic Patients. *J. Ment. Sci.* 107:575-582, May 1961.
2. Michaux, W.W.: Side Effects, Resistance and Dosage Deviations in Psychiatric Outpatients Treated With Tranquilizers. *J. Nerv. Ment. Dis.* 133: 203-212, Sept. 1961.
3. Janecek, J., Schiele, B.C., Bellville, T.P., Vestre, N.D., Raths, O.: A Controlled Study of 4-[1-phenyl-4-piperazinyl]-butyl 3, 4, 5-trimethoxybenzate hydrochloride (MA 568) and Meprobamate in Psychiatric Outpatients. *J. New Drugs* 5: 51-56, Jan.-Feb., 1965.
4. Lorr, M., McNair, D.M., Weinstein, G.J.: Early Effects of Chlordiazepoxide (Librium) Used With Psychotherapy. *J. Psychiat. Res.* 1:257-270, 1963.
5. Payne, R.W., Sorenson, E.J., Smalley, T.K., Brandt, Jr., E.N.: Diazepam, Meprobamate, and Placebo in Musculoskeletal Disorders. *JAMA*, 188:157-160, April, 1964.
6. Rickels, K., Snow, L.: Meprobamate and Phenobarbital Sodium in Anxious Neurotic Psychiatric and Medical Clinic Out-patients. *Psychopharmacologia* 5:339-348, 1964.
7. Rickels, K., Baumm, C., Raab, E., Taylor, W., Moore E.: A Psychopharmacological Evaluation of Chlordiazepoxide, LA-1 and Placebo, Carried Out With Anxious, Neurotic Medical Clinic Patients. *Medical Times*, 93:238-245, March, 1965.
8. Pogge, R.C.: The Toxic Placebo, I. Side and Toxic Effects Reported During the Administration of Placebo Medicine, II. The Case of the Partial Patient. *Medical Times*, 91: 773-781, August 1963.
9. Busfield, Jr. B.L., Schneller, P., Capra, D.: Depressive Symptom or Side Effect? A Comparative Study of Symptoms During Pre-Treatment and Treatment Periods of Patients on Three Antidepressant Medications. *J. Nerv. Ment. Dis.* 134:339-345, April 1962.
10. Green, D.M.: Side Effects — Quantification. *Fed. Proc.* 21:179, 1962.
11. Park, L.C., Covi, L.: Nonblind Placebo Trial. *Arch. Gen. Psychiat.*, 12:336-345, 1965.
12. Fisher, S., Cole, J.O., Rickels, K., Uhlenhuth, E.H.: Drug-Set Interaction: The Effect of Expectations on Drug Response in Outpatients. "Neuropsychopharmacology." (Bradley, Fluegel & Hoch, eds.) *Elsevier Pub. Co.*, Amsterdam 3:149-156, 1964.
13. Uhlenhuth, E.H., Rickels, K., Fisher, S., Park, L.C., Lipman, R.S., Mock, J.: Drug, Doctor's Verbal Attitude and Clinic Setting in the Symptomatic Response to Pharmacotherapy. *Psychopharmacologia* 9:392-418, 1966.
14. Rickels, K., Cattell, R.B., Weise, C., Gray, B., Yee, R., Mallin, A., Aaronson, H. G.: Controlled Psychopharmacological Research in Private Psychiatric Practice. *Psychopharmacologia* 9:288-306, 1966.
15. Rickels, K., Boren, R. Stuart, H.M.: Controlled Psychopharmacological Research in General Practice. *J. New Drugs* 4:138-147, May-June 1964.
16. Siegel, S.: "Nonparametric Statistics for the Behavioral Sciencies," *McGraw-Hill Book Co.*, Inc., N.Y. 1956.
17. Letermendia, F.J.J., Harris, A. D.: The Influence of Side-Effects on the Reporting of Symptoms. *Psychopharmacologia* 1:39-47, 1959.
18. Rao, C.R.: "Advanced Statistical Methods in Biometric Research." *Wiley*, New York, 1952, p. 192.
19. Park, L.C.. Uhlenhuth, E.H., Lipman, R. S., Rickels, K., Fisher, S.: A Comparison of Doctor and Patient Improvement Ratings in a Double-Blind Drug Trial. *Brit. J. Psychiat.*, 111:535-540, June 1965.
20. Rickels, K., Carranza, J., MacAfee, A.: Placebo Responses in Different Neurotic Patient Populations. Presented at the 4th *Congress of the Collegium Internationale Neuro-Psychopharmacologicum*, Birmingham, England, September, 1964.

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