

# Is Flumazenil an Effective Treatment for Hepatic Encephalopathy?

## EBEM Commentator Contact

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## SYSTEMATIC REVIEW SOURCE

This is a systematic review abstract, a regular feature of the *Annals'* Evidence-Based Emergency Medicine (EBEM) series. Each features an abstract of a systematic review from the Cochrane Database of Systematic Reviews and a commentary by an emergency physician knowledgeable in the subject area.

The source for this systematic review abstract is: Als-Nielsen B, Gluud LL, Gluud C. *Benzodiazepine Receptor Antagonists for Hepatic Encephalopathy (Cochrane Review)*. Cochrane Library, Issue 1. Chichester, UK: John Wiley & Sons, Ltd; 2005.

The *Annals'* EBEM editors prepared the abstract of this Cochrane systematic review, as well as the Evidence-Based Medicine Teaching Points.

## OBJECTIVE

To evaluate the beneficial and harmful effects of benzodiazepine receptor antagonists for patients with hepatic encephalopathy.

## DATA SOURCES

The Cochrane Hepato-Biliary Group Controlled Trials Register, the Cochrane Central Register of Controlled Trials, MEDLINE on Silver Platter, EMBASE, reference lists of relevant articles, inquiry with authors of trials, and pharmaceutical companies were used. The review is updated to January 12, 2004.

## STUDY SELECTION

Studies were considered if they were randomized controlled trials that included persons with hepatic encephalopathy caused by liver disease or hepatic failure in which all patients received a benzodiazepine antagonist, placebo, or no treatment. Blinding, publication status, language, subject sex, age, or ethnicity was not considered as criteria for study selection. Outcomes included complete resolution or improvement of clinical

symptoms, time to recovery or improvement, quality of life, survival and adverse effects.

## DATA EXTRACTION AND ANALYSES

Two reviewers independently selected articles for inclusion, evaluated methodologic quality of the studies, and abstracted the data. Dichotomous variables were reported as risk difference with associated 95% confidence intervals (CIs). A random-effects model was used, based on the study's heterogeneity. Statistical heterogeneity was explored by a  $\chi^2$  test, with significance set at  $P < .1$ . The inconsistency across trials was also assessed by  $I^2$ . Potential sources of heterogeneity were explored through subgroup analyses.

## MAIN RESULTS

Thirteen randomized trials involving 805 patients were included, and 8 trials used a crossover design.<sup>1-5</sup> All trials were double blind and assessed flumazenil, median dose 2 mg, versus placebo, for a median duration of 10 minutes. The included patients had a favorable prognosis (361/390 [93%] survived in the flumazenil group versus 345/376 [92%] in the placebo group). Flumazenil had a significant beneficial effect on improvement of hepatic encephalopathy at the end of treatment ( $n = 8$  trials; risk difference 0.28; 95% CI 0.20 to 0.37). Flumazenil had no significant effect on recovery ( $n = 2$  trials; risk difference 0.13; 95% CI  $-0.09$  to 0.36) or mortality ( $n = 10$  trials; risk difference 0.01; 95% CI  $-0.05$  to 0.07). Flumazenil may be associated with adverse events; however, these trial results were heterogeneous.

## CONCLUSIONS

Flumazenil had a significant beneficial effect on short-term improvement of hepatic encephalopathy in patients with cirrhosis and a highly favorable prognosis; however, it failed to demonstrate a significant effect on recovery or survival. Until this has been demonstrated, flumazenil may be considered for patients with chronic liver disease and hepatic encephalopathy but cannot be recommended for routine clinical use.

**Table 1.** Main results.

Outcome	No. of Studies Pooled (Total N)	Description	Risk Difference (CI)
Complete resolution	2 (35)	Trend towards favoring flumazenil	0.13 (−0.09 To 0.36)
Improvement/all	8 (736)	Favors flumazenil	0.28 (0.20–0.37)
Improvement/high-quality studies	5 (640)		0.29 (0.17–0.40)
Improvement/hepatic encephalopathy grade II-IV	2 (43)		0.40 (0.04–0.76)
Improvement/hepatic encephalopathy grade III-IV	4 (604)		0.22 (0.17–0.28)
Improvement/positives for benzodiazepines excluded	3 (597)		0.19 (0.14–0.24)
Survival at maximum follow-up	10 (766)	No difference	0.01 (−0.05 To 0.07)
Adverse events	6 (672)	No difference	0.06 (−0.06 To 0.18)
Adverse events/exclusion of Barbaro et al <sup>1</sup> trial	5 (145)		0.06 (−0.02 To 0.14)

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### COMMENTARY: CLINICAL IMPLICATION

Hepatic encephalopathy is a syndrome characterized by depressed level of consciousness, cognitive impairment, and personality changes induced by circulating neurotoxic substances that have bypassed normal hepatic detoxification because of diversion of portal blood flow into the systemic circulation. Hepatic encephalopathy most commonly occurs in the setting of hepatic cirrhosis or in those who have undergone portocaval shunt surgery. Up to two thirds of patients with cirrhosis may have subclinical hepatic encephalopathy.<sup>6</sup> About 30% of patients with end-stage liver disease develop clinically significant hepatic encephalopathy. The emergency department (ED) presentation of a patient with decompensated hepatic encephalopathy is commonly triggered by infection, increased dietary protein load, alcohol use, or gastrointestinal bleeding. ED treatment of hepatic encephalopathy usually consists of supportive care and identification and treatment of infection and gastrointestinal bleeding. Administration of lactulose (orally, by nasogastric tube, or by enema) or oral neomycin has been advocated to reduce the nitrogen load. Treatment of hepatic encephalopathy with flumazenil, a benzodiazepine receptor antagonist, has been described in the literature but has not yet made its way into routine clinical practice in the ED.

This Cochrane review collected the best available evidence on the use of flumazenil for the treatment of hepatic encephalopathy caused by liver disease or hepatic failure. The authors report comprehensive and appropriate selection criteria and data sources, indicating that the likelihood that all important studies on this topic were identified is high. Studies were evaluated for methodologic quality, indicating that the

likelihood that poor-quality data were unrecognized as such is low. Heterogeneity among studies was assessed using the random-effects model. The results indicate that flumazenil was associated with a significant beneficial effect on the improvement of hepatic encephalopathy at the end of treatment but no significant long-term effect on recovery or mortality. These findings are summarized and expanded in [Table 1](#). An important result for the practicing emergency physician is the lack of a difference in adverse outcomes in patients with hepatic encephalopathy who are treated with flumazenil compared with those who are treated with placebo (risk difference 0.06; 95% CI −0.06 to 0.18) and the persistence of this lack of difference after the single study that represents a source of heterogeneity was removed from the analysis (risk difference 0.06; 95% CI −0.02 to 0.14). Caution is advised interpreting these results, since the sample size is small and adverse events often emerge with larger samples.

The use of flumazenil to improve hepatic encephalopathy caused by cirrhosis for the short term may prove helpful to patients and clinicians alike. For example, it may provide an opportunity for patients to provide a better history of their condition and treatment; allow patients to make their values, preferences, and rights (including preferences related to advance directives or surgical consent) known to providers; and improve their compliance with medical treatment regimens. To our knowledge, these outcomes have never been addressed in a primary study and were not addressed by the review. The lack of a difference in adverse events compared to placebo between groups, a result that may be questioned on the basis of heterogeneity of studies, persisted even when the trial that was a source of heterogeneity<sup>1</sup> was removed. Because there were no seizures reported in any group, it appears that flumazenil may be cautiously considered for the treatment of hepatic encephalopathy caused by cirrhosis for clinical situations for which short-term improvement is desirable or sufficient and for which there are no overriding contraindications to flumazenil.

**Table 2.** Design of a crossover trial.

Group	Period 1	Washout Period	Period 2
Group 1	Treatment A (a)	No treatment	Treatment B (b)
Group 2	Treatment B (c)	No treatment	Treatment A (d)

\*In a crossover design, patients in each group receive each treatment in turn. Differences in outcomes can be measured across treatments [(a-b)+(d-c)] or across periods [(a+c)-(b+d)].

## TAKE HOME MESSAGE

The use of flumazenil for the treatment of hepatic encephalopathy appears to cause short-term improvement and is not associated with more adverse events than placebo. In clinical situations in which short-term improvement is desirable or sufficient, flumazenil may be considered for patients with hepatic encephalopathy.

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## EBEM TEACHING POINT

Of the 13 included trials, 5 used a parallel group design and 8 used a crossover design. In a randomized controlled trial using a parallel design, patients are randomly assigned to the intervention or control treatment, and the measured outcomes are compared between groups. In a randomized controlled trial using a crossover design, patients are randomly assigned to the intervention or control treatment, as in the previous example. The difference is that patients in a crossover study act as their own controls. For example, the initial treatment is followed by a washout period in which neither treatment is administered, and then the patient receives the opposite treatment from that originally assigned. In a crossover design, measured outcomes can be compared both between groups and within individual patients because each patient receives both treatments. This comparison can be visualized in tabular form (Table 2). Treatments are compared by combining the difference between the measured outcomes for the intervention and the control treatments from within each group.

A crossover design is appropriate when the washout period is sufficiently long, the disease process is sufficiently predictable and stable, and the treatment effects are sufficiently short to permit a return to a physiologic baseline at the end of the washout. Not surprisingly, many diseases and treatments encountered in emergency medicine cannot use a crossover design.

There are several threats to the validity of a crossover trial. First, a *period effect* may exist whereby the effect is seen during one or the other period, irrespective of the treatment received. The periods (period 1 or period 2) can also be compared by looking at the difference between the measured outcomes between periods. A *carryover effect* occurs when the residual effect of the first treatment persists beyond the washout period to confound the second treatment. Carryover effects may result in a difference in outcomes between the 2 groups.

A crossover design is particularly useful for determining dose-response curves and for controlling for interpatient outcome variability, such as one might encounter when trying to quantify "improvement in hepatic encephalopathy." In general, a crossover design can reduce the total number of patients needed for a study and can increase the statistical power of a study relative to the number of patients enrolled. The fluctuating nature of hepatic encephalopathy makes a crossover design both a reasonable and a suboptimal design choice. On one hand, the crossover design's ability to reduce interpatient outcome variability is well suited to the study of hepatic encephalopathy. Conversely, its dependence on a clear return to physiologic baseline during the washout period makes the crossover design ill-suited to the study of hepatic encephalopathy. Evidence from well-designed, larger parallel group randomized controlled trials is needed to answer this question.<sup>7,8</sup>

## REFERENCES

1. Barbaro G, Di Lorenzo G, Soldini M, et al. Flumazenil for hepatic encephalopathy grade II and IVa in patients with cirrhosis: an Italian multicenter double-blind placebo-controlled, cross-over study. *Hepatology*. 1998;28:374-378.
2. Dursun M, Caliskan M, Canoruc F, et al. The efficacy of flumazenil in subclinical to mild hepatic encephalopathic ambulatory patients: a prospective, randomised, double-blind, placebo-controlled study. *Swiss Med Weekly*. 2003;133:118-123.
3. Goulenok C, Bernard B, Cadranel JF, et al. Flumazenil vs. placebo in hepatic encephalopathy in patients with cirrhosis: a meta-analysis. *Aliment Pharmacol Ther*. 2002;16:361-372.
4. Gyr K, Haussler J, Bouletreau P, et al. Evaluation of the efficacy and safety of flumazenil in the treatment of portal systemic encephalopathy: a double blind, randomised placebo controlled multicentre study. *Gut*. 1996;39:319-324.
5. Pomier-Layrargues G, Giguere JF, Lavoie J, et al. Flumazenil in cirrhotic patients in hepatic coma: a randomized double-blind placebo-controlled crossover trial. *Hepatology*. 1994;19:32-37.
6. Gitlin N, Lewis DC, Hinkley L. The diagnosis and prevalence of subclinical hepatic encephalopathy in apparently healthy ambulant, non-shunted patients with cirrhosis. *J Hepatol*. 1986;3:75-82.
7. Dallal GE. The little handbook of statistical practice. Available at: <http://www.StatisticalPractice.com>. Accessed December 26, 2005.
8. Max MB, Lynn J, eds. *Interactive Textbook of Symptom Research*. Bethesda, MD: National Institute of Dental and Craniofacial Research; 2000.