Recently there has been a renewed interest in optimizing the use of benzodiazepines for acute treatment of seizure clusters, status epilepticus, or both in either the inpatient or outpatient setting. A number of different benzodiazepines as well as different routes of administration have been pitted against each other. Studies have compared rectal diazepam versus intranasal and buccal midazolam, intravenous lorazepam versus intravenous diazepam, and buccal midazolam versus intravenous diazepam, to name a few (1–4). The current study takes a slightly different tack, as it compares two different routes of administration of the same benzodiazepine, namely, lorazepam. The authors selected lorazepam for their study based on results from the Veterans Affairs status epilepticus study, which demonstrated that lorazepam was significantly superior to phenytoin in stopping status epilepticus, as well as the study of intravenous lorazepam versus diazepam, which showed that lorazepam was superior in the out-of-hospital setting (4, 5). The present study shows no difference between intravenous and intranasal administration in the ability to stop seizures within 10 minutes.

There are a few issues with the present study that need to be taken into account when assessing the outcome. First, the authors made the interesting choice of using time of administration rather than time of decision to treat as the starting point. In a recent study comparing intravenous diazepam with intranasal midazolam, the time of emergency room admission was used to highlight the point that intravenous access may take time to achieve; therefore, seizures may continue for a longer time (6). In the current study, not only did it take a median of 4 minutes and up to 25 minutes to achieve peripheral venous access, but one child was considered to have a “protocol violation” because venous access could not be achieved within 10 minutes. The decision of whether to count this time or not depends on the intent of the study. Pragmatically, to a treating physician, the most important number would be the time from when the patient enters the emergency room to when seizures cease, and it would seem that in this study in particular, when two routes of administration of the same drug were compared, the above might be the most relevant outcome.

Why compare two routes of administration of the same drug? There are many things to consider when addressing which benzodiazepine would be optimal when treating acute seizures. The first, as indicated above, is the time necessary to actually deliver a drug to the patient. The second, is the amount of time it takes for the drug, once delivered, to reach its intended target in the central nervous system. Notably, this time depends on both the benzodiazepine selected, as well as its route of administration. What many people do not realize, is that benzodiazepines differ in their physiochemical characteristics, and these differences may make one benzodiazepine optimal under some circumstances but less optimal under others. Lorazepam is an excellent case in point. Lorazepam...
is preferred for the treatment of status epilepticus because of its ability to suppress seizures over a relatively extended period, which reduces the likelihood of relapse. Compared with the other benzodiazepines, diazepam and midazolam, lorazepam has a slower redistribution from the brain owing to lower lipid solubility and also has a reasonably long half-life (7). Thus, with intravenous administration, it is an excellent choice for treatment of status epilepticus. However, the very characteristics that make it the champion under these circumstances (its lower lipid solubility) may make it a less optimal choice for intranasal administration. It is likely that, since lipid solubility is an important characteristic for getting a drug across a mucous membrane such as the nasal cavity, intranasal lorazepam would have a slower rate of absorption and onset of action than its cousins, midazolam and diazepam.

Yet, in this study, the time to seizure cessation after intranasal administration was similar to the intravenous route. Is this “proof” that lorazepam is indeed a good choice for intranasal administration? While this study is promising, there are some important reasons why the results may not be definitive. First, the study selected children who “presented convulsing to the emergency room or develop a seizure during an ER stay.” Since patients were not required to be in status epilepticus to be enrolled in the study, it is possible (or maybe even likely) that their seizures would have ceased even without administration of a benzodiazepine. In the absence of a placebo arm, this cannot be known. Second, fully half of the children in this study, which was performed in India, were having seizures as a result of neurocysticercosis. Thus, it is unclear whether the results would be generalizable to other populations.

The choice of the ideal benzodiazepine will depend on the speed at which therapy must be initiated, the necessity for prolonged protection against seizures, the use in the emergency room versus by patients or caregivers at home, and the ease of use of a given formulation. It is quite likely that the optimal benzodiazepine may differ depending on situation and user. Thus, it is to be hoped that different formulations of a number of benzodiazepines will be available in the future.

by Jacqueline A. French, MD

References
Instructions
The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. Each author should submit a separate form and is responsible for the accuracy and completeness of the submitted information. The form is in four parts.

1. Identifying information.
   Enter your full name. If you are NOT the main contributing author, please check the box “no” and enter the name of the main contributing author in the space that appears. Provide the requested manuscript information.

2. The work under consideration for publication.
   This section asks for information about the work that you have submitted for publication. The time frame for this reporting is that of the work itself, from the initial conception and planning to the present. The requested information is about resources that you received, either directly or indirectly (via your institution), to enable you to complete the work. Checking “No” means that you did the work without receiving any financial support from any third party – that is, the work was supported by funds from the same institution that pays your salary and that institution did not receive third-party funds with which to pay you. If you or your institution received funds from a third party to support the work, such as a government granting agency, charitable foundation or commercial sponsor, check “Yes”. Then complete the appropriate boxes to indicate the type of support and whether the payment went to you, or to your institution, or both.

3. Relevant financial activities outside the submitted work.
   This section asks about your financial relationships with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. For example, if your article is about testing an epidermal growth factor receptor (DGFR) antagonist in lung cancer, you should report all associations with entities pursuing diagnostic or therapeutic strategies in cancer in general, not just in the area of EGFR or lung cancer.

   Report all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. This should include all monies from sources with relevance to the submitted work, not just monies from the entity that sponsored the research. Please note that your interactions with the work’s sponsor that are outside the submitted work should also be listed here. If there is any question, it is usually better to disclose a relationship than not to do so.

   For grants you have received for work outside the submitted work, you should disclose support ONLY from entities that could be perceived to be affected financially by the published work, such as drug companies, or foundations supported by entities that could be perceived to have a financial stake in the outcome. Public funding sources, such as government agencies, charitable foundations or academic institutions, need not be disclosed. For example, if a government agency sponsored a study in which you have been involved and drugs were provided by a pharmaceutical company, you need only list the pharmaceutical company.

4. Other relationships
   Use this section to report other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work.
**American Epilepsy Society**  
*Epilepsy Currents Journal*  
Disclosure of Potential Conflicts of Interest

**Section #1 Identifying Information**

1. Today’s Date: 10/18/2011

2. First Name: Jacqueline  Last Name: French  Degree: MD

3. Are you the Main Assigned Author?  ✔ Yes  ☐ No
   
   If no, enter your name as co-author:

4. Manuscript/Article Title: Benzo vs benzo: and the winner is…

5. Journal Issue you are submitting for: 11.5

**Section #2 The Work Under Consideration for Publication**

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc.)?

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

<table>
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<th>Type</th>
<th>No</th>
<th>Money Paid to You</th>
<th>Money to Your Institution*</th>
<th>Name of Entity</th>
<th>Comments**</th>
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* This means money that your institution received for your efforts on this study.

** This section to provide any needed explanation.

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10/18/2011
### Section #3 Relevant financial activities outside the submitted work.
Place a check in the appropriate boxes in the table to indicate whether you have financial relationships (regardless of amount of compensation) with entities as described in the instructions. Use one line for each entity; add as many lines as you need by clicking the “Add” box. You should report relationships that were present during the 36 months prior to submission.

Complete each row by checking “No” or providing the requested information. If you have more than one relationship just add rows to this table.

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* This means money that your institution received for your efforts.
** For example, if you report a consultancy above there is no need to report travel related to that consultancy on this line.

### Section #4 Other relationships
Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?

- [ ] No other relationships/conditions/circumstances that present a potential conflict of interest.
- [x] Yes, the following relationships/conditions/circumstances are present:

I receive 25% salary support for my work for the Consortium, but this is from work performed for 10 companies, not just the two listed which have projects related to benzodiazepines.

Thank you for your assistance.
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