Acute repetitive seizures (ARS) are also sometimes termed serial, repetitive, recurrent, cluster, or crescendo seizures (1). Although there is not a universally agreed upon definition, the essential features of ARS include multiple seizures (usually three or more) over a relatively short period of time (usually <24 hours). The seizures that compose ARS may be different from the patient’s usual isolated seizures, and the patient or family may be able to use these features to identify the onset of ARS. The type, duration, or severity of seizure may be characteristic at onset of ARS, or alternatively, ARS may be identified simply by increased frequency of typical seizures. ARS are distinguished from status epilepticus by recovery between the discrete seizures. ARS may be seen with nearly any seizure type, but the term is less often applied to myoclonic or absence seizures, which prototypically involve multiple seizures.

The prevalence of ARS is not well known. Certain epilepsy syndromes are more likely to include ARS, namely symptomatic generalized and refractory localization-related epilepsy syndromes. A population-based study of ARS in the United Kingdom estimated that the crude prevalence in the general population was 2.3 per 10,000 (2). The prevalence was highest in the very young (ages 0–4) at 5.9 per 10,000, and declined with age to 0.5 per 10,000 in those aged 70 and older. They estimated that ARS affect about 3 percent of the epilepsy population, which corresponds to about 0.02 percent of the general population. There is evidence that the prevalence of ARS in

**A Double-Blind, Randomized, Placebo-Controlled Trial of a Diazepam Auto-Injector Administered by Caregivers to Patients With Epilepsy Who Require Intermittent Intervention for Acute Repetitive Seizures.**


**PURPOSE:** A diazepam auto-injector (AI) has been developed for intramuscular administration to treat acute repetitive seizures (ARS). The objective of this study was to evaluate the efficacy and safety of the diazepam AI when administered by caregivers to control an episode of ARS. **METHODS:** In this phase III, randomized, double-blind, parallel-group, placebo-controlled, multicenter study, subjects with epilepsy on a stable antiepileptic drug regimen who required intermittent medical intervention to control ARS were randomized 1:1 to the placebo AI or the diazepam AI group. Subjects were stratified according to age (2–5, 6–11, ≥12 years). Dose (5, 10, 15, or 20 mg) was based on age and weight. A single dose of study medication was dispensed to be administered by caregivers in an outpatient setting when required. The primary end point was time to next seizure or rescue from 15 min to 12 h postdose. Secondary end points included rescue medication use, number of seizures postdose, caregiver and physician treatment assessments, and safety measures. **KEY FINDINGS:** Of 234 subjects randomized, 81/110 in the placebo AI group and 82/124 in the diazepam AI group were included in the intent-to-treat analysis. Baseline characteristics were similar for both groups. Time to next seizure or rescue was significantly longer in the diazepam AI group compared with the placebo AI group, with a hazard ratio of 0.55 (95% confidence interval (CI) 0.34–0.88; p = 0.012) for diazepam AI versus placebo AI, adjusted for age group. The 25th percentile for time to the next seizure or rescue was 1.18 h (95% CI 0.38–2.03) for placebo AI and 2.70 h (95% CI 0.48–11.42) for diazepam AI; the median was 5.9 h for placebo AI and was inestimable for diazepam AI due to the low number of events experienced by subjects in that group. The proportion of subjects using rescue medication postdose was 30% (24/81) placebo AI versus 17% (14/82) diazepam AI (p = 0.066). An event (seizure or rescue) occurred in 55.6% of subjects in the placebo AI group and 35.4% in the diazepam AI group. The number of seizures experienced during the 12-h postdose period was significantly lower for diazepam AI (median 0.0) compared with placebo AI (median 1.0; p = 0.010). **SIGNIFICANCE:** The diazepam AI was significantly more effective than placebo AI at delaying the next seizure or rescue. Secondary efficacy end points were generally supportive of the primary outcome. Diazepam AI administered by trained caregivers was effective for the treatment of ARS and was well-tolerated, with a safety profile similar to placebo.
an epilepsy-center population is much higher (3). Although the overall proportion of patients with ARS is relatively small, those with ARS are at risk for medical complications, including injury and progression to status epilepticus, and require disproportionate resources, often including emergency department care. Optimal management of ARS begins at home, before the need for emergency department care arises.

A flurry of publications appeared in the period from 1998 to 2002 supporting the development of rectal diazepam for acute repetitive seizures. Two randomized-controlled trials (RCTs) of rectal diazepam for ARS established the safety and efficacy of out of hospital benzodiazepine administration by this route (4, 5). Two follow-up studies, one in children (6) and one in adults (7), used combined subset data from the two RCTs to confirm efficacy and safety in each of these age groups.

Rectal diazepam provided a much needed treatment option for ARS, but the route of administration may be cumbersome and problematic in social settings. An often quoted study by Tatum (8) examined the attitude of adult patients toward the use of rectal diazepam. The survey is frequently cited to highlight problems with the rectal route of administration; however, the responses in fact represented a glass half empty/glass half full proposition. When asked whether seizures or use of rectal medications was more embarrassing, responses were equally split. Two-thirds of respondents denied embarrassment related to use of rectal medications. There was a strong preference among respondents to avoid trips to the emergency department. This relative acceptance notwithstanding, options for other routes of administration for acute therapy in ARS are desirable.

Several alternative routes for acute administration of benzodiazepines have been and are being explored. Buccal administration of midazolam for ARS has been used widely in many parts of the world, but is not approved by the FDA for this use. Midazolam is rapidly absorbed following buccal administration, with reasonably high bioavailability in controlled settings, but carries at least theoretical risks of aspiration or inconsistent absorption in the setting of ictal hypersalivation. Intranasal administration of benzodiazepines provides rapid absorption and levels comparable with rectal dosing, and is under active investigation. Intramuscular (IM) administration also permits rapid administration, and there is a longstanding experience with lay use of auto-injectors such as the epinephrine auto-injector (EpiPen) for treatment of acute anaphylaxis. Although past studies have raised concerns about delayed or inconsistent absorption of benzodiazepines following IM injection, findings from studies using current technology have allayed these fears (9).

The RAMPART study, using auto-injector IM administration of midazolam by medical personnel for the treatment of pre-hospital status epilepticus, demonstrated safety and efficacy of benzodiazepine administration by auto-injection and the results compared favorably with intravenous administration of lorazepam (10).

The study by Abou-Khalil and colleagues investigated use of a diazepam intramuscular auto-injector for patients with ARS (1). The study design was similar to the previous studies of rectal diazepam (4). This was a randomized, double-blind, placebo-controlled study that included 73 pediatric (≥ age 2) and 90 adult patients with ARS, randomized to treatment with IM diazepam (with weight-adjusted doses) or placebo. ARS were not strictly defined, but seizures had to be readily identified and repetitive, requiring intermittent medical intervention. Appropriate safety exclusions were in place, including for patients who were known to consistently progress to status epilepticus. A reliable, trained caregiver administered the study drug and recorded seizures for 12 hours following dosing. The primary efficacy endpoint was time to next seizure or need for rescue medication over the 12 hours following IM injection of the study drug. Several other objective and subjective secondary end points were also examined.

Intramuscular injection of diazepam for ARS appeared effective. Compared with placebo, the hazard ratio for an event (next seizure or rescue) in the diazepam treated group was 0.55 (95% CI 0.34–0.88; p = 0.012), and Kaplan-Meier curves showed early separation of the diazepam and placebo groups. Overall, a next seizure or rescue event was more common in the placebo group (55.6%) than the diazepam group (35.4%), representing an absolute risk reduction of 20.2 percent. Fewer diazepam-treated subjects required rescue therapy or emergency department care, but the difference was not statistically significant. Both caregiver and physician global assessments favored the diazepam group; only the latter finding was statistically significant. Safety data were favorable, including no serious respiratory problems; most adverse events related to local pain at the injection site.

Rectal administration of therapy for ARS is acceptable to many patients when there are no approved alternatives. However, safe and effective treatment of ARS delivered by an alternative route (e.g., intranasal, intramuscular) would likely be widely and preferentially adopted by most patients. Findings in this study of IM administration of diazepam using an auto-injector were roughly comparable with those obtained in studies of rectal administration. As this and several other products advance in the pipeline, new options for treatment of ARS are likely to become available soon.

by David Spencer, MD

References
6. Kriel RL, Cloyd JC, Pellock JM, Mitchell WG, Cereghino JJ, Rosman NP. Rectal diazepam gel for treatment of acute repetitive


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.**
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2. First Name  David     Last Name Spencer  Degree MD

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4. Manuscript/Article Title: Hope for New Treatments for Acute Repetitive Seizures

5. Journal Issue you are submitting for:  14-3

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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.)?

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* This means money that your institution received for your efforts on this study.
** Use this section to provide any needed explanation.
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<td>PI for studies sponsored by NeuroPace and Upsher-Smith Laboratories. Neither I nor my institution receive direct compensation</td>
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<td>6. Payment for lectures including service on speakers bureaus</td>
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<td>12. Travel/accommodations/meeting expenses unrelated to activities listed.**</td>
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David Spencer, MD

Thank you for your assistance.
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