for assisted ventilation because of a drop in oxygen saturation or a reduction in respiratory rate or effort, was reported in 1.2% and 4.6% of patients in these studies (42, 47). Two of the class III IM or intranasal midazolam studies reported significant respiratory depression (36–39, 43, 45, 46, 53). Single children in each study (6.25% and 2%) in the IM midazolam group experienced respiratory failure resulting in artificial ventilation (51, 55).

Two class III studies involved intranasal lorazepam. In one study of 80 children, a drop of ≥5 mm Hg in systolic and diastolic blood pressure was noted in 15 (18.8%) and 12 (15%) children, respectively, while only two (2.5%) had a fall in oxygen saturation below 92% (44). In a second study of 71 children, none developed significant hypotension and only one (1.4%) required assisted ventilation (52).

The following conclusions were drawn. Respiratory depression is the most common clinically significant treatment-emergent adverse event associated with anticonvulsant drug treatment in status epilepticus in children (level A). No substantial difference probably exists between midazolam, lorazepam, and diazepam administration by any route in children with respect to rates of respiratory depression (level B). Adverse events, including respiratory depression, with benzodiazepine administration for status epilepticus have been reported less frequently in children than in adults (level B).

Q3. Which Is the Most Effective Benzodiazepine?

Adult Studies

In a class I prehospital status epilepticus study (23), the percentage of patients' status epilepticus stopped by lorazepam was higher but not significantly different than with diazepam (odds ratio [OR], 1.9; 95% CI: 0.8–4.4). However, the study's sample size was selected to be able to detect a difference between the active drugs and placebo, not to detect a difference between the two active drugs (23). In a class II lorazepam–diazepam comparative trial (25), there was no difference between the two arms in the percentage of patients having control of seizures after either one injection (lorazepam, 78%; diazepam, 58%; not significant [NS]) or two injections (lorazepam, 89%; diazepam, 76%; NS). There was no significant difference between the two arms in the latency of action (lorazepam median, 3 minutes; diazepam median, 2 minutes; NS) (25).

The class I RAMPART trial (24) reported seizures were absent in 73% of subjects in the IM midazolam group compared with 63% in the IV lorazepam group, resulting in an absolute difference of 10% (95% CI: 4.0–16.1; $p < 0.001$) that met the prespecified noninferiority requirements plus additional superiority for both per protocol and ITT analyses. Median time from active treatment to cessation of convulsions was shorter for IV lorazepam (1.6 minutes) compared with IM midazolam (3.3 minutes), which was offset by more rapid IM midazolam administration (IV lorazepam, 4.8 minutes, vs intranasal midazolam, 1.2 minutes) (24).

There is no difference in the treatment-emergent adverse-event profiles between lorazepam and diazepam in the three adult class I and class II status epilepticus studies (22, 23, 25). No differences in treatment-emergent adverse-event profiles were found between IM midazolam and IV lorazepam (24). There is pharmacokinetic evidence to suggest a longer duration of action (but not longer half-life) for lorazepam compared with diazepam (61).

The following conclusions were drawn. In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam (level A). No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus (level A).

Pediatric Studies

As described in detail in Question 1, one class I trial enrolled and randomized 273 children to either IV diazepam or IV lorazepam (34). Efficacy was similar between IV diazepam (101/140, 72.1%) and IV lorazepam (97/133, 72.9%). As described in detail in Question 2, side-effect profiles of the two treatments were similar (34).

A meta-analysis of six class III pediatric studies (36, 38–40, 42, 47) found non-IV midazolam (IM/intranasal/buccal) was more effective than diazepam (IV/rectal) at achieving seizure cessation (relative risk [RR] =1.52, 95% CI: 1.27–1.82) with similar respiratory complications (RR = 1.49; 95% CI: 0.25–8.72) (62). Time to seizure cessation was shorter for intranasal midazolam compared with IV diazepam in two studies (38, 46) and longer in one study (39). Comparing intranasal midazolam and rectal diazepam, intranasal midazolam was more effective in terminating seizures (37) and demonstrated a shorter time to seizure termination (45). Comparing IM midazolam to IV diazepam, a shorter interval to seizure cessation was found for IM midazolam in both studies (36, 43). Only one study found a significantly shorter time to seizure cessation for buccal midazolam compared with rectal diazepam (42).

One study comparing lorazepam to diazepam found no difference between the treatments in the time for the initial (presenting) seizure to stop after anticonvulsant administration but did find fewer lorazepam patients required multiple doses (lorazepam, 8/33, vs diazepam, 25/53; $p < 0.05$) or additional anticonvulsants (lorazepam, 1/33, vs diazepam, 17/53; $p < 0.01$) for seizure cessation (35).

The following conclusions were drawn. In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam (level A). In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal) (level B).

Q4. Is IV Fosphenytoin More Effective Than IV Phenytoin?

Three class III RCTs examined the comparative tolerability of IV fosphenytoin and IV phenytoin (63). A single-dose, randomized, double-blind, class III tolerability study in patients needing infusion of phenytoin compared fosphenytoin ($n = 39$, 12.7 mg/kg, 82 mg phenytoin equivalent [PE]/min [range, 40–103 mg PE/min]) to phenytoin ($n = 13$, 11.3 mg/kg, 42.4 mg/min). In contrast to phenytoin, there were no fosphenytoin-related significant cardiac arrhythmias, change in heart rate, respiration or blood pressure (63). A second study involved patients requiring a phenytoin loading dose and