class III RCT was conducted across nine hospitals in Sub-Saharan Africa and involved 436 children. The efficacy of sublingual lorazepam (131/234, 56%) was significantly lower than that for rectal diazepam (160/202, 79%; $p < 0.001$) for terminating seizures within 10 minutes of study drug administration (54).

Sixteen class III studies compared midazolam with diazepam. In five studies, buccal midazolam was compared with rectal diazepam (40–42, 47, 50). In one study, in 177 children experiencing 219 separate seizures, buccal midazolam was more effective than rectal diazepam in stopping seizures whether all seizures were considered (56% vs 27%) or just initial episodes (42). The largest study of 330 children in Uganda found a lower rate of treatment failure (seizures lasting longer than 10 minutes after medication administration or seizure recurrence within 1 hour) for buccal midazolam compared with rectal diazepam (30.3% vs 43%; $p = 0.016$). This superiority was limited to a subgroup of patients without malaria, with buccal midazolam superior to rectal diazepam with respect to treatment failure (26.2% vs 55.9%; $p = 0.002$) (47). In an RCT of 98 children (aged 3 months to 12 years), buccal midazolam was superior to rectal diazepam for control of seizures within 5 minutes of administration (49/49, 100%, vs 40/49, 82%; $p < 0.001$), treatment initiation time (median 2 vs 3 minutes; $p < 0.001$), and drug effect time (median 4 vs 5 minutes; $p < 0.001$) (50). In the two smaller studies ($n = 79$ and $n = 43$), there was no difference in efficacy between buccal midazolam and rectal diazepam (40, 41).

Intranasal midazolam was compared with IV diazepam in four class III pediatric studies (38, 39, 46, 53). In one study involving children with prolonged febrile seizures, time to drug administration of intranasal midazolam was faster ($p < 0.001$) but the time period between drug administration and seizure cessation was shorter for IV diazepam ($p < 0.001$) (38). The second study found that the mean time to achieve seizure control was faster for IV diazepam compared with intranasal midazolam ($p < 0.007$) (39). A third study found intranasal midazolam was significantly faster to administer than IV diazepam, with a slower mean time to seizure cessation after medication administration for intranasal midazolam compared with IV diazepam, but a faster time to seizure cessation after hospital arrival with intranasal midazolam ($p < 0.001$ for all comparisons) (46). Lastly, an RCT of 60 children (aged 2 months to 15 years), equally divided between intranasal midazolam (0.2 mg/kg) and IV diazepam (0.3 mg/kg), found the time to control seizures was shorter using intranasal midazolam compared with IV diazepam (3.16 ± 1.24 minutes vs 6.42 ± 2.59 minutes; $p < 0.001$) when the time needed to establish IV access was included (53).

Three trials examined the efficacy of intranasal midazolam compared with rectal diazepam (37, 45, 51). Intranasal midazolam (0.2 mg/kg, maximum dose, 10 mg) was compared with rectal diazepam (0.3 to 0.5 mg/kg, maximum dose, 20 mg) for prehospital seizures lasting longer than 5 minutes. Overall, 92 children received study medication, and no difference in total seizure time after medication administration between therapies was identified (51). Another trial involving 46 children experiencing 188 seizures compared the efficacy of intranasal midazolam 0.3 mg/kg (92 episodes) to rectal diazepam 0.2 mg/kg (96 episodes) for terminating seizures within 10 minutes of drug administration. The time to seizure cessation was significantly faster for intranasal midazolam (116.7 ± 126.9 seconds vs 178.6 ± 179.5 seconds; $p = 0.005$), with a trend toward a higher success rate with intranasal midazolam (89/92, 96.7%) compared with rectal diazepam (85/96, 88.5%; $p = 0.060$) (45). A third smaller trial ($n = 45$) found intranasal midazolam was more effective than rectal diazepam (87% vs 60%; $p < 0.05$) (37).

Intramuscular midazolam was compared with IV diazepam in three class III studies (36, 43, 55). In all three studies, IM midazolam had a shorter interval to seizure cessation, but there was no significant difference in overall efficacy for termination of seizures (36, 43, 55).

One study compared buccal midazolam 0.2 mg/kg with IV diazepam 0.3 mg/kg, with no significant difference found in overall efficacy (defined as complete cessation of seizures 5 minutes after administration of study treatment) (48). Time to seizure cessation from identification of the seizure in the emergency department was significantly shorter for buccal midazolam compared with IV diazepam (2.39 minutes vs 2.98 minutes, respectively), with most of the difference driven by more rapid time to initiation of treatment (48).

Intravenous lorazepam (0.1 mg/kg over 2–4 minutes) was compared with IV levetiracetam (20 mg/kg over 15 minutes) in a class III RCT involving children with either convulsive or subtle convulsive status epilepticus (30). As first therapy, lorazepam success rate (29/38, 76.3%) was similar to that for levetiracetam (31/41, 75.6%) (30).

In one RCT, children with convulsive seizures at time of presentation received either IV valproic acid (20 mg/kg) with diazepam (0.3 mg/kg) ($n = 16$) or IV phenytoin (20 mg/kg) with diazepam (0.3 mg/kg) ($n = 17$) (56). There was no difference in efficacy outcomes between these two arms (56).

The only class III pediatric RCT not involving a benzodiazepine compared IV phenytoin ($n = 33$) and IV valproic acid ($n = 35$). Overall, valproic acid had higher efficacy than phenytoin (valproic acid, 66%, vs phenytoin, 42%; $p = 0.046$), but only 23% and 12% of the cohorts were 15 years old or younger, with no statistical adjustment for these dissimilar proportions (27).

Two RCTs (one class II [58] and one class III [31]) addressed second-therapy efficacy in children after failure of initial benzodiazepine therapy. The class II study compared IV valproic acid (20 mg/kg, $n = 30$) with IV phenobarbital (20 mg/kg, $n = 30$) in children 3 to 16 years old whose seizures did not respond to IV diazepam (0.2 mg/kg) within 5 minutes. No significant difference was noted in efficacy between valproic acid and phenobarbital (27/30, 90%, vs 23/30, 77%; $p = 0.189$) for terminating seizures within 20 minutes, but the valproic acid group experienced significantly fewer clinically significant adverse effects (24% vs 74%; $p < 0.001$) (58). The second study involved both adults and children and found that the efficacy of IV valproic acid was similar to that of IV phenytoin (88% vs 84%) in patients whose seizures did not respond to 0.2 mg/kg of IV diazepam (31).

The following conclusions were drawn. In children, IV lorazepam and IV diazepam are established as efficacious