continuous ECG monitoring, pulse oximetry, and continuous waveform capnography as soon as the situation safely allows.

Of note, the evidence surrounding emergency physician use of ketamine for procedural sedation was reviewed in a 2014 clinical policy.[44] Ketamine is widely and safely administered for procedural sedation in EDs, and emergency physicians are already familiar with the drug's desired effects and potential complications. As such, the authors made a consensus recommendation for its use for sedation of agitated patients in the ED.

Other Agents

Whereas the vast majority of the literature has focused on the use of antipsychotics and benzodiazepines for the management of acute agitation in the out-of-hospital and ED settings, other modalities have been studied and may be considered. This brief review is included to frame an understanding of alternatives to the more traditional medications described above.

One Class III study by Asadollahi et al[45] investigated the efficacy of intravenous sodium valproate versus intramuscular haloperidol in the treatment of acute agitation in the ED. This single university hospital double-blind parallel group included agitated adult patients as confirmed by an attending emergency physician or a psychiatrist. Of note, physiologic causes of agitation were excluded. The primary outcome was agitation measured at baseline and 30 minutes after injection using 3 different agitation scales. The valproate study arm (80 patients) received 20 mg/kg intravenous valproate compared with 5-mg intramuscular haloperidol in the second haloperidol study arm (80 patients). No significant difference was found in the sedation scores between valproate and haloperidol arms with regard to decreased levels of agitation. The endpoint change in efficacy measures at 30 minutes after the first injection (intention-to-treat, N=160) was larger for the valproate-treated patients (4.73±1.93) compared with haloperidol-treated patients (5.45±2.09). The authors did note that the haloperidol treatment group had a significantly larger proportion of patients who showed at least one adverse event (37 of 80, 46.2%) than the valproate treatment group (24 of 80, 30%), with intense sedation 30 minutes after intervention representing the most frequent adverse event. Of note, they also found a vomiting and headache incidence of 16.2% (13 of 80) and 11.2% (9 of 80), respectively, in the valproate treatment group compared with none in the haloperidol group. The authors conclude that valproate may be a viable alternative agent for treatment of agitation; however, the side effects of headache, vomiting, and teratogenicity may limit its utility.

Two other Class III studies evaluated supplementing intramuscular haloperidol with additional agents for the treatment of agitation.[46,47] In the first Class III study, Raveendran et al[46] utilized intramuscular promethazine in addition to haloperidol compared with intramuscular olanzapine with the intent that the addition of promethazine will reduce the acute dystonic reactions sometimes seen with haloperidol. In this single-site trial performed in a psychiatric ED in south India, patients with acute agitation were randomized to receive either intramuscular olanzapine or intramuscular haloperidol plus promethazine. Both were equally effective for the primary outcome of tranquillization or sedation at 15 minutes and 4 hours. Additional findings demonstrated that the combination of haloperidol plus promethazine sedated patients more rapidly, and the effects lasted longer. Seventeen percent more patients given olanzapine compared with haloperidol plus promethazine required repeated physician involvement for increased aggression (number needed to treat=6, 95% CI 4 to 13), and additional medications were required to manage aggression over the 4 hours of the study period in 20% more patients who were administered olanzapine than those given haloperidol plus promethazine (number needed to treat=6; 95% CI 3 to 10), 65 of 150 (43%) versus 31 of 150 (21%); relative risk, 2.07; 95% CI 1.43 to 2.97).[45] The authors concluded that both olanzapine and haloperidol plus promethazine provided effective sedation with similar adverse events, but haloperidol plus promethazine resulted in longer sedation over 4 hours without the need for additional sedative agents.

In the second Class III study, the TREC (tranquilização rápida-ensaio clínico [rapid tranquillisation-clinical trial]) Collaborative Group (2003)[47] compared intramuscular midazolam with the combination of intramuscular haloperidol and promethazine. This pragmatic randomized clinical trial enrolled aggressive or agitated patients with mental illness in 3 psychiatric EDs in Brazil. The primary outcome was patient tranquility or sedation at 20 minutes. Numerous secondary outcomes were evaluated: patients tranquil or asleep at later intervals, patients restrained or given extra drugs within 2 hours, and severe adverse events. With regard to the primary outcome, 134 of 151 (89%) of patients given midazolam were tranquil or asleep after 20 minutes compared with 101 of 150 (67%) of patients given haloperidol plus promethazine (relative risk 1.32; 95% CI 1.16 to 1.49). The midazolam study arm continued to demonstrate statistically and clinically significant superiority with 13% tranquil or asleep (relative advantage