

Pharmacological Treatment for Paroxysmal Sympathetic Hyperactivity

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BACKGROUND Paroxysmal sympathetic hyperactivity, which affects up to 10% of all acquired brain injury survivors, is characterized by elevated heart rate, blood pressure, respiratory rate, and temperature; diaphoresis; and increased posturing. Pharmacological agents that have been studied in the management of this disorder include opiates, γ -aminobutyric acid agents, dopaminergic agents, and β blockers. Although paroxysmal sympathetic hyperactivity is a relatively common complication after acquired brain injury, there is a paucity of recommendations or comparisons of agents for the management of this disorder.

OBJECTIVE To evaluate all relevant literature on pharmacological therapies used to manage patients with paroxysmal sympathetic hyperactivity to help elucidate possible best practices.

METHODS Of the 27 studies evaluated for inclusion, 10 studies received full review: 4 retrospective cohort studies, 5 single case studies, and 1 case series.

RESULTS Monotherapy is usually not effective in the management of paroxysmal sympathetic hyperactivity and multiple agents with different mechanisms of action should be considered. α_2 -Agonists such as dexmedetomidine may hold some slight clinical efficacy over agents like propofol, and with respect to oral medications, propranolol might convey some slight advantage compared to others. However, with the limited data available, these results must be interpreted with caution.

CONCLUSIONS As the treatment of paroxysmal sympathetic hyperactivity is reactive to symptomatic evolution over time, critical care nurses play a vital role in the monitoring and treatment of these patients. Limited data exist on the management of paroxysmal sympathetic hyperactivity and larger robust data sets are needed to guide decision-making. (*Critical Care Nurse*. 2020;40[3]:e9-e16)

CE 1.0 hour, Pharma 0.5, CERP A

This article has been designated for CE contact hour(s). The evaluation tests your knowledge of the following objectives:

1. Describe 2 different agents used in the management of paroxysmal sympathetic hyperactivity.
2. Analyze current literature addressing paroxysmal sympathetic hyperactivity management.
3. Discuss 2 pros and cons to each agent that can be used in management of paroxysmal sympathetic hyperactivity.

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Episodic sympathetic hyperactivity following traumatic brain injury (TBI) has been described in the literature as early as the 1950s.¹ Previously described by several terms such as *sympathetic storming*, *autonomic storming*, and *dysautonomia*, the nomenclature has since been revised to paroxysmal sympathetic hyperactivity (PSH) disorder.² This disorder affects up to 10% of all TBI survivors.³ Along with increased morbidity, PSH disorder is associated with higher health care costs and longer hospitalizations.³⁻⁵

Although there are several theories regarding the mechanisms of PSH, the pathophysiology is not well delineated and remains an area of ongoing research.³ The disorder is characterized by a constellation of non-specific symptoms including tachycardia, hypertension, tachypnea, pyrexia, diaphoresis, and increased posturing (Figure 1). Paroxysmal sympathetic hyperactivity was considered to be a diagnosis of exclusion until Baguley's 11-point probabilistic diagnostic scale, the PSH-Assessment Measure (PSH-AM), was published in 2014. The PSH-AM includes both a Diagnosis Likelihood Tool and Clinical Feature Scale and aids in the diagnosis of PSH when confronted with these nonspecific symptoms.²

With a solidified nomenclature and diagnostic criteria, this condition has the potential to be treated more effectively to decrease morbidity associated with secondary brain damage. Presently, treatment strategies for PSH are focused on symptomatic management and include opiates, γ -aminobutyric acid-mediated agents, dopaminergic agents, and β blockers. Although PSH is a relatively

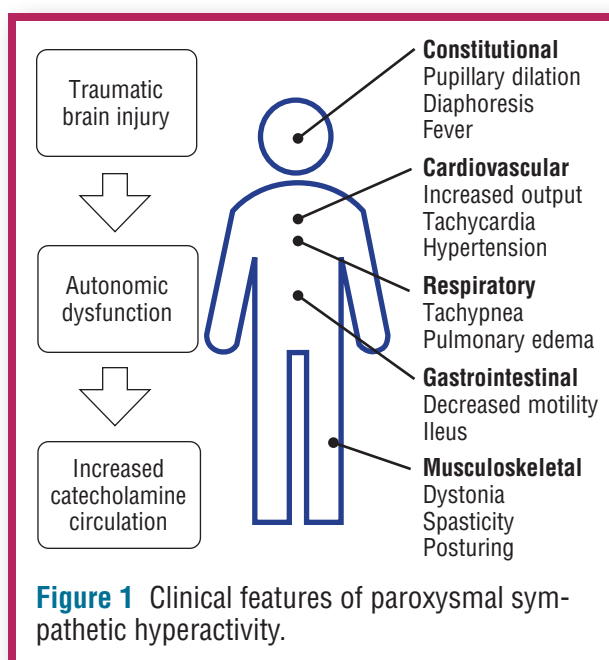


Figure 1 Clinical features of paroxysmal sympathetic hyperactivity.

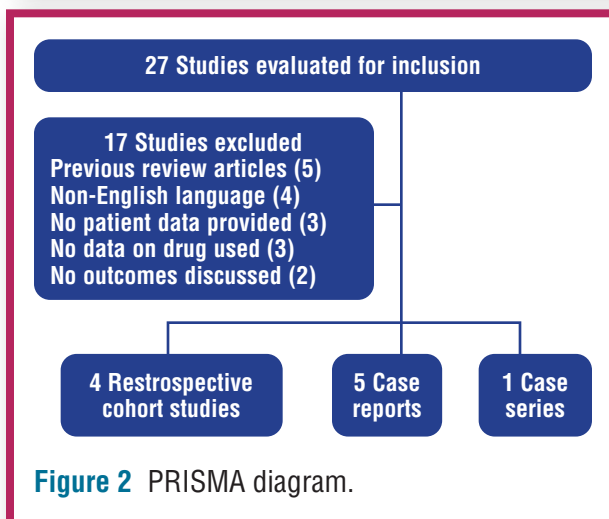


Figure 2 PRISMA diagram.

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common complication after TBI, a paucity of recommendations or head-to-head comparisons of agents for the management of PSH exists. This review aimed to evaluate all relevant literature to help elucidate possible best practices with the limited data that exist.

Methods

A systematic literature search of MEDLINE was conducted from 1970 to February 14, 2018, using the search terms *traumatic brain injury*, *sympathetic storming*, *paroxysmal sympathetic hyperactivity disorder*, *storming*, and *episodic sympathetic hyperactivity* to identify suitable studies. Only articles in the English language were considered. Figure 2 shows the PRISMA (Preferred Reporting Items

for Systematic Reviews and Meta-Analyses) diagram of studies included and excluded from review. Articles were included for review if they were in the English language, were not a previous review article, described therapies in actual clinical cases, and were full texts (abstracts were excluded from review). Two independent reviewers identified relevant articles and graded them for inclusion. If there was disagreement between the 2 reviewers regarding article inclusion, a third independent reviewer made the final decision. Because of the large heterogeneity among the studies, a meta-analysis was considered futile and therefore not performed.

Literature Evaluation

A total of 27 studies were evaluated for inclusion, with 10 studies ultimately receiving full review. Among the nearly 600 patients evaluated in the 10 studies, 99.1% had TBI as their primary diagnosis, 0.56% had stroke listed as the primary diagnosis, and 0.34% had anoxic injury listed as the primary insult. There were 4 retrospective cohort studies included in the final analysis, which comprised the majority of the patients analyzed (> 99%), 5 single case studies, and 1 case series.

Retrospective Studies

In a retrospective cohort study by Pozzi et al,⁶ children and adolescents with acquired brain injury of various etiology who had at least 1 PSH episode for 7 consecutive days were evaluated and compared to controls admitted during the same time frame who did not experience signs of PSH. A total of 407 patients were included: 26 patients who experienced an episode of PSH and 381 controls. Statistically significantly greater numbers of patients with PSH versus controls scored more than 21 on the Disability Rating Scale (17/26, 70.8% vs 118/381, 34.4%; $P = .001$) and experienced higher incidence of death (5/26, 19.2% vs 8/381, 2.1%; $P < .001$). Only medications specifically administered to patients as needed for acute PSH symptoms were recorded, and the decision on which drugs and doses to administer was left to the discretion of each treating physician. Acetaminophen was the most frequently administered medication (140 administrations), but did not have significantly superior effects versus control (odds ratio [OR] 0.98, 95% CI 0.53-1.82) with regard to reduction of symptoms. The administration of clonazepam and lorazepam had large effect sizes with ORs

greater than 2 with respect to symptom cessation; however, these failed to reach statistical significance. Hydroxyzine was the only medication that demonstrated statistically significant benefit versus controls in reduction in overall symptoms of PSH (OR 2.88, 95% CI 1.01-8.25). The authors concluded that PSH episodes cannot be controlled by analgesia alone and may require additional abortive medications such as benzodiazepines and hydroxyzine.

The study by Pozzi et al⁶ highlights the need for multimodal treatment to control PSH symptoms, as single classes of medications may not effectively abate PSH symptoms. Critical care nurses should be cognizant of the adjunctive medications available when caring for patients with acquired brain injury and request medications with different mechanisms of action when caring for patients who display PSH symptoms.

In a retrospective cohort study, Peng et al⁷ examined the efficacy of dexmedetomidine versus propofol for PSH symptom relief. The investigation included 72 patients (32 patients in dexmedetomidine cohort, 40 patients in propofol cohort) who all experienced a TBI and required neurosurgical intervention. Patients in the dexmedetomidine group received a loading dose of 1 µg/kg and a maintenance dose of 0.3 to 0.6 µg/kg per hour as needed, whereas patients in the propofol group received a continuous intravenous (IV) infusion of 0.3 to 4 mg/kg per hour that was adjusted according to sedation scores (not to exceed 4 mg/kg per hour). Although patients in both groups showed an acute response to the medications, the dexmedetomidine group was superior to propofol in controlling several characteristics of PSH. Mean (SD) time to paroxysmal hypertension resolution (29.03 [8.86] minutes vs

42.0 [14.77] minutes; $P < .01$), time to paroxysmal hypermyotonia remission (3.97 [1.73] minutes vs 5.56 [1.51] minutes; $P < .01$), paroxysmal hypermyotonia remission rate (61.22% [10.8%] vs 41.52% [14.15%]; $P < .01$), paroxysmal hypermyotonia duration (9.31 [2.66] days vs 13.05 [4.19] days; $P < .01$), time for body temperature to return to normal (10.62 [4.14] days vs 15.31 [4.58] days; $P < .01$), time for heart rate to return to normal (11.34 [3.90] days vs 15.72 [4.10] days; $P < .01$), and time for respiration

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rate to return to normal (7.00 [1.74] days vs 15.32 [5.87] days; $P < .01$) were all statistically in favor of the dexmedetomidine group. Additionally, dexmedetomidine was superior to propofol in decreasing time from drug administration to complete remission, defined as absence of PSH symptoms for 5 consecutive days (mean 9.31 [2.66] days vs 13.05 [4.19] days; $P \leq .01$). Although dexmedetomidine was shown to be superior to propofol at controlling the aforementioned symptoms, logistical regression analysis of factors relating to recurrence suggested that dexmedetomidine does not protect against recurrence of PSH (OR 0.878, 95% CI 0.248-3.107; $P = .84$).

Dexmedetomidine and propofol both have multimodal mechanisms of action that are helpful in the management of PSH. The Peng et al⁷ study is one of the few studies to provide a direct comparison of these agents. Because of the small sample size, definitive conclusions cannot be drawn from these results; however, given the available evidence it would be reasonable to use dexmedetomidine for management of PSH symptoms over propofol.

Tang et al⁸ evaluated the prevention of PSH using various sedatives in a retrospective study, which included 90 adult patients with a severe TBI requiring neurosurgical intervention. Patients who received dexmedetomidine (continuous infusion of 0.8 $\mu\text{g}/\text{kg}$ over 10 min followed by 0.25-0.75 $\mu\text{g}/\text{kg}$ per hour) were compared to patients in a control group, who received either propofol (2 mg/kg per hour) or midazolam (0.1 mg/kg per hour). Withdrawal of sedation was initiated on day 5 in both groups. Patients were assessed for probability of developing PSH using the PSH-AM score, and therapeutic efficacy was

assessed by hospital length of stay and the Glasgow Outcomes Score (GOS). Authors

found a statistically significant difference in the number of “unlikely” PSH diagnoses in the dexmedetomidine group versus the control group (42 vs 25; $P = .03$); a trend suggesting a difference in the number of “probable” PSH diagnoses in the dexmedetomidine group versus the control group (3 vs 8; $P = .06$); and a statistically significant difference in the mean (SD) PSH-AM scores of patients with “probable” diagnoses (18.33 [1.53] vs 22.63 [2.97]; $P = .04$). Overall, the mean (SD) PSH-AM score was lower in the dexmedetomidine group versus

the control group (5.26 [4.66] vs 8.58 [8.09]; $P = .02$); however, there was no statistically significant difference between mean (SD) intensive care unit length of stay (15.70 [13.07] days vs 20.65 [16.74] days; $P = .12$), hospital length of stay (23.50 [16.58] days vs 28.53 [20.28] days; $P = .17$), days of sedation (5.46 [2.82] vs 6.08 [2.95]; $P = .32$), GOS at discharge (3.00 [1.28] vs 2.75 [1.15]; $P = .34$), or after 3 months (3.42 [1.47] vs 3.05 [1.43]; $P = .23$). Symptomatic management of PSH was carried out as needed, although this study focused on sedatives in the prevention of PSH.

The data from the Tang et al⁸ study suggest that administration of dexmedetomidine for sedation confers a lower risk of PSH development compared to administration of propofol or midazolam in patients with severe TBI requiring surgery, although neither medication was superior regarding hospital length of stay or functional outcomes. These results must be interpreted with caution given the lack of randomization, small sample size, and use of GOS as an outcome measure for PSH. Nonetheless, these data must be considered given the paucity of information regarding the use of pharmaceuticals for the prevention of PSH.

In a retrospective cohort study by Pozzi et al,⁹ 23 pediatric patients with postacute TBI injuries were assessed for PSH and remission of symptoms following medication administration. Only patients who exhibited at least 1 PSH episode per day for 7 consecutive days in the absence of possible alternative causes were included in the study. Numerous medications were administered because of the high variability in PSH symptoms, but only medications administered to at least 5 patients were included in the analysis. By nonparametric correlation, remission was found to be correlated with conservative doses of propranolol ($r = 0.072$; $P = .02$), baclofen ($r = 0.094$; $P = .002$), and diazepam ($r = 0.185$; $P < .001$). Of these medications, a logistic regression model was used to test if any individual therapy predicted remission. Remission was found to be more probable with higher propranolol doses (OR 1.22, 95% CI 1.04-1.42; $P < .01$) and diazepam doses (OR 8.89, 95% CI 3.37-23.44; $P < .001$); however, neither of these medications was administered at the maximum dosage. The authors postulated that the beneficial effects from lower scheduled doses of diazepam (around 0.1 mg/kg) were due to myorelaxant and anxiolytic properties that are less prone to developing tolerance.⁹ Propranolol doses were

Dexmedetomidine and propofol both have multimodal mechanisms of action that are helpful in the management of PSH.

also maintained at lower concentrations (up to 2.5 mg/kg) because of the profound hypotension and bradycardia induced at higher doses. There were no significant correlations between baclofen, niaprazine, clonazepam, or phenobarbital doses and PSH remission. The analysis was aimed at detecting dosage changes from nonremission to remission; therefore, a lack of significance indicates that similar doses were used in both states of recovery and should not be equated with a lack of efficacy.⁹

Although Pozzi et al⁹ did not find robust data because of the limited sample size, they did demonstrate that moderate dosing strategies might be beneficial in patients with TBI who experience PSH. Maximum doses were not needed to achieve remission and these dosing strategies conveyed a wide therapeutic index without significant adverse events. Given these data and the role of critical care nurses in the evaluation of PSH symptoms and medication side effects, nurses are in the ideal position to recommend more conservative dosing or alternative medications when observed side effects outweigh therapeutic benefit for any given patient.

Case Series

In a case series by Baguley et al,⁴ the management of PSH symptoms with gabapentin was described in 6 patients. All patients were men in their late teens or early 20s with severe TBI who had received several different medications in attempts to improve symptomatic control. In 4 of the described cases, reduced spasticity, posturing, and presumed neuropathic pain was attributed to the introduction of gabapentin earlier in the course of treatment. The mechanism of gabapentin in this setting is not fully understood. The authors suggested these effects may be attributed to a reduction in neuropathic pain.⁴ Alternatively, gabapentin may be involved in controlling afferent stimuli by increasing activation of inhibitory pathways within the spinal cord.⁴ For patients displaying severe ongoing posturing, gabapentin may be considered early in the treatment regimen.

Case Reports

In a case report by Liu et al,¹⁰ a 27-year-old Hispanic man with subarachnoid hemorrhage was placed on the institution's hypothermia protocol with paralytics. After rewarming, the patient started exhibiting signs of PSH including hypertension, tachycardia, and fluctuations in

temperature. Intravenous labetalol 10 mg was given twice, but the patient continued to experience symptoms. Intravenous labetalol as needed, bromocriptine as needed, dexmedetomidine, fentanyl, and midazolam were administered for symptomatic management; however, this combination of medications did not attenuate symptoms. Propranolol 10 mg twice a day was added to the regimen, bromocriptine was adjusted to 5 mg 3 times a day, and IV

labetalol was continued as needed. At this time, the

patient was transferred to an intermediate care unit with minimal neurological and vital checks. After sustained symptomatic resolution, propranolol and bromocriptine were reserved for as-needed usage, and eventually were discontinued. The authors concluded that scheduled doses of bromocriptine and propranolol were superior to as-needed doses regarding resolution of PSH symptoms.¹⁰ This case again highlights the importance of multimodal therapies in the management of PSH because monotherapy, although not studied in a causative fashion, has been shown less effective than multiple agents in the limited data available.¹⁰

Lemke¹¹ reported a case involving a 24-year-old man who was in an unrestrained motor vehicle accident; he developed a subsequent subdural hematoma and began experiencing PSH symptoms after having a neurosurgical evaluation. Caregivers initiated administration of IV fentanyl 25 to 50 µg/h as needed (1300 µg/24 h) and IV midazolam 2 to 4 mg/hour (35 mg/24 h), which achieved adequate control of PSH symptoms. On day 4 of admission, metoprolol 12.5 mg twice a day and clonidine 0.1 mg twice a day were initiated to further control symptoms. By day 6, phenytoin was initiated for potential nonconvulsive seizures, clonidine dosing was increased to 0.1 mg 3 times per day, and oxycodone 5 to 10 mg every 4 hours as needed was added. On day 8, the patient was weaned off of mechanical ventilation and ultimately extubated. After transfer of the patient from the intensive care unit to the general neurological unit, he experienced a prolonged storming episode, which was abated with administration of acetaminophen, supplemental oxycodone, and morphine 10 mg intramuscularly. By recommendation of the rehabilitation facility, bromocriptine 10 mg was scheduled every 8 hours, metoprolol was

For patients displaying severe ongoing posturing, gabapentin may be considered early in the treatment regimen.

discontinued, and propranolol 20 mg twice a day was initiated. On day 13, the propranolol dose was increased to 20 mg 3 times a day. By day 21, storming episodes had stabilized and medications were slowly weaned. This report demonstrates the transient nature of PSH episodes and the need for continuous reassessment of medication choice and dosing on the basis of frequent evaluations of PSH symptoms. Again, critical care nurses are in an ideal position to assess the treatment effects and side effects of medications administered for PSH symptoms and to subsequently suggest modifications to the treatment regimen, if needed.

In a case report by Raitchel et al,¹² a 9-year-old African American boy was hospitalized for hypoxic brain injury, resulting from pulseless arrest lasting longer than 10 minutes. The patient received fentanyl and midazolam continuous infusions while intubated; these medications were then weaned over the next 2 to 3 days. On day 4 of admission, the patient started experiencing signs of PSH, which were attributed to opiate and benzodiazepine withdrawal at the time, and therefore fentanyl and midazolam continuous infusions were restarted. On hospital day 5, severe cerebral edema was noted on imaging. Several interventions to decrease intracranial pressure were instituted, including hyperventilation and administration of hypertonic saline, mannitol, and vecuronium; however, symptoms worsened as cerebral edema resolved. The patient received clonidine 0.1 mg twice a day and lorazepam 1 mg as

Initiating IV morphine in patients who are refractory to nonselective β blockers, α_2 -agonists, or benzodiazepines could be an efficacious method of attenuating acute PSH episodes.

needed for developing PSH episodes. With increasing number and

duration of PSH episodes, clonidine was increased to 0.2 mg 3 times a day, but eventually discontinued because of bradycardia. To control symptoms, caregivers initiated administration of propranolol 5 mg every 8 hours, clonazepam 0.5 mg every 8 hours, and baclofen 5 mg twice a day. The patient's episodes did not subside until morphine 2.5 mg IV as needed was initiated. The patient was discharged receiving propranolol 10 mg in the morning, 5 mg in the afternoon, and 10 mg at night; baclofen 20 mg every 8 hours; clonazepam 0.5 mg every 8 hours; and morphine 15 mg as needed. The authors concluded that in this case, lorazepam and labetalol were ineffective

at aborting acute PSH episodes. Propranolol and clonidine both reduced the frequency and severity of episodes but resulted in occasional bradycardia between episodes. Baclofen was found to be efficacious at preventing episodes, and clonazepam assisted in preventing autonomic storms. The authors suggested initiating IV morphine in patients who are refractory to nonselective β blockers, α_2 -agonists, or benzodiazepines as an efficacious method of attenuating acute PSH episodes.

Siefferman and Lai¹³ describe a 41-year-old man with right middle cerebral ischemic stroke, who during his course of recovery began experiencing symptoms of PSH. The patient's PSH-AM score totaled 13, which translates to a "possible" diagnosis of PSH, and he subsequently received propranolol 10 mg twice daily (later increased to 10 mg 3 times a day when symptoms returned). After increasing the dose of propranolol, the patient's PSH symptoms were alleviated within 1 day. Propranolol was later discontinued, and several PSH symptoms returned; therefore, propranolol was restarted and continued for symptomatic relief. The authors concluded that scheduled propranolol successfully alleviated PSH symptoms.¹³ Propranolol's exact mechanism for cessation of PSH symptoms is not fully understood. The drug's lipophilicity may enable it to freely cross the blood-brain barrier and blunt the neuronal responses that contribute to PSH symptoms.¹⁴

A report by May et al¹⁵ describes the case of a 15-year-old white boy who sustained multiple intra-abdominal injuries from an all-terrain vehicle rollover. On hospital day 40 in the operating room, the patient appeared to seize, followed by pulseless ventricular tachycardia requiring advanced cardiac life support. Because of the prolonged events, the patient was thought to have developed an anoxic brain injury. Providers administered 1 dose of lorazepam 2 mg and fosphenytoin 20 mg/kg for the patient's seizure activity and then a midazolam continuous infusion and fentanyl continuous infusion. Continuous electroencephalogram (EEG) showed no seizure activity, so the midazolam continuous infusion was discontinued. The next day, the patient developed tachycardia, fever, posturing, and muscle rigidity. At this time, PSH was considered. Three doses of IV propranolol were administered and the patient received an esmolol continuous infusion. Despite several days of continuous esmolol and fentanyl infusions, the patient remained tachycardic and febrile and continued to display episodes of PSH

Table Drug comparison chart

Drug	Mechanism of action	Dose	Onset	Duration	Common side effects
Dexmedetomidine	α_2 -agonist	0.25-1.4 ug/kg/h	5-10 min	60-120 min (dose dependent)	Bradycardia, hypotension, sedation
Propofol	GABA-A agonist	5-50 ug/kg/min	30 s	3-10 min depending on dose, rate, and duration of administration	Bradycardia, hypotension, sedation, PRIS, respiratory depression
Midazolam	GABA-A agonist	0.1 mg/kg/h	IV, 3-5 min Oral, 10-30 min	IV, 30-45 min Oral, 1 h	Bradycardia, hypotension, sedation, respiratory depression, delirious
Clonidine	α_2 -agonist	6-18 ug/kg/d	Oral, 30-60 min Patch, 3 d	Oral, 8-12 h Patch, 7 d	Bradycardia, hypotension, rebound hypertension
Bromocriptine	Dopamine agonist	5-10 mg 2-3 times a day	60-90 min	8-12 h	Dyskinesia, hypertension, metabolic abnormalities
Propranolol	Nonselective β blocker	0.1-0.5 mg/kg/d	Oral, 1-2 h IV, immediate	Oral, 8-12 h IV, 2-4 h	Hypotension, bradycardia, insomnia, constipation
Morphine	Opiate	1-10 mg PRN	PO, 30-60 min IV, 5-10 min	Oral, 3-5 h IV, 3-6 h	Respiratory depression, hypotension, delirious, pruritus
Fentanyl	Opiate	25-100 μ g PRN	IV, 1-2 min Patch, 12-24 h	IV, 30-60 min Patch, 72-96 h	Respiratory depression, hypotension, delirious
Labetalol	Nonselective β blocker	10 mg PRN	Oral, 20 min - 2 h IV, 2-5 min	Oral, 8-24 h IV, 2-4 h	Hypotension, bradycardia
Gabapentin	GABA analog, does not interact with GABA receptor	300-600 mg 2-3 times a day	2-4 hours	6 h	Ataxia, sedation
Hydroxyzine	Histamine-1 antagonist	6.25-25 mg	Oral, 15-60 min	Oral, 4-6 h	Sedation, urinary retention
Baclofen	GABA-B agonist	5-20 mg 2-3 times a day	Oral, 2-3 h Intrathecal, 30-60 min	Oral, 8-12 h Intrathecal, 4-8 h	Confusion, dizziness, drowsiness, hypotonia

Abbreviations: GABA, γ -aminobutyric acid; IV, intravenous; PRIS, propofol-related infusion syndrome; PRN, as needed.

with posturing. The continuous fentanyl infusion was discontinued and the patient received a continuous infusion of morphine, midazolam, dexmedetomidine, transdermal clonidine, and IV propranolol (with discontinuation of esmolol). On hospital day 52, IV propranolol became unavailable to the hospital and the patient could not tolerate oral medications; therefore, rectal propranolol was compounded in the hospital pharmacy and administered to the patient every 8 hours, then titrated up to every 6 hours. This dose of rectal propranolol together with a continuous infusion of morphine, midazolam, and dexmedetomidine and a clonidine patch every 24 hours reduced the patient's PSH symptoms to 1 to 3 episodes per day, each lasting 30 minutes or less. Although not optimal, rectal propranolol was a novel treatment that proved to be an effective option in this particular case. These conclusions must be interpreted with caution and reserved for situations wherein other routes of

administration are not available, as they are derived from a single case report.

Discussion

On the basis of the available evidence, it is clear that monotherapy is not effective in the management of PSH patients and that management with multiple agents with different mechanisms of action should be considered. The Table compares characteristics of medications commonly used in the management of PSH, including mechanism of action, dose, onset, duration of action, and side effects. As it stands currently, α_2 -agonists such as dexmedetomidine may hold some slight clinical efficacy over agents like propofol; however, because of limited data, this conclusion must be interpreted with caution. With respect to oral medications, it would appear from these data that propranolol might convey some slight advantage compared to others, yet again, this must be interpreted

with caution. Because limited data exist on the management of PSH and larger robust data sets are needed to guide decision-making, bedside critical care nurses must understand the most relevant pharmacological treatment options based on the available information.

Conclusions

Paroxysmal sympathetic hyperactivity is a complex hyperdynamic syndrome that consists of multiple presentations; the goal of treatment is to decrease the frequency and intensity of symptoms and attenuate further morbidity and mortality. As the treatment of PSH is reactive to symptomatic evolution over time, critical care nurses play a vital role in the monitoring and treatment of these patients. A paucity of literature exists on how to appropriately manage these patients pharmacologically and more data are needed to define appropriate clinical pathways. [CCN](#)

Financial Disclosures

None reported.

See also

To learn more about caring for patients with brain injury, read "Intensive Care Unit Readmission in Patients With Primary Brain Injury and Tracheostomy" by Pandian et al in the *American Journal of Critical Care*, 2019;28(1):56-63. Available at www.ajconline.org.

References

1. Penfield W, Jasper H. Autonomic seizures. In: Penfield W, Jasper H, eds. *Epilepsy and Functional Anatomy of the Human Brain*. London, United Kingdom: J & A Churchill Ltd; 1954:412-437.
2. Baguley IJ, Perkes IE, Fernandez-Ortega JF, Rabinstein AA, Dolce G, Hendricks HT; Consensus Working Group. Paroxysmal sympathetic hyperactivity after acquired brain injury: consensus on conceptual definition, nomenclature, and diagnostic criteria. *J Neurotrauma*. 2014; 31(17):1515-1520.
3. Fernandez-Ortega JF, Prieto-Palomino MA, Garcia-Caballero M, Galeas-Lopez JL, Quesada-Garcia G, Baguley IJ. Paroxysmal sympathetic hyperactivity after traumatic brain injury: clinical and prognostic implications. *J Neurotrauma*. 2012;29(7):1364-1370.
4. Baguley IJ, Heriseanu RE, Gurka JA, Nordenbo A, Cameron ID. Gabapentin in the management of dysautonomia following severe traumatic brain injury: a case series. *J Neurol Neurosurg Psychiatry*. 2007;78(5):539-541.
5. Baguley IJ, Nicholls JL, Felmingham KL, Crooks J, Gurka JA, Wade LD. Dysautonomia after traumatic brain injury: a forgotten syndrome? *J Neurol Neurosurg Psychiatry*. 1999;67(1):39-43.
6. Pozzi M, Conti V, Locatelli F, et al. Paroxysmal sympathetic hyperactivity in pediatric rehabilitation: clinical factors and acute pharmacological management. *J Head Trauma Rehabil*. 2015;30(5):357-363.
7. Peng Y, Zhu H, Chen H, et al. Dexmedetomidine attenuates acute paroxysmal sympathetic hyperactivity. *Oncotarget*. 2017;8(40):69012-69019.
8. Tang Q, Wu X, Weng W, et al. The preventive effect of dexmedetomidine on paroxysmal sympathetic hyperactivity in severe traumatic brain injury patients who have undergone surgery: a retrospective study. *PeerJ*. 2017; 5:e2986. doi:10.7717/peerj.2986
9. Pozzi M, Conti V, Locatelli F, et al. Paroxysmal sympathetic hyperactivity in pediatric rehabilitation: pathological features and scheduled pharmacological therapies. *J Head Trauma Rehabil*. 2017;32(2):117-124.
10. Liu Y, Jolly S, Pokala K. Prolonged paroxysmal sympathetic storming associated with spontaneous subarachnoid hemorrhage. *Case Rep Med*. 2013;2013:358182.
11. Lemke DM. Sympathetic storming after severe traumatic brain injury. *Crit Care Nurse*. 2007;27(1):30-37.
12. Raithe DS, Ohler KH, Porto I, Bicknese AR, Kraus DM. Morphine: an effective abortive therapy for pediatric paroxysmal sympathetic hyperactivity after hypoxic brain injury. *J Pediatr Pharmacol Ther*. 2015;20(4):335-340.
13. Siefferman JW, Lai G. Propranolol for paroxysmal sympathetic hyperactivity with lateralizing hyperhidrosis after stroke. *Case Rep Neurol Med*. 2015;2015:421563.
14. Rabinstein AA, Benarroch EE. Treatment of paroxysmal sympathetic hyperactivity. *Curr Treat Options Neurol*. 2008;10(2):151-157.
15. May CC, Oyler DR, Parli SE, Talley CL. Rectal propranolol controls paroxysmal sympathetic hyperactivity: a case report. *Pharmacotherapy*. 2015;35(4):e27-e31. doi:10.1002/phar.1568