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PAROXYSMAL SYMPATHETIC HYPERACTIVITY MANAGEMENT

Evidence Based Medicine Guideline

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SUMMARY

Paroxysmal sympathetic hyperactivity (PSH), often referred to as "neurostorming," is a complex hyperdynamic syndrome characterized by paroxysmal episodes of sympathetic overactivity affecting up to 33% of patients with severe traumatic brain injury (TBI) (1,2). PSH leads to increased morbidity, prolonged hospital stays, and higher healthcare costs (3,4). Despite its prevalence and clinical significance, PSH remains underrecognized and inconsistently managed due to its nonspecific presentation and the lack of universally accepted treatment protocols.

These evidence-based guidelines aim to standardize the diagnosis and management of PSH in adult patients following severe acquired brain injury. We provide a framework for pharmacological and non-pharmacological interventions to improve early recognition, optimize treatment strategies, and enhance patient outcomes. The guidelines incorporate current evidence, including the PSH-Assessment Measure (PSH-AM), a valuable tool for diagnosis and severity assessment (5).

RECOMMENDATIONS

- **Level 1**
  - **Propranolol is a first-line agent for PSH management and should be initiated within 24 hours of PSH diagnosis when clinically appropriate.**
- **Level 2**
  - **The PSH-Assessment Measure (PSH-AM) should be used for standardized diagnosis and monitoring.**
  - **Alpha-2 agonists (clonidine or dexmedetomidine) may be used as either adjunctive therapy or alternative first-line agents.**
  - **Morphine may be used for acute symptom control and as part of multimodal therapy.**
  - **Environmental modification strategies should be employed to reduce external stimuli.**
  - **Nutritional support should be provided to address the hypermetabolic state.**
- **Level 3**
  - **Gabapentin reduces posturing and neuropathic pain.**
  - **Intrathecal baclofen may be considered for severe refractory spasticity.**
  - **Bromocriptine is a second-line agent for hyperthermia.**
  - **Early mobilization and physiotherapy should be implemented.**
  - **Reassess PSH symptoms regularly and adjust therapy based on individual patient response.**
  - **Benzodiazepines may be used for acute symptom control as part of a multimodal approach.**
  - **Refractory hyperthermia should be treated with targeted temperature strategies.**

PHARMACOLOGICAL MANAGEMENT

Recent studies have significantly advanced our understanding of pharmacological interventions for PSH, involving several drug classes, each targeting different aspects of sympathetic hyperactivity.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Supported by multiple, prospective randomized clinical trials or strong prospective, non-randomized evidence if randomized testing is inappropriate.
- **Level 2:** Supported by prospective data or a preponderance of strong retrospective evidence.
- **Level 3:** Supported by retrospective data or expert opinion.

Beta-blockers

Beta-blockers, particularly propranolol, have emerged as a cornerstone in PSH management. Recent studies provide strong evidence for their efficacy and safety in treating PSH following TBI. Fernandez-Ortega et al. demonstrated that catecholamine levels increase dramatically during PSH paroxysms, providing a physiological rationale for β-blocker use (7). Building on this, Ding et al. conducted a comprehensive systematic review and meta-analysis of 15 studies with 12,721 patients exposed to beta-blockers after TBI (8). They found a significant reduction in adjusted in-hospital mortality (OR 0.39, 95% CI 0.30-0.51, p<0.001) and improved long-term (≥6 months) functional outcome (OR 1.75, 95% CI 1.09-2.80, p=0.02). Notably, there was no significant difference in cardiopulmonary adverse events between beta-blocker and control groups (OR 0.91, 95% CI 0.55-1.50, p=0.702), suggesting the overall safety of beta-blocker use in TBI patients. Ahl et al. conducted a matched case-control study showing better long-term functional outcomes (GOS >3 at 12 months) in severe TBI patients treated with beta-blockers (57.9% vs 40.8%, p=0.03) (9). Edavettal et al. found that non-selective beta-blockers had a greater reduction in odds of mortality compared to selective beta-blockers in TBI patients (10).

Propranolol, a non-selective beta-blocker, has shown particular promise in treating PSH. Khalili et al. performed a randomized controlled trial with 219 patients, demonstrating that propranolol improved both in-hospital mortality (4.4% vs 18.6%, p=0.012) and long-term functional outcomes in isolated severe TBI patients (11). Schroeppel et al. conducted a retrospective case-control study of 1,755 patients, finding propranolol superior to other beta-blockers in TBI patients, with significantly lower mortality rates (3% vs 15%, p=0.002) (12). They attributed this superiority to propranolol's lipophilicity, allowing it to cross the blood-brain barrier. Do et al. reported a case where propranolol effectively controlled PSH symptoms refractory to other treatments, including selective β-blockers (13). This case highlighted the potential superiority of non-selective β-blockade in PSH management.

Early administration of propranolol appears to be beneficial. Ko et al. and Murray et al. showed that early (within 24 hours) administration of low-dose propranolol was safe and improved outcomes in severe TBI (14,15). Rabinstein and Benarroch's review emphasized propranolol's efficacy in reducing heart rate, blood pressure, and temperature in PSH patients (16). They recommended a dosage range of 20-60 mg every 4-6 hours.

In a pediatric study by Pozzi et al., propranolol was found to be one of the most effective medications for PSH symptom control. Higher propranolol doses were associated with a higher probability of PSH remission (OR 1.22, 95% CI 1.04-1.42, p<0.01) (6).

May et al. reported a case where rectal propranolol was effectively used when the intravenous form was unavailable, demonstrating the potential for alternative administration routes in challenging clinical scenarios (17).

While propranolol has the most robust evidence, other β-blockers have also been studied. Metoprolol, a β1-selective antagonist, was less effective when used alone in a case report by Do et al., suggesting that β1-selective antagonism may be insufficient for PSH management (13). Labetalol, a combined alpha- and beta-blocker, has shown some efficacy after metoprolol failure by Do et al., but comparative studies with propranolol are lacking. While less studied in PSH, esmolol’s short half-life makes it potentially useful for acute symptom control or in hemodynamically unstable patients (18). Cruickshank et al. conducted an early RCT showing no significant difference in hypotension, bradycardia, or other adverse events between atenolol and control groups in TBI patients (19).

In conclusion, the current literature strongly supports using β-blockers, particularly propranolol, as a first-line pharmacological intervention for PSH. Their efficacy, favorable side effect profile, and potential mortality benefit make them crucial in PSH management strategies. However, more randomized controlled trials are needed to definitively establish their role and compare different β-blockers head-to-head in PSH treatment.

Alpha-2 agonists

Alpha-2 (α2) agonists have emerged as a significant beneficial pharmacological intervention in managing PSH. Recent studies have focused primarily on two α2 agonists: clonidine and dexmedetomidine. Tang et al. and Peng et al. suggest that α2-agonists may have preventive and acute treatment effects on PSH (20,21).

Clonidine has shown efficacy in reducing circulating plasma catecholamine levels in patients with severe head injury. Payen et al. reported significant decreases in plasma epinephrine and norepinephrine concentrations following clonidine administration (22). Nordess et al. conducted a randomized controlled trial on 47 severe TBI patients, combining propranolol and clonidine treatment (23). While the study did not show a significant difference

in ventilator-free days, it demonstrated an improvement in CFS scores in the treatment group (mean difference 1.7 points, 95% CI 0.4-2.9, p=0.012), supporting the safety and feasibility of clonidine administration in severe TBI patients.

Baguley et al. reviewed clonidine's effectiveness in controlling hypertension and tachycardia associated with PSH (24). They noted that while clonidine is effective for these symptoms, it may be less efficacious for other manifestations of PSH. Rabinstein and Benarroch recommended clonidine as a first-line agent for PSH management, suggesting a 0.1-0.3 mg dosage every 6-8 hours (16). They emphasized its usefulness in combination therapy due to its different mechanism of action compared to β-blockers. Nguembu et al. performed a scoping review examining the role of β-blockers in PSH management, including studies that used clonidine in combination with β-blockers (25). Their findings indicated that clonidine was often used in combination with propranolol or other β-blockers, with some studies reporting improved outcomes (e.g., reduced length of stay, lower mortality) with combined therapy, but the evidence was limited. The review highlighted the common practice of using clonidine in combination with other medications for PSH management.

Alshaya et al. performed a retrospective cohort study comparing clonidine to a control in 169 PSH patients after severe TBI (26). The clonidine group improved functional outcomes (higher delta Glasgow Coma Score), suggesting potential benefits in improving functional outcomes in PSH patients. However, Pozzi et al.'s pediatric study found no significant correlation between clonidine dosage and PSH remission, suggesting potential limitations in its efficacy or the need for combination therapy in that population (27).

Dexmedetomidine has shown promising results in recent studies. Peng et al. conducted a retrospective study comparing dexmedetomidine to propofol in 72 patients with PSH after neurosurgery (21). They found dexmedetomidine had shorter times to control paroxysmal hypertension (29.03 ± 8.86 vs. 42.0 ± 14.77 min, $p<0.01$), higher remission rates of paroxysmal hypermyotonia (61 ± 11% vs. 42 ± 14%, $p<0.01$), shorter duration of paroxysmal hypermyotonia (9 ± 3 vs. 13 ± 4 days, $p<0.01$), and faster normalization of temperature, heart rate, and respiratory rate in the dexmedetomidine group. This study supports the efficacy of dexmedetomidine in managing PSH symptoms.

Tang et al. found that patients sedated with dexmedetomidine had significantly lower PSH-AM scores compared to the control group (5 ± 5 vs. 9 ± 8, p=0.017), suggesting a potential preventive effect on PSH in severe TBI patients (20). Goddeau et al. reported a case where dexmedetomidine (initiated at 0.1 μg/kg/hour and titrated to 0.7 μg/kg/hour) significantly improved PSH symptoms within 24 hours in a patient with refractory PSH (18). May et al. described the successful use of dexmedetomidine as part of a multimodal regimen for refractory PSH in a pediatric patient (17).

In conclusion, α2-agonists, particularly dexmedetomidine, have shown promising results in PSH management. Their unique mechanism of action, complementary to other agents like β-blockers, makes them valuable in multimodal treatment approaches. However, larger randomized controlled trials are needed to definitively establish their role in PSH management.

Opioids

Opioids, particularly morphine, have been a cornerstone in the management of PSH since its early recognition. Severe studies and case reports support their role in PSH management. Baguley et al., in a comprehensive review, highlighted morphine as a first-line agent for PSH management (24). They noted its efficacy in reducing heart rate, blood pressure, and temperature, attributing these effects to both analgesic action and increased cholinergic effects. Bullard's case series demonstrated morphine's effectiveness in controlling PSH symptoms, particularly when combined with bromocriptine (28). The author suggested that morphine's action on medullary vagal nuclei contributes to its efficacy. Raithel et al. reported a case of refractory PSH in a pediatric patient where intravenous morphine (2.5 mg as needed) effectively aborted acute episodes when other treatments had failed (29). This case highlighted morphine's potential as a rescue medication in severe cases. Ko et al. described successful management of PSH using morphine in a patient with pontine hemorrhage, demonstrating its utility beyond traumatic brain injury cases (30). Lemke's case report detailed the use of morphine as part of a multimodal regimen, effectively controlling PSH symptoms in combination with other agents (31).

While morphine is the most studied opioid in PSH, others have also shown promise. Lee et al. described the use of fentanyl patches (10-30 mcg/h) in managing PSH symptoms associated with brainstem-compressing tumors (32).

Although less commonly used, remifentanyl's ultra-short half-life may be advantageous in certain clinical scenarios, allowing for rapid titration (33).

In conclusion, opioids, particularly morphine, remain a crucial component in the pharmacological management of PSH. Their rapid onset of action makes them valuable for acute symptom control and ongoing management. However, their use must be balanced against potential side effects and the risk of dependence. The integration of opioids into multimodal treatment regimens, with careful monitoring and individualized dosing, appears to be the most effective approach based on current evidence. Future research should focus on optimizing opioid dosing strategies and exploring the potential of newer opioid formulations in PSH management.

Gabapentin

Gabapentin, originally developed as an anticonvulsant, has emerged as a promising agent in the management of PSH. Several studies and case reports support its use in PSH treatment. Baguley et al. conducted a seminal case series examining gabapentin's efficacy in PSH management (34). This study included six male patients with severe TBI who had failed to respond adequately to conventional PSH treatments. They found that gabapentin significantly reduced spasticity, dystonia, and presumed neuropathic pain, improved responsiveness and cognitive functioning in some patients, and effective doses ranged from 300 mg to 2400 mg daily, titrated based on clinical response. Thomas and Greenwald's comprehensive review highlighted gabapentin as a valuable option for PSH management, particularly for spasticity and allodynic responses (35). They noted its efficacy in the acute and recovery phases of brain injury. Cuny et al., while primarily focusing on intrathecal baclofen, mentioned gabapentin as part of multimodal therapy for refractory PSH cases (36). This underscores its role in combination treatment approaches. Rabinstein and Benarroch's review of PSH treatments included gabapentin as a potential adjunctive therapy, particularly for its effects on neuropathic pain and spasticity (16). Although primarily focused on dexmedetomidine, Peng et al.'s study mentioned gabapentin as part of the treatment regimen for some PSH patients, indicating its integration into standard care protocols in some centers (21).

In conclusion, gabapentin represents a valuable addition to the pharmacological armamentarium for PSH management. Its unique mechanism of action, efficacy in managing multiple PSH symptoms, and favorable side effect profile make it an attractive option, particularly as part of multimodal treatment approaches. However, more robust clinical evidence is needed to fully elucidate its role and optimize its use in PSH management.

Baclofen

Baclofen, a GABA-B receptor agonist, has emerged as a significant pharmacological intervention in managing PSH, particularly for cases involving severe spasticity and dystonia. The literature primarily focuses on intrathecal baclofen (ITB), with some studies examining oral administration. Cuny et al. conducted a pivotal study on ITB for PSH management in 8 patients with severe traumatic brain injury (TBI) (36). They found a significant reduction in dysautonomic episodes within 24-48 hours of ITB initiation, improved Glasgow Outcome Scale scores at 1-year follow-up, and a mean ITB dose of 570 µg/day (range 300-800 µg/day). Becker et al. reported on seven patients with severe spasticity and autonomic dysfunction treated with ITB (37). They observed immediate improvement in spasticity (>65%) and autonomic symptoms, reduction in oral medication requirements, and ITB doses ranging from 100 to 800 µg/day. Goddeau et al. described a case where ITB (initial dose 50 µg/day, increased to 125 µg/day) effectively controlled refractory PSH symptoms when combined with propranolol and bromocriptine (18). A long-term follow-up study by Hoarau et al. on 15 patients with severe TBI and dysautonomia treated with ITB reported sustained efficacy in controlling spasticity and autonomic symptoms for up to 19 years, improved functional outcomes and quality of life, and a mean ITB dose of 280 µg/day at last follow-up (38).

While less studied, oral baclofen has been mentioned in several reviews. Baguley et al.'s review on pharmacological management of dysautonomia following TBI included oral baclofen as a potential treatment option, particularly for spasticity (24). Rabinstein and Benarroch's review mentioned oral baclofen as part of multimodal therapy for PSH but noted its limited efficacy compared to ITB (16). Pozzi et al.'s study on pediatric PSH found no significant correlation between oral baclofen doses and PSH remission, suggesting potential limitations in its oral form (27).

In conclusion, baclofen, particularly in its intrathecal form, represents a valuable option for managing severe spasticity and autonomic symptoms in PSH. Its efficacy in refractory cases and potential for long-term symptom control make it an important consideration in PSH management algorithms. However, the invasive nature of ITB and the limited efficacy of oral baclofen necessitate careful patient selection and close monitoring. Future research should focus on optimizing baclofen therapy and exploring its role in combination treatment approaches for PSH.

Bromocriptine

Bromocriptine, a dopamine agonist, has been utilized in the management of PSH since the early descriptions of the syndrome. Several studies and case reports support its use, although the overall body of evidence is less robust than that of other agents. Bullard's seminal case report in 1987 described the successful use of bromocriptine in combination with morphine for managing PSH symptoms in a patient with TBI (28). This report highlighted efficacy in controlling temperature fluctuations and autonomic instability, dosage of 2.5 mg three times daily (increased to 5 mg three times daily), and a synergistic effect when combined with morphine. Russo and O'Flaherty reported on the use of bromocriptine in a pediatric case of severe TBI with autonomic dysfunction (39). Their findings included rapid resolution of hyperpyrexia and other dysautonomic symptoms within 24 hours of bromocriptine initiation, an initial dose of 1.25 mg twice daily (increased to 2.5 mg three times daily), and successful weaning off the medication after 2 months without symptom recurrence. Baguley et al.'s review on pharmacological management of dysautonomia following TBI included bromocriptine as a second-line agent, particularly for managing hyperpyrexia and sweating (24). They noted a typical dosing range of 2.5-5 mg three times daily and the potential for enhancing the effectiveness of other medications when used in combination therapy. Rabinstein and Benarroch's review highlighted bromocriptine's role in PSH management, particularly for cases with prominent hyperthermia (16). They suggested a starting dose of 1.25 mg twice daily, with gradual titration up to 40 mg/day, and consideration of bromocriptine in cases refractory to first-line treatments. Liu et al. described a case of prolonged PSH associated with subarachnoid hemorrhage where bromocriptine (5 mg three times daily) was successfully used as part of a multimodal regimen, including propranolol and morphine (40).

In conclusion, bromocriptine represents a valuable option in the pharmacological management of PSH, particularly for cases with prominent hyperthermia or those refractory to first-line treatments. Its unique mechanism of action and potential synergistic effects with other medications, like morphine, make it an important consideration in multimodal treatment approaches. However, the limited robust clinical evidence and potential for side effects necessitate careful patient selection and close monitoring. Future research should focus on optimizing bromocriptine's use in PSH and exploring its potential neuroprotective properties in the context of brain injury.

Benzodiazepines

Benzodiazepines have been utilized in the management of PSH due to their sedative, anxiolytic, and muscle relaxant properties. While not considered first-line agents, they play a role in multimodal treatment approaches, particularly for acute symptom control. Baguley et al.'s comprehensive review of the pharmacological management of dysautonomia following TBI included benzodiazepines as potential agents for PSH management (24). They noted efficacy in controlling agitation, hypertension, tachycardia, and posturing and the potential for worsening neurological functioning, necessitating cautious use. Blackman et al. reported on the use of benzodiazepines in a case series of pediatric patients with paroxysmal autonomic instability with dystonia (PAID), a term previously used to describe PSH-like syndromes (41). Their findings included the efficacy of diazepam in controlling dystonic posturing and autonomic symptoms and the use of scheduled doses rather than as-needed administration for better symptom control. Rabinstein and Benarroch's review highlighted the role of benzodiazepines in PSH management, particularly for acute symptom control (16). They suggested short-acting benzodiazepines like midazolam for breakthrough episodes and longer-acting agents like clonazepam for maintenance therapy. Pozzi et al.'s study on pediatric PSH found a significant correlation between clonazepam administration and PSH remission ($r = 0.185$; $P < .001$) (27). However, logistic regression did not identify clonazepam as an independent predictor of remission. Samuel et al.'s review on pharmacologic management of PSH after brain injury included benzodiazepines as part of multimodal therapy, particularly for managing agitation and posturing (5).

In conclusion, benzodiazepines remain a valuable tool in the management of PSH, particularly for acute symptom control and as part of multimodal treatment approaches. Their rapid onset of action and efficacy in controlling multiple PSH symptoms make them useful in many clinical scenarios. However, their potential for adverse effects, particularly on cognition and respiratory function, necessitates careful patient selection, close monitoring, and judicious use. Individual patient characteristics, symptom severity, and overall treatment goals should guide the integration of benzodiazepines into PSH management protocols.

Dantrolene

Dantrolene is the most reported peripherally acting muscle relaxant in PSH management. Its use primarily focuses on managing severe dystonic posturing associated with sympathetic storms. Blackman et al. included dantrolene in their case series of patients with paroxysmal autonomic instability with dystonia (PAID), reporting that it effectively managed severe dystonic posturing associated with sympathetic storms (22). The typical dosing range for dantrolene in PSH management is 0.5-2 mg/kg intravenously every 6-12 hours, with a maximum daily dose of 10

mg/kg (24). The use of dantrolene in PSH management highlights the importance of addressing motor symptoms, particularly dystonia, which can be a significant source of distress and potential secondary complications.

Propofol

Propofol is the most used anesthetic agent in PSH management, typically reserved for severe, refractory cases. Case reports and clinical experience support its use. Goddeau et al. reported a case of successful use of propofol for refractory PSH in a patient with severe TBI (18). They reported effectively controlling sympathetic storms at a dose of 30-50 µg/kg/min without causing significant hemodynamic compromise. The use of propofol in PSH management underscores the sometimes necessary escalation to anesthetic agents in severe, treatment-resistant cases. However, its use requires careful monitoring due to potential cardiovascular and respiratory effects.

NON-PHARMACOLOGICAL MANAGEMENT

Non-pharmacological approaches, while less studied, are recognized as important adjuncts to medication:

- Environmental modification: Reducing external stimuli by controlling room temperature, minimizing noise, and limiting unnecessary interventions may help prevent PSH episodes (42).
- Early mobilization: Physiotherapy and range of motion exercises may help prevent complications such as contractures and heterotopic ossification (42).
- Nutritional support: PSH is associated with a hypermetabolic state. Caldwell et al.'s case series highlighted the importance of adequate caloric intake to prevent weight loss and malnutrition (43).
- Temperature management: External cooling measures may be necessary to manage hyperthermia resistant to pharmacological interventions (16).

Synthesis of Current Evidence

The current body of evidence supports several key principles in PSH management:

- Early recognition and diagnosis using standardized tools like the PSH-AM is crucial for timely intervention (2).
- A multimodal approach combining pharmacological and non-pharmacological strategies is more effective than monotherapy (5).
- Propranolol and dexmedetomidine have the strongest supporting evidence as first-line agents, with propranolol showing potential mortality benefits (12,21).
- Opioids, particularly morphine, remain important for acute symptom control but require careful monitoring due to side effect profiles (24).
- Gabapentin shows promise, especially for managing posturing and neuropathic pain symptoms associated with PSH (34).
- Intrathecal baclofen may be effective for refractory cases, particularly those with severe spasticity (36).
- Non-pharmacological interventions, including environmental modification and nutritional support, should be integrated into comprehensive management plans (43).
- Treatment should be individualized and adjusted based on symptom severity and response, as PSH presentations can vary significantly between patients (3).

Despite these advances, the overall quality of evidence remains limited. Most recommendations are based on retrospective analyses, case series, and expert opinion. The heterogeneity in PSH definitions and outcome measures across studies further complicates the synthesis of the evidence. Large-scale, randomized controlled trials are needed to establish the efficacy of various interventions and develop standardized treatment protocols.

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Management Algorithm for Paroxysmal Sympathetic Hyperactivity (Modified from Samuel et al., 2016; Godoy et al., 2017; Zheng et al., 2020)

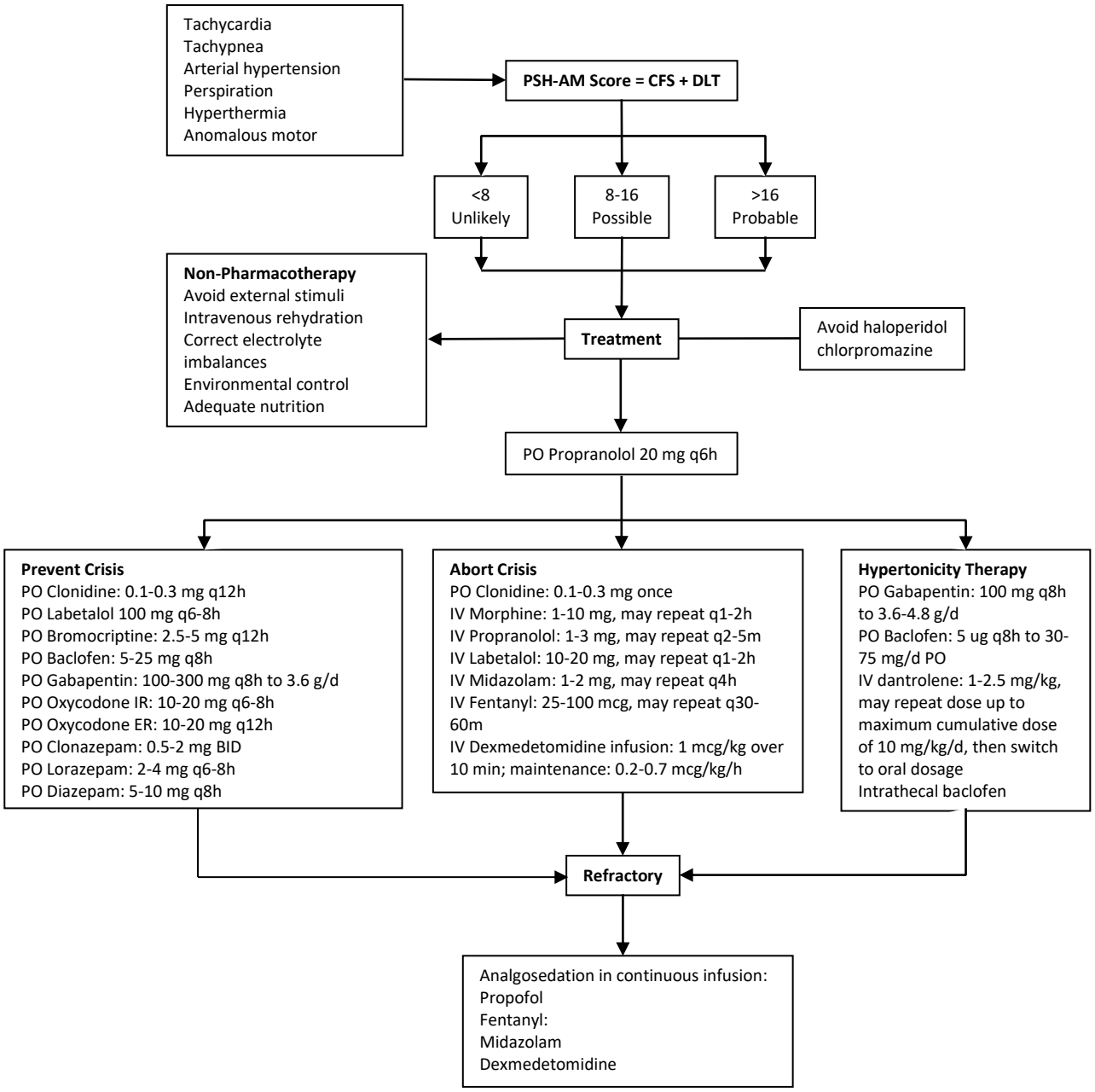

Table 1: Clinical Feature Scale (CFS). *The sum of scores for each feature ranges from 0 to 3 points each, with a maximum score of 18. Modified from Samuel et al., 2016; Godoy et al., 2017; Zheng et al., 2020*

	0	1	2	3
Heart rate (bpm)	<100	100-119	129-139	≥140
Respiratory rate (bpm)	<18	18-23	24-29	≥30
Systolic pressure (mmHg)	<140	140-159	160-179	≥180
Temperature (ºC)	<37.0	37.0-37.9	38.0-38.9	≥39.0
Sweating	No visible sweating	Moist or glistening skin	Beads of sweat	Profuse sweating
Posturing during episodes	Unchanged	Hypertonicity increases Tone is easily overcome	Hypertonicity Tone is difficult to overcome	Inescapable hypertonicity

Table 2: Diagnosis Likelihood Tool (DLT). *The sum of scores for each feature is given 1 point each for a max score of 11 points. Modified from Samuel et al., 2016; Godoy et al., 2017; Zheng et al., 2020*

1. Clinical features occur simultaneously
2. Episodes are paroxysmal in nature
3. Sympathetic hyperactivity to normally non-painful stimuli
4. Features persist ≥3 consecutive days
5. Features persist ≥2 weeks after brain injury
6. Features persist despite treatment of alternative differential diagnoses
7. Features ≥2 episodes daily
8. Medication administered to decrease sympathetic features
9. Absence of parasympathetic features during episodes
10. Absence of other presumed cause of features
11. History of acquired brain injury
The presence of per item being scored as 1 and their absence as 0, range from 0-11 points.

Table 3: Paroxysmal Sympathetic Hyperactivity Assessment Measure (PSH-AM). *Modified from Samuel et al., 2016; Godoy et al., 2017; Zheng et al., 2020*

	Probability of Diagnosis of PSH	
PSH-AM Score (CSF score + DLT score)	<8	Improbable
	8-16	Possible
	>16	Probable
CSF score: Assesses the severity of the six core features of PSH with points ranging from 0 to 18		
DLT score: Estimates the likelihood of PSH by identifying the presence of observed features		
PSH-AM Score: Uses combined total from the CFS and DLT scores for a diagnostic likelihood of PSH		

Table 4: Abortive Pharmacological Management for PSH. (Modified from Samuel et al., 2016 and Zheng et al., 2020)

Drug Class	Medications	Dosage	Target Symptoms	Key Considerations
Opioids	Morphine	1-10 mg IV every 1-2 hours, up to 20 mg in severe cases	Hypertension, tachycardia, allodynia	Risk of respiratory depression; monitor closely
	Fentanyl	25-100 mcg IV, may repeat every 30-60 minutes	Hypertension, tachycardia, allodynia	Shorter duration of action compared to morphine
Benzodiazepines	Midazolam	1-2 mg IV, may repeat every 4 hours	Agitation, hypertension, tachycardia, posturing	Risk of respiratory depression; may interfere with neurological assessment
	Diazepam	1-10 mg IV	Agitation, hypertension, tachycardia, dystonia, spasticity	Longer duration of action compared to midazolam
Beta-Blockers	Propranolol	1-3 mg IV, may repeat every 2-5 minutes	Hypertension, tachycardia, diaphoresis	Monitor for bradycardia and hypotension
	Labetalol	10-20 mg IV, may repeat every 1-2 hours	Tachycardia, hypertension	Less likely to cause severe bradycardia
Alpha-2 Agonists	Clonidine	0.1-0.3 mg PO once	Hypertension, tachycardia	Monitor for rebound hypertension upon discontinuation
	Dexmedetomidine	Loading dose: 1 mcg/kg over 10 min; Maintenance: 0.2-0.7 mcg/kg/hr IV	Hypertension, tachycardia, agitation	Monitor for bradycardia and hypotension
Anesthetics	Propofol	10-20 mg IV bolus	Refractory symptoms, severe agitation	Use with caution; may require mechanical ventilation
Muscle Relaxants	Dantrolene	0.5-2 mg/kg IV every 6-12 hours	Severe muscular spasms, hyperthermia	Monitor liver function; max daily dose 10 mg/kg

Note: All medications should be titrated based on individual patient response and tolerability. Close monitoring is essential during the administration of these medications.

Table 5: Preventive Pharmacological Management for PSH. (Modified from Samuel et al., 2016 and Zheng et al., 2020)

Drug Class	Medication	Dosage	Target Symptoms	Key Considerations
Beta-Blockers	Propranolol	20-60 mg orally every 4-6 hours	Hypertension, tachycardia, diaphoresis	Monitor for bradycardia and hypotension; may affect glucose metabolism
	Metoprolol	25-100 mg orally twice daily	Hypertension, tachycardia	More cardioselective than propranolol
	Labetalol	100 mg PO every 6-8 hours	Tachycardia, hypertension	Less likely to cause severe bradycardia
Alpha-2 Agonists	Clonidine	0.1-0.3 mg orally or transdermally every 12 hours	Hypertension, tachycardia	Monitor for rebound hypertension upon discontinuation
	Dexmedetomidine	0.2-0.7 mcg/kg/hr IV infusion	Hypertension, tachycardia, agitation	Requires continuous IV administration; monitor for bradycardia
Neuromodulators	Gabapentin	100-300 mg orally three times daily, up to 3600 mg/day	Allodynia, spasticity, paroxysms	May cause sedation; adjust dose in renal impairment
	Baclofen	5-25 mg orally three times daily	Spasticity, dystonia	Monitor for sedation and muscle weakness
	Bromocriptine	2.5-5 mg orally twice daily	Hyperthermia, diaphoresis	May cause nausea and orthostatic hypotension
Benzodiazepines	Clonazepam	0.5-2 mg orally twice daily	Anxiety, spasticity	Risk of dependence; may impair cognition
	Lorazepam	2-4 mg PO every 6-8 hours per day	Agitation, hypertension, spasticity	Fast acting, short duration
	Diazepam	5-10 mg PO every 8 hours a day	Agitation, hypertension, tachycardia, dystonia, spasticity	Longer duration of action compared to midazolam Most useful for hypertonicity
Opioids	Morphine Sulfate ER	15-30 mg orally twice daily	Persistent pain, allodynia	Monitor for constipation and respiratory depression
	Oxycodone IR	10-20 mg PO every 6-8 hours a day	Pain, agitation	Fast acting
	Oxycodone ER	10-20 mg every 12 hours a day	Pain, agitation	Extended action
Antispasmodics	Tizanidine	2-4 mg orally three times daily	Spasticity, muscle spasms	May cause dry mouth and sedation
Anesthetics	Propofol	Up to 80 mcg/kg/minute continuous infusion	Refractory symptoms, severe agitation	Deep sedation (only permissible in patients who are intubated and ventilated) Propofol infusion

Note: Dosages should be titrated based on individual patient response and tolerability. Regular monitoring of vital signs, neurological status, and potential side effects is essential. Combination therapy may be necessary for optimal symptom control.

Table 6. Refractory Pharmacological Management for PSH

Drug Class	Medications	Dosage	Target Symptoms	Key Considerations
Anesthetics	Propofol	5-50 mcg/kg/min IV continuous infusion	Severe agitation, refractory symptoms	Requires mechanical ventilation; monitor for propofol infusion syndrome
Barbiturates	Pentobarbital	Loading: 5-15 mg/kg IV; Maintenance: 0.5-5 mg/kg/hr	Refractory intracranial hypertension, severe PSH	Prolonged sedation; may cause hypotension
Alpha-2 Agonists	Dexmedetomidine	0.2-1.5 mcg/kg/hr IV continuous infusion	Refractory agitation, tachycardia	May cause bradycardia; allows for neurological assessment
Opioids	Remifentanil	0.05-0.25 mcg/kg/min IV continuous infusion	Severe pain, refractory sympathetic hyperactivity	Ultra-short acting; rapid offset
Muscle Relaxants	Cisatracurium	1-2 mcg/kg/min IV continuous infusion	Severe posturing, refractory spasticity	Non-depolarizing; minimal cardiovascular effects
Intrathecal Therapy	Baclofen (IT)	Initial test dose: 50-100 mcg; titrate as needed	Severe, refractory spasticity	Requires implanted pump; risk of withdrawal if abruptly stopped
Neuromodulators	Pregabalin	75-150 mg orally twice daily, up to 600 mg/day	Refractory allodynia, anxiety	May cause dizziness and somnolence
Antipsychotics	Quetiapine	25-200 mg orally twice daily	Severe agitation, delirium	Monitor for QT prolongation
Combination Therapy	Morphine + Midazolam	Individualized dosing	Refractory pain and agitation	High risk of respiratory depression; use with caution

Note: These medications should be considered only when standard treatments have failed for refractory PSH. Close monitoring in an ICU setting is essential. Dosages should be individualized based on patient response and tolerability.