Sjögren's Foundation Clinical Practice Guideline

December 2025

Peripheral Nervous System Manifestations in Sjögren's

Peripheral nervous system (PNS)* manifestations are increasingly recognized as a significant aspect of Sjögren's disease (SjD), an autoimmune disorder that affects multiple organ systems. Clinical practice guidelines for PNS manifestations in SjD were developed under the leadership of the Sjögren's Foundation to improve early identification, evaluation, and consistency of care by primary care physicians, rheumatologists, and neurologists. Of note:

- PNS manifestations in SjD are reported to affect between 8% and 60% of patients, with impacts extending far beyond discomfort and significantly diminishing patients' overall quality of life. However, this prevalence might be underestimated due to the lack of early diagnosis and awareness of the neuropathies seen in SjD. PNS symptoms can precede the diagnosis of SjD in up to 90% of cases.
- PNS manifestations of SjD include cranial neuropathies (such as trigeminal neuropathy, acute facial neuropathy), polyneuropathies (such as large fiber [axonal] neuropathy, small fiber neuropathy, demyelinating polyradiculoneuropathy), and autonomic nervous system neuropathies (including postural tachycardia, orthostatic hypotension, and gastrointestinal & urogynecology autonomic nerve dysfunction). Additionally, some patients with SjD may develop vasculitic neuropathy or ganglionopathy, which can be rapidly debilitating.
- Autonomic disorders in SjD can greatly diminish quality of life and overall function. These conditions are frequently overlooked or mistaken as anxiety or other functional disorders.
- To accurately diagnose and manage PNS manifestations, it is crucial to understand the specific subtype of peripheral neuropathy and its underlying pathophysiological mechanisms. Patients with SjD can suffer from several types of peripheral neuropathies at the same time.
- In all, 31 good practices are provided for the evaluation of PNS manifestations, along with 20 evidence-based treatment recommendations.
- A multidisciplinary approach to evaluating these complex cases is essential and can include a primary care physician, rheumatologist, neurologist, and other specialists as indicated, such as neurogastroenterologist, otolaryngologist, urologist, or urogynecologist.

* Corneal neuropathy will be included in the forthcoming update to the Sjögren's Foundation ocular clinical practice guideline.

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Sjögren's FOUNDATION®

Clinical Practice Guidelines Development

The development of this guideline reflects careful and rigorous work over a multi-year period and including multi-specialty collaboration and patient advocacy by the Sjögren's Foundation and our partners. The Sjögren's Foundation launched its initiative to develop clinical practice guidelines more than a decade ago, with a goal to improve the quality of Sjögren's care in the United States. The initiative brings together leading experts in evidence-based medicine, major medical organizations, practicing clinicians, and patient representatives.

The PNS Guideline involved over 95 collaborators, including rheumatologists, neurologists, other healthcare professionals, and Sjögren's patients. The Topic Review Group that developed the PNS Guideline involved the following:

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The Foundation used a rigorous, transparent process that included a comprehensive review of published research to incorporate the most up-to-date science in developing treatment recommendations for PNS manifestations in Sjögren's. The group followed a consensus-building process to engage feedback from experts who were not involved in recommendation development and to ensure alignment across the recommendations. The Consensus Expert Panel was made up of 69 members, including 39 rheumatologists, 20 neurologists, and 10 Sjogren's patients or family of patients.

Citation

Deboo A, Fox R, Hammitt KM, Frantsve-Hawley J, Baker MC, Danielides S, De Sousa E, Goodman BP, King JK, Mandel S, Noaiseh G, Pavlakis PP, Sarka G, Scofield RH, Varadhachary A, Wallace DJ, Makara M, Carteron N, Carsons S; Consensus Expert Panel (CEP) members. Clinical Practice Guideline for Evaluation and Management of Peripheral Nervous System Manifestations in Sjogren's Disease. Arthritis Care Res (Hoboken). 2025 Dec 1. doi: 10.1002/acr.70004. Online ahead of print. PMID: 41327784.

Recommendations for Aligned Nomenclature of Peripheral Nervous System Disorders Across Rheumatology and Neurology

During development of the Peripheral Nervous System Clinical Practice Guideline, inconsistent nomenclature across rheumatology and neurology emerged as a recurring barrier to communication and guideline implementation. This led to a separate, independently published effort to align terminology across specialties (Arthritis & Rheumatology, Noaiseh et al., 2024).

Definitions of Peripheral Neuropathies in Sjögren's Disease

Type of Neuropathy	Other Nomenclature	Presentation
Mononeuropathy	• Neuropathy • Focal neuropathy	Patients will present with sensory and/or motor symptoms and signs in the distribution of a single nerve. Sensory symptoms can include negative (numbness) or positive (tingling paresthesias or pins and needles) symptoms or neuropathic pain. Motor symptoms would be weakness or loss of muscle bulk. On examination, sensory loss should be restricted to the cutaneous distribution of the single nerve, and weakness or atrophy should be found in muscles innervated by the affected nerve. If the nerve mediates a deep tendon reflex, that reflex may be reduced or absent. A Tinel sign may be elicited by tapping on the affected nerve, which would result in electric or pins and needles paresthesias in the cutaneous distribution of the nerve. Signs and symptoms can affect the face if a cranial nerve, such as the facial or trigeminal, is involved.
Large Fiber (Axonal) Neuropathy	• Sensory polyneuropathy (Pure sensory axonal neuropathy of the distal nerves) • Sensory motor polyneuropathy (Axonal sensorimotor polyneuropathy)	Large fiber neuropathy results from the dysfunction or damage of Aβ fibers, which mediate the sensations of proprioception, vibration, and touch. Abnormal proprioception may result in problems with balance and an ataxic gait (wide-based, unsteady).
Small Fiber Neuropathy	• Small fiber polyneuropathy • Small fiber sensory neuropathy	Small fiber neuropathy typically presents with pain, burning, numbness, and tingling in a stocking glove distribution. Symptoms usually begin starting in the feet and can ascend. Examination will show diminished pain and temperature sensations in the distal limbs. Less frequently, there can be early proximal or patchy evolution. Because large fibers that mediate proprioceptive (balance) and motor functions are not involved, these patients should not have ataxia or muscle weakness. Fibers of the peripheral autonomic nervous system are also small caliber fibers, and small fiber neuropathy can affect these autonomic fibers, leading to autonomic dysfunction. This will result in autonomic symptoms that otherwise can be difficult to localize.
Demyelinating Polyradiculoneuropathy	• Demyelinating polyradiculoneuropathy (including chronic inflammatory demyelinating polyradiculoneuropathy: CIDP)	The presentation can be progressive or relapsing and remitting. Sensory symptoms can include numbness, burning pain, throbbing, or dysesthesias. Motor complaints are weakness and loss of muscle bulk. Characteristic features of the examination include motor findings of weakness and muscle atrophy and sensory deficits in vibration and proprioception with loss of reflexes. Patients with demyelinating polyradiculoneuropathy will most commonly have a combination of proximal and distal findings on neurological examination and electrodiagnostic testing. This proximal involvement often distinguishes demyelinating polyradiculoneuropathy from the more common length-dependent polyneuropathies that have only distal involvement initially.

Type of Neuropathy	Other Nomenclature	Presentation
Mononeuropathy	• Neuropathy • Focal neuropathy	Patients will present with sensory and/or motor symptoms and signs in the distribution of a single nerve. Sensory symptoms can include negative (numbness) or positive (tingling paresthesias or pins and needles) symptoms or neuropathic pain. Motor symptoms would be weakness or loss of muscle bulk. On examination, sensory loss should be restricted to the cutaneous distribution of the single nerve, and weakness or atrophy should be found in muscles innervated by the affected nerve. If the nerve mediates a deep tendon reflex, that reflex may be reduced or absent. A Tinel sign may be elicited by tapping on the affected nerve, which would result in electric or pins and needles paresthesias in the cutaneous distribution of the nerve. Signs and symptoms can affect the face if a cranial nerve, such as the facial or trigeminal, is involved.

Evaluating Sjögren's Patients for Mononeuropathies

Good Practices for Patient Evaluation

Good Practice 1

Sjögren's patients with persistent facial pain or numbness should be assessed for dysfunction of the 5th cranial nerve which can manifest as either trigeminal neuralgia or trigeminal neuropathy.

- Physical examination: assess for numbness or pain of the face in the distribution of one or more branches of the trigeminal nerve, unilateral or bilateral, by testing for loss of light touch and either pin prick or cold sensation.
- If the distribution of symptoms or findings on physical examination is consistent with trigeminal neuralgia or trigeminal neuropathy, a contrast-enhanced brain MRI with attention to brainstem/skull base and exiting cranial nerves should be performed to exclude structural or other etiologies of trigeminal dysfunction.
- Consider electrophysiological testing, including blink reflex.

Good Practice 2

Sjögren's patients with unilateral facial weakness should be assessed for facial (cranial nerve 7) neuropathy.

- Symptoms and physical examination findings: weakness of the upper and ipsilateral lower face. Upper facial weakness manifests as an inability to raise the eyebrows, inability to wrinkle the forehead, weakness of eye closure, or a widened palpebral fissure. Involvement of the lower facial muscles manifests as lip closure weakness, and facial droop. Some patients experience a loss of taste on the anterior two-thirds of the tongue and/or hyperacusis (hearing sensitivity) on the affected side.
- Physical examination findings that may suggest an alternative etiology include coexisting cranial mononeuropathies, ear canal vesicles, neck stiffness, headaches, and fevers. These findings should prompt an evaluation for Lyme disease, herpes zoster, sarcoidosis, or variants of Guillain-Barre Syndrome (GBS), which may include lumbar puncture.
- Perform a contrast-enhanced brain MRI with attention to the brainstem/skull base and exiting cranial nerves to exclude structural or other etiologies of facial neuropathy.
- Consider electrophysiological testing with nerve conduction study, including blink reflex, and electromyography (EMG).
- Facial neuropathy rarely presents bilaterally. If the manifestations are bilateral or recurrent, an aggressive evaluation for more generalized systemic disease should be pursued.

Good Practice 3

Patients with Sjögren's who present with cranial mononeuropathies of other cranial nerves should be evaluated for alternative etiologies. Work-up should include referral to the appropriate specialist, such as a neurologist, otolaryngologist, ophthalmologist, speech pathologist, or gastroenterologist for evaluation.

Good Practice 4

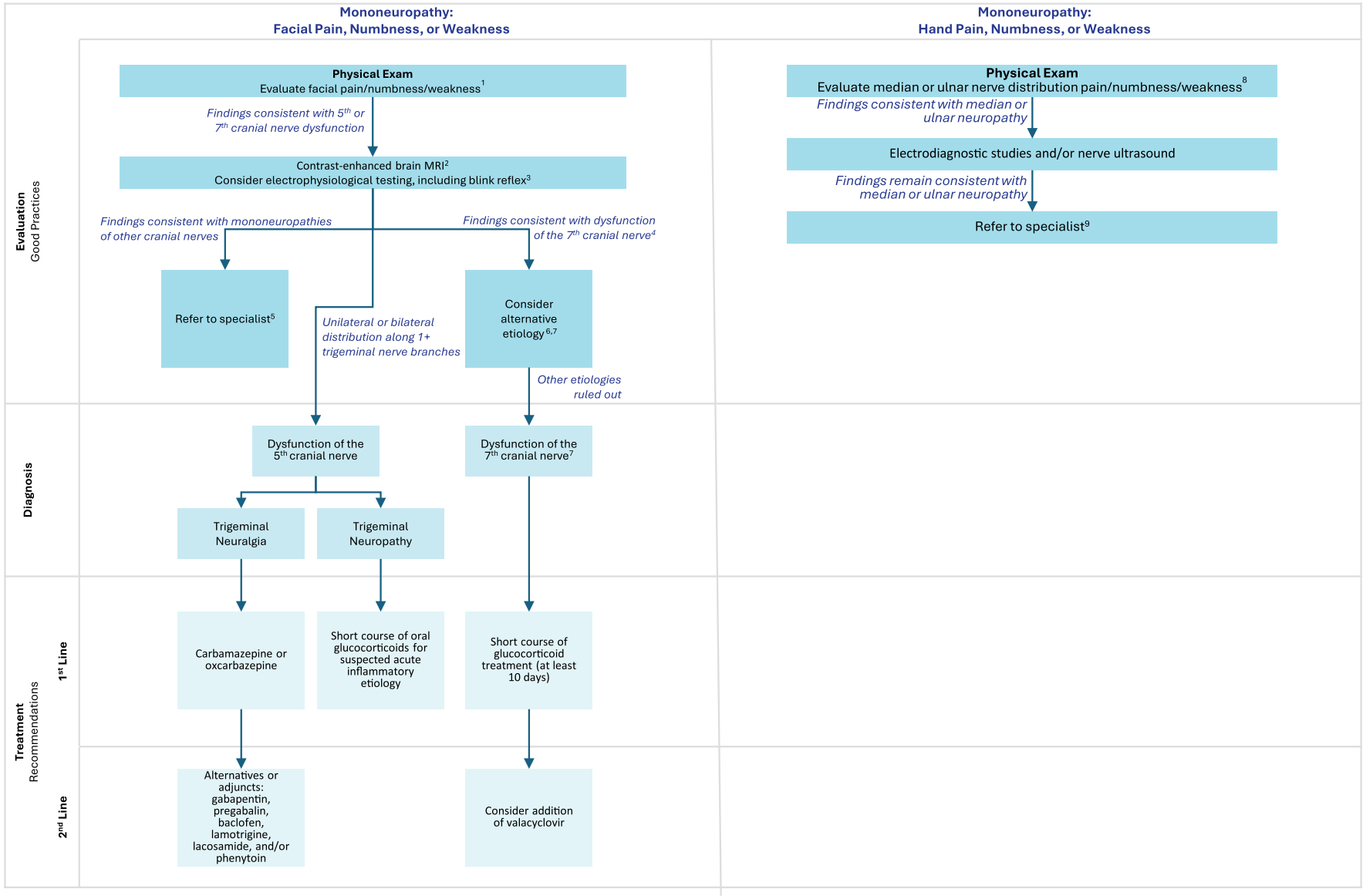
Sjögren's patients with numbness, pain, or weakness of the hand should be evaluated for median or ulnar neuropathy.

- Physical examination: Median neuropathy presents with sensory loss of the lateral (medial) three and ½ digits, atrophy of the thenar eminence, and weakness of thumb abduction. Ulnar neuropathy presents with sensory loss of the medial one and ½ digits, atrophy of intrinsic hand muscles, a "claw-hand" appearance, and weakness of the fingers.
- If a median or ulnar neuropathy is suspected, consider electrodiagnostic studies and/or nerve ultrasound.
- Referral to a hand surgeon or other specialist who evaluates and treats carpal tunnel syndrome or ulnar neuropathy should be considered.
- If carpal tunnel surgical release is performed, a tenosynovial biopsy may be obtained to exclude amyloidosis.

Recommendations for Mononeuropathies in Sjögren's

Recommendations for Mononeuropathies		Strength of Recommendation
Recommendation 1	**For patients with Sjögren's related trigeminal neuropathy, we recommend a short course of oral glucocorticoids for suspected acute inflammatory etiology.**	**CONDITIONAL**
Recommendation 2	**For patients with Sjögren's-related trigeminal neuralgia (neuropathic pain), we recommend:** • First-line treatment with carbamazepine or oxcarbazepine. • Second-line treatments, either as alternatives or adjuncts, may include gabapentin, pregabalin, baclofen, lamotrigine, lacosamide, or phenytoin.	**CONDITIONAL**
Recommendation 3	**For patients with Sjögren's who develop an acute facial neuropathy, we recommend:** • A short course of glucocorticoid treatment for at least 10 days. • Consider the addition of valacyclovir.	**CONDITIONAL**

Figure 1: Evaluation and Management of Patients with Sjögren's who Exhibit Symptoms and/or Physical Examination Signs of Mononeuropathy



References to Figure 1: Evaluation and Management of Patients with Sjögren's Who Exhibit Symptoms and/or Physical Examination Signs of Mononeuropathies

1 Loss of light touch, pinprick, or cold sensation.

2 Attention should be paid to the brainstem/skull base and exiting cranial nerves to exclude structural or other etiologies.

3 Electrodiagnostic studies include nerve conduction studies (NCS) and electromyography (EMG) and should be performed by an experienced electromyographer.

4 Patients with unilateral facial weakness should be assessed for facial (cranial nerve 7) neuropathy. Physical exam findings include weakness of the upper and ipsilateral lower face. Upper facial weakness manifests as inability to raise the eyebrows, inability to wrinkle the forehead, weakness of eye closure or a widened palpebral fissure. Involvement of the lower facial muscles manifests as lip closure weakness and facial droop. Some patients experience a loss of taste on the anterior two-thirds of the tongue and/or hyperacusis (hearing sensitivity) on the affected side. Facial neuropathy rarely presents bilaterally. If the manifestations are bilateral or recurrent, an evaluation for more generalized systemic disease should be pursued.

5 Specialists may include neurologist, otolaryngologist, ophthalmologist, speech pathologist, or gastroenterologist.

6 Physical examination findings that suggest an alternative etiology include coexisting cranial mononeuropathies, ear canal vesicles, neck stiffness, headaches and fevers. These findings should prompt an evaluation for Lyme disease, herpes zoster, sarcoidosis, or variants of Guillain-Barre Syndrome (GBS), which may include lumbar puncture.

7 If the manifestations are bilateral or recurrent, an evaluation for more generalized systemic disease should be pursued.

8 Median neuropathy presents with sensory loss of the lateral (radial) three and ½ digits, atrophy of the thenar eminence, and weakness of thumb abduction. Ulnar neuropathy presents with sensory loss of the medial one and ½ digits, atrophy of intrinsic hand muscles, a "claw-hand" appearance, and weakness of the fingers.

9 Refer to a hand surgeon or other specialist who evaluates and treats carpal tunnel syndrome or ulnar neuropathy. If carpal tunnel surgical release is performed, a tenosynovial biopsy may be obtained to exclude amyloidosis.

Evaluating Sjögren's Patients for Polyneuropathies

Good Practices for Patient Evaluation

Good Practice 5	**Recognize that neuropathies can have many causes, including Sjögren's disease. Potential alternative etiologies should be identified, such as diabetes, hypothyroidism, B-12 deficiency, monoclonal gammopathies, infectious etiologies, toxins, and medications. Labs related to these etiologies should be ordered.**
Good Practice 6	**Recognize that Sjögren's patients can present with a wide range of symptoms, including diverse presentations of peripheral neuropathies. For abnormal sensations suspected of being neuropathic, ask the following questions to characterize the neuropathy:** 1. Do you have numbness, tingling, pins and needles or buzzing sensation, burning pain, other abnormal sensations and/or weakness? 2. Are the symptoms symmetric or asymmetric? 3. Where is it worse—hands, feet, or all over? 4. Where did you notice it first? (distal onset?) 5. How long have symptoms been present? 6. Do you have any gait disturbances/abnormalities? **Additional questions that may be useful in screening are:** 7. Was the onset of neuropathy gradual or abrupt? 8. How have symptoms changed? (Worse? Persistent? Intermittent? More proximal?) 9. Do symptoms awaken you from sleep? 10. Under what circumstances did symptoms begin (i.e. Did they start before or after new medication or infection?) 11. Have there been any exposures to medications, supplements, complementary and alternative medicine, or occupational exposures that could be neurotoxic?
Good Practice 7	**Sjögren's patients who have symptoms suggesting a peripheral neuropathy should have a comprehensive neurological examination.**
Good Practice 8	**For Sjögren's patients who have a history and physical examination findings suggesting a peripheral neuropathy, consider referral to a neurologist.**
Good Practice 9	**For Sjögren's patients with persistent neuropathic symptoms, electrodiagnostic studies [nerve conduction studies (NCS) and electromyography (EMG)], should be performed by an experienced electromyographer. The study is best timed at 1-4 weeks from the onset of symptoms, depending on the type, progression, and severity of the neuropathy.**
Good Practice 10	**For Sjögren's patients with suspected small fiber neuropathy, consider evaluation of epidermal nerve fiber density with punch skin biopsy to support this diagnosis.**

Good Practices for Patient Evaluation *Continued*

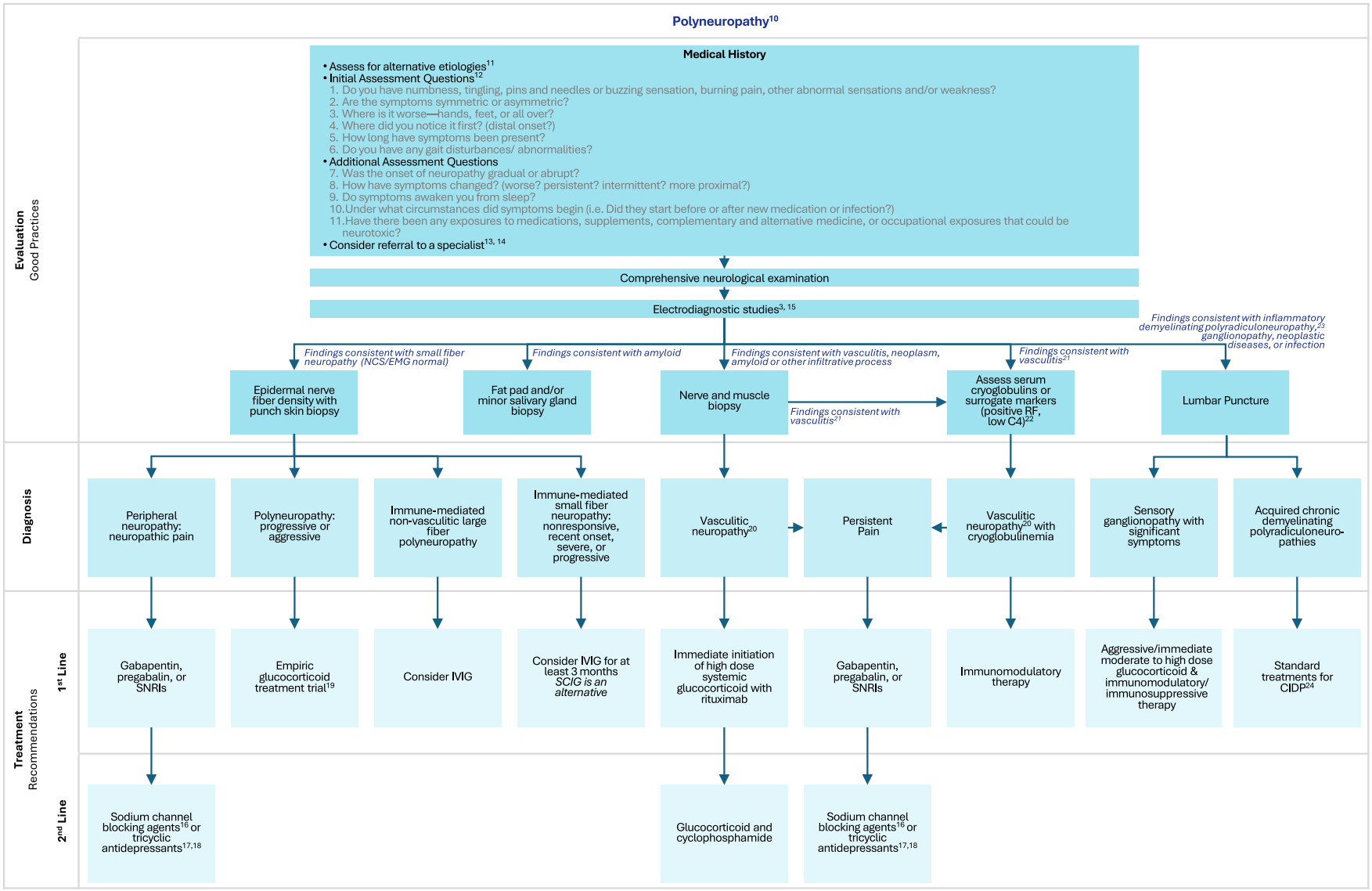
Good Practice 11	**For Sjögren's patients with suspected peripheral neuropathy and electrodiagnostic studies (NCS/EMG) warranting additional evaluation or when there is no response to treatment, the following should be considered:** • Fat pad and/or minor salivary gland biopsy if amyloid is suspected. • Nerve and muscle biopsy if vasculitis, neoplasm, amyloid, or other infiltrative processes are suspected. • Lumbar puncture should be reserved for assessing suspected cases of inflammatory demyelinating polyradiculoneuropathy (including AIDP and CIDP), ganglionopathy, neoplastic diseases, or infection.
Good Practice 12	**For Sjögren's patients with gait disturbance due to weakness, sensory loss, ataxia, or imbalance, consider assessments for gait & balance training and for assistive devices by physical therapy, PMR (physical medicine rehabilitation), and/or other related healthcare professionals.**
Good Practice 13	**For Sjögren's patients with polyneuropathy with neuropathic pain who have not benefited from initial treatments for neuropathic pain, referral to a neurologist and/or a pain specialist may be warranted.**
Good Practice 14	**For Sjögren's patients with confirmed polyneuropathy, treatment choice depends on the type and location of neuropathy, disease severity, and degree of systemic involvement (e.g., vasculitis).**
Good Practice 15	**Vasculitic neuropathy should be considered in Sjögren's patients with polyneuropathy and the following clinical scenarios: Acute, painful, rapid onset, or stepwise progression of neurological deficit, clinical and electromyographic evidence of multiple mononeuropathies, evidence of single-organ or systemic vasculitis, or immunologically active disease as defined by cryoglobulinemia, hypocomplementemia, monoclonal gammopathy, positive rheumatoid factor, and elevated Inflammatory markers.**
Good Practice 16	**We recognize the technical difficulties in correctly identifying serum cryoglobulins. Therefore, other surrogate markers associated with the presence of cryoglobulinemia (i.e., positive rheumatoid factor and hypocomplementemia C4), in the appropriate clinical context, may also be suggestive in those negative for serum cryoglobulins.**
Good Practice 17	**For any Sjögren's patients with a suspicion of vasculitic neuropathy, electromyography (EMG) and nerve conduction studies (NCS) should be performed. The timing of this study is based on the severity and tempo of presentation, typically 1-4 weeks after the onset of symptoms.**
Good Practice 18	**For Sjögren's patients with clinical and electrodiagnostic findings suggestive of a vasculitic etiology, a nerve and muscle biopsy is warranted.**
Good Practice 19	**For Sjögren's patients with vasculitic neuropathy with cryoglobulinemia, repeat serum cryoglobulin as a biomarker for therapeutic response, along with complement C4 and rheumatoid factor (RF), as markers of biological response.**

Recommendations for Polyneuropathies in Sjögren's

Recommendations for Polyneuropathies		Strength of Recommendation
Recommendation 4	For Sjögren's patients with neuropathic pain in the setting of a peripheral neuropathy, we recommend first-line symptomatic treatment that includes gabapentin, pregabalin, or serotonin-norepinephrine re-uptake inhibitors (SNRIs), depending on individual patient tolerance, comorbidities, and side effect risk.	STRONG
Recommendation 5	For Sjögren's patients with neuropathic pain in the setting of a peripheral neuropathy who are not helped by first-line treatments, we recommend sodium channel blocking agents (carbamazepine, oxcarbazepine, lamotrigine) or tricyclic antidepressants (nortriptyline and desipramine may be better tolerated). For patients who are refractory to, or intolerant of, first- and second-line neuropathic pain medications, referral to a neurologist and/or pain management specialist may be warranted.	CONDITIONAL
Recommendation 6	For Sjögren's-related polyneuropathy with a progressive or aggressive presentation, we recommend an empiric glucocorticoid treatment trial. The specific dose and length of treatment with glucocorticoids will depend on the individual circumstances. Factors such as the response to treatment, and the potential side effects of the medication should be considered when determining the appropriate duration of treatment.	CONDITIONAL
Recommendation 7	For Sjögren's-related immune-mediated non-vasculitic large fiber polyneuropathy, we recommend considering intravenous immunoglobulin (IVIG).	CONDITIONAL
Recommendation 8	For Sjögren's-related immune-mediated small fiber neuropathies that do not respond to symptomatic treatment and have recent onset, severe, or progressive disease, we recommend considering treatment with IVIG for a duration of at least 3 months. Treatment with subcutaneous immunoglobulin (SCIG) is an alternative.	CONDITIONAL
Recommendation 9	For Sjögren's patients with acquired chronic demyelinating polyradiculoneuropathies, we recommend offering standard treatments for CIDP.	STRONG
Recommendation 10	For Sjögren's patients with sensory ganglionopathy who manifest significant symptoms, we recommend instituting aggressive and immediate treatment with moderate to high dose glucocorticoids and immunomodulatory/ immunosuppressive therapy.	STRONG
Recommendation 11	For Sjögren's patients with high suspicion of vasculitic neuropathy, we recommend immediate initiation of high-dose systemic glucocorticoids with rituximab as the first line of therapy.	STRONG

Recommendations for Polyneuropathies *Continued*		Strength of Recommendation
Recommendation 12	**For Sjögren's patients with vasculitic neuropathy unresponsive to first-line therapy with glucocorticoids and rituximab, we recommend glucocorticoids and cyclophosphamide as a second line of therapy.**	**CONDITIONAL**
Recommendation 13	**For Sjögren's patients with vasculitic neuropathy with cryoglobulinemia, we recommend maintenance with immunomodulatory therapy.**	**CONDITIONAL**
Recommendation 14	**For Sjögren's patients with vasculitic neuropathy and persistent neuropathic pain, we recommend symptomatic management as discussed in Therapy Recommendations 4 and 5: Polyneuropathies.**	**STRONG**
Recommendation 15	**We do not recommend IVIG as a first line of therapy for Sjögren's patients with vasculitic neuropathy.**	**CONDITIONAL**

Figure 2: Evaluation and Management of Patients with Sjögren's who Exhibit Symptoms and/or Physical Examination Signs of Polyneuropathy



References to Figure 2: Evaluation and Management of Patients with Sjögren's who Exhibit Symptoms and/or Physical Examination Signs of Polyneuropathy

3 Electrodiagnostic studies include nerve conduction studies (NCS) and electromyography (EMG) and should be performed by an experienced electromyographer.

10 For Sjögren's patients with confirmed polyneuropathy, treatment choice depends on the type and location of neuropathy, disease severity, and degree of systemic involvement (e.g., vasculitis).

11 Potential alternative etiologies include diabetes, hypothyroidism, B-12 deficiency, monoclonal gammopathies, infectious etiologies, toxins, and medications. Labs related to these etiologies should be ordered.

12 Recognize that Sjögren's patients can present with a wide range of symptoms, including diverse presentations of peripheral neuropathies. For abnormal sensations suspected of being neuropathic, these questions should be asked to characterize the neuropathy.

13 Consider referral to a neurologist for initial assessment and if the patient has not benefited from initial treatments for neuropathic pain.

14 Consider assessments for gait & balance training and assistive devices by physical therapy, physical medicine rehabilitation, and/or related healthcare professionals if gait disturbance due to weakness, sensory loss, ataxia or imbalance is present.

15 The studies are best timed at 1-4 weeks from onset of symptoms, depending on the type, progression, and severity of the neuropathy.

16 Sodium channel blocking agents include carbamazepine, oxcarbazepine, and lamotrigine.

17 Tricyclic antidepressants that may be better tolerated due to less anticholinergic side effects include nortriptyline and desipramine.

18 If patients are refractory to, or intolerant of, first and second line treatments, refer to a neurologist and/or pain management specialist.

19 The specific dose and length of treatment with glucocorticoid will depend on the individual circumstances. Factors such as the response to treatment and the potential side effects of the medication should be considered when determining the appropriate duration of treatment.

20 We do not recommend intravenous immunoglobulin (IVIG) as a first line of therapy for Sjögren's patients with vasculitic neuropathy.

21 Vasculitic neuropathy should be considered in Sjögren's patients with polyneuropathy and the following clinical scenarios: Acute, painful, rapid onset, or stepwise progression of neurological deficit, clinical and electromyographic evidence of multiple mononeuropathies, evidence of single-organ or systemic vasculitis, immunologically active disease as defined by cryoglobulinemia, hypocomplementemia, monoclonal gammopathy, positive rheumatoid factor and elevated Inflammatory markers.

22 Repeat serum cryoglobulin as a biomarker for therapeutic response, along with complement C4 and rheumatoid factor (RF), as markers of biological response.

23 Including acute inflammatory demyelinating polyneuropathy (AIDP) and chronic inflammatory demyelinating polyneuropathy (CIDP).

24 Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

Evaluating Sjögren's Patients for ANS Neuropathies

Good Practices for Patient Evaluation

Good Practice 20

The following screening process is recommended for the initial assessment of potential autonomic nervous system (ANS) involvement in Sjögren's:

For primary screening, ask the following questions:

1. Do you experience postural lightheadedness, syncope (fainting), near-syncope, or a racing heart when upright?
2. Do you experience problems with sweating too little, or too much?
3. Do you have chronic GI symptoms or problems, such as:
   - Difficulty swallowing
   - Nausea
   - Abdominal pain
   - Feel like you fill up more quickly than you ought to when eating a meal (early satiety)
   - Diarrhea or constipation. If yes, does diarrhea occur at night?
   - Significant abdominal bloating
4. Do you have genitourinary problems, such as:
   - Sexual dysfunction
   - Difficulty emptying your bladder completely or incontinence
   - Frequent urination, particularly frequent nocturnal enuresis
   - Urogenital problems and/or pelvic pain

Good Practice 21

For Sjögren's patients with suspected ANS involvement, conduct further assessments with the Composite Autonomic Symptom Scale (COMPASS-31) questionnaire and orthostatic blood pressure and pulse measurements (postural vital signs).

Good Practice 22

For Sjögren's patients with suspected ANS involvement and abnormal Composite Autonomic Symptom Scale (COMPASS-31) or abnormal postural vital sign results, refer to a neurologist, neurogastroenterologist, cardiologist, urologist, or ANS testing center for further evaluation.

Good Practice 23

For Sjögren's patients with symptoms of orthostatic intolerance, including postural lightheadedness, syncope, and near-syncope, conduct formal autonomic testing at centers or facilities where this testing is available. Autonomic testing should include tilt table, the Quantitative Sudomotor Axon Reflex Test (QSART), measures of heart rate variability, and assessments of blood pressure changes, including the Valsalva maneuver, to characterize the nature of the autonomic nervous system involvement.

Good Practice 24

If formal autonomic testing is performed, a Composite Autonomic Severity Scale (CASS) could be calculated to quantify the severity of autonomic nervous system impairment in Sjögren's.

Good Practice 25

For Sjögren's patients with significant autonomic neuropathy, the following should be considered to exclude other causes: B-12 and B-6 measurement, Hemoglobin A1C, serum immunofixation, serum-free light chains, and an autoimmune dysautonomia panel (screen of antibodies associated with autonomic neuropathy other than Sjögren's, such as acetylcholine receptor ganglionic antibody, ANNA-1, CASPR-2IgG CBA, CRMP-5, DPPX, LGI1-IgG CBA, PCA-2, AP3B2 IFA). Testing for supine and standing catecholamines (norepinephrine) may be considered.

Good Practices for Patient Evaluation *Continued*

Good Practice 26	**For Sjögren's patients where there is concern for autonomic neuropathy or symptoms of abnormal sweating, a skin biopsy could be considered to assess sweat gland nerve fiber density.**
Good Practice 27	**Provided the initial study was abnormal, quantitative autonomic testing [such as tilt table, the Quantitative Sudomotor Axon Reflex Test (QSART), measures of heart rate variability, and assessments of blood pressure changes, including the Valsalva maneuver] could be repeated in 6-12 months after institution of immunomodulatory therapy to assess peripheral nervous system remodeling in Sjögren's patients.**
Good Practice 28	**Autonomic failure in conjunction with sensory neuropathy and sensory ataxia may indicate an autonomic ganglionopathy. Providers should recognize that this may require an urgent referral to a neurologist and aggressive treatment.**
Good Practice 29	**For Sjögren's patients with complex gastrointestinal symptoms, refer to a gastroenterologist or neurogastroenterologist for evaluation and treatment. Motility testing to look for esophageal, gastric, or intestinal dysmotility should be considered.**
Good Practice 30	**For Sjögren's patients with genitourinary symptoms, refer to a urologist, urogynecologist, or neurologist for evaluation and treatment.**
Good Practice 31	**Symptoms related to problematic sweating may result from autonomic neuropathy in Sjögren's. Nocturnal sweating, hyperhidrosis, hypohidrosis, and heat intolerance may be reported by patients. A careful history and examination, supplemented by autonomic tests of sweating function (such as QSART) can be helpful in identifying severity and pattern of impairment.**

‡ ANNA-1 = anti-neuronal nuclear antibody, type 1

CASPR2-IgG CBA, S = contacting-associated response protein 2

CRMP-5 IgG Western Blot, S = collapsing response-mediator protein – 5

DPPX = dipeptidyl-peptidase-like protein-6 (regulatory subunit neuronal Kv4.2 potassium channel)

LGI1-IgG CBA, S = leucine-rich glioma inactivated 1 protein antibody

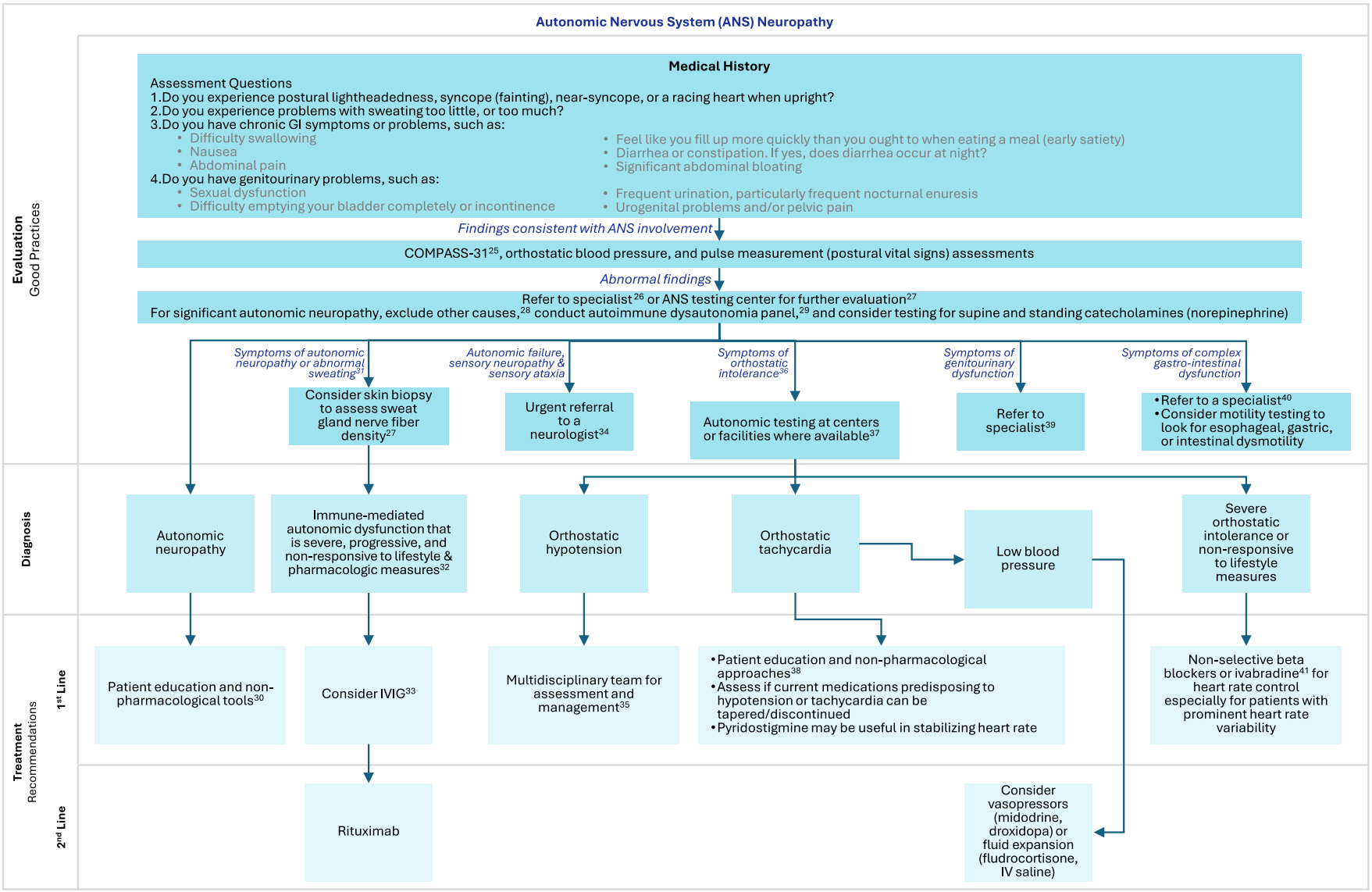
PCAB-2 = Purkinje cell cytoplasmic antibody, type 2

AP3B2 IFA Titer, S = adaptor protein 3 beta 2 antibody by IFA (immunofluorescence)

Recommendations for ANS Neuropathies in Sjögren's

Recommendations for Autonomic Nervous System Neuropathies		Strength of Recommendation
Recommendation 16	**For Sjögren's patients with autonomic neuropathy, we recommend patient education about autonomic dysfunction and non-pharmacologic tools such as lifestyle measures and therapies that target symptoms caused by their disease.**	**STRONG**
Recommendation 17	**For Sjögren's patients with orthostatic tachycardia, we recommend providing patient education to facilitate lifestyle management and initiating non-pharmacologic approaches such as increased fluid intake, abdominal and lower limb compression garments, increased salt intake, and gentle graded exercise in a seated or supine position. Assess if current medications predisposing to hypotension or tachycardia can be tapered/discontinued (stimulants, diuretics, vasodilators). For patients with severe symptoms of orthostatic intolerance or those who do not respond to lifestyle measures, consider the following:** • For heart rate control, use non-selective beta blockers or ivabradine, which is a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker, especially for those patients with prominent heart rate variability. • For individuals with orthostatic tachycardia with low blood pressures thought to potentially contribute to tachycardia, consider vasopressors (midodrine, droxidopa) or fluid expansion (fludrocortisone, IV saline). • Pyridostigmine may be useful in stabilizing heart rate and blood pressure in individuals with orthostatic tachycardia.	**CONDITIONAL**
Recommendation 18	**For Sjögren's patients with orthostatic hypotension, we recommend a multidisciplinary team (could include a rheumatologist, cardiologist, and neurologist) for assessment (tilt table, QSART, etc.) and management, depending on services available regionally.**	**CONDITIONAL**
Recommendation 19	**For Sjögren's-related immune-mediated autonomic dysfunction that is severe, progressive, and not responsive to lifestyle and pharmacologic measures, we recommend considering IVIG, with frequency and dosage that manages symptoms.**	**CONDITIONAL**
Recommendation 20	**For Sjögren's-related immune-mediated autonomic dysfunction that is severe and not responsive to IVIG, we recommend rituximab.**	**CONDITIONAL**

Figure 3: Evaluation and Management of Patients with Sjögren's who Exhibit Symptoms and/or Physical Examination Signs of Autonomic Nervous System (ANS) Neuropathy



References to Figure 3: Evaluation and Management of Patients with Sjögren's who Exhibit Symptoms and/or Physical Examination Signs of Autonomic Nervous System (ANS) Neuropathy

25 Composite Autonomic Severity Scale questionnaire.

26 Neurologist, neurogastroenterologist, cardiologist, urologist.

27 Provided the initial study was abnormal, quantitative autonomic testing [such as tilt table, the Quantitative Sudomotor Axon Reflex Test (QSART), measures of heart rate variability, and assessments of blood pressure changes, including the Valsalva maneuver] could be repeated in 6-12 months after institution of immunomodulatory therapy to assess peripheral nervous system remodeling in Sjögren's patients.

28 Other potential causes include B-12 and B-6 measurement, hemoglobin A1C, serum immunofixation, serum-free light chains.

29 Screen for antibodies associated with autonomic neuropathy other than Sjögren's, such as acetylcholine receptor ganglionic antibody, ANNA-1, CASPR-2IgG CBA, CRMP-5, DPPX, LGI1-IgG CBA, PCA-2, AP3B2 IFA

30 Lifestyle measures and therapies that target symptoms caused by their disease.

31 Problematic sweating may result from autonomic neuropathy in Sjögren's. Nocturnal sweating, hyperhidrosis, hypohidrosis, and heat intolerance may be reported by patients. A careful history and examination, supplemented by autonomic tests of sweating function (such as QSART) can be helpful in identifying severity and pattern of impairment.

32 For Sjögren's patients with significant autonomic neuropathy the following should be considered to exclude other causes: B-12 and B-6 measurement, hemoglobin A1C, serum immunofixation, serum-free light chains, and an autoimmune dysautonomia panel (screen for antibodies associated with autonomic neuropathy other than Sjögren's, such as acetylcholine receptor ganglionic antibody, ANNA-1, CASPR-2IgG CBA, CRMP-5, DPPX, LGI1-IgG CBA, PCA-2, AP3B2 IFA). Testing for supine and standing catecholamines (norepinephrine) may be considered.

33 Dose & frequency should be sufficient to manage symptoms.

34 Autonomic failure in conjunction with sensory neuropathy and sensory ataxia may indicate autonomic ganglionopathy. Providers should recognize that this may require an urgent referral to a neurologist and aggressive treatment.

35 May include rheumatologist, cardiologist, and neurologist. Assessment includes tilt table, QSART, etc.

36 Including postural lightheadedness, syncope, and near-syncope.

37 Autonomic testing should include tilt table, the Quantitative Sudomotor Axon Reflex Test (QSART), measures of heart rate variability, blood pressure changes including the Valsalva maneuver to characterize the nature of the autonomic nervous system involvement. A Composite Autonomic Severity Scale (CASS) could be calculated to quantify the severity of autonomic nervous system impairment.

38 Increased fluid intake, abdominal and lower limb compression garments, increased salt intake, gentle graded exercise in seated or supine position.

39 Urologist, urogynecologist, or neurologist.

40 Gastroenterologist or neuro-gastroenterologist.

41 Ivabradine is a hyperpolarization-activated cyclic nucleotide-gated (HCN) channel blocker.