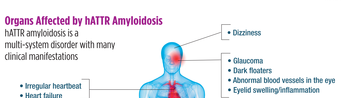
Identifying Signs and Symptoms of Hereditary Transthyretin Amyloidosis in Pharmacy Practice

Clinical Pearls

- **Hereditary transthyretin (hATTR) amyloidosis is genetic, systemic, progressive, debilitating disease with cardiomyopathy-predominant, neurological-predominant, and mixed phenotypes**
  - hATTR amyloidosis polyneuropathy and cardiomyopathy lead to substantial morbidity and mortality
- **Presenting symptoms of hATTR amyloidosis may be variable, nonspecific, and often attributed to other conditions**
  - Diagnosis is often delayed up to 8 years, during which time patients often use ineffective therapies
- **Pharmacists can facilitate diagnosis and direct patients to disease-specific therapies**
  - Early recognition of symptoms and prevalent use of medications to address common symptoms may be indicative of hATTR amyloidosis

hATTR Amyloidosis: Overview of Disease Pathogenesis

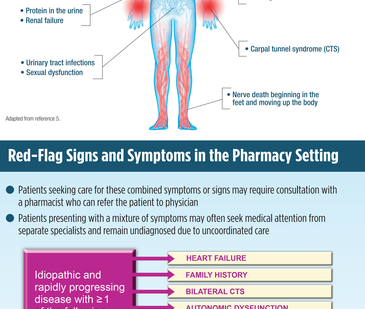
- Mutations in the *TTR* gene destabilize the folded TTR monomer, promoting the lifespan of an aggregate-prone monomer, and eventually result in the buildup of amyloid fibrils in organs throughout the body
- More than 50 missense mutations can cause hATTR amyloidosis. Different mutations can result in cardiac-predominant, neurological-predominant, or mixed phenotypes



Adapted from reference 4.

Organs Affected by hATTR Amyloidosis

hATTR amyloidosis is a multi-system disorder with many clinical manifestations



Adapted from reference 5.

Red-Flag Signs and Symptoms in the Pharmacy Setting

- Patients seeking care for these combined symptoms or signs may require consultation with a pharmacist who can refer the patient to physician
- Patients presenting with a mixture of symptoms may often seek medical attention from separate specialists and remain undiagnosed due to uncoordinated care

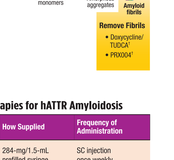
Idiopathic and rapidly progressing disease with ≥ 1 of the following signs/symptoms:

- HEART FAILURE
- FAMILY HISTORY
- BILATERAL CTS
- AUTONOMIC DYSFUNCTION
- UNEXPLAINED WEIGHT LOSS
- RENAL ABNORMALITIES

Adapted from reference 1.

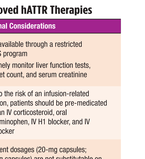
Potential Indicators of hATTR Amyloidosis in the Outpatient Setting

- Multiple therapeutic failures with antihypertensive medications
- Over-the-counter use of:
  - Antidiarrheal/anti-constipation therapies
  - Eye drops for eye "floaters"
  - Topical pain creams
- Progressive worsening of of neuropathy or heart failure despite therapy



Potential Indicators of hATTR Amyloidosis in the Inpatient Setting

- Failure to improve after multiple interventions for heart failure or neuropathy
- Patients with the following diagnoses who fail to improve despite treatment specific to that diagnosis:
  - Chronic inflammatory demyelinating polyradiculoneuropathy
  - Idiopathic axonal polyneuropathy
  - Lumbar spinal stenosis
  - Diabetic neuropathy



Pharmacotherapy for hATTR Amyloidosis

- Management of hATTR amyloidosis includes the use of disease-specific therapies, based on the underlying predominant manifestations, as well as appropriate supportive care and symptom management

hATTR Amyloidosis

Cardiomyopathy **ONLY**	Cardiomyopathy **AND** neuropathy	Neuropathy **ONLY**
Tafamidis	Tafamidis	Patisiran
Diflunisal *Off-label usage*	Patisiran	Inotersen
	Inotersen	Diflunisal *Off-label usage*
	Diflunisal *Off-label usage*	

Mechanism of Action of Therapies Used to Treat hATTR Amyloidosis

*Off-label, †investigational
Adapted from reference 1.

FDA-Approved Disease-Specific Therapies for hATTR Amyloidosis

Medication	Mechanism	Indication	How Supplied	Frequency of Administration
Inotersen	ASO inhibitor of TTR	Polyneuropathy of hATTR	284-mg/1.5-mL prefilled syringe	SC injection once weekly
Patisiran	TTR mRNA inhibitor	Polyneuropathy of hATTR	10-mg/5-mL single-dose vial	80-minute IV infusion once every 3 weeks
Tafamidis	TTR stabilizer	Amyloid cardiomyopathy	20-mg oral capsule; 61-mg oral capsule	Daily

ASO: antisense oligonucleotide; IV: intravenous; mRNA: messenger RNA; SC: subcutaneous; TTR: transthyretin.

Management Considerations for FDA-Approved hATTR Therapies

Medication	Common AEs	Additional Considerations
Inotersen	Injection site reactions Nausea Headache Fatigue Thrombocytopenia	• Only available through a restricted REMS program • Routinely monitor liver function tests, platelet count, and serum creatinine
Patisiran	Infusion-related reactions Upper respiratory tract infections Dyspepsia Dyspnea Muscle spasms	• Due to the risk of an infusion-related reaction, patients should be pre-medicated with an IV corticosteroid, oral acetaminophen, IV H1 blocker, and IV H2 blocker
Tafamidis	In clinical trials, the incidence of AEs was similar between tafamidis and placebo	• Different dosages (20-mg capsules; 61-mg capsules) are not substitutable on a per-mg basis

AE: adverse event; IV: intravenous; REMS: Risk Evaluation and Mitigation Strategy

Conclusions

- **The advent of disease-specific therapies for hATTR amyloidosis allows for improved outcomes for patients**
- **Pharmacists can facilitate access to these therapies through prompt recognition of symptoms and signs and by encouraging physician follow-up, as well as by providing expertise on the pharmacologic management of patients receiving these therapies**

References

1. Adams D et al. *J Neurol*. 2020. doi:10.1007/s00415-019-09688-0. 2. Kapoor M et al. *J Neuromuscul Dis*. 2019;6:189-199. 3. Kachur E. *US Pharm*. 2019;44:8-10. 4. Ruberg FL et al. *J Am Coll Cardiol*. 2019;73:2872-2891. 5. www.amyloidosis.org. 6. Inotersen. Package insert. Akcea Therapeutics; 2020. 7. Patisiran. Package insert. Alnylam Pharmaceuticals, Inc; 2020. 8. Tafamidis. Package insert. Pfizer Inc; 2019.